AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews®

Clin Microbiol Rev. 2007 Oct; 20(4): 660–694.
doi: 10.1128/CMR.00023-07

PMCID: PMC2176051
PMID: 17934078

Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection

Vincent C. C. Cheng, Susanna K. P. Lau, Patrick C. Y. Woo, and Kwok Yung Yuen*

State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, Research Centre of Infection and Immunology, The University of Hong Kong, Hong Kong Special Administrative Region, China

*Corresponding author. Mailing address: State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, Research Centre of Infection and Immunology, The University of Hong Kong, Hong Kong Special Administrative Region, China. Phone: (852) 2855 4892. Fax: (852) 2855 1241. E-mail: hkumicro@hkucc.hku.hk

ABSTRACT

Before the emergence of severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) in 2003, only 12 other animal or human coronaviruses were known. The discovery of this virus was soon followed by the discovery of the civet and bat SARS-CoV and the human coronaviruses NL63 and HKU1. Surveillance of coronaviruses in many animal species has increased the number on the list of coronaviruses to at least 36. The explosive nature of the first SARS epidemic, the high mortality, its transient reemergence a year later, and economic disruptions led to a rush on research of the epidemiological, clinical, pathological, immunological, virological, and other basic scientific aspects of the virus and the disease. This research resulted in over 4,000 publications, only some of the most representative works of which could be reviewed in this article. The marked increase in the understanding of the virus and the disease within such a short time has allowed the development of diagnostic tests, animal models, antivirals, vaccines, and epidemiological and infection control measures, which could prove to be useful in randomized control trials if SARS should return. The findings that horseshoe bats are the natural reservoir for SARS-CoV-like virus and that civets are the amplification host highlight the importance of wildlife and biosecurity in farms and wet markets, which can serve as the source and amplification centers for emerging infections.

INTRODUCTION

Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) is a novel virus that caused the first major pandemic of the new millennium (89, 180, 259). The rapid economic growth in southern China has led to an increasing demand for animal proteins including those from exotic game food animals such as civets. Large numbers and varieties of these wild game mammals in overcrowded cages and the lack of biosecurity measures in wet markets allowed the jumping of this novel virus from animals to human (353, 376). Its capacity for human-to-human transmission, the lack of awareness in hospital infection control, and international air travel facilitated the rapid global dissemination of this agent. Over 8,000 people were affected, with a crude fatality rate of 10%. The acute and dramatic impact on health care systems, economies, and societies of affected countries within just a few months of early 2003 was unparalleled since the last plague. The small reemergence of SARS in late 2003 after the resumption of the wildlife market in southern China and the recent discovery of a very similar virus in horseshoe bats, bat SARS-CoV, suggested that SARS can return if conditions are fit for the introduction, mutation, amplification, and transmission of this dangerous virus (45, 190, 215, 347). Here, we review the biology of the virus in relation to the epidemiology, clinical presentation, pathogenesis, laboratory diagnosis, animal models or hosts, and options for treatment, immunization, and infection control.

TAXONOMY AND VIROLOGY OF SARS-COV

SARS-CoV is one of 36 coronaviruses in the family *Coronaviridae* within the order *Nidovirales*. Members of the *Coronaviridae* are known to cause respiratory or intestinal infections in humans and other animals (Fig. 1). Despite a marked degree of phylogenetic divergence from other known coronaviruses, SARS-CoV together with bat SARS-CoV are now considered group 2b coronaviruses (190, 282). Primary isolation of SARS-CoV was achieved by inoculation of patients' specimens into embryonal monkey kidney cell lines such as FRhK-4 or Vero E6 cell lines, which produced cytopathic changes at foci, where cells become round and refractile within 5 to 14 days (259). These initial cytopathic changes spread throughout the cell monolayers, leading to cell detachment within 24 to 48 h. Subcultures can be made on Vero (monkey kidney), Huh-7 (liver cancer) (301), CACO-2 (colonic carcinoma) (79) or other colorectal cancer, MvLu (mink lung epithelial) (104), and POEK and PS (pig) cell lines (122). Transmission electron microscopy of infected cell lines showed characteristic coronavirus particles within dilated cisternae of rough endoplasmic reticulum and double-membrane vesicles. Clusters of extracellular viral particles adhering to the surface of the plasma membrane were also seen. Negatively stained electron microscopy showed viral particles of 80 to 140 nm with characteristic surface projections of surface proteins from the lipid envelope (89, 180, 259). SARS-CoV has a higher degree of stability in the environment than other known human coronaviruses (91, 276). It can survive for at least 2 to 3 days on dry surfaces at room temperature and 2 to 4 days in stool (276). The electron microscopic appearance and genome order of 5′-replicase (Orf1ab)-structural proteins (spike [S]-envelope [E]-membrane [M]-nucleocapsid [N])-poly(T)-3′ are similar to those of other members of the *Coronaviridae* (236). Similar to other coronaviruses, it is an enveloped positive-sense single-stranded RNA virus with a genome size of almost 30 kb (Fig. 2). The genome is predicted to have 14 functional open reading frames (ORFs) (290). Their functions and putative roles are outlined in Table 1. Two large 5′-terminal ORFs, ORFs 1a and 1b, encode 16 nonstructural proteins, 7 of which are likely to be involved in the transcription and replication of the largest genome among all

RNA viruses (92, 95, 158, 166, 242, 284, 309, 316, 343, 414). The two proteases are involved in posttranslational proteolytic processing of the viral polyprotein (5, 15, 121, 224, 394). The surface S protein is involved in the attachment and entry of the host cell and is therefore the main target for neutralizing antibody and antiviral peptides (159, 206, 227, 301, 334). N together with M, E, and Orf7a are involved in the assembly of the virion (97, 147, 150, 245, 359). Orf3a is an ion channel protein that is likely to be involved in viral budding and release (234). Analysis of genome sequences of many isolates of SARS-CoV from humans with civet SARS-CoV and bat SARS-CoV showed that the most variable genes with nucleotide homologies of less than 90% are the S gene, *Orf3*, *Orf8*, *nsp2*, *nsp3*, and *nsp4* (190, 215, 282). Deletions of 82 and 415 nucleotides in *Orf8* were found in some human isolates, whereas a unique 29-nucleotide signature insertion in *Orf8* can be found in animal isolates (64, 117). Therefore, the more conserved *Orf1b* is generally chosen to be the molecular target for the design of clinical diagnostic tests rather than these less conserved regions.

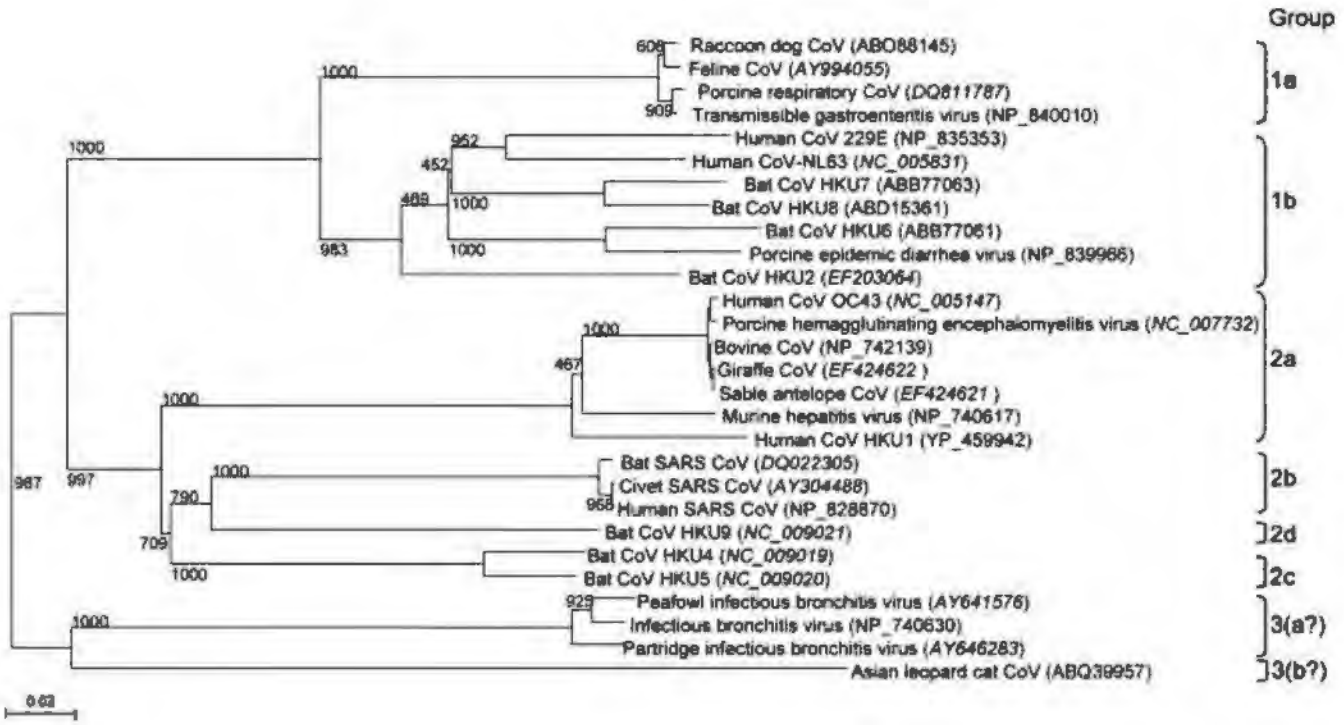


FIG. 1.

Phylogenetic tree of 28 coronaviruses with complete protein sequences of helicase. Their accession numbers are shown in parentheses. Italic type indicates the complete genome accession numbers since helicase protein sequence accession numbers of these coronaviruses are not available. The helicase of another eight coronaviruses of spotted hyena, cheetah, ferret, puffinosis, rat, pigeon, goose, and duck are not included because no complete protein sequence is available. The classification of Asian leopard cat coronavirus is undefined. The tree was constructed by the neighbor-joining method using clustalX 1.83. The scale bar indicates the estimated number of substitutions per 50 nucleotides. (Data are from references 265, 326, 339, 367, 368, and 375.)

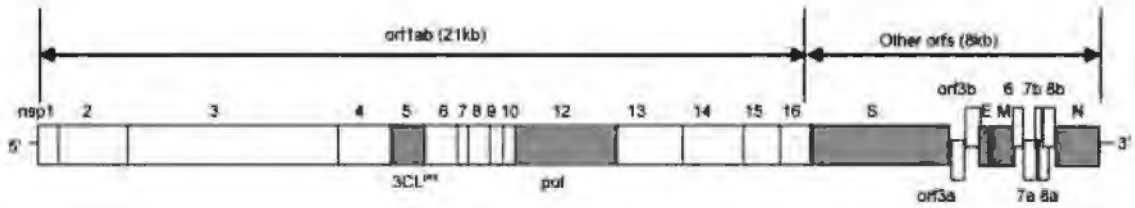


FIG. 2.

Genome arrangement of SARS-CoV. Gray boxes indicate 3CL protease ($3CL^{pro}$), polymerase (pol), spike (S), envelope (E), membrane (M), and nucleocapsid (N) genes.

TABLE 1.

Nomenclature and functional characteristics of SARS-CoV gene products and their interactions with host cells in disease pathogenesis

Gene nomenclature (no. of amino acid residues in product)	Gene product and/or characteristic(s) (reference[s])	Effect on cellular response of host (reference[s])
Orf1a/b		
nsp1 (180)	Expression promoted degradation of host endogenous mRNAs, which may inhibit host protein synthesis and prevented endogenous IFN-β mRNA accumulation (167)	Induce CCL5, CXCL10 (IP10), and CCL3 expression in human lung epithelial cells via activation of NF-κB; increases cellular RNA degradation, which might facilitate SARS-CoV replication or block immune responses (81, 192)
nsp2 (638)	Deletion attenuates viral growth and RNA synthesis (106)	
nsp3 (1,922)	Papain-like protease 2; proteolytic processing of the viral polyprotein at 3 sites and participation in synthesis of subgenomic RNA segment (15, 121, 224)	
ADP-ribose 1-phosphatase; dephosphorylates Appr-1‴-p, a side product of cellular tRNA splicing, to ADP-ribose (271)		Putative catalytic triad (Cys1651-His1812-Asp1826) and zinc-binding site have deubiquitinating activity; this unexpected activity in addition to its papain-like protease suggests a novel viral strategy to modulate the host cell ubiquitination machinery to its advantage (15, 224, 279)
nsp4	Not known	

Open in a separate window

VIRAL LIFE CYCLE

Trimers of the S protein form the peplomers that radiate from the lipid envelope and give the virus a characteristic corona solis-like appearance under an electron microscope. S is a class I fusion protein that consists of the amino-terminal S1 and carboxyl-terminal S2 subunits connected by a fusion peptide. The two subunits are indispensable for receptor binding and membrane fusion, respectively. The receptor binding domain of S1 has been mapped to residues 318 to 510 (9, 365). The binding of S1 to the cellular receptor will trigger conformational changes, which collocate the fusion peptide upstream of the two heptad repeats of S2 to the transmembrane domain, and, finally, fusion of the viral and cellular lipid envelopes. Moreover, this process could be facilitated by the infected cell membrane-associated protease, such as factor Xa, which can cleave S into S1 and S2. This proteolytic cleavage is specifically inhibited by a protease inhibitor, Ben-HCl (90).

The key receptor of the host cell attached by S is angiotensin-converting enzyme 2 (ACE2), which is a metalloprotease expressed in the cells of the lung, intestine, liver, heart, vascular endothelium, testis, and kidney (119). Since ACE2 was shown to protect against acute lung injury in a mouse model and since the binding of the S protein to host cells results in the downregulation of ACE2, this mechanism may contribute to the severity of lung damage in SARS (181). Cells expressing some lectins, including DC-SIGN, L-SIGN, and LSECtin, have been shown to augment the cellular entry of pseudotype virus expressing S but only in the concomitant presence of ACE2 (40, 107, 162, 398). Nonsusceptible cells expressing these lectins in the absence of ACE2, such as dendritic cells, were able to promote the cell-mediated transfer of SARS-CoV to susceptible cells (40). Although lysosomotropic agents can block viral entry, which indicates that endosomal acidification is required for entry, the activation of the S protein by protease can bypass this inhibition and result in cell-to-cell fusion. Despite the role of the pH-sensitive endosomal protease cathepsin L in the entry pathway (151, 300), viral culture does not require pretreatment with trypsin. However, this pH-sensitive cathepsin L may be a target for agents such as chloroquine, which elevates endosomal pH (174, 341).

The process of viral disassembly in the cytoplasm for the release of viral RNA for translation and replication remains elusive. Translation starts with two large polyproteins from *Orf1a* and *Orf1ab*, which are posttranslationally cleaved by the two viral proteases into nsp1 to nsp16. These cleavage products form the replication-transcription complex, which replicates the viral genome and transcribes a 3′-coterminal nested set of eight subgenomic RNAs. It is therefore conceivable that infected cells contain a higher number of transcripts containing genes towards the 3′ terminus of the viral genome. On this basis, reverse transcriptase PCR (RT-PCR) using the N gene may have a better sensitivity than those using the other genes.

As in other coronaviruses, SARS-CoV may attach by the hydrophobic domains of their replication machinery to the limiting membrane of autophagosomes and form double-membrane vesicles. Once sufficient viral genomic RNA and structural proteins are accumulated, viral assembly by budding of the helical nucleocapsid at the endoplasmic reticulum to the Golgi intermediate compartment occurs. Here, the triple-membrane-spanning M protein interacts with the N protein and viral RNA to generate the basic structure. It also interacts with the E and S proteins to induce viral budding and release. Unlike other coronaviruses, the M protein of SARS-CoV also incorporates another triple-membrane-spanning protein of *Orf3a* into the virion (161). The N protein is the most abundantly expressed viral protein in infected cells in which the mRNA levels were amplified 3 to 10 times higher at 12

h postinfection than other structural genes (138) and is therefore an important target for immunohistochemistry and antigen detection in clinical specimens. Various diagnostic tests, antiviral agents, and vaccines are designed on the basis of our understanding of the structure and function of the various viral proteins involved in the life cycle of this virus.

SEQUENCE OF THE SARS EPIDEMIC AND MOLECULAR EVOLUTION OF THE VIRUS

Sequence of Events

SARS was the first known major pandemic caused by a coronavirus. During the epidemic in 2003, 8,096 cases with 774 deaths had occurred in over 30 countries among five continents (89, 117, 144, 180, 182, 197, 236, 250, 259, 260, 270, 290, 292, 303, 336, 377). The disease emerged in late 2002, when an outbreak of acute community-acquired atypical pneumonia syndrome was first noticed in the Guangdong Province (Table 2). Retrospective surveillance revealed severe cases of the disease in five cities around Guangzhou over a period of 2 months (431). The index case was reported in Foshan, a city 24 km away from Guangzhou. The second case involved a chef from Heyuan who worked in a restaurant in Shenzhen. The patient had regular contact with wild game food animals. His wife, two sisters, and seven hospital staff members who had contact with him were also affected. From 16 November 2002 to 9 February 2003, a total of 305 cases were reported in mainland China, with 105 of those cases involving health care workers. The devastating pandemic started in Hong Kong, Special Administrative Region (HKSAR), when a professor of nephrology from a teaching hospital in Guangzhou who had acquired the disease from his patients came to HKSAR on 21 February 2003. Within a day, he transmitted the infection to 16 other people in the hotel where he resided. His brother-in-law, one of the secondary cases, underwent an open lung biopsy from which the etiological agent was discovered and first isolated (259). It was a novel coronavirus, named SARS-CoV.

TABLE 2.

Sequence of events and molecular evolution of SARS-CoV throughout the epidemic[a]

Phase and date	Important event, phase of evolution, and genotypic marker(s)[b]
Early	Most isolates had SNV genotypic marker of the GZ02 reference nucleotide at positions 17564, 21721, 22222, 23823, and 27827 of G:A:C:G:C; some initial cases had the 29-bp insertion or 82-bp deletion at *Orf8*; avg K_a/K_s ratio of >1, which was higher than that of the middle phase, which indicates strong positive selection
16 November 2002	First case that fulfilled the WHO definition of SARS at Foshan, Guangdong Province, China
17 December 2002	Chef from Heyuan who worked at a restaurant in Shenzhen had atypical pneumonia
26 December 2002 to 20 January 2003	Outbreak of similar cases at Zhongshan
Middle	SNV genotypic marker of G:A:C:T:C; avg K_a/K_s ratio was higher than that of the late phase but was <1, which indicates purifying selection
12 January 2003	Outbreak in Guangzhou resulted in complicated SARS cases transferred to the major hospitals in Guangzhou
31 January 2003	Outbreak in Guanzhou hospitals involving patients and health care workers
Late	SNV marker of T:G:T:T:T; avg K_a/K_s ratio shows stabilization of nonsynonymous mutation rate; some isolates had 415-bp deletion at *Orf8*
21 February 2003	65-yr-old doctor from Guangdong Province resided at "hotel M" in Hong Kong (index patient); unwell since 15 February and admitted to the hospital on 22 February; infected 17 residents at hotel M, some of whom traveled to Vietnam, Singapore, and Toronto, where they started new local clusters of cases
26 February 2003	Hotel M contact was admitted to a hospital in Hanoi and started a nosocomial outbreak

Open in a separate window

[a]See references 27, 89, 117, 182, 190, 197, 215, 218, 221, 236, 251, 252, 259, 277, 304, 377, 378, 422, and 431.
[b]K_a/K_s ratio refers to the ratio of nonsynonymous nucleotide substitutions to synonymous nucleotide substitutions during the molecular evolution of SARS-CoV.

The secondary cases unknowingly carried the disease to hospitals in the HKSAR and to other countries and continents including Vietnam, Canada, Singapore, the Philippines, the United Kingdom, the United States, and back again to China. Carlo Urbani, a physician working at the World Health Organization (WHO) office in Hanoi, Vietnam, was the first to notify the WHO of cases outside Guangdong after witnessing an explosive nosocomial outbreak of SARS in a hospital in Hanoi, which resulted from a person who had returned from the hotel in HKSAR. Carlo Urbani's description of the disease, to which he later succumbed, alerted health authorities throughout the world and accelerated collaborative research to identify the virus and combat the disease (281).

Molecular Evolution

Soon after the isolation of SARS-CoV, SARS-CoV-like viruses were found in palm civets and a raccoon dog from wild-animal markets in the Guangdong Province of China (117), suggesting that these animals could be the source of human infections. As a result, massive numbers of palm civets were culled to remove sources for the reemergence of SARS in Guangdong in January 2004. The virus was found in many civets and raccoon dogs from the wildlife market prior to culling but not in over 1,000 civets later sampled at 25 farms in 12 provinces (168). The evolutionary starting point was a prototype group consisting of three viral genome sequences of animal origin. This prototype group representing low-pathogenicity virus has seven single-nucleotide variation (SNV) sites that caused six amino acid changes, at positions 147, 228, 240, 479, 821, and 1080 of the S protein, which were involved in generating the early phase of the 2002 and 2003 epidemic. One of these was found in the first SARS patient in the subsequent epidemic of 2003 to 2004. A further 14 SNVs caused 11 amino acid residue changes, at positions 360, 462, 472, 480, 487, 609, 613, 665, 743, 765, and 1163. This resulting high-pathogenicity virus group caused the middle phase of the epidemic of 2003. Finally, the remaining six SNVs caused four amino acid changes, at positions 227, 244, 344, and 778, which resulted in the group of viruses responsible for the late phase and the global epidemic (168). The neutral mutation rate of this virus during the epidemic in 2003 is almost constant, at around 8×10^{-6} nt^{-1} day^{-1}, which is similar to those of most known RNA viruses (64, 304). The most recent common ancestor was estimated to be present around mid-November, which is epidemiologically compatible with the first case of SARS found in Foshan.

After the epidemic was over, a second interspecies-jumping event occurred in late 2003 to early 2004, resulting in the reemergence of four human cases in China (45, 347). These four cases were believed to be due to an independent interspecies transmission event, instead of residual cases of the major epidemic, because of the much lower affinity for human ACE2 (bACE2) of the S proteins of SARS-CoV isolated from these patients and palm civets than that of the major 2003 epidemic isolates from SARS patients, which utilized both human and palm civet ACE2 efficiently (216). Since S contains the receptor binding domain for the host receptor and is immunogenic, it is under selection in the host and becomes the most rapidly evolving protein, with most mutations located in the S1 domain and especially the receptor binding domain. Bioinformatic analysis has identified three key amino acid residues at positions 360, 479, and 487 that are responsible for host-specific binding (17). Most human isolates in the 2003 epidemic have N479 and T487 in their S, whereas most civet isolates have K/R479 and S487. The low affinity of the S proteins bearing K479 and S487 combinations for hACE2 was confirmed by pseudotype binding assays. However, the human and

civet isolates of the outbreak of 2003 to 2004 had N479 and S487, which suggested that this is an intermediate stage of mutation of the S protein. Further change to the N479 and T487 combination will allow efficient human-to-human transmission (275). Apart from the subsequent minor outbreak, three laboratory-associated outbreaks were reported in Singapore, Taiwan, and Beijing from September 2003 to May 2004 (221, 251, 252, 256). In Beijing, the outbreak also involved secondary and tertiary cases.

Phylogenetic analysis of the S protein of 139 SARS-CoV isolates in the Hong Kong outbreak showed that several introductions of viruses had occurred but that only one of them was associated with the major outbreak in HKSAR and the rest of the world (116). Some of the strains found in the early stages of the outbreak were phylogenetically distinct from the major cluster and were closer to some of the Guangdong and Beijing strains. This concurred with the fact that the index patient of the HKSAR outbreak was a Guangzhou medical doctor who had traveled to HKSAR. Another molecular epidemiological study of the Guangdong outbreak suggested that the disease spread from Guangdong to HKSAR and the rest of the world, and the index case was a chef who handled game animals (431). Subsequent animal surveillance in China recovered coronavirus isolates that had 99.8% nucleotide identity with SARS-CoV (117). A characteristic 29-bp insertion between *Orf8a* and *Orf8b* (also initially known as *Orf10* and *Orf11*) was found in these animal isolates (117, 302). This 29-nucleotide segment was deleted either before or soon after crossing the species barrier to humans. The biological effect of this deletion remains elusive. A number of SARS-CoV isolates in the later stages of the epidemic showed larger deletions around this site (64). Two independent molecular epidemiological studies comparing the complete genomes of 12 and 63 virus isolates also found evidence of strong positive selection at the beginning of the epidemic, which was followed by a purifying selection, as indicated by the amino acid substitution rate at S, Orf3a, and nsp3 (64, 304, 402). Both studies suggested that molecular adaptation of the virus had occurred after interspecies transmission from animals to humans. In the small outbreak in Guangzhou in 2004, all four human isolates belonged to a separate sublineage of the concurrent animal isolates that were distinct from the human pandemic or animal viruses in 2003. Although SARS-CoV is distinct from the three existing groups of coronaviruses, it may be closer to group II because 19 out of 20 cysteines found in the S1 domain of the S protein are spatially conserved compared with the group II consensus sequence, whereas only five cysteine residues are conserved compared with those of groups I and III (93, 302). Since coronaviruses are believed to have coevolved with their animal hosts, it is possible that rats, mice, and cattle harboring group II coronaviruses are more likely to be the animal host for SARS-CoV than cats, which harbor group I coronavirus. However, when a comparison of the phylogenetic trees for 11 known host species and nucleocapsid sequences of 36 coronaviruses was done using an inference approach with sliding-window analysis, there was statistical incongruence, which indicates multiple host species shifts between the coronaviruses of many animals that are phylogenetically distant (283). Thus, it would not be too unexpected if other mammals are the true animal reservoir rather than mice and rats. Nevertheless, civets and other related mammals had at least served as a major amplification host in the markets of southern China irrespective of the original animal reservoir. The control of these animals and the markets played a pivotal role in the epidemiological control of SARS (304). In view of the low rate of detection of SARS-CoV in wild and farm civets (338), in contrast to a very high rate in caged civets in wildlife markets, efforts were made to find the natural reservoir of SARS-CoV in birds, pig, cattle, sheep, mice, and rats, which all turned out to be negative. However, SARS-CoV-like viruses with around 90% genomic identity with SARS-CoV were independently discovered in horseshoe bats (*Rhinolophus* spp.) in HKSAR and mainland

China (190). The high seroprevalence and viral load of infected Chinese horseshoe bats, *Rhinolophus sinicus*, strongly suggested that bats are the natural reservoir of SARS-CoV-like viruses, similar to the situation of fruit bats carrying Hendra virus or Nipah virus (363).

EPIDEMIOLOGICAL CHARACTERISTICS

The epidemiological linkage of the initial human cases of the 2003 pandemic to wild game animals suggested that SARS-CoV is zoonotic in origin (431). The isolation of SARS-CoV-like viruses from palm civets and subsequently horseshoe bats further supported this contention (117, 190). It was reported that a seroprevalence rate of about 80% was found in civets in animal markets in Guangzhou (338). However, person-to-person transmission has been the primary mode of spread of the epidemic, which has occurred in health care facilities, workplaces, homes, and public transportation. The most important route of person-to-person spread appears to be direct or indirect contact of the mucosae with infectious respiratory droplets or fomites (296). SARS-CoV has been detected in respiratory secretions, feces, urine, and tears of infected individuals (42, 229). Nosocomial transmission of SARS was facilitated by the use of nebulizers, suction, intubation, bronchoscopy, or cardiopulmonary resuscitation on SARS patients, when large numbers of infectious droplets were generated (70, 197, 340). In fact, almost half of the SARS cases in HKSAR were nosocomial infections that were acquired within health care facilities and institutions (202). The attack rate among health care workers was higher where the number of SARS patients was greater (187). Although airborne transmission is considered uncommon, a unique form of airborne transmission was considered a likely explanation for a large community outbreak in a private housing estate called Amoy Garden in HKSAR. Contaminated aerosols generated in toilets by exhaust fans coupled with dried U traps of sewage drains, which ascended the light well connecting different floors, caused an explosive outbreak affecting hundreds of people (71, 405). The presence of viruses in stool, often with high viral loads (156, 258), also suggested the possibility of feco-oral transmission, although this has not been proven conclusively. It was suggested that SARS was transmitted in commercial aircraft during the epidemic. Out of a total of 40 flights investigated, 5 were associated with probable in-flight SARS transmission, affecting 37 passengers (254). Most of the affected passengers sat within five rows of the index case. The overall risk of transmission appears to be low, at around 1 in 156 (358). In the largest incident, during a 3-h flight carrying 120 passengers traveling from HKSAR to Beijing, a superspreading event (SSE) infected 22 passengers (254). The pattern of involvement was atypical, considering the short duration of exposure of 3 h and the widespread involvement of patients sitting within seven rows in front of and five rows behind the index case. Although airborne transmission was considered to be a possible explanation, other potential modes of transmission, such as contact of passengers with the index case before or after the flight, cannot be excluded, especially since 17 out of the 22 people infected were from two tourist groups (254). In another study, a SARS patient traveled between HKSAR and European countries during the presymptomatic and early symptomatic period, and no transmission among passengers seated in close proximity to the index patient was found, suggesting that in-flight transmission of SARS is not common (23). Symptomatic SARS patients appeared to transmit infections on board much more readily than presymptomatic ones (23, 254, 358). Initiation of screening procedures to detect people with fever prior to boarding has been used in an attempt to reduce the risk of in-flight transmission of SARS, but the efficacy is still uncertain (342).

In 17 studies that reported on seroepidemiology, the seroprevalence varied from 0 to 1.81% for the general population, 0 to 2.92% for asymptomatic health care workers, 0 to 0.19% for asymptomatic household contacts, and 12.99 to 40% for asymptomatic animal handlers (28, 37, 45, 69, 117, 141, 198, 201, 203, 207, 209, 228, 352, 369, 387, 406, 429). The last finding is quite expected, since frequent zoonotic challenges by low-level-pathogenic strains of SARS-CoV before 2003 in animal handlers of southern China would probably have caused such a high seroprevalence in this at-risk group. Genuine asymptomatic infection with antigenemia detected by enzyme immunoassay (EIA) and seroconversion confirmed by neutralization antibody assay was documented in a restaurant worker who worked in the same restaurant as the index case of the outbreak of 2003 to 2004 (45). However, in 2003, sustained exposure of the animal handlers to these infected civets and other wild animals would result in the introduction of a moderately transmissible and more virulent SARS-CoV strain, which would have mutated from the animal strain and adapted to infect humans more efficiently. The result was a massive global outbreak, but the overall asymptomatic infection rate was still relatively low with this more virulent human-adapted virus in the general population, health care workers, and household contacts. A meta-analysis gave overall seroprevalence rates of 0.1% for the general population and 0.23% for health care workers (203). It is also important to remember that these seroprevalence studies are not directly comparable since different serological methods of various sensitivities or specificities were used with or without confirmation by another test. Thus, the true incidence of asymptomatic infection remains elusive.

The incubation period of SARS is 2 to 14 days, although occasional cases with longer incubation periods have been reported (41). The average number of secondary cases resulting from a single case was two to four (225, 285). Unlike influenza virus, where the patients were most infectious in the first 2 days of illness, transmission from symptomatic SARS patients usually occurred on or after the fifth day of onset of disease, which is in line with the rising viral load in nasopharyngeal secretions that peaked at around day 10 (258). There have been speculations about the incidence of SARS and ambient temperature (319), but a definite seasonality could not be concluded. SSEs have been noted to play an important role in the propagation of the SARS outbreak, which gives rise to a disproportionate number of secondary cases, as in the Amoy Garden of HKSAR. A study comparing the clinical and environmental features of SSE and non-SSE cases showed that SSEs were likely to be related to a combination of factors including delayed isolation, admission to a nonisolation ward, and severe disease at the time of isolation (53).

CLINICAL FEATURES

The typical clinical presentation of SARS is that of viral pneumonia with rapid respiratory deterioration (Table 3). Fever, chills, myalgia, malaise, and nonproductive cough are the major presenting symptoms, whereas rhinorrhea and sore throat are less frequently seen (7, 21, 37, 149, 197, 258, 259, 270, 278, 336, 411, 425). Clinical deterioration, often accompanied by watery diarrhea, commonly occurs 1 week after the onset of illness (58, 258). Similar to other causes of atypical pneumonia, physical signs upon chest examination are minimal compared with the radiographical findings. Chest radiographs typically show ground-glass opacities and focal consolidations, especially in the periphery and subpleural regions of the lower zones. Progressive

involvement of both lungs is not uncommon (113, 148, 184, 362). Shifting of radiographic shadows and spontaneous pneumomediastinum may occur (74, 258). A retrospective analysis of serial chest radiographs in all SARS patients from HKSAR showed that the initial extent and progression of radiographic opacities may be useful for prognostic prediction (6).

TABLE 3.

Correlation between clinical, virological, immunological, and histopathological findings

Clinical and laboratory features (% positive isolates [no. of isolates studied/total no.]) (reference)[a]	Viral load for indicated day(s) after onset of symptoms (reference)	Blood immune profile or histopathological feature (reference)
Systemic involvement Fever (99.9 [751/752]) Chill or rigors (51.5 [377/732]) Malaise (58.8 [317/539])	Mean 1.1 log copies/ml between days 10 and 15 in serum (156)	Increased mean serum concentrations of IL-16, TNF-α, and transforming growth factor β1 but decreased IL-18 between days 3 and 27 (16); increased IFN-γ and inflammatory cytokines IL-1, IL-6, and IL-12 for at least 2 wk; chemokine profile demonstrated increased neutrophil chemokine IL-8, MCP-1, and Th1 chemokine IP-10 (360); increased serum concn of IP10, MIG, and IL-8 during the first wk was associated with adverse outcome or death (325)
Respiratory involvement Rhinorrhea (13.8 [50/362]) Sore throat (16.5 [91/552]) Cough	Mean 2.4 log copies/ml between days 10 and 15 for NPA (156), 9.58×10^2-5.93×10^6 copies/ml for throat swab and 7.08×10^2-6.38×10^8 copies/ml for saliva between days 2 and 9 (349), and 2×10^4-1×10^{10} copies/ml between days 5 and 51 for lung tissue (96)	IP10 highly expressed in both lung and lymphoid tissues, with monocyte-macrophage infiltration and depletion of lymphocytes (163); increased alveolar macrophages and CD8 cells, decreased CD4-to-CD8 ratio, and increased TNF-α, IL-6, IL-8, RANTES, and MCP-1 levels in bronchoalveolar lavage samples (124, 344); IP10 was increased in lung tissue from patients who died of SARS (325); increased differential expression of cytokines within these pulmonary tissues, including Stat1, IFN-regulatory factor 1, IL-6, IL-8, and IL-18, often characteristic of

Open in a separate window

[a]See references 7, 21, 37, 149, 197, 258, 259, 270, 278, 336, and 425 for clinical and laboratory features unless otherwise specified in the table.

Diarrhea is the most common extrapulmonary manifestation, followed by hepatic dysfunction; dizziness, which may be related to diastolic cardiac impairment and pulmonary arterial thrombosis; abnormal urinalysis; petechiae; myositis; neuromuscular abnormalities; and epileptic fits (44, 58, 188, 211, 248, 335, 346, 383). The elderly may present atypically without fever or respiratory symptoms (68, 361). While infections in children appear to be milder than those in adults (20, 144, 183), SARS in pregnant women carries a significant risk of mortality (364, 410). Higher nasopharyngeal and serum viral loads were associated with oxygen desaturation, mechanical ventilation, and mortality; higher stool viral loads were associated with diarrhea; and higher urine viral loads were associated with abnormal urinalysis (58, 75, 156). The significant correlation of the viral loads in these specimens to the severity of clinical or laboratory findings suggested that extrapulmonary viral replication was contributing to clinical manifestations (156).

As for hematological parameters, peripheral blood lymphopenia and elevated hepatic parenchymal enzymes are common with or without thrombocytopenia or increases in D dimers and activated partial thromboplastin time (197). About 20% to 30% of patients developed respiratory failure requiring mechanical ventilation, and the overall mortality rate was around 15%. Age, presence of comorbidities, increased lactate dehydrogenase level, hypouricemia, acute renal failure, more extensive pulmonary radiological involvement at presentation, and a high neutrophil count at the time of admission are poor prognostic indicators (153, 197, 385). Restrictive lung function abnormalities due to residual lung fibrosis and muscle weakness are common in the convalescent phase (34, 247, 255). Among survivors of SARS in HKSAR 1 year after illness, significant impairment in diffusion capacity was noted in 23.7% of studied subjects. The exercise capacity and health status of SARS survivors were also remarkably lower than those of the healthy population (154). A study on the pathological changes of testes from six patients who died of SARS indicated that orchitis was also a complication and suggested that reproductive functions in male patients who recovered from SARS should be monitored (388). Depression and posttraumatic stress disorder are especially common among health care workers and patients with affected family members (57, 66, 238, 310). Complications due to the use of corticosteroids including psychosis, adrenal insufficiency, and avascular osteonecrosis were also reported (36, 112, 145, 195, 200).

HISTOPATHOLOGICAL CHANGES OF SARS

Histological Changes

Acute diffuse alveolar damage with air space edema was the most prominent feature in patients who died before the 10th day after onset of illness (99, 250). Hyaline membranes, interstitial edema, interstitial infiltrates of inflammatory cells, bronchiolar injury with loss of cilia, bronchiolar epithelial denudation, and focal deposition of fibrin on the exposed basement membranes were other observed features (157). Patients who died after the 10th day of illness exhibited a mixture of acute changes and those of the organizing phase of diffuse alveolar damage. There was interstitial and airspace fibrohlast proliferation, type II pneumocyte hyperplasia, and squamous metaplasia of bronchial epithelium. The alveolar spaces contained a combination of macrophages, desquamated pneumocytes, and multinucleated giant cells. Hemophagocytosis in the alveolar exudates and thrombosis of venules

were noted in some cases. Other pulmonary complications might include secondary bacterial bronchopneumonia and invasive aspergillosis (345). Systemic vasculitis involving the walls of small veins with edema, fibrinoid necrosis, and infiltration by monocytes, lymphocytes, and plasma cells were noted in one report (87).

No tissue destruction or severe inflammatory process associated with viral infection was noted in other organs or tissues, but viral particles could be detected in pneumocytes and enterocytes by in situ hybridization (331). Inflammation, cellular apoptosis, or microvillus atrophy of a significant degree was not found in the intestinal mucosa to account for the watery diarrhea. Immunohistochemical staining showed the presence of viral nucleoproteins in type II pneumocytes and occasionally pulmonary macrophages. Necrosis or atrophy in the lymphoid tissue of lymph nodes and white pulp of the spleen are commonly observed extrapulmonary pathologies.

Immunological Profiles

Flow cytometric examination of the peripheral blood at the time of admission before the use of steroid showed decreases in levels of dendritic cell subsets, natural killer cells, $CD4^+$ and $CD8^+$ T lymphocytes, and B lymphocytes (82, 213, 420). A study of three SARS patients suggested that a self-limiting or abortive infection of peripheral blood mononuclear cells can occur, as evident by the presence of minus-strand RNA, the replicative intermediate of the virus during the initial week of illness (208). Studies of the cytokine profile of SARS patients showed conflicting results, which may be due to the use of many immunomodulators including steroids. However, those studies generally showed consistent and significant elevations of the plasma chemokines gamma interferon (IFN-γ)-inducible protein 10 (IP10 [CXCL10]), monocyte chemotactic protein 1 (MCP-1 [CCL2]), and interleukin-8 (IL-8). In some studies, levels of the Th1-related cytokines IFN-γ and IL-12 and the inflammatory cytokines IL-1β and IL-6, which can induce an intense inflammatory response, were also increased (63, 152, 163, 165, 325, 360). In one study, patients with severe disease tended to have increased plasma levels of IFN-α, IFN-γ, and CXCL10 and decreased levels of IL-12p70, IL-2, and tumor necrosis factor alpha (TNF-α) during the acute phase. In the late phase, patients with severe disease had significantly increased plasma chemokine levels of IL-8, CXCL10, and CCL2 but decreased cytokine levels of IL-12p70, IL-2, TNF-α, and IFN-γ compared with mild cases of SARS (26). These host responses may account for the recruitment and accumulation of alveolar macrophages and polymorphs and the activation of Th1 cell-mediated immunity by the stimulation of natural killer and cytotoxic T lymphocytes, respectively. Since SARS-CoV appears to evade the triggering of IFN-α and IFN-β in human macrophages in vitro (61, 280), the lack of an antiviral innate immune response may permit uncontrolled viral replication with progressive increases in viral load and the accompanying proinflammatory systemic response. This situation continues into the second week of illness until the appearance of the adaptive immune response, which brings viral replication under control. Moreover, comparative transcriptomal microarray analysis showed that SARS-CoV rather than CoV-229E markedly upregulated genes associated with apoptosis, inflammation, the stress response, and procoagulation during the early phase of infection of a human liver cancer cell line (Huh7) (322). Both observations help to explain the clinical severity of SARS in relation to the high viral load at up to 2 weeks of illness and the intense inflammatory response as evident from serum cytokine profiles and histopathology. The majority of SARS patients resolved the proinflammatory cytokine and chemokine responses at the acute

phase and expressed adaptive immune genes. In contrast, patients who later succumbed showed deviated IFN-stimulated gene and immunoglobulin gene expression levels, persistent chemokine levels, and deficient anti-SARS spike antibody production. It was speculated that unregulated IFN responses during the acute phase may lead to a malfunction of the switch from innate immunity to adaptive immunity. Indeed, recovered patients were found to have higher and sustainable levels of N-specific antibody and S-specific neutralizing antibody responses, whereas patients who later succumbed had an initial rise and then a fall in antibody levels just before death, suggesting that antibody response is likely to play an important role in determining the ultimate disease outcome (417).

PATHOGENESIS, IMMUNE RESPONSE, AND HOST SUSCEPTIBILITY

Interaction between Viral and Cellular Factors

The exact mechanism of how the virus produces damage at cells, tissue, and organs to clinical levels remains elusive. Similar to other viruses such as influenza A virus, Nipah virus, or Ebola virus, SARS-CoV must possess the ability to evade the innate antiviral response of the cells in order to replicate efficiently in the host. Transfection experiments with Orf3b, Orf6, and N in 293T cells showed that these viral proteins are IFN antagonists that can interfere with the synthesis of IFN and its downstream signaling pathways (178). However, this cannot explain the apparent discrepancy of IFN-β/α production in infected human intestinal Caco-2 cell line (253) and the lack of such production in SARS patients' peripheral blood mononuclear cells or in human primary macrophages abortively infected with SARS-CoV despite the activation of several IFN-stimulated genes in the latter case (61). On the other hand, this may explain the increased serum level of IFN of some SARS patients, which may have an intestinal source. Due to the lack of a type 2 pneumocyte cell line that is susceptible to SARS-CoV, the relevance of these findings cannot be ascertained for lung epithelial cells.

Once the virus can overcome the innate immune response at the cellular level, it can take over the host metabolic apparatus through the degradation of host mRNA by nsp1 and the modulation of the ubiquitination pathway of the host by nsp3 (15, 81, 192, 224, 279). Efficient viral replication ensues, and cell damage occurs by virus-induced cytolysis or immunopathology. Infected cell lines and postmortem lung tissues have shown cytopathic changes due to apoptosis, necrosis, or occasionally syncytium formation. Expression of nsp5, nsp10, Orf3a, Orf3b, Orf7a, Orf8a, E, M, and N in different cell lines by transfection can cause cellular apoptosis (Table 1). Expression of S in transfected cells can lead to syncytium formation with cells expressing ACE2 (181). Paradoxically, little cytopathic effect or inflammation was found in intestinal biopsy specimens of SARS patients despite marked viral replication seen with electron microscopy (205). The transcriptomal profile of infected Caco-2 cells showed a marked upregulation of the potent immunosuppressive cytokine transforming growth factor β and the antiapoptotic host cellular response, which may explain the noninflammatory secretory diarrhea and huge amount of viral shedding in stool (79). Therefore, the clinical or histopathological manifestations at various organs or tissues do not depend solely on the presence of the relevant receptor and coreceptors or the viral productivity as reflected by the viral load. The inflammatory and apoptotic responses of the cell triggered by the virus and the compensatory regenerative power or functional reserve of that organ may be equally important

in determining the manifestations and the outcome of infection. nsp1 expression in human lung epithelial A549 cells can increase the expression of the chemokines IP10, CCL3, and CCL5 through the NF-κB pathway (192). This correlated well with the plasma chemokine profile of SARS patients and the immunohistochemical staining of infected lungs. IP10 expressed on pneumocytes is a potent chemoattractant for activated cytotoxic T lymphocytes, natural killer cells, and monocytes, which may therefore infiltrate the interstitium and alveoli of lungs of SARS patients. Administration of a recombinant S fragment between positions 324 and 688 and Orf3a expression in lung cells can excite the production of IL-8 (43, 169). The expression of N in transfected cells can also activate the Cox2 inflammatory cascade (393). If SARS-CoV can indeed suppress the early innate immune response of IFN-β/α in type 2 pneumocytes without activating the IFN-stimulated genes and therefore also allowing an uncontrolled viral replication in the adjacent cells, the concomitant activation of proinflammatory chemokines and cytokines would explain the dominant and highly fatal manifestation of SARS in the lungs.

Adaptive Immune Response

In general, specific serum antibody against whole SARS-CoV by indirect immunofluorescence or neutralization tests starts to appear at around day 7, plateaus at around the second month, and is maintained for over 12 months. Immunoglohulin M (IgM) and IgG appeared at around the same time, but the former was not detected after 2 to 3 months (371). Serum testing by recombinant nucleocapsid EIA can detect such an antibody as early as the fifth day after the onset of symptoms (46). The virus-specific T-cell-mediated immune response is not clearly defined. In one study, S-specific cell-mediated immunity mediated by CD4 and CD8 cells was found to last for more than 1 year (395).

Host Susceptibility

Some studies suggested a possible association of HLA-B*4601 with susceptibility to and severity of SARS among the Chinese population in Taiwan (223), but the finding was not confirmed in HKSAR SARS cases. Among the Chinese population in HKSAR, similar associations with HLA-B*0703 and the genetic variant ICAM3 Gly143 have been found (35, 249). Low-mannose-binding lectin producing the YB haplotype has an increased risk of acquiring SARS (160, 416). On the other hand, individuals with HLA-DRB1*0301 or that are homozygous for CLEC4M tandem repeats were found to be less susceptible to SARS-CoV infection (40, 249). However, the latter finding was strongly disputed in two subsequent studies (324, 430).

LABORATORY DIAGNOSIS OF SARS-COV INFECTION

No pathognomonic signs or symptoms of SARS can be used to differentiate SARS from other causes of community- or hospital-acquired pneumonia. Etiological diagnosis and differentiation from other causes of atypical pneumonia can be made only by laboratory confirmation. A positive viral culture from respiratory, fecal, and, occasionally, urine or tissue specimens or a fourfold rise in the neutralizing antibody titer in serum samples taken upon admission and 28 days afterward is the most definitive evidence of infection. However, both viral culture and neutralizing antibody testing required a biosafety level 3 laboratory, which is not

available in most hospitals. Rapid detection by nucleic acid amplification such as RT-PCR or antigen detection by EIA is the alternative. It is important that most of these rapid tests have never been thoroughly investigated in prospective field trials due to the short-lasting nature of the SARS epidemic. Thus, most of our data on these assays came from evaluations of stored clinical specimens. As for the collection of clinical specimens, although bronchoalveolar lavage fluid and lung biopsy tissue should be the ideal specimens at the onset of illness, such procedures are invasive and can be hazardous to health care workers. Nasopharyngeal aspirates and throat washings, taken with respiratory precautions and preserved in viral transport medium, remain the most important diagnostic specimens.

Nucleic Acid Amplification Assays

Most nucleic acid amplification tests are designed with the *Orf1b* or nucleoprotein gene (32, 56, 88, 108, 155, 189, 264, 266, 268, 349, 384, 391, 413). The latter gene has the theoretical advantage of being more abundant in infected cells and therefore of higher sensitivity, but this has not been clearly proven in clinical studies. Of these methods, real-time quantitative RT-PCR (Table 4) of the nasopharyngeal aspirate is the most sensitive and rapid method for aiding in clinical diagnosis and may achieve a sensitivity of 80% with good specificity even if it is collected within the first 5 days of illness (266). In-house qualitative RT-PCR tests are generally less sensitive and prone to contamination. Positive test results from a single sample must be confirmed by a repeat test detecting a different region of the SARS-CoV genome on the same sample. If possible, another repeat sample should also be tested to exclude false-positive results due to amplicon carryover. Since the viral load in nasopharyngeal aspirate usually peaked on the 10th day after the onset of symptoms, suspected SARS cases must have the tests repeated as the disease evolves to avoid false-negative results (32, 258). Stool specimens should also be routinely sent for testing since a very high percentage of patients develop diarrhea and shed virus during the second week of illness (58). Viral load determination of nasopharyngeal specimens or serum upon presentation might have clinical value, as it is an important prognostic factor (72, 73, 75, 156). Longitudinal monitoring of viral load would be an important part of any treatment trials in the future.

TABLE 4.

Clinical evaluation of molecular diagnostic tests for SARS-CoV

Diagnostic method and target gene	Clinical specimen	Diagnostic gold standard	Collection time after onset of symptoms (no. of samples)	% Sensitivity (viral load [copies/ml])	Reference
In-house RT-PCR					
RNA pol[a]	NPA	Laboratory confirmed[b]	Days 1-5[c] (72)	59.7[d]	391
			Days 1-5 (98)	29.6	32
RNA pol	NPA	WHO criteria, probable SARS	Days 0-5 (501)	41.1	56
			Days 6-11 (211)	58.8	
			Days 12-20 (62)	37.1	
			Day >21 (15)	13.3	
RNA pol	Throat swab	WHO criteria, probable SARS	Days 1-13 (590)	37.5	384
RNA pol[a]	Nose and throat swab	Laboratory confirmed[b]	Days 1-5[c] (54)	61.1[d]	391
			Days 1-5 (53)	28.3	32
RNA pol	Upper respiratory[e]	WHO criteria, probable SARS	Days 0-5 (212)	31.1	56
			Days 6-11 (73)	37	
			Days 12-20 (45)	31.1	
			Day >21 (159)	5.7	
RNA pol[a]	Respiratory[f]	Laboratory confirmed[b]	1 wk (243)	26.3	39
			2 wk (134)	30.6	
			3-4 wk (94)	18.1	

Open in a separate window

[a]For the RNA extraction protocol, 140 μl of nasopharyngeal aspirate (NPA) was used.
[b]A rise of fourfold or more in antibody titer against SARS-CoV.
[c]Day after admission.
[d]Specificity of the test was 100%.

[e]Upper respiratory specimens consisted of throat and nasal swabs ($n = 216$), throat swabs ($n = 164$), nasopharyngeal swabs ($n = 47$), and nasal swabs ($n = 62$).
[f]Respiratory specimens consisted of tracheal aspirate ($n = 7$), pooled throat and nasal swabs ($n = 25$), nasal swabs ($n = 58$), NPA ($n = 192$), throat swabs ($n = 43$), and throat washing ($n = 146$).
[g]For the modified RNA extraction protocol, 560 μl of NPA was used.
[h]Respiratory specimens consisted of saliva ($n = 3$), nasopharyngeal swabs ($n = 16$), sputum ($n = 8$), endotracheal aspirate ($n = 2$), and bronchoalveolar lavage fluid ($n = 2$).
[i]The test adopted the SARS1S_AS TaqMan assay design (Applied Biosystems, Foster City, CA), and 280 μl of plasma was used for RNA extraction.
[j]LAMP, real-time loop-mediated amplification.
[k]Respiratory specimens consisted of throat wash ($n = 15$), throat swabs ($n = 13$), and throat and nasal swabs ($n = 21$).
[l]Roche kit indicates a LightCycler SARS-CoV quantification kit (b-Test_Lot) (Roche Diagnostics, Germany).
[m]There was no result for one sample due to failed internal control. The sample was omitted from the sensitivity evaluation of this assay.
[n]Commercial kit indicates a RealArt HPA-Coronavirus LC RT PCR kit (Artus GmbH, Hamburg, Germany) and a SARS-CoV POL assay (EraGen Biosciences, Madison, WI) with different extraction methods (QIAGEN viral RNA Minikit, bioMerieux miniMg, and Cortex MagaZorb).
[o]Artus kit indicates a RealArt HPA-Coronavirus LC RT-PCR kit (Artus GmbH, Hamburg, Germany).

Antigen Detection Assays

Antigen detection with monoclonal antibodies or monospecific polyclonal antibody against the N protein was found to be a sensitive and specific test for the diagnosis of SARS (Table 5). In a large study with sera collected from 317 SARS patients at different time points of illness, EIA detection of SARS N was performed using a panel of three monoclonal antibodies (46). Over 80% of SARS cases can be detected within the first 7 days after the onset of illness. As serum antibody levels started to rise at day 7, the sensitivity of the serum antigen assay progressively decreased to 0% at day 21 (46). Antigen detection with EIA in nonserum specimens is generally less sensitive than RT-PCR because the cutoff value is usually set at a much higher level than that of serum specimens to overcome the high background optical density values in nonserum specimens (189, 191).

TABLE 5.

Clinical evaluation of antigen detection for SARS-CoV

Diagnostic method and detection target	Diagnostic gold standard	Collection time after onset of symptoms (days)[a] (no. of samples)	Sensitivity (%)	Overall specificity (%)	Reference
EIA					
N protein	WHO criteria, probable SARS	3-5 (8)	50	98.5	48
		6-10 (14)	71.4		
		11-20 (9)	44.4		
N protein	WHO criteria, probable SARS	1-5 (84)	92.9	100	86
		6-10 (63)	69.8		
		11-20 (52)	30.8		
N protein	WHO criteria, probable SARS	1-5 (85)	94	99.9	46
		6-10 (60)	78		
N protein	WHO criteria, probable SARS	NM (18)	100	100	127
N protein	Laboratory confirmed[b]	6-24 (66) (NPA)	52	96.7	191
		11-31 (94) (urine)	5	99	
		8-32 (65) (stool)	55	96	
Immunofluorescence assay					
N protein	WHO criteria,	2-9 (17) (throat wash)	65	100	226

Open in a separate window

[a]Serum samples collected unless specified. NM, not mentioned.
[b]Positive for IgG antibodies against SARS-CoV by indirect immunofluorescence assay in serum sample during the course of illness.

Antibody Detection Assays

For antibody testing (Table 6), the indirect immunofluorescent antibody test is more commonly performed than the neutralizing antibody test since the former involves minimal manipulation of infectious virus and therefore carries less risk of a biohazard. The test is generally not useful during the first week of illness. Single low-titer positive results can be related to cross-reactions with other human coronaviruses (31, 47). A recombinant nucleocapsid EIA may be used as a rapid screening test and possesses a higher sensitivity, with detection as early as day 5 after onset of illness (46), but again, false-positive results due to cross-reactions with HCoV-O43 and HCoV-229E can occur and require confirmation by Western blotting against the S polypeptide of SARS-CoV (372). Serum IgG, IgM, and IgA appeared at around the same time, between days 5 and 17 after the onset of symptoms, and paralleled the appearance of neutralizing antibody activity, but one study reported that IgM appeared 3 days earlier using an IgM capture EIA against nucleoprotein (404). The titer of neutralizing antibody peaked at days 20 to 30 and was sustained for a long time. It is interesting that the neutralizing antibody level of those who died peaked at day 14 and then started to fall, whereas those who survived had a sustained level of antibody (417). A new immunofluorescence assay using the S protein and a recombinant N-S fusion protein as an antigen has been described. The results are comparable to those obtained with whole-virus-based immunofluorescence assays (128, 235). The three laboratory outbreaks of SARS prompted the use of pseudotype viruses for research and neutralization antibody testing, but data on systematic evaluation are lacking.

TABLE 6.

Clinical evaluation of antibody detection for SARS-CoV

Diagnostic method and detection target	Diagnostic gold standard	Collection time (days) after onset of symptoms[a] (no. of samples)	Sensitivity (%)	Overall specificity (%)	Reference
EIA					
Anti-N protein antibodies	WHO criteria, probable SARS	1-5 (27)	14.8	100	299
		6-10 (38)	68.4		
		11-61 (135)	89.6		
Anti-N protein antibodies	WHO criteria, probable SARS	10 (16)	81.3	100	330
		20 (16)	100		
		30 (16)	100		
Anti-N protein antibodies	WHO criteria, probable SARS	12-72 (280)	89.3	NM	273
Anti-N protein antibodies	Laboratory confirmed[b]	12-43 (106)	95.3/96.6/96.6[f]	94.3/59.4/60.4[f]	373
Anti-N protein antibodies	Laboratory confirmed[b]	NM[c] (106)	94.3	100	369
Anti-N protein antibodies	Laboratory confirmed[d]	First wk (36) (IgM)	33	100	404
		Second wk (36) (IgM)	97		
		Third wk (36) (IgM)	100		
Anti-N protein antibodies	WHO criteria, probable SARS	NM (407)	70.2	99.9	54

Open in a separate window

[a]Serum samples were collected.
[b]Positive for IgG antibodies against SARS-CoV by indirect immunofluorescence assay in serum sample during the course of illness.
[c]NM, not mentioned.
[d]Details not specified.
[e]True SARS is defined as WHO criteria for probable cases of SARS and/or at least one specimen positive for SARS-CoV by RT-PCR.

[f]IgG/IgM/IgA.
[g]IgG/IgM.

CLINICAL MANAGEMENT AND ANTIVIRALS

Since there is no proven effective antiviral agent by randomized placebo control trial (Table 7), clinical management of SARS has relied largely upon supportive care. Broad-spectrum antimicrobial coverage for community-acquired pneumonia should be given while virological confirmation is pending. Such antibiotics should be stopped once the diagnosis of SARS is confirmed, but nosocomial infections as a result of prolonged intubation and the use of corticosteroids should be appropriately managed.

TABLE 7.

Antiviral agents and immunomodulators against SARS-CoV in vivo

Antiviral agent and/or immunomodulator (no. of subjects) (study design)	Main findings[a]	Reference
Ribavirin (144 patients) (retrospective case series)	126 patients (88%) treated; side effects of hemolysis (76%) and lowered hemoglobin of 2 g/dl (49%)	21
Ribavirin (229 patients) (retrospective uncontrolled cohort analysis)	97 patients (42.2%) treated; crude death rate of 10.3% (treatment) vs 12.9% (control) (P = 0.679)	199
Ribavirin and corticosteroids (75 patients) (prospective case series)	9 patients (12%) had spontaneous pneumomediastinum; 20% developed ARDS in wk 3	258
Ribavirin and MP (31 patients[b]) (retrospective case series)	No patient required intubation or mechanical ventilation; no mortality noted in this series	303
Ribavirin and corticosteroids[c] (71 patients[d]) (prospective cohort study)	Crude mortality rate of 3.4% (only in patients aged >65 yr); none of the discharged survivors required continuation of oxygen therapy	186
Ribavirin and corticosteroids[e] (138 patients) (prospective uncontrolled study)	None responded to antibacterials; 25 patients (18.1%) responded to ribavirin and low-dose corticosteroid; 107 patients required high-dose MP, 88.8% of whom responded; 21 patients (15.2%) required mechanical ventilation; mortality rate, 10.9%	314
Ribavirin and MP (72	Patients treated with initial pulse MP therapy had no better rate of mechanical ventilation (5.9%	120

Open in a separate window

[a]ARDS, acute respiratory distress syndrome; MP, methylprednisolone; NS, P value was not significant.
[b]One patient recovered on antibacterial treatment alone.
[c]A 3-week step-down course of corticosteroids and pulsed methylprednisolone rescue for deterioration.
[d]Three patients recovered on antibacterial treatment alone.
[e]Low-dose corticosteroid and selective use of high-dose methylprednisolone.

[f]Initially treated with high-dose pulse ($n = 17$) versus nonpulse ($n = 55$) methylprednisolone.
[g]One hundred eleven patients treated with ribavirin as a historical control.
[h]Six hundred thirty-four patients selected as matched cohort.
[i]Three hundred forty-three patients selected as matched cohort.
[j]Patients who continued to deteriorate despite ribavirin and corticosteroid therapy.
[k]Patient who continued to deteriorate despite ribavirin and corticosteroid therapy.

The correlation between viral loads and clinical outcome suggests that suppression of viral replication by effective antiviral drugs should be the key to preventing morbidity and mortality. However, in vitro susceptibility test results were often conflicting, as in the case of IFN-β1a (78, 137, 318) and IFN-α2b (308, 318). Nevertheless, it appears that IFN-β, IFN-αn1, IFN-αn3, and leukocytic IFN-α have some potential activity and warrant evaluation by clinical trials (50, 305, 426). Although a very high 50% cytotoxic concentration exceeding 1,000 mg/liter has been demonstrated for ribavirin (77), and although its low level of in vitro activity against SARS-CoV was initially attributed to cellular toxicity (318), ribavirin has good activity when tested in other human Caco-2 and pig kidney cell lines despite its lack of activity in Vero cells (243). The use of different cell lines, testing conditions, and virus strains may have contributed to these discrepancies.

Numerous other potential antiviral agents have been identified using different approaches (Table 8). Replication of SARS-CoV requires proteolytic processing of the replicase polyprotein by two viral cysteine proteases, a chymotrypsin-like protease ($3CL^{pro}$) and a papain-like protease (PL^{pro}). These proteases are important targets for the development of antiviral drugs. Protease inhibitors (especially nelfinavir) (386, 392), glycyrrhizin (77), baicalin (50), reserpine (381), aescin (381), valinomycin (381), niclosamide (380), aurintricarboxylic acid (129), mizoribine (293), indomethacin (4), chloroquine (174), and many herbal formulations, have also been found to possess some antiviral activity against SARS-CoV in vitro. In addition, an organic nitric oxide donor, *S*-nitro-*N*-acetylpenicillamine, appeared to have inhibitory activity against SARS-CoV (2), which has formed the basis for the use of nitric oxide inhalation as an experimental form of rescue therapy for SARS (52). Several agents with good in vitro antiviral activities, including ACE2 analogues, helicase inhibitors, and nucleoside analogues, were also reported to have some activity in vitro (14, 332). Antiviral peptides designed against the S protein and especially those derived from heptad repeat region 2 of S2 were shown to inhibit membrane fusion and cell entry (22, 177, 227). Small interfering RNA (siRNA) also demonstrated activities in reducing cytopathic effects, viral replication, and viral protein expression in cell lines (125, 232, 351, 418, 419, 428). Screening of chemical libraries has identified several inhibitors of protease, helicase, and spike-mediated cell entry (170). Most of the above-mentioned chemicals or approaches have not been evaluated in human or animal models. In mouse models, nelfinavir, β-D-N^4-hydroxycytidine, calpain inhibitor VI, 3-deazaneplanocin A, human leukocyte IFN-αn3, and anti-inflammatory agents including chloroquine, amodiaquin, and pentoxifylline did not significantly reduce lung virus titers in mice. When not given in combination with other antivirals, the IMP dehydrogenase inhibitors, including ribavirin, suppress the proinflammatory response while augmenting viral replication in this mouse model (13).

TABLE 8.

Antiviral agents and immunomodulators tested against SARS-CoV in animals and in vitro

Antiviral agent(s) and/or immunomodulator(s)	Study setting and methods (virus strain)	Main findings[a]	Reference

Antiviral agent(s) and/or immunomodulator(s)	Study setting and methods (virus strain)	Main findings[a]	Reference
IFN-αB/D (hybrid IFN)	BALB/c mice (Urbani)	i.p. IFN-αB/D once daily for 3 days beginning 4 h after virus exposure reduced SARS-CoV replication in lungs by 1 $\log_{10}$ at 10,000 and 32,000 IU; at the highest dose of 100,000 IU, virus lung titers were not detectable	13
Ampligen [poly(I:C124)] (mismatched double-stranded RNA IFN inducer)	BALB/c mice (Urbani)	i.p. Ampligen at 10 mg/kg 4 h after virus exposure reduced virus lung titers to undetectable levels	13
Pegylated IFN-α as prophylactic treatment	Cynomolgus macaques (*Macaca fascicularis*) (patient 5668)	Significantly reduced viral replication and excretion, viral antigen expression by type 1 pneumocytes, and pulmonary damage; postexposure treatment with pegylated IFN-α yielded intermediate results	118
IFN-α2b (Intron A)	Vero (FFM-1, HK isolate)	Mean (SD) EC_{50} = 4,950 (890) IU/ml (SI of >2) for FFM-1 isolate; mean (SD) EC_{50} = 6,500 (980) IU/ml (SI of >105) for HK isolate	78
	Caco2 (FFM-1, HK isolate)	Mean (SD) EC_{50} = 1,530 (220) IU/ml (SI of >6.5) for FFM-1 isolate; mean (SD) EC_{50} = 880 (130) IU/ml (SI of >11.4) for HK isolate	78
IFN-β1b (Betaferon)	Vero (FFM-1, HK	Mean (SD) EC_{50} = 95 (17) IU/ml (SI of >105) for FFM-1 isolate; mean (SD)	78

Open in a separate window

[a]i.p., intraperitoneal; EC_{50}, 50% effective concentration; SI, selectivity index; NA, not available; p.i., preincubation; NM, not mentioned; IC_{50}, 50% inhibitory concentration; $TCID_{50}$, 50% tissue culture infective dose; CI, combination index (combination index of <1 indicates synergism); CPE, cell culture cytopathic effect; aa, amino acids; RP, RNA polymerase; CC_{50}, 50% cytotoxic concentration; ↓, decreased.
[b]MP576, HE602, and VE607 were validated to be inhibitors of SARS-CoV M^{pro}, Hel, and viral entry, respectively.
[c]Bananin, iodobananin, vanillinbananin, and eubananin were effective inhibitors of the ATPase activity of the SCV helicase.

Before the demonstration of viral load as an important factor in determining clinical outcome, immunomodulators were empirically used for the treatment of SARS during the initial epidemic (59). These immunomodulators include corticosteroids, intravenous immunoglobulins, pentaglobulin, thymosin, thalidomide, and anti-TNF (140, 421). Corticosteroids were previously found to reduce mortality in patients with pneumonia due to varicella-zoster virus and influenza virus (1, 109). High-dose hydrocortisone was shown to reduce the expression of the proinflammatory chemokines CXCL8 and CXCL10 in infected Caco-2 cells (80). However, without an effective antiviral agent, the early use of high doses of corticosteroids for prolonged periods could be detrimental. It may increase the plasma viral load and the risk of nosocomial infections and avascular osteonecrosis (196). Pegylated IFN-α2a was shown to be useful for prophylaxis and reducing respiratory viral shedding and lung pathology when used as an early treatment in a monkey model (118). Among clinical treatments studied, combinations of steroid with either alfacon-1, a recombinant consensus IFN-α (231), or protease inhibitors and ribavirin were found to improve outcomes in two different treatment trials using historical controls (33, 72). Due to the very short time course of this epidemic and the initial lack of suitable animal models, randomized control treatment trials are difficult to be organized and executed despite the finding of some commercially available candidate agents that appeared to be active in vitro.

INFECTION CONTROL AND LABORATORY SAFETY

Because of the physical stability of SARS-CoV in the environment, the absence of protective immunity in the general population, and the lack of effective antivirals or vaccines, infection control against SARS remains the primary means to prevent person-to-person transmission in future epidemics. Early recognition, triage, and prompt isolation of suspected cases are the principal measures against nosocomial transmission (142). Although respiratory droplet and contact precautions are effective under most circumstances (296), airborne precautions should be considered for aerosol-generating procedures such as bronchoscopy, tracheostomy, and suctioning of the airway. The virus can be easily inactivated by commonly used disinfectants such as household bleach, which reduced the viral load by more than 3 logs within 5 min (185). In a study on the survival of SARS-CoV, fecal and respiratory samples were shown to be infectious for 4 and >7 days at room temperature, respectively. Survival was found to be longer on disposable gowns than on cotton gowns. Therefore, absorbent material such as cotton is preferred over nonabsorptive material for personal protective clothing in routine patient care. In contrast, the virus cannot be recovered after the drying of a paper request form even with a high inoculum. Therefore, the risk of infection via contact with droplet-contaminated paper is small (185). When managing patients, oxygen delivery by low-flow nasal cannula instead of high-flow face masks should be used to reduce the risk of airborne transmission. Mechanical ventilation, including noninvasive modalities such as continuous positive airway pressure and bilevel positive airway pressure, should be carried out only in negative-pressure isolation rooms under strict airborne precautions (62). All health care personnel caring for patients with suspected or confirmed SARS must have daily temperature checks in the late afternoon and be quarantined after unprotected exposure to achieve early detection and to avoid nosocomial and community outbreaks. Upon discharge of patients, adherence to strict personal hygiene is important. Clinical specimens of patients remained RT-PCR positive for a substantial period of time, although the clinical significance of this finding is unknown (73). At the community level, contact tracing and quarantine of contacts, temperature checks at borders, health

declarations for travelers, social distancing by suspension of schools and closing of workplaces, public education, and effective communication of information have been used to control community spread. Although screening of suspected cases at international borders and airports was widely practiced during the epidemic, the value of doing so has been questioned (307). To prevent laboratory-acquired infections, all laboratories handling live SARS-CoV should strictly comply with WHO standards for biosafety level 3 laboratories.

PASSIVE IMMUNIZATION AND DEVELOPMENT OF A SARS-COV VACCINE

Use of Convalescent-Phase Serum and Neutralizing Antibody

Passive immunization using convalescent plasma with high titers of neutralizing antibody has been used for SARS patients who continued to deteriorate. No significant adverse reactions were noted, with perhaps some clinical benefit in a retrospective analysis (60, 401). Currently, only hyperimmune globulin produced from plasma from convalescent patients and equine plasma produced by immunization with inactivated SARS-CoV are available for prophylactic trials in humans (233, 421). A human monoclonal IgG1 produced from a single-chain variable region fragment against the S1 domain from two nonimmune human antibody libraries has also been produced (312). One of the single-chain variable region fragments, 80R, blocks spike-ACE2 receptor interactions through binding to the S1 domain. In a murine model of asymptomatic SARS infection, passive immunization by high titers of neutralizing antibody prevented viral replication in the lungs but was not as effective in nasal turbinates (311). Similarly, passive immunization of mice and ferrets with human IgG1 monoclonal antibody CR3014 was effective in preventing the development of lung pathology but less effective in reducing pharyngeal excretion (329). Recently, potent cross-reactive monoclonal antibodies against highly conserved sites within the spike protein, which can neutralize zoonotic or epidemic SARS-CoV, were reported (131, 434). These new weapons should be considered for clinical testing if SARS returns. Currently, there are no randomized placebo-controlled trials on the role of antibody therapy for pre- or postexposure prophylaxis in at-risk groups during the SARS epidemic.

Of all the surface proteins, only the ectodomains of S and Orf3a can induce significant neutralizing antibody with some augmentation from the M and E proteins (3, 24). The S1 fragment between amino acids 318 and 510 is the receptor binding domain for ACE2. This fragment induces the majority of the neutralizing antibody in convalescent SARS patients (135). The minor epitope for the neutralizing antibody is found at amino acids 1055 to 1192 around heptad repeat 2 of the S2 subunit. However, this minor neutralizing epitope was implicated in the induction of an infection-enhancing antibody (400). The risk of immune enhancement should not be underestimated because ferrets immunized by whole S protein carried in modified vaccinia virus Ankara developed hepatitis (355). Most of the highly immunodominant sites in S generate only nonneutralizing antibodies. It is important that only three to five amino acid changes in the receptor binding domain of S are found between the early and late isolates of human SARS (64), and even reverse-genetically-made isogenic viruses made with the spike protein from zoonotic variants and the early but not the late phase of the SARS epidemic can produce fatal disease in 1-year-old mice (289). Therefore, the receptor binding domain of S1 remains the best target for the development of a vaccine.

Active Immunization

As expected, the importance of the S protein was confirmed in the murine model using either intramuscular or intranasal administration of highly attenuated modified vaccinia virus Ankara carrying the S protein (18). Mucosal immunization of African green monkeys with recombinant attenuated parainfluenza virus-SARS-CoV S protein chimeric virus resulted in a good neutralizing antibody response and protection from viral replication in the upper and lower respiratory tracts following live SARS-CoV challenge (25). Other approaches to active immunization involved the use of an adenoviral vector carrying the S, M, and N proteins in rhesus macaques (102); subunit vaccine with S fragments in rabbits and mice (415); other vaccines derived from the SARS-CoV genome using reverse genetics, such as the attenuated rabies vector (94)-, attenuated vesicular stomatitis virus (171)-, or Venezuelan equine encephalitis virus (12, 85)-based vaccines; and S1 vaccine expressed in tomato and low-nicotine tobacco plants as a mucosal vaccine (262). A plasmid DNA vaccine carrying the S protein encoded by humanized codons was highly protective in a mouse model (412). The use of other targets such as inactivated whole virus in mice (323), DNA vaccine linking the N protein to calreticulin (176), DNA vaccination with the N gene in mice (433), and virus-like particles has also been reported. Only the inactivated whole-virus vaccine was tested in healthy Chinese volunteers, who showed good neutralizing antibodies with little side effects, but the data have not been published. However, the protective efficacy and risk of immune enhancement are still unknown in the situation of an epidemic.

As for the key protective immune effector in the mouse model, T-cell depletion with specific monoclonal antibodies against CD4 or CD8, alone or in combination with CD90, did not affect protective immunity, which was confirmed by adoptive T-cell transfer (399). Donor T cells alone did not inhibit pulmonary viral replication in recipient mice, whereas passive transfer of purified IgG from immunized mice achieved similar protection. In summary (Table 9), all vaccines based on the S protein appeared to be capable of inducing neutralizing antibody responses, and those based on nucleoprotein can induce nucleoprotein-specific cell-mediated immunity. However, only vaccines based on the S protein were shown to be protective in animal models, whereas a DNA vaccine based on the N protein induced immunopathology of lungs in mice after challenge with live virus (85).

TABLE 9.

Passive and active immunization against SARS

Type of vaccine	Target (animal model)	Response[a]	Reference(s)
Passive immunization			
Human monoclonal antibody	S protein (ferret)	Decrease in lung viral titer, decrease in viral shedding, prevention of virally induced tissue pathology	329
	S protein (BALB/c mice)	Decrease in lung/nasal viral titers	333
	S protein (BALB/c mice)	Decrease in lung viral titers	313
Human monoclonal antibody from transgenic (HuMantibody) mice	S protein (BALB/c mice)	Decrease in lung/nasal viral titers	110
Active immunization			
Inactivated whole virus	Inactivated SARS-CoV (BALB/c mice)	Neutralizing antibodies	323
	Inactivated SARS-CoV (BALB/c mice)	Neutralizing antibodies; specific IgA in tracheal/lung wash fluid with adjuvant-added or PEG-precipitated vaccine only	274
	Inactivated SARS-CoV (BALB/c mice, rabbits)	Specific antibodies recognizing RBD of S1; blocked binding of RBD to ACE2; significant decrease in S protein-mediated cell entry in pseudotyped virus assay	134
	Inactivated SARS-CoV (BALB/c mice)	Neutralizing antibodies	306,317
Recombinant protein fragment	S protein (BALB/c mice)	Neutralizing antibodies	19
	S protein (BALB/c	Neutralizing antibodies	415

Open in a separate window

[a]PEG, polyethylene glycol; RBD, receptor-binding domain; DTH, delayed-type hypersensitivity; CTL, cytotoxic T cell.

The relative importance of systemic or mucosal immunity in terms of the neutralizing antibody or cytotoxic T-lymphocyte response against S, N, or other targets in terms of recovery from SARS is unknown. Nevertheless, neutralizing antibody against S1 appears to be crucial for prophylactic immunity. Live-attenuated virus is not a good choice because of the concern about reversion to virulence or recombination with wild strains to form new wild types. An inactivated SARS-CoV strain is the easiest and most likely candidate for clinical trials if SARS returns. Irrespective of the approach to immunization, the phenomenon of immune enhancement of disease in feline peritonitis coronavirus infection is also a cause for concern in view of the immunopathology seen in immunized ferrets and mice after challenge with wild-type SARS-CoV.

ANIMAL MODELS AND ANIMALS SUSCEPTIBLE TO SARS-COV

Reproducible and consistent animal models that mimic the clinical, viral load, and histopathological changes of SARS are essential for proving causation, studying pathogenesis, and testing antivirals or immunization (Table 10). The Koch's postulates for SARS-CoV as a causative agent of SARS were fulfilled with a primate model using cynomolgus macaques (*Macaca fascicularis*), which demonstrated clinical and pathological features with some similarities to those found in humans (182). On the contrary, African green monkeys (*Cercopithecus aethiops*) did not develop significant lung pathology after inoculation with the SARS-CoV. The lack of consistency in primate animal models of rhesus, cynomolgus, and African green monkeys for experimental SARS was noted in another study (239). Moreover, these large mammals are expensive and difficult to handle. BALB/c mice demonstrated asymptomatic or mild infections in lungs and nasal turbinates by intranasal inoculation, which was not significantly different from the findings with inoculation of immunological Th1-biased C57BL/6 mice (105). BALB/c mice that were 12 to 14 months old developed symptomatic pneumonia, which correlated with the age-related susceptibility to acute SARS in humans (287). As expected, STAT-1 knockout-immunodeficient mice had fatal and disseminated disease (143). Transgenic mice expressing human ACE2 receptors also developed fatal disease, with extrapulmonary dissemination to many organs including the brain (240, 337). It is interesting that mouse-adapted SARS-CoV strains with six amino acid mutations can also cause fatal disseminated disease in young BALB/c mice (286). Adult F344 rats developed symptomatic disease after inoculation with passaged SARS-CoV strains containing one mutation in the receptor binding domain of S (244). Ferrets (*Mustela furo*) and domestic cats (*Felis domesticus*) were also susceptible to infection by SARS-CoV (237). The cats remained asymptomatic, and only some of the infected ferrets died of the disease. Very high levels of viral replication were found in infected golden Syrian hamsters, but they generally did not develop overt clinical disease (288). Similarly, inoculated common marmosets generally had mild clinical disease and histopathological changes of pneumonia with extrapulmonary dissemination and high levels of viral replication in affected tissues (111). As expected, palm civets (*Paguma larvata*) were shown to be susceptible to symptomatic infection by SARS-CoV with or without the 29-bp signature sequence (382). Pigs and chickens are not susceptible to SARS-CoV (356). Since different SARS-CoV isolates were used by different groups, it is therefore still uncertain whether one particular animal would be better than others as a model for SARS-CoV. It appears that the senescent BALB/c mouse is an inexpensive and relatively easily reproduced animal model for testing vaccines and antivirals for SARS. An important observation of this review is the diverse range of mammalian species that are susceptible to experimental infection by SARS-CoV,

which again demonstrated that SARS-CoV is highly capable of jumping interspecies barriers and is an excellent candidate as an emerging or reemerging pathogen. Indeed, our first report on animal SARS-CoV showed that Chinese ferret badgers (*Melogale moschata*) and raccoon dogs (*Nyctereutes procyonoides*) were also infected with SARS-CoV (117). The recent discovery of a high proportion of Chinese horseshoe bats and subsequently other horseshoe bats shedding SARS-CoV-like viruses or being seropositive strongly suggested that the bats could be the natural reservoir of this group of viruses (190, 215).

TABLE 10.

Animals tested for susceptibility to SARS-CoV in experimental and natural infection[a]

Animal species and age	Dose and route of inoculation (virus strain)	Point of evaluation (days)	Main findings	Reference
Cynomolgus macaques (*Macaca fascicularis*)	10^3 to 10^6 $TCID_{50}$; i.n., i.v., conjunctival (NM)	Up to 16	Lethargy from 3 dpi, respiratory distress from 4 dpi, died with severe multifocal pulmonary consolidation and histologically interstitial pneumonia, diffuse alveolar damage, necrosis of alveolar and bronchiolar epithelium, and alveolar edema with proteinaceous fluid admixed with fibrin, erythrocytes, alveolar macrophages, and neutrophils	98
Cynomolgus macaques (*Macaca fascicularis*); adult	10^6 $TCID_{50}$; i.n., IT, conjunctiva (strain from patient 5688)	6	Excreted SARS-CoV from nose, mouth, and pharynx from 2 dpi; diffuse alveolar damage with epithelial necrosis, serosanguineous exudate, hyaline membrane formation, type 2 pneumocyte hyperplasia, and syncytium formation	182
Cynomolgus macaques and rhesus macaques	10^7 PFU; IT, i.v. (Tor2)	12	Mild self-limited respiratory infection	291
African green, rhesus, and cynomolgus monkeys; juvenile	10^6 $TCID_{50}$; i.n., IT (Urbani)	Up to 28	SARS-CoV replicated in the respiratory tract but did not induce illness; moderate to high titers of SARS-CoV excretion with associated interstitial pneumonitis detected in lungs of African green monkeys on 2 dpi and resolved by 4 dpi	239
Rhesus	10^3, 10^5,	Up to 60	Transient fever occurred 2-3 dpi; SARS-CoV-specific IgGs detected in sera	272

Open in a separate window

[a]$TCID_{50}$, 50% tissue culture infective dose; i.n., intranasal; i.v., intravenous; NM, not mentioned; dpi, day postinfection; IT, intratracheal. i.p., intraperitoneal; NA, not applicable.
[b]All mice died that day after infection.
[c]Concentration of virus inoculation was not mentioned.
[d]SARS-CoV Frankfurt 1 isolate was serially passaged in young F344 rats (4 weeks) 10 times before experimental inoculation.

[e]BJ01, with a 29-nucleotide deletion.
[f]GZ01, without the 29-nucleotide deletion.

SHOULD WE BE READY FOR THE REEMERGENCE OF SARS?

The medical and scientific community demonstrated marvelous efforts in the understanding and control of SARS within a short time, as evident by over 4,000 publications available online. Despite these achievements, gaps still exist in terms of the molecular basis of the physical stability and transmissibility of this virus, the molecular and immunological basis of disease pathogenesis in humans, screening tests for early or cryptic SARS cases, foolproof infection control procedures for patient care, effective antivirals or antiviral combinations, the usefulness of immunomodulatory agents for late presenters, an effective vaccine with no immune enhancement, and the immediate animal host that transmitted the virus to caged civets in the market at the beginning of the epidemic. Coronaviruses are well known to undergo genetic recombination (375), which may lead to new genotypes and outbreaks. The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, together with the culture of eating exotic mammals in southern China, is a time bomb. The possibility of the reemergence of SARS and other novel viruses from animals or laboratories and therefore the need for preparedness should not be ignored.

ACKNOWLEDGMENTS

This review is dedicated to the late Henry Fok for his generous support to the research on emerging infections.

We acknowledge research funding from Hui Hoy and Hui Ming, Richard Y. H. Yu and family, the HKU Special Research Achievement Award, and the Croucher Senior Medical Research Fellowship 2006-2007.

We also acknowledge the help of Huang Yi for her assistance in preparing the phylogenetic tree.

REFERENCES

1. **Ahmed, R., Q. A. Ahmed, N. A. Adhami, and Z. A. Memish.** 2002. Varicella pneumonia: another 'steroid responsive' pneumonia? J. Chemother. 14:220-222. [PubMed] [Google Scholar]

2. **Akerstrom, S., M. Mousavi-Jazi, J. Klingstrom, M. Leijon, A. Lundkvist, and A. Mirazimi.** 2005. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. J. Virol. 79:1966-1969. [PMC free article] [PubMed] [Google Scholar]

3. **Akerstrom, S., Y. J. Tan, and A. Mirazimi.** 2006. Amino acids 15-28 in the ectodomain of SARS coronavirus 3a protein induces neutralizing antibodies. FEBS Lett. 580:3799-3803. [PubMed] [Google Scholar]

4. **Amici, C., A. Di Coro, A. Ciucci, L. Chiappa, C. Castilletti, V. Martella, N. Decaro, C. Buonavoglia, M. R. Capobianchi, and M. G. Santoro.** 2006. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir. Ther. 11:1021-1030. [PubMed] [Google Scholar]

5. **Anand, K., J. Ziebuhr, P. Wadhwani, J. R. Mesters, and R. Hilgenfeld.** 2003. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. Science 300:1763-1767. [PubMed] [Google Scholar]

6. **Antonio, G. E., C. G. Ooi, K. T. Wong, E. L. Tsui, J. S. Wong, A. N. Sy, J. Y. Hui, C. Y. Chan, H. Y. Huang, Y. F. Chan, T. P. Wong, L. L. Leong, J. C. Chan, and A. T. Ahuja.** 2005. Radiographic-clinical correlation in severe acute respiratory syndrome: study of 1373 patients in Hong Kong. Radiology 237:1081-1090. [PubMed] [Google Scholar]

7. **Avendano, M., P. Derkach, and S. Swan.** 2003. Clinical course and management of SARS in health care workers in Toronto: a case series. CMAJ 168:1649-1660. [PMC free article] [PubMed] [Google Scholar]

8. **Baas, T., J. K. Taubenberger, P. Y. Chong, P. Chui, and M. G. Katze.** 2006. SARS-CoV virus-host interactions and comparative etiologies of acute respiratory distress syndrome as determined by transcriptional and cytokine profiling of formalin-fixed paraffin-embedded tissues. J. Interf. Cytok. Res. 26:309-317. [PMC free article] [PubMed] [Google Scholar]

9. **Babcock, G. J., D. J. Esshaki, W. D. Thomas, Jr., and D. M. Ambrosino.** 2004. Amino acids 270 to 510 of the severe acute respiratory syndrome coronavirus spike protein are required for interaction with receptor. J. Virol. 78:4552-4560. [PMC free article] [PubMed] [Google Scholar]

10. **Balzarini, J., E. Keyaerts, L. Vijgen, H. Egberink, E. De Clercq, M. Van Ranst, S. S. Printsevskaya, E. N. Olsufyeva, S. E. Solovieva, and M. N. Preobrazhenskaya.** 2006. Inhibition of feline (FIPV) and human (SARS) coronavirus by semisynthetic derivatives of glycopeptide antibiotics. Antivir. Res. 72:20-33. [PubMed] [Google Scholar]

11. **Balzarini, J., E. Keyaerts, L. Vijgen, F. Vandermeer, M. Stevens, E. De Clercq, H. Egberink, and M. Van Ranst.** 2006. Pyridine N-oxide derivatives are inhibitory to the human SARS and feline infectious peritonitis coronavirus in cell culture. J. Antimicrob. Chemother. 57:472-481. [PubMed] [Google Scholar]

12. **Baric, R. S., T. Sheahan, D. Deming, E. Donaldson, B. Yount, A. C. Sims, R. S. Roberts, M. Frieman, and B. Rockx.** 2006. SARS coronavirus vaccine development. Adv. Exp. Med. Biol. 581:553-560. [PubMed] [Google Scholar]

13. **Barnard, D. L., C. W. Day, K. Bailey, M. Heiner, R. Montgomery, L. Lauridsen, P. K. Chan, and R. W. Sidwell.** 2006. Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. Antivir. Chem. Chemother. 17:275-284. [PubMed] [Google Scholar]

14. **Barnard, D. L., V. D. Hubbard, J. Burton, D. F. Smee, J. D. Morrey, M. J. Otto, and R. W. Sidwell.** 2004. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARSCoV) by calpain inhibitors and beta-D-N4-hydroxycytidine. Antivir. Chem. Chemother. 15:15-22. [PubMed] [Google Scholar]

15. **Barretto, N., D. Jukneliene, K. Ratia, Z. Chen, A. D. Mesecar, and S. C. Baker.** 2005. The papain-like protease of severe acute respiratory syndrome coronavirus has deubiquitinating activity. J. Virol. 79:15189-15198. [PMC free article] [PubMed] [Google Scholar]

16. **Beijing Group of National Research Project for SARS.** 2003. Dynamic changes in blood cytokine levels as clinical indicators in severe acute respiratory syndrome. Chin. Med. J. 116:1283-1287. [PubMed] [Google Scholar]

17. **Bernini, A., O. Spiga, A. Ciutti, S. Chiellini, L. Bracci, X. Yan, B. Zheng, J. Huang, M. L. He, H. D. Song, P. Hao, G. Zhao, and N. Niccolai.** 2004. Prediction of quaternary assembly of SARS coronavirus peplomer. Biochem. Biophys. Res. Commun. 325:1210-1214. [PubMed] [Google Scholar]

18. **Bisht, H., A. Roberts, L. Vogel, A. Bukreyev, P. L. Collins, B. R. Murphy, K. Subbarao, and B. Moss.** 2004. Severe acute respiratory syndrome coronavirus spike protein expressed by attenuated vaccinia virus protectively immunizes mice. Proc. Natl. Acad. Sci. USA 101:6641-6646. [PMC free article] [PubMed] [Google Scholar]

19. **Bisht, H., A. Roberts, L. Vogel, K. Subbarao, and B. Moss.** 2005. Neutralizing antibody and protective immunity to SARS coronavirus infection of mice induced by a soluble recombinant polypeptide containing an N-terminal segment of the spike glycoprotein. Virology 334:160-165. [PubMed] [Google Scholar]

20. **Bitnun, A., U. Allen, H. Heurter, S. M. King, M. A. Opavsky, E. L. Ford-Jones, A. Matlow, I. Kitai, R. Tellier, S. Richardson, D. Manson, P. Babyn, and S. Read.** 2003. Children hospitalized with severe acute respiratory syndrome-related illness in Toronto. Pediatrics 112:e261. [PubMed] [Google Scholar]

21. **Booth, C. M., L. M. Matukas, G. A. Tomlinson, A. R. Rachlis, D. B. Rose, H. A. Dwosh, S. L. Walmsley, T. Mazzulli, M. Avendano, P. Derkach, I. E. Ephtimios, I. Kitai, B. D. Mederski, S. B. Shadowitz, W. L. Gold, L. A. Hawryluck, E. Rea, J. S. Chenkin, D. W. Cescon, S. M. Poutanen, and A. S. Detsky.** 2003. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 289:2801-2809. [PubMed] [Google Scholar]

22. **Bosch, B. J., B. E. Martina, R. Van Der Zee, J. Lepault, B. J. Haijema, C. Versluis, A. J. Heck, R. De Groot, A. D. Osterhaus, and P. J. Rottier.** 2004. Severe acute respiratory syndrome coronavirus (SARS-CoV) infection inhibition using spike protein heptad repeat-derived peptides. Proc. Natl. Acad. Sci. USA 101:8455-8460. [PMC free article] [PubMed] [Google Scholar]

23. **Breugelmans, J. G., P. Zucs, K. Porten, S. Broll, M. Niedrig, A. Ammon, and G. Krause.** 2004. SARS transmission and commercial aircraft. Emerg. Infect. Dis. 10:1502-1503. [PMC free article] [PubMed] [Google Scholar]

24. **Buchholz, U. J., A. Bukreyev, L. Yang, E. W. Lamirande, B. R. Murphy, K. Subbarao, and P. L. Collins.** 2004. Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity. Proc. Natl. Acad. Sci. USA 101:9804-9809. [PMC free article] [PubMed] [Google Scholar]

25. **Bukreyev, A., E. W. Lamirande, U. J. Buchholz, L. N. Vogel, W. R. Elkins, M. St. Claire, B. R. Murphy, K. Subbarao, and P. L. Collins.** 2004. Mucosal immunisation of African green monkeys (Cercopithecus aethiops) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. Lancet 363:2122-2127. [PubMed] [Google Scholar]

26. **Cameron, M. J., L. Ran, L. Xu, A. Danesh, J. F. Bermejo-Martin, C. M. Cameron, M. P. Muller, W. L. Gold, S. E. Richardson, S. M. Poutanen, B. M. Willey, M. E. Devries, Y. Fang, C. Seneviratne, S. E. Bosinger, D. Persad, P. Wilkinson, L. D. Greller, R. Somogyi, A. Humar, S. Keshavjee, M. Louie, M. B. Loeb, J. Brunton, A. J. McGeer, and D. J. Kelvin.** 2007. Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. J. Virol. 81:8692-8706. [PMC free article] [PubMed] [Google Scholar]

27. **Centers for Disease Control and Prevention.** 2003. Outbreak of severe acute respiratory syndrome—worldwide, 2003. Morb. Mortal. Wkly. Rep. 52:226-228. [PubMed] [Google Scholar]

28. **Centers for Disease Control and Prevention.** 2003. Prevalence of IgG antibody to SARS-associated coronavirus in animal traders—Guangdong Province, China, 2003. Morb. Mortal. Wkly. Rep. 52:986-987. [PubMed] [Google Scholar]

29. **Chan, C. M., C. W. Ma, W. Y. Chan, and H. Y. Chan.** 2007. The SARS-coronavirus membrane protein induces apoptosis through modulating the Akt survival pathway. Arch. Biochem. Biophys. 459:197-207. [PubMed] [Google Scholar]

30. **Chan, C. P., K. L. Siu, K. T. Chin, K. Y. Yuen, B. Zheng, and D. Y. Jin.** 2006. Modulation of the unfolded protein response by the severe acute respiratory syndrome coronavirus spike protein. J. Virol. 80:9279-9287. [PMC free article] [PubMed] [Google Scholar]

31. **Chan, K. H., V. C. Cheng, P. C. Woo, S. K. Lau, L. L. Poon, Y. Guan, W. H. Seto, K. Y. Yuen, and J. S. Peiris.** 2005. Serological responses in patients with severe acute respiratory syndrome coronavirus infection and cross-reactivity with human coronaviruses 229E, OC43, and NL63. Clin. Diagn. Lab. Immunol. 12:1317-1321. [PMC free article] [PubMed] [Google Scholar]

32. **Chan, K. H., L. L. Poon, V. C. Cheng, Y. Guan, I. F. Hung, J. Kong, L. Y. Yam, W. H. Seto, K. Y. Yuen, and J. S. Peiris.** 2004. Detection of SARS coronavirus in patients with suspected SARS. Emerg. Infect. Dis. 10:294-299. [PMC free article] [PubMed] [Google Scholar]

33. **Chan, K. S., S. T. Lai, C. M. Chu, E. Tsui, C. Y. Tam, M. M. Wong, M. W. Tse, T. L. Que, J. S. Peiris, J. Sung, V. C. Wong, and K. Y. Yuen.** 2003. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med. J. 9:399-406. [PubMed] [Google Scholar]

34. **Chan, K. S., J. P. Zheng, Y. W. Mok, Y. M. Li, Y. N. Liu, C. M. Chu, and M. S. Ip.** 2003. SARS: prognosis, outcome and sequelae. Respirology 8:S36-S40. [PubMed] [Google Scholar]

35. **Chan, K. Y., J. C. Ching, M. S. Xu, A. N. Cheung, S. P. Yip, L. Y. Yam, S. T. Lai, C. M. Chu, A. T. Wong, Y. Q. Song, F. P. Huang, W. Liu, P. H. Chung, G. M. Leung, E. Y. Chow, E. Y. Chan, J. C. Chan, H. Y. Ngan, P. Tam, L. C. Chan, P. Sham, V. S. Chan, M. Peiris, S. C. Lin, and U. S. Khoo.** 2007. Association of ICAM3 genetic variant with severe acute respiratory syndrome. J. Infect. Dis. 196:271-280. [PubMed] [Google Scholar]

36. **Chan, M. H., P. K. Chan, J. F. Griffith, I. H. Chan, L. C. Lit, C. K. Wong, G. E. Antonio, E. Y. Liu, D. S. Hui, M. W. Suen, A. T. Ahuja, J. J. Sung, and C. W. Lam.** 2006. Steroid-induced osteonecrosis in severe acute respiratory syndrome: a retrospective analysis of biochemical markers of bone metabolism and corticosteroid therapy. Pathology 38:229-235. [PubMed] [Google Scholar]

37. **Chan, P. K., M. Ip, K. C. Ng, C. W. Rickjason, A. Wu, N. Lee, T. H. Rainer, G. M. Joynt, J. J. Sung, and J. S. Tam.** 2003. Severe acute respiratory syndrome-associated coronavirus infection. Emerg. Infect. Dis. 9:1453-1454. [PMC free article] [PubMed] [Google Scholar]

38. **Chan, P. K., K. C. Ng, R. C. Chan, R. K. Lam, V. C. Chow, M. Hui, A. Wu, N. Lee, F. H. Yap, F. W. Cheng, J. J. Sung, and J. S. Tam.** 2004. Immunofluorescence assay for serologic diagnosis of SARS. Emerg. Infect. Dis. 10:530-532. [PMC free article] [PubMed] [Google Scholar]

39. **Chan, P. K., W. K. To, K. C. Ng, R. K. Lam, T. K. Ng, R. C. Chan, A. Wu, W. C. Yu, N. Lee, D. S. Hui, S. T. Lai, E. K. Hon, C. K. Li, J. J. Sung, and J. S. Tam.** 2004. Laboratory diagnosis of SARS. Emerg. Infect. Dis. 10:825-831. [PMC free article] [PubMed] [Google Scholar]

40. **Chan, V. S., K. Y. Chan, Y. Chen, L. L. Poon, A. N. Cheung, B. Zheng, K. H. Chan, W. Mak, H. Y. Ngan, X. Xu, G. Screaton, P. K. Tam, J. M. Austyn, L. C. Chan, S. P. Yip, M. Peiris, U. S. Khoo, and C. L. Lin.** 2006. Homozygous L-SIGN (CLEC4M) plays a protective role in SARS coronavirus infection. Nat. Genet. 38:38-46. [PubMed] [Google Scholar]

41. **Chan, W. M., Y. W. Kwan, H. S. Wan, C. W. Leung, and M. C. Chiu.** 2004. Epidemiologic linkage and public health implication of a cluster of severe acute respiratory syndrome in an extended family. Pediatr. Infect. Dis. J. 23:1156-1159. [PubMed] [Google Scholar]

42. **Chan, W. M., K. S. Yuen, D. S. Fan, D. S. Lam, P. K. Chan, and J. J. Sung.** 2004. Tears and conjunctival scrapings for coronavirus in patients with SARS. Br. J. Ophthalmol. 88:968-969. [PMC free article] [PubMed] [Google Scholar]

43. **Chang, Y. J., C. Y. Liu, B. L. Chiang, Y. C. Chao, and C. C. Chen.** 2004. Induction of IL-8 release in lung cells via activator protein-1 by recombinant baculovirus displaying severe acute respiratory syndrome-coronavirus spike proteins: identification of two functional regions. J. Immunol. 173:7602-7614. [PubMed] [Google Scholar]

44. **Chau, T. N., K. C. Lee, H. Yao, T. Y. Tsang, T. C. Chow, Y. C. Yeung, K. W. Choi, Y. K. Tso, T. Lau, S. T. Lai, and C. L. Lai.** 2004. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology 39:302-310. [PubMed] [Google Scholar]

45. **Che, X. Y., B. Di, G. P. Zhao, Y. D. Wang, L. W. Qiu, W. Hao, M. Wang, P. Z. Qin, Y. F. Liu, K. H. Chan, V. C. Cheng, and K. Y. Yuen.** 2006. A patient with asymptomatic severe acute respiratory syndrome (SARS) and antigenemia from the 2003-2004 community outbreak of SARS in Guangzhou, China. Clin. Infect. Dis. 43:e1-e5. [PubMed] [Google Scholar]

46. **Che, X. Y., W. Hao, Y. Wang, B. Di, K. Yin, Y. C. Xu, C. S. Feng, Z. Y. Wan, V. C. Cheng, and K. Y. Yuen.** 2004. Nucleocapsid protein as early diagnostic marker for SARS. Emerg. Infect. Dis. 10:1947-1949. [PMC free article] [PubMed] [Google Scholar]

47. **Che, X. Y., L. W. Qiu, Z. Y. Liao, Y. D. Wang, K. Wen, Y. X. Pan, W. Hao, Y. B. Mei, V. C. Cheng, and K. Y. Yuen.** 2005. Antigenic cross-reactivity between severe acute respiratory syndrome-associated coronavirus and human coronaviruses 229E and OC43. J. Infect. Dis. 191:2033-2037. [PubMed] [Google Scholar]

48. **Che, X. Y., L. W. Qiu, Y. X. Pan, K. Wen, W. Hao, L. Y. Zhang, Y. D. Wang, Z. Y. Liao, X. Hua, V. C. Cheng, and K. Y. Yuen.** 2004. Sensitive and specific monoclonal antibody-based capture enzyme immunoassay for detection of nucleocapsid antigen in sera from patients with severe acute respiratory syndrome. J. Clin. Microbiol. 42:2629-2635. [PMC free article] [PubMed] [Google Scholar]

49. **Chen, C. Y., Y. H. Ping, H. C. Lee, K. H. Chen, Y. M. Lee, Y. J. Chan, T. C. Lien, T. S. Jap, C. H. Lin, L. S. Kao, and Y. M. Chen.** 2007. Open reading frame 8a of the human severe acute respiratory syndrome coronavirus not only promotes viral replication but also induces apoptosis. J. Infect. Dis. 196:405-415. [PubMed] [Google Scholar]

50. **Chen, F., K. H. Chan, Y. Jiang, R. Y. Kao, H. T. Lu, K. W. Fan, V. C. Cheng, W. H. Tsui, I. F. Hung, T. S. Lee, Y. Guan, J. S. Peiris, and K. Y. Yuen.** 2004. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J. Clin. Virol. 31:69-75. [PubMed] [Google Scholar]

51. **Chen, L., C. Gui, X. Luo, Q. Yang, S. Gunther, E. Scandella, C. Drosten, D. Bai, X. He, B. Ludewig, J. Chen, H. Luo, Y. Yang, Y. Yang, J. Zou, V. Thiel, K. Chen, J. Shen, X. Shen, and H. Jiang.** 2005. Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication in vitro. J. Virol. 79:7095-7103. [PMC free article] [PubMed] [Google Scholar]

52. **Chen, L., P. Liu, H. Gao, B. Sun, D. Chao, F. Wang, Y. Zhu, G. Hedenstierna, and C. G. Wang.** 2004. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. Clin. Infect. Dis. 39:1531-1535. [PubMed] [Google Scholar]

53. **Chen, M. I., S. C. Loon, H. N. Leong, and Y. S. Leo.** 2006. Understanding the super-spreading events of SARS in Singapore. Ann. Acad. Med. Singapore 35:390-394. [PubMed] [Google Scholar]

54. **Chen, S., D. Lu, M. Zhang, J. Che, Z. Yin, S. Zhang, W. Zhang, X. Bo, Y. Ding, and S. Wang.** 2005. Double-antigen sandwich ELISA for detection of antibodies to SARS-associated coronavirus in human serum. Eur. J. Clin. Microbiol. Infect. Dis. 24:549-553. [PubMed] [Google Scholar]

55. **Chen, Z., L. Zhang, C. Qin, L. Ba, C. E. Yi, F. Zhang, Q. Wei, T. He, W. Yu, J. Yu, H. Gao, X. Tu, A. Gettie, M. Farzan, K. Y. Yuen, and D. D. Ho.** 2005. Recombinant modified vaccinia virus Ankara expressing the spike glycoprotein of severe acute respiratory syndrome coronavirus induces protective neutralizing antibodies primarily targeting the receptor binding region. J. Virol. 79:2678-2688. [PMC free article] [PubMed] [Google Scholar]

56. **Cheng, P. K., D. A. Wong, L. K. Tong, S. M. Ip, A. C. Lo, C. S. Lau, E. Y. Yeung, and W. W. Lim.** 2004. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. Lancet 363:1699-1700. [PubMed] [Google Scholar]

57. **Cheng, S. K., C. W. Wong, J. Tsang, and K. C. Wong.** 2004. Psychological distress and negative appraisals in survivors of severe acute respiratory syndrome (SARS). Psychol. Med. 34:1187-1195. [PubMed] [Google Scholar]

58. **Cheng, V. C., I. F. Hung, B. S. Tang, C. M. Chu, M. M. Wong, K. H. Chan, A. K. Wu, D. M. Tse, K. S. Chan, B. J. Zheng, J. S. Peiris, J. J. Sung, and K. Y. Yuen.** 2004. Viral replication in the nasopharynx is associated with diarrhea in patients with severe acute respiratory syndrome. Clin. Infect. Dis. 38:467-475. [PubMed] [Google Scholar]

59. **Cheng, V. C., B. S. Tang, A. K. Wu, C. M. Chu, and K. Y. Yuen.** 2004. Medical treatment of viral pneumonia including SARS in immunocompetent adult. J. Infect. 49:262-273. [PubMed] [Google Scholar]

60. **Cheng, Y., R. Wong, Y. O. Soo, W. S. Wong, C. K. Lee, M. H. Ng, P. Chan, K. C. Wong, C. B. Leung, and G. Cheng.** 2005. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur. J. Clin. Microbiol. Infect. Dis. 24:44-46. [PubMed] [Google Scholar]

61. **Cheung, C. Y., L. L. Poon, I. H. Ng, W. Luk, S. F. Sia, M. H. Wu, K. H. Chan, K. Y. Yuen, S. Gordon, Y. Guan, and J. S. Peiris.** 2005. Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. J. Virol. 79:7819-7826. [PMC free article] [PubMed] [Google Scholar]

62. **Cheung, T. M., L. Y. Yam, L. K. So, A. C. Lau, E. Poon, B. M. Kong, and R. W. Yung.** 2004. Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. Chest 126:845-850. [PubMed] [Google Scholar]

63. **Chien, J. Y., P. R. Hsueh, W. C. Cheng, C. J. Yu, and P. C. Yang.** 2006. Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. Respirology 11:715-722. [PubMed] [Google Scholar]

64. **Chinese SARS Molecular Epidemiology Consortium.** 2004. Molecular evolution of the SARS coronavirus during the course of the SARS epidemic in China. Science 303:1666-1669. [PubMed] [Google Scholar]

65. **Cho, J. H., D. L. Bernard, R. W. Sidwell, E. R. Kern, and C. K. Chu.** 2006. Synthesis of cyclopentenyl carbocyclic nucleosides as potential antiviral agents against orthopoxviruses and SARS. J. Med. Chem. 49:1140-1148. [PubMed] [Google Scholar]

66. **Chong, M. Y., W. C. Wang, W. C. Hsieh, C. Y. Lee, N. M. Chiu, W. C. Yeh, O. L. Huang, J. K. Wen, and C. L. Chen.** 2004. Psychological impact of severe acute respiratory syndrome on health workers in a tertiary hospital. Br. J. Psych. 185:127-133. [PubMed] [Google Scholar]

67. **Chong, P. Y., P. Chui, A. E. Ling, T. J. Franks, D. Y. Tai, Y. S. Leo, G. J. Kaw, G. Wansaicheong, K. P. Chan, L. L. E. Oon, E. S. Teo, K. B. Tan, N. Nakajima, T. Sata, and W. D. Travis.** 2004. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. Arch. Pathol. Lab. Med. 128:195-204. [PubMed] [Google Scholar]

68. **Chow, K. Y., C. E. Lee, M. L. Ling, D. M. Heng, and S. G. Yap.** 2004. Outbreak of severe acute respiratory syndrome in a tertiary hospital in Singapore, linked to an index patient with atypical presentation: epidemiological study. BMJ 328:195. [PMC free article] [PubMed] [Google Scholar]

69. **Chow, P. K., E. E. Ooi, H. K. Tan, K. W. Ong, B. K. Sil, M. Teo, T. Ng, and K. C. Soo.** 2004. Healthcare worker seroconversion in SARS outbreak. Emerg. Infect. Dis. 10:249-250. [PMC free article] [PubMed] [Google Scholar]

70. **Christian, M. D., M. Loutfy, L. C. McDonald, K. F. Martinez, M. Ofner, T. Wong, T. Wallington, W. L. Gold, B. Mederski, K. Green, and D. E. Low.** 2004. Possible SARS coronavirus transmission during cardiopulmonary resuscitation. Emerg. Infect. Dis. 10:287-293. [PMC free article] [PubMed] [Google Scholar]

71. **Chu, C. M., V. C. Cheng, I. F. Hung, K. S. Chan, B. S. Tang, T. H. Tsang, K. H. Chan, and K. Y. Yuen.** 2005. Viral load distribution in SARS outbreak. Emerg. Infect. Dis. 11:1882-1886. [PMC free article] [PubMed] [Google Scholar]

72. **Chu, C. M., V. C. Cheng, I. F. Hung, M. M. Wong, K. H. Chan, K. S. Chan, R. Y. Kao, L. L. Poon, C. L. Wong, Y. Guan, J. S. Peiris, and K. Y. Yuen.** 2004. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 59:252-256. [PMC free article] [PubMed] [Google Scholar]

73. **Chu, C. M., W. S. Leung, V. C. Cheng, K. H. Chan, A. W. Lin, V. L. Chan, J. Y. Lam, K. S. Chan, and K. Y. Yuen.** 2005. Duration of RT-PCR positivity in severe acute respiratory syndrome. Eur. Respir. J. 25:12-14. [PubMed] [Google Scholar]

74. **Chu, C. M., Y. Y. Leung, J. Y. Hui, I. F. Hung, V. L. Chan, W. S. Leung, K. I. Law, C. S. Chan, K. S. Chan, and K. Y. Yuen.** 2004. Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. Eur. Respir. J. 23:802-804. [PubMed] [Google Scholar]

75. **Chu, C. M., L. L. Poon, V. C. Cheng, K. S. Chan, I. F. Hung, M. M. Wong, K. H. Chan, W. S. Leung, B. S. Tang, V. L. Chan, W. L. Ng, T. C. Sim, P. W. Ng, K. I. Law, D. M. Tse, J. S. Peiris, and K. Y. Yuen.** 2004. Initial viral load and the outcomes of SARS. CMAJ 171:1349-1352. [PMC free article] [PubMed] [Google Scholar]

76. **Chu, K. H., W. K. Tsang, C. S. Tang, M. F. Lam, F. M. Lai, K. F. To, K. S. Fung, H. L. Tang, W. W. Yan, H. W. Chan, T. S. Lai, K. L. Tong, and K. N. Lai.** 2005. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 67:698-705. [PubMed] [Google Scholar]

77. **Cinatl, J., B. Morgenstern, G. Bauer, P. Chandra, H. Rabenau, and H. W. Doerr.** 2003. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361:2045-2046. [PubMed] [Google Scholar]

78. **Cinatl, J., B. Morgenstern, G. Bauer, P. Chandra, H. Rabenau, and H. W. Doerr.** 2003. Treatment of SARS with human interferons. Lancet 362:293-294. [PubMed] [Google Scholar]

79. **Cinatl, J., Jr., G. Hoever, B. Morgenstern, W. Preiser, J. U. Vogel, W. K. Hofmann, G. Bauer, M. Michaelis, H. F. Rabenau, and H. W. Doerr.** 2004. Infection of cultured intestinal epithelial cells with severe acute respiratory syndrome coronavirus. Cell. Mol. Life Sci. 61:2100-2112. [PMC free article] [PubMed] [Google Scholar]

80. **Cinatl, J., Jr., M. Michaelis, B. Morgenstern, and H. W. Doerr.** 2005. High-dose hydrocortisone reduces expression of the pro-inflammatory chemokines CXCL8 and CXCL10 in SARS coronavirus-infected intestinal cells. Int. J. Mol. Med. 15:323-327. [PubMed] [Google Scholar]

81. **Connor, R. F., and R. L. Roper.** 2007. Unique SARS-CoV protein nsp1: bioinformatics, biochemistry and potential effects on virulence. Trends Microbiol. 15:51-53. [PubMed] [Google Scholar]

82. **Cui, W., Y. Fan, W. Wu, F. Zhang, J. Y. Wang, and A. P. Ni.** 2003. Expression of lymphocytes and lymphocyte subsets in patients with severe acute respiratory syndrome. Clin. Infect. Dis. 37:857-859. [PubMed] [Google Scholar]

83. **Dahl, H., A. Linde, and O. Strannegard.** 2004. In vitro inhibition of SARS virus replication by human interferons. Scand. J. Infect. Dis. 36:829-831. [PubMed] [Google Scholar]

84. **de Lang, A., A. D. Osterhaus, and B. L. Haagmans.** 2006. Interferon-gamma and interleukin-4 downregulate expression of the SARS coronavirus receptor ACE2 in Vero E6 cells. Virology 353:474-481. [PubMed] [Google Scholar]

85. **Deming, D., T. Sheahan, M. Heise, B. Yount, N. Davis, A. Sims, M. Suthar, J. Harkema, A. Whitmore, R. Pickles, A. West, E. Donaldson, K. Curtis, R. Johnston, and R. Baric.** 2006. Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. PLoS Med. 3:e525. [PMC free article] [PubMed] [Google Scholar]

86. **Di, B., W. Hao, Y. Gao, M. Wang, Y. D. Wang, L. W. Qiu, K. Wen, D. H. Zhou, X. W. Wu, E. J. Lu, Z. Y. Liao, Y. B. Mei, B. J. Zheng, and X. Y. Che.** 2005. Monoclonal antibody-based antigen capture enzyme-linked immunosorbent assay reveals high sensitivity of the nucleocapsid protein in acute-phase sera of severe acute respiratory syndrome patients. Clin. Diagn. Lab. Immunol. 12:135-140. [PMC free article] [PubMed] [Google Scholar]

87. **Ding, Y., H. Wang, H. Shen, Z. Li, J. Geng, H. Han, J. Cai, X. Li, W. Kang, D. Weng, Y. Lu, D. Wu, L. He, and K. Yao.** 2003. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J. Pathol. 200:282-289. [PubMed] [Google Scholar]

88. **Drosten, C., L. L. Chiu, M. Panning, H. N. Leong, W. Preiser, J. S. Tam, S. Gunther, S. Kramme, P. Emmerich, W. L. Ng, H. Schmitz, and E. S. Koay.** 2004. Evaluation of advanced reverse transcription-PCR assays and an alternative PCR target region for detection of severe acute respiratory syndrome-associated coronavirus. J. Clin. Microbiol. 42:2043-2047. [PMC free article] [PubMed] [Google Scholar]

89. **Drosten, C., S. Gunther, W. Preiser, S. van der Werf, H. R. Brodt, S. Becker, H. Rabenau, M. Panning, L. Kolesnikova, R. A. Fouchier, A. Berger, A. M. Burguiere, J. Cinatl, M. Eickmann, N. Escriou, K. Grywna, S. Kramme, J. C. Manuguerra, S. Muller, V. Rickerts, M. Sturmer, S. Vieth, H. D. Klenk, A. D. Osterhaus, H. Schmitz, and H. W. Doerr.** 2003. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N. Engl. J. Med. 348:1967-1976. [PubMed] [Google Scholar]

90. **Du, L., R. Y. Kao, Y. Zhou, Y. He, G. Zhao, C. Wong, S. Jiang, K. Y. Yuen, D. Y. Jin, and B. J. Zheng.** 2007. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. Biochem. Biophys. Res. Commun. 359:174-179. [PMC free article] [PubMed] [Google Scholar]

91. **Duan, S. M., X. S. Zhao, R. F. Wen, J. J. Huang, G. H. Pi, S. X. Zhang, J. Han, S. L. Bi, L. Ruan, and X. P. Dong.** 2003. Stability of SARS coronavirus in human specimens and environment and its sensitivity to heating and UV irradiation. Biomed. Environ. Sci. 16:246-255. [PubMed] [Google Scholar]

92. **Egloff, M. P., F. Ferron, V. Campanacci, S. Longhi, C. Rancurel, H. Dutartre, E. J. Snijder, A. E. Gorbalenya, C. Cambillau, and B. Canard.** 2004. The severe acute respiratory syndrome-coronavirus replicative protein nsp9 is a single-stranded RNA-binding subunit unique in the RNA virus world. Proc. Natl. Acad. Sci. USA 101:3792-3796. [PMC free article] [PubMed] [Google Scholar]

93. **Eickmann, M., S. Becker, H. D. Klenk, H. W. Doerr, K. Stadler, S. Censini, S. Guidotti, V. Masignani, M. Scarselli, M. Mora, C. Donati, J. H. Han, H. C. Song, S. Abrignani, A. Covacci, and R. Rappuoli.** 2003. Phylogeny of the SARS coronavirus. Science 302:1504-1505. [PubMed] [Google Scholar]

94. **Faber, M., E. W. Lamirande, A. Roberts, A. B. Rice, H. Koprowski, B. Dietzschold, and M. J. Schnell.** 2005. A single immunization with a rhabdovirus-based vector expressing severe acute respiratory syndrome coronavirus (SARS-CoV) S protein results in the production of high levels of SARS-CoV-neutralizing antibodies. J. Gen. Virol. 86:1435-1440. [PMC free article] [PubMed] [Google Scholar]

95. **Fan, Z., K. Peng, X. Tan, B. Yin, X. Dong, F. Qiu, Y. Shen, H. Wang, J. Yuan, B. Qiang, and X. Peng.** 2005. Molecular cloning, expression, and purification of SARS-CoV nsp13. Protein Expr. Purif. 41:235-240. [PubMed] [Google Scholar]

96. **Farcas, G. A., S. M. Poutanen, T. Mazzulli, B. M. Willey, J. Butany, S. L. Asa, P. Faure, P. Akhavan, D. E. Low, and K. C. Kain.** 2005. Fatal severe acute respiratory syndrome is associated with multiorgan involvement by coronavirus. J. Infect. Dis. 191:193-197. [PubMed] [Google Scholar]

97. **Fielding, B. C., V. Gunalan, T. H. Tan, C. F. Chou, S. Shen, S. Khan, S. G. Lim, W. Hong, and Y. J. Tan.** 2006. Severe acute respiratory syndrome coronavirus protein 7a interacts with hSGT. Biochem. Biophys. Res. Commun. 343:1201-1208. [PubMed] [Google Scholar]

98. **Fouchier, R. A., T. Kuiken, M. Schntten, G. van Amerongen, G. J. van Doornum, B. G. van den Hoogen, M. Peiris, W. Lim, K. Stohr, and A. D. Osterhaus.** 2003. Aetiology: Koch's postulates fulfilled for SARS virus. Nature 423:240. [PubMed] [Google Scholar]

99. **Franks, T. J., P. Y. Chong, P. Chui, J. R. Galvin, R. M. Lourens, A. H. Reid, E. Selbs, C. P. McEvoy, C. D. Hayden, J. Fukuoka, J. K. Taubenberger, and W. D. Travis.** 2003. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. Hum. Pathol. 34:743-748. [PubMed] [Google Scholar]

100. **Frieman, M., B. Yount, M. Heise, S. A. Kopecky-Bromberg, P. Palese, and R. S. Baric.** 2007. SARS-CoV ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rER/Golgi membrane. J. Virol. 81:9812-9824. [PMC free article] [PubMed] [Google Scholar]

101. **Gan, Y. R., H. Huang, Y. D. Huang, C. M. Rao, Y. Zhao, J. S. Liu, L. Wu, and D. Q. Wei.** 2006. Synthesis and activity of an octapeptide inhibitor designed for SARS coronavirus main proteinase. Peptides 27:622-625. [PubMed] [Google Scholar]

102. **Gao, W., A. Tamin, A. Soloff, L. D'Aiuto, E. Nwanegbo, P. D. Robbins, W. J. Bellini, S. Barratt-Boyes, and A. Gambotto.** 2003. Effects of a SARS-associated coronavirus vaccine in monkeys. Lancet 362:1895-1896. [PubMed] [Google Scholar]

103. **Ghosh, A. K., K. Xi, K. Ratia, B. D. Santarsiero, W. Fu, B. H. Harcourt, P. A. Rota, S. C. Baker, M. E. Johnson, and A. D. Mesecar.** 2005. Design and synthesis of peptidomimetic severe acute respiratory syndrome chymotrypsin-like protease inhibitors. J. Med. Chem. 48:6767-6771. [PubMed] [Google Scholar]

104. **Gillim-Ross, L., J. Taylor, D. R. Scholl, J. Ridenour, P. S. Masters, and D. E. Wentworth.** 2004. Discovery of novel human and animal cells infected by the severe acute respiratory syndrome coronavirus by replication-specific multiplex reverse transcription-PCR. J. Clin. Microbiol. 42:3196-3206. [PMC free article] [PubMed] [Google Scholar]

105. **Glass, W. G., K. Subbarao, B. Murphy, and P. M. Murphy.** 2004. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. J. Immunol. 173:4030-4039. [PubMed] [Google Scholar]

106. **Graham, R. L., A. C. Sims, S. M. Brockway, R. S. Baric, and M. R. Denison.** 2005. The nsp2 replicase proteins of murine hepatitis virus and severe acute respiratory syndrome coronavirus are dispensable for viral replication. J. Virol. 79:13399-13411. [PMC free article] [PubMed] [Google Scholar]

107. **Gramberg, T., H. Hofmann, P. Moller, P. F. Lalor, A. Marzi, M. Geier, M. Krumbiegel, T. Winkler, F. Kirchhoff, D. H. Adams, S. Becker, J. Munch, and S. Pohlmann.** 2005. LSECtin interacts with filovirus glycoproteins and the spike protein of SARS coronavirus. Virology 340:224-236. [PubMed] [Google Scholar]

108. **Grant, P. R., J. A. Garson, R. S. Tedder, P. K. Chan, J. S. Tam, and J. J. Sung.** 2003. Detection of SARS coronavirus in plasma by real-time RT-PCR. N. Engl. J. Med. 349:2468-2469. [PubMed] [Google Scholar]

109. **Greaves, I. A., H. J. Colebatch, and T. A. Torda.** 1981. A possible role for corticosteroids in the treatment of influenzal pneumonia. Aust. N. Z. J. Med. 11:271-276. [PubMed] [Google Scholar]

110. **Greenough, T. C., G. J. Babcock, A. Roberts, H. J. Hernandez, W. D. Thomas, Jr., J. A. Coccia, R. F. Graziano, M. Srinivasan, I. Lowy, R. W. Finberg, K. Subbarao, L. Vogel, M. Somasundaran, K. Luzuriaga, J. L. Sullivan, and D. M. Ambrosino.** 2005. Development and characterization of a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody that provides effective immunoprophylaxis in mice. J. Infect. Dis. 191:507-514. [PubMed] [Google Scholar]

111. **Greenough, T. C., A. Carville, J. Coderre, M. Somasundaran, J. L. Sullivan, K. Luzuriaga, and K. Mansfield.** 2005. Pneumonitis and multi-organ system disease in common marmosets (Callithrix jacchus) infected with the severe acute respiratory syndrome-associated coronavirus. Am. J. Pathol. 167:455-463. [PMC free article] [PubMed] [Google Scholar]

112. **Griffith, J. F., G. E. Antonio, S. M. Kumta, D. S. Hui, J. K. Wong, G. M. Joynt, A. K. Wu, A. Y. Cheung, K. H. Chiu, K. M. Chan, P. C. Leung, and A. T. Ahuja.** 2005. Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. Radiology 235:168-175. [PubMed] [Google Scholar]

113. **Grinblat, L., H. Shulman, A. Glickman, L. Matukas, and N. Paul.** 2003. Severe acute respiratory syndrome: radiographic review of 40 probable cases in Toronto, Canada. Radiology 228:802-809. [PubMed] [Google Scholar]

114. **Guan, M., K. H. Chan, J. S. Peiris, S. W. Kwan, S. Y. Lam, C. M. Pang, K. W. Chu, K. M. Chan, H. Y. Chen, E. B. Phuah, and C. J. Wong.** 2004. Evaluation and validation of an enzyme-linked immunosorbent assay and an immunochromatographic test for serological diagnosis of severe acute respiratory syndrome. Clin. Diagn. Lab. Immunol. 11:699-703. [PMC free article] [PubMed] [Google Scholar]

115. **Guan, M., H. Y. Chen, S. Y. Foo, Y. J. Tan, P. Y. Goh, and S. H. Wee.** 2004. Recombinant protein-based enzyme-linked immunosorbent assay and immunochromatographic tests for detection of immunoglobulin G antibodies to severe acute respiratory syndrome (SARS) coronavirus in SARS patients. Clin. Diagn. Lab. Immunol. 11:287-291. [PMC free article] [PubMed] [Google Scholar]

116. **Guan, Y., J. S. Peiris, B. Zheng, L. L. Poon, K. H. Chan, F. Y. Zeng, C. W. Chan, M. N. Chan, J. D. Chen, K. Y. Chow, C. C. Hon, K. H. Hui, J. Li, V. Y. Li, Y. Wang, S. W. Leung, K. Y. Yuen, and F. C. Leung.** 2004. Molecular epidemiology of the novel coronavirus that causes severe acute respiratory syndrome. Lancet 363:99-104. [PubMed] [Google Scholar]

117. **Guan, Y., B. J. Zheng, Y. Q. He, X. L. Liu, Z. X. Zhuang, C. L. Cheung, S. W. Luo, P. H. Li, L. J. Zhang, Y. J. Guan, K. M. Butt, K. L. Wong, K. W. Chan, W. Lim, K. F. Shortridge, K. Y. Yuen, J. S. Peiris, and L. L. Poon.** 2003. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science 302:276-278. [PubMed] [Google Scholar]

118. **Haagmans, B. L., T. Kuiken, B. E. Martina, R. A. Fouchier, G. F. Rimmelzwaan, G. van Amerongen, D. van Riel, T. de Jong, S. Itamura, K. H. Chan, M. Tashiro, and A. D. Osterhaus.** 2004. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat. Med. 10:290-293. [PubMed] [Google Scholar]

119. **Hamming, I., W. Timens, M. L. Bulthuis, A. T. Lely, G. J. Navis, and H. van Goor.** 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J. Pathol. 203:631-637. [PubMed] [Google Scholar]

120. **Han, D. P., A. Penn-Nicholson, and M. W. Cho.** 2006. Identification of critical determinants on ACE2 for SARS-CoV entry and development of a potent entry inhibitor. Virology 350:15-25. [PubMed] [Google Scholar]

121. **Harcourt, B. H., D. Jukneliene, A. Kanjanahaluethai, J. Bechill, K. M. Severson, C. M. Smith, P. A. Rota, and S. C. Baker.** 2004. Identification of severe acute respiratory syndrome coronavirus replicase products and characterization of papain-like protease activity. J. Virol. 78:13600-13612. [PMC free article] [PubMed] [Google Scholar]

122. **Hattermann, K., M. A. Muller, A. Nitsche, S. Wendt, O. D. Mantke, and M. Niedrig.** 2005. Susceptibility of different eukaryotic cell lines to SARS-coronavirus. Arch. Virol. 150:1023-1031. [PubMed] [Google Scholar]

123. **He, H., Y. Tang, X. Qin, W. Xu, Y. Wang, X. Liu, X. Liu, S. Xiong, J. Li, M. Zhang, and M. Duan.** 2005. Construction of a eukaryotic expression plasmid encoding partial S gene fragments of the SARS-CoV and its potential utility as a DNA vaccine. DNA Cell Biol. 24:516-520. [PubMed] [Google Scholar]

124. **He, L., Y. Ding, Q. Zhang, X. Che, Y. He, H. Shen, H. Wang, Z. Li, L. Zhao, J. Geng, Y. Deng, L. Yang, J. Li, J. Cai, L. Qiu, K. Wen, X. Xu, and S. Jiang.** 2006. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. J. Pathol. 210:288-297. [PubMed] [Google Scholar]

125. **He, M. L., B. Zheng, Y. Peng, J. S. Peiris, L. L. Poon, K. Y. Yuen, M. C. Lin, H. F. Kung, and Y. Guan.** 2003. Inhibition of SARS-associated coronavirus infection and replication by RNA interference. JAMA 290:2665-2666. [PubMed] [Google Scholar]

126. **He, Q., K. H. Chong, H. H. Chng, B. Leung, A. E. Ling, T. Wei, S.-W. Chan, E. E. Ooi, and J. Kwang.** 2004. Development of a Western blot assay for detection of antibodies against coronavirus causing severe acute respiratory syndrome. Clin. Diagn. Lab. Immunol. 11:417-422. [PMC free article] [PubMed] [Google Scholar]

127. **He, Q., Q. Du, S. Lau, I. Manopo, L. Lu, S. W. Chan, B. J. Fenner, and J. Kwang.** 2005. Characterization of monoclonal antibody against SARS coronavirus nucleocapsid antigen and development of an antigen capture ELISA. J. Virol. Methods 127:46-53. [PubMed] [Google Scholar]

128. **He, Q., I. Manopo, L. Lu, B. P. Leung, H. H. Chng, A. E. Ling, L. L. Chee, S. W. Chan, E. E. Ooi, Y. L. Sin, B. Ang, and J. Kwang.** 2005. Novel immunofluorescence assay using recombinant nucleocapsid-spike fusion protein as antigen to detect antibodies against severe acute respiratory syndrome coronavirus. Clin. Diagn. Lab. Immunol. 12:321-328. [PMC free article] [PubMed] [Google Scholar]

129. **He, R., A. Adonov, M. Traykova-Adonova, J. Cao, T. Cutts, E. Grudesky, Y. Deschambaul, J. Berry, M. Drebot, and X. Li.** 2004. Potent and selective inhibition of SARS coronavirus replication by aurintricarboxylic acid. Biochem. Biophys. Res. Commun. 320:1199-1203. [PubMed] [Google Scholar]

130. **He, R., A. Leeson, A. Andonov, Y. Li, N. Bastien, J. Cao, C. Osiowy, F. Dobie, T. Cutts, M. Ballantine, and X. Li.** 2003. Activation of AP-1 signal transduction pathway by SARS coronavirus nucleocapsid protein. Biochem. Biophys. Res. Commun. 311:870-876. [PubMed] [Google Scholar]

131. **He, Y., J. Li, W. Li, S. Lustigman, M. Farzan, and S. Jiang.** 2006. Cross-neutralization of human and palm civet severe acute respiratory syndrome coronaviruses by antibodies targeting the receptor-binding domain of spike protein. J. Immunol. 176:6085-6092. [PubMed] [Google Scholar]

132. **He, Y., H. Lu, P. Siddiqui, Y. Zhou, and S. Jiang.** 2005. Receptor-binding domain of severe acute respiratory syndrome coronavirus spike protein contains multiple conformation-dependent epitopes that induce highly potent neutralizing antibodies. J. Immunol. 174:4908-4915. [PubMed] [Google Scholar]

133. **He, Y., Y. Zhou, S. Liu, Z. Kou, W. Li, M. Farzan, and S. Jiang.** 2004. Receptor-binding domain of SARS-CoV spike protein induces highly potent neutralizing antibodies: implication for developing subunit vaccine. Biochem. Biophys. Res. Commun. 324:773-781. [PubMed] [Google Scholar]

134. **He, Y., Y. Zhou, P. Siddiqui, and S. Jiang.** 2004. Inactivated SARS-CoV vaccine elicits high titers of spike protein-specific antibodies that block receptor binding and virus entry. Biochem. Biophys. Res. Commun. 325:445–452. [PubMed] [Google Scholar]

135. **He, Y., Q. Zhu, S. Liu, Y. Zhou, B. Yang, J. Li, and S. Jiang.** 2005. Identification of a critical neutralization determinant of severe acute respiratory syndrome (SARS)-associated coronavirus: importance for designing SARS vaccines. Virology 334:74-82. [PubMed] [Google Scholar]

136. **He, Z., C. Zhao, Q. Dong, H. Zhuang, S. Song, G. Peng, and D. E. Dwyer.** 2005. Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets. Int. J. Infect. Dis. 9:323-330. [PubMed] [Google Scholar]

137. **Hensley, L. E., L. E. Fritz, P. B. Jahrling, C. L. Karp, J. W. Huggins, and T. W. Geisbert.** 2004. Interferon-beta 1a and SARS coronavirus replication. Emerg. Infect. Dis. 10:317-319. [PMC free article] [PubMed] [Google Scholar]

138. **Hiscox, J. A., D. Cavanagh, and P. Britton.** 1995. Quantification of individual subgenomic mRNA species during replication of the coronavirus transmissible gastroenteritis virus. Virus Res. 36:119-130. [PubMed] [Google Scholar]

139. **Ho, J. C., G. C. Ooi, T. Y. Mok, J. W. Chan, I. Hung, B. Lam, P. C. Wong, P. C. Li, P. L. Ho, W. K. Lam, C. K. Ng, M. S. Ip, K. N. Lai, M. Chan-Yeung, and K. W. Tsang.** 2003. High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. Am. J. Respir. Crit. Care Med. 168:1449-1456. [PubMed] [Google Scholar]

140. **Ho, J. C., A. Y. Wu, B. Lam, G. C. Ooi, P. L. Khong, P. L. Ho, M. Chan-Yeung, N. S. Zhong, C. Ko, W. K. Lam, and K. W. Tsang.** 2004. Pentaglobin in steroid-resistant severe acute respiratory syndrome. Int. J. Tuberc. Lung Dis. 8:1173-1179. [PubMed] [Google Scholar]

141. **Ho, K. Y., K. S. Singh, A. G. Habib, B. K. Ong, T. K. Lim, E. E. Ooi, B. K. Sil, A. E. Ling, X. L. Bai, and P. A. Tambyah.** 2004. Mild illness associated with severe acute respiratory syndrome coronavirus infection: lessons from a prospective seroepidemiologic study of health-care workers in a teaching hospital in Singapore. J. Infect. Dis. 189:642-647. [PubMed] [Google Scholar]

142. **Ho, P. L., X. P. Tang, and W. H. Seto.** 2003. SARS: hospital infection control and admission strategies. Respirology 8:S41-S45. [PubMed] [Google Scholar]

143. **Hogan, R. J., G. Gao, T. Rowe, P. Bell, D. Flieder, J. Paragas, G. P. Kobinger, N. A. Wivel, R. G. Crystal, J. Boyer, H. Feldmann, T. G. Voss, and J. M. Wilson.** 2004. Resolution of primary severe acute respiratory syndrome-associated coronavirus infection requires Stat1. J. Virol. 78:11416-11421. [PMC free article] [PubMed] [Google Scholar]

144. **Hon, K. L., C. W. Leung, W. T. Cheng, P. K. Chan, W. C. Chu, Y. W. Kwan, A. M. Li, N. C. Fong, P. C. Ng, M. C. Chiu, C. K. Li, J. S. Tam, and T. F. Fok.** 2003. Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet 361:1701-1703. [PubMed] [Google Scholar]

145. **Hong, N., and X. K. Du.** 2004. Avascular necrosis of bone in severe acute respiratory syndrome. Clin. Radiol. 59:602-608. [PubMed] [Google Scholar]

146. **Hong, T. C., Q. L. Mai, D. V. Cuong, M. Parida, H. Minekawa, T. Notomi, F. Hasebe, and K. Morita.** 2004. Development and evaluation of a novel loop-mediated isothermal amplification method for rapid detection of severe acute respiratory syndrome coronavirus. J. Clin. Microbiol. 42:1956-1961. [PMC free article] [PubMed] [Google Scholar]

147. **Hsieh, P. K., S. C. Chang, C. C. Huang, T. T. Lee, C. W. Hsiao, Y. H. Kou, I. Y. Chen, C. K. Chang, T. H. Huang, and M. F. Chang.** 2005. Assembly of severe acute respiratory syndrome coronavirus RNA packaging signal into virus-like particles is nucleocapsid dependent. J. Virol. 79:13848-13855. [PMC free article] [PubMed] [Google Scholar]

148. **Hsieh, S. C., W. P. Chan, J. C. Chien, W. S. Lee, M. S. Yao, W. M. Choi, C. Y. Chen, and C. Yu.** 2004. Radiographic appearance and clinical outcome correlates in 26 patients with severe acute respiratory syndrome. Am. J. Roentgenol. 182:1119-1122. [PubMed] [Google Scholar]

149. **Hsu, L. Y., C. C. Lee, J. A. Green, B. Ang, N. I. Paton, L. Lee, J. S. Villacian, P. L. Lim, A. Earnest, and Y. S. Leo.** 2003. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. Emerg. Infect. Dis. 9:713-717. [PMC free article] [PubMed] [Google Scholar]

150. **Huang, C., N. Ito, C. T. Tseng, and S. Makino.** 2006. Severe acute respiratory syndrome coronavirus 7a accessory protein is a viral structural protein. J. Virol. 80:7287-7294. [PMC free article] [PubMed] [Google Scholar]

151. **Huang, I. C., B. J. Bosch, F. Li, W. Li, K. H. Lee, S. Ghiran, N. Vasilieva, T. S. Dermody, S. C. Harrison, P. R. Dormitzer, M. Farzan, P. J. Rottier, and H. Choe.** 2006. SARS coronavirus, but not human coronavirus NL63, utilizes cathepsin L to infect ACE2-expressing cells. J. Biol. Chem. 281:3198-3203. [PubMed] [Google Scholar]

152. **Huang, K. J., I. J. Su, M. Theron, Y. C. Wu, S. K. Lai, C. C. Liu, and H. Y. Lei.** 2005. An interferon-gamma-related cytokine storm in SARS patients. J. Med. Virol. 75:185-194. [PubMed] [Google Scholar]

153. **Hui, D. S., K. T. Wong, G. E. Antonio, N. Lee, A. Wu, V. Wong, W. Lau, J. C. Wu, L. S. Tam, L. M. Yu, G. M. Joynt, S. S. Chung, A. T. Ahuja, and J. J. Sung.** 2004. Severe acute respiratory syndrome: correlation between clinical outcome and radiologic features. Radiology 233:579-585. [PubMed] [Google Scholar]

154. **Hui, D. S., K. T. Wong, F. W. Ko, L. S. Tam, D. P. Chan, J. Woo, and J. J. Sung.** 2005. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest 128:2247-2261. [PubMed] [Google Scholar]

155. **Hui, R. K., F. Zeng, C. M. Chan, K. Y. Yuen, J. S. Peiris, and F. C. Leung.** 2004. Reverse transcriptase PCR diagnostic assay for the coronavirus associated with severe acute respiratory syndrome. J. Clin. Microbiol. 42:1994-1999. [PMC free article] [PubMed] [Google Scholar]

156. **Hung, I. F., V. C. Cheng, A. K. Wu, B. S. Tang, K. H. Chan, C. M. Chu, M. M. Wong, W. T. Hui, L. L. Poon, D. M. Tse, K. S. Chan, P. C. Woo, S. K. Lau, J. S. Peiris, and K. Y. Yuen.** 2004. Viral loads in clinical specimens and SARS manifestations. Emerg. Infect. Dis. 10:1550-1557. [PMC free article] [PubMed] [Google Scholar]

157. **Hwang, D. M., D. W. Chamberlain, S. M. Poutanen, D. E. Low, S. L. Asa, and J. Butany.** 2005. Pulmonary pathology of severe acute respiratory syndrome in Toronto. Mod. Pathol. 18:1-10. [PubMed] [Google Scholar]

158. **Imbert, I., J. C. Guillemot, J. M. Bourhis, C. Bussetta, B. Coutard, M. P. Egloff, F. Ferron, A. E. Gorbalenya, and B. Canard.** 2006. A second, non-canonical RNA-dependent RNA polymerase in SARS coronavirus. EMBO J. 25:4933-4942. [PMC free article] [PubMed] [Google Scholar]

159. **Ingallinella, P., E. Bianchi, M. Finotto, G. Cantoni, D. M. Eckert, V. M. Supekar, C. Bruckmann, A. Carfi, and A. Pessi.** 2004. Structural characterization of the fusion-active complex of severe acute respiratory syndrome (SARS) coronavirus. Proc. Natl. Acad. Sci. USA 101:8709-8714. [PMC free article] [PubMed] [Google Scholar]

160. **Ip, W. K., K. H. Chan, H. K. Law, G. H. Tso, E. K. Kong, W. H. Wong, Y. F. To, R. W. Yung, E. Y. Chow, K. L. Au, E. Y. Chan, W. Lim, J. C. Jensenius, M. W. Turner, J. S. Peiris, and Y. L. Lau.** 2005. Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. J. Infect. Dis. 191:1697-1704. [PubMed] [Google Scholar]

161. **Ito, N., E. C. Mossel, K. Narayanan, V. L. Popov, C. Huang, T. Inoue, C. J. Peters, and S. Makino.** 2005. Severe acute respiratory syndrome coronavirus 3a protein is a viral structural protein. J. Virol. 79:3182-3186. [PMC free article] [PubMed] [Google Scholar]

162. **Jeffers, S. A., S. M. Tusell, L. Gillim-Ross, E. M. Hemmila, J. E. Achenbach, G. J. Babcock, W. D. Thomas, Jr., L. B. Thackray, M. D. Young, R. J. Mason, D. M. Ambrosino, D. E. Wentworth, J. C. Demartini, and K. V. Holmes.** 2004. CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus. Proc. Natl. Acad. Sci. USA 101:15748-15753. [PMC free article] [PubMed] [Google Scholar]

163. **Jiang, Y., J. Xu, C. Zhou, Z. Wu, S. Zhong, J. Liu, W. Luo, T. Chen, Q. Qin, and P. Deng.** 2005. Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome. Am. J. Respir. Crit. Care Med. 171:850-857. [PubMed] [Google Scholar]

164. **Jin, H., C. Xiao, Z. Chen, Y. Kang, Y. Ma, K. Zhu, Q. Xie, Y. Tu, Y. Yu, and B. Wang.** 2005. Induction of Th1 type response by DNA vaccinations with N, M, and E genes against SARS-CoV in mice. Biochem. Biophys. Res. Commun. 328:979-986. [PubMed] [Google Scholar]

165. **Jones, B. M., E. S. Ma, J. S. Peiris, P. C. Wong, J. C. Ho, B. Lam, K. N. Lai, and K. W. Tsang.** 2004. Prolonged disturbances of in vitro cytokine production in patients with severe acute respiratory syndrome (SARS) treated with ribavirin and steroids. Clin. Exp. Immunol. 135:467-473. [PMC free article] [PubMed] [Google Scholar]

166. **Joseph, J. S., K. S. Saikatendu, V. Subramanian, B. W. Neuman, A. Brooun, M. Griffith, K. Moy, M. K. Yadav, J. Velasquez, M. J. Buchmeier, R. C. Stevens, and P. Kuhn.** 2006. Crystal structure of nonstructural protein 10 from the severe acute respiratory syndrome coronavirus reveals a novel fold with two zinc-binding motifs. J. Virol. 80:7894-7901. [PMC free article] [PubMed] [Google Scholar]

167. **Kamitani, W., K. Narayanan, C. Huang, K. Lokugamage, T. Ikegami, N. Ito, H. Kubo, and S. Makino.** 2006. Severe acute respiratory syndrome coronavirus nsp1 protein suppresses host gene expression by promoting host mRNA degradation. Proc. Natl. Acad. Sci. USA 103:12885-12890. [PMC free article] [PubMed] [Google Scholar]

168. **Kan, B., M. Wang, H. Jing, H. Xu, X. Jiang, M. Yan, W. Liang, H. Zheng, K. Wan, Q. Liu, B. Cui, Y. Xu, E. Zhang, H. Wang, J. Ye, G. Li, M. Li, Z. Cui, X. Qi, K. Chen, L. Du, K. Gao, Y. T. Zhao, X. Z. Zou, Y. J. Feng, Y. F. Gao, R. Hai, D. Yu, Y. Guan, and J. Xu.** 2005. Molecular evolution analysis and geographic investigation of severe acute respiratory syndrome coronavirus-like virus in palm civets at an animal market and on farms. J. Virol. 79:11892-11900. [PMC free article] [PubMed] [Google Scholar]

169. **Kanzawa, N., K. Nishigaki, T. Hayashi, Y. Ishii, S. Furukawa, A. Niiro, F. Yasui, M. Kohara, K. Morita, K. Matsushima, M. Q. Le, T. Masuda, and M. Kannagi.** 2006. Augmentation of chemokine production by severe acute respiratory syndrome coronavirus 3a/X1 and 7a/X4 proteins through NF-kappaB activation. FEBS Lett. 580:6807-6812. [PubMed] [Google Scholar]

170. **Kao, R. Y., W. H. Tsui, T. S. Lee, J. A. Tanner, R. M. Watt, J. D. Huang, L. Hu, G. Chen, Z. Chen, L. Zhang, T. He, K. H. Chan, H. Tse, A. P. To, L. W. Ng, B. C. Wong, H. W. Tsoi, D. Yang, D. D. Ho, and K. Y. Yuen.** 2004. Identification of novel small-molecule inhibitors of severe acute respiratory syndrome-associated coronavirus by chemical genetics. Chem. Biol. 11:1293-1299. [PubMed] [Google Scholar]

171. **Kapadia, S. U., J. K. Rose, E. Lamirande, L. Vogel, K. Subbarao, and A. Roberts.** 2005. Long-term protection from SARS coronavirus infection conferred by a single immunization with an attenuated VSV-based vaccine. Virology 340:174-182. [PubMed] [Google Scholar]

172. **Keng, C. T., Y. W. Choi, M. R. Welkers, D. Z. Chan, S. Shen, S. G. Lim, W. Hong, and Y. J. Tan.** 2006. The human severe acute respiratory syndrome coronavirus (SARS-CoV) 8b protein is distinct from its counterpart in animal SARS-CoV and down-regulates the expression of the envelope protein in infected cells. Virology 354:132-142. [PubMed] [Google Scholar]

173. **Keyaerts, E., L. Vijgen, L. Chen, P. Maes, G. Hedenstierna, and M. Van Ranst.** 2004. Inhibition of SARS-coronavirus infection in vitro by S-nitroso-N-acetylpenicillamine, a nitric oxide donor compound. Int. J. Infect. Dis. 8:223-226. [PubMed] [Google Scholar]

174. **Keyaerts, E., L. Vijgen, P. Maes, J. Neyts, and M. Van Ranst.** 2004. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem. Biophys. Res. Commun. 323:264-268. [PubMed] [Google Scholar]

175. **Khan, S., B. C. Fielding, T. H. Tan, C. F. Chou, S. Shen, S. G. Lim, W. Hong, and Y. J. Tan.** 2006. Over-expression of severe acute respiratory syndrome coronavirus 3b protein induces both apoptosis and necrosis in Vero E6 cells. Virus Res. 122:20-27. [PubMed] [Google Scholar]

176. **Kim, T. W., J. H. Lee, C. F. Hung, S. Peng, R. Roden, M. C. Wang, R. Viscidi, Y. C. Tsai, L. He, P. J. Chen, D. A. Boyd, and T. C. Wu.** 2004. Generation and characterization of DNA vaccines targeting the nucleocapsid protein of severe acute respiratory syndrome coronavirus. J. Virol. 78:4638-4645. [PMC free article] [PubMed] [Google Scholar]

177. **Kliger, Y., and E. Y. Levanon.** 2003. Cloaked similarity between HIV-1 and SARS-CoV suggests an anti-SARS strategy. BMC Microbiol. 3:20. [PMC free article] [PubMed] [Google Scholar]

178. **Kopecky-Bromberg, S. A., L. Martinez-Sobrido, M. Frieman, R. A. Baric, and P. Palese.** 2007. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. J. Virol. 81:548-557. [PMC free article] [PubMed] [Google Scholar]

179. **Kopecky-Bromberg, S. A., L. Martinez-Sobrido, and P. Palese.** 2006. 7a protein of severe acute respiratory syndrome coronavirus inhibits cellular protein synthesis and activates p38 mitogen-activated protein kinase. J. Virol. 80:785-793. [PMC free article] [PubMed] [Google Scholar]

180. **Ksiazek, T. G., D. Erdman, C. S. Goldsmith, S. R. Zaki, T. Peret, S. Emery, S. Tong, C. Urbani, J. A. Comer, W. Lim, P. E. Rollin, S. F. Dowell, A. E. Ling, C. D. Humphrey, W. J. Shieh, J. Guarner, C. D. Paddock, P. Rota, B. Fields, J. DeRisi, J. Y. Yang, N. Cox, J. M. Hughes, J. W. LeDuc, W. J. Bellini, and L. J. Anderson.** 2003. A novel coronavirus associated with severe acute respiratory syndrome. N. Engl. J. Med. 348:1953-1966. [PubMed] [Google Scholar]

181. **Kuba, K., Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W. Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A. Leibbrandt, T. Wada, A. S. Slutsky, D. Liu, C. Qin, C. Jiang, and J. M. Penninger.** 2005. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat. Med. 11:875-879. [PubMed] [Google Scholar]

182. **Kuiken, T., R. A. Fouchier, M. Schutten, G. F. Rimmelzwaan, G. van Amerongen, D. van Riel, J. D. Laman, T. de Jong, G. van Doornum, W. Lim, A. E. Ling, P. K. Chan, J. S. Tam, M. C. Zambon, R. Gopal, C. Drosten, S. van der Werf, N. Escriou, J. C. Manuguerra, K. Stohr, J. S. Peiris, and A. D. Osterhaus.** 2003. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 362:263-270. [PubMed] [Google Scholar]

183. **Kwan, M. Y., W. M. Chan, P. W. Ko, C. W. Leung, and M. C. Chiu.** 2004. Severe acute respiratory syndrome can be mild in children. Pediatr. Infect. Dis. J. 23:1172-1174. [PubMed] [Google Scholar]

184. **Lai, E. K., H. Deif, E. A. LaMere, D. H. Pham, B. Wolff, S. Ward, B. Mederski, and M. R. Loutfy.** 2005. Severe acute respiratory syndrome: quantitative assessment from chest radiographs with clinical and prognostic correlation. Am. J. Roentgenol. 184:255-263. [PubMed] [Google Scholar]

185. **Lai, M. Y., P. K. Cheng, and W. W. Lim.** 2005. Survival of severe acute respiratory syndrome coronavirus. Clin. Infect. Dis. 41:e67-e71. [PubMed] [Google Scholar]

186. **Lau, A. C., L. K. So, F. P. Miu, R. W. Yung, E. Poon, T. M. Cheung, and L. Y. Yam.** 2004. Outcome of coronavirus-associated severe acute respiratory syndrome using a standard treatment protocol. Respirology 9:173-183. [PubMed] [Google Scholar]

187. **Lau, J. T., X. Yang, P. C. Leung, L. Chan, E. Wong, C. Fong, and H. Y. Tsui.** 2004. SARS in three categories of hospital workers, Hong Kong. Emerg. Infect. Dis. 10:1399-1404. [PMC free article] [PubMed] [Google Scholar]

188. **Lau, K. K., W. C. Yu, C. M. Chu, S. T. Lau, B. Sheng, and K. Y. Yuen.** 2004. Possible central nervous system infection by SARS coronavirus. Emerg. Infect. Dis. 10:342-344. [PMC free article] [PubMed] [Google Scholar]

189. **Lau, S. K., X. Y. Che, P. C. Woo, B. H. Wong, V. C. Cheng, G. K. Woo, I. F. Hung, R. W. Poon, K. H. Chan, J. S. Peiris, and K. Y. Yuen.** 2005. SARS coronavirus detection methods. Emerg. Infect. Dis. 11:1108-1111. [PMC free article] [PubMed] [Google Scholar]

190. **Lau, S. K., P. C. Woo, K. S. Li, Y. Huang, H. W. Tsoi, B. H. Wong, S. S. Wong, S. Y. Leung, K. H. Chan, and K. Y. Yuen.** 2005. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc. Natl. Acad. Sci. USA 102:14040-14045. [PMC free article] [PubMed] [Google Scholar]

191. **Lau, S. K., P. C. Woo, B. H. Wong, H. W. Tsoi, G. K. Woo, R. W. Poon, K. H. Chan, W. I. Wei, J. S. Peiris, and K. Y. Yuen.** 2004. Detection of severe acute respiratory syndrome (SARS) coronavirus nucleocapsid protein in SARS patients by enzyme-linked immunosorbent assay. J. Clin. Microbiol. 42:2884-2889. [PMC free article] [PubMed] [Google Scholar]

192. **Law, A. H., D. C. Lee, B. K. Cheung, H. C. Yim, and A. S. Lau.** 2007. Role for nonstructural protein 1 of severe acute respiratory syndrome coronavirus in chemokine dysregulation. J. Virol. 81:416-422. [PMC free article] [PubMed] [Google Scholar]

193. **Law, P. T., C. H. Wong, T. C. Au, C. P. Chuck, S. K. Kong, P. K. Chan, K. F. To, A. W. Lo, J. Y. Chan, Y. K. Suen, H. Y. Chan, K. P. Fung, M. M. Waye, J. J. Sung, Y. M. Lo, and S. K. Tsui.** 2005. The 3a protein of severe acute respiratory syndrome-associated coronavirus induces apoptosis in Vero E6 cells. J. Gen. Virol. 86:1921-1930. [PubMed] [Google Scholar]

194. **Lawler, J. V., T. P. Endy, L. E. Hensley, A. Garrison, E. A. Fritz, M. Lesar, R. S. Baric, D. A. Kulesh, D. A. Norwood, L. P. Wasieloski, M. P. Ulrich, T. R. Slezak, E. Vitalis, J. W. Huggins, P. B. Jahrling, and J. Paragas.** 2006. Cynomolgus macaque as an animal model for severe acute respiratory syndrome. PLoS Med. 3:e149. [PMC free article] [PubMed] [Google Scholar]

195. **Lee, D. T., Y. K. Wing, H. C. Leung, J. J. Sung, Y. K. Ng, G. C. Yiu, R. Y. Chen, and H. F. Chiu.** 2004. Factors associated with psychosis among patients with severe acute respiratory syndrome: a case-control study. Clin. Infect. Dis. 39:1247-1249. [PubMed] [Google Scholar]

196. **Lee, N., K. C. A. Chan, D. S. Hui, E. K. Ng, A. Wu, R. W. Chiu, V. W. Wong, P. K. Chan, K. T. Wong, E. Wong, C. S. Cockram, J. S. Tam, J. J. Sung, and Y. M. Lo.** 2004. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. J. Clin. Virol. 31:304-309. [PubMed] [Google Scholar]

197. **Lee, N., D. Hui, A. Wu, P. Chan, P. Cameron, G. M. Joynt, A. Ahuja, M. Y. Yung, C. B. Leung, K. F. To, S. F. Lui, C. C. Szeto, S. Chung, and J. J. Sung.** 2003. A major outbreak of severe acute respiratory syndrome in Hong Kong. N. Engl. J. Med. 348:1986-1994. [PubMed] [Google Scholar]

198. **Lee, P. P., W. H. Wong, G. M. Leung, S. S. Chiu, K. H. Chan, J. S. Peiris, T. H. Lam, and Y. L. Lau.** 2006. Risk-stratified seroprevalence of severe acute respiratory syndrome coronavirus among children in Hong Kong. Pediatrics 117:e1156-e1162. [PubMed] [Google Scholar]

199. **Leong, H. N., B. Ang, A. Earnest, C. Teoh, W. Xu, and Y. S. Leo.** 2004. Investigational use of ribavirin in the treatment of severe acute respiratory syndrome, Singapore, 2003. Trop. Med. Int. Health 9:923-927. [PubMed] [Google Scholar]

200. **Leow, M. K., D. S. Kwek, A. W. Ng, K. C. Ong, G. J. Kaw, and L. S. Lee.** 2005. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin. Endocrinol. (Oxford) 63:197-202. [PubMed] [Google Scholar]

201. **Leung, G. M., P. H. Chung, T. Tsang, W. Lim, S. K. Chan, P. Chau, C. A. Donnelly, A. C. Ghani, C. Fraser, S. Riley, N. M. Ferguson, R. M. Anderson, Y. L. Law, T. Mok, T. Ng, A. Fu, P. Y. Leung, J. S. Peiris, T. H. Lam, and A. J. Hedley.** 2004. SARS-CoV antibody prevalence in all Hong Kong patient contacts. Emerg. Infect. Dis. 10:1653-1656. [PMC free article] [PubMed] [Google Scholar]

202. **Leung, G. M., A. J. Hedley, L. M. Ho, P. Chau, I. O. Wong, T. Q. Thach, A. C. Ghani, C. A. Donnelly, C. Fraser, S. Riley, N. M. Ferguson, R. M. Anderson, T. Tsang, P. Y. Leung, V. Wong, J. C. Chan, E. Tsui, S. V. Lo, and T. H. Lam.** 2004. The epidemiology of severe acute respiratory syndrome in the 2003 Hong Kong epidemic: an analysis of all 1755 patients. Ann. Intern. Med. 141:662-673. [PubMed] [Google Scholar]

203. **Leung, G. M., W. W. Lim, L. M. Ho, T. H. Lam, A. C. Ghani, C. A. Donnelly, C. Fraser, S. Riley, N. M. Ferguson, R. M. Anderson, and A. J. Hedley.** 2006. Seroprevalence of IgG antibodies to SARS-coronavirus in asymptomatic or subclinical population groups. Epidemiol. Infect. 134:211-221. [PMC free article] [PubMed] [Google Scholar]

204. **Leung, T. W., K. S. Wong, A. C. Hui, K. F. To, S. T. Lai, W. F. Ng, and H. K. Ng.** 2005. Myopathic changes associated with severe acute respiratory syndrome: a postmortem case series. Arch. Neurol. 62:1113-1117. [PubMed] [Google Scholar]

205. **Leung, W. K., K. F. To, P. K. Chan, H. L. Chan, A. K. Wu, N. Lee, K. Y. Yuen, and J. J. Sung.** 2003. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology 125:1011-1017. [PubMed] [Google Scholar]

206. **Li, F., W. Li, M. Farzan, and S. C. Harrison.** 2005. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science 309:1864-1868. [PubMed] [Google Scholar]

207. **Li, G., X. Chen, and A. Xu.** 2003. Profile of specific antibodies to the SARS-associated coronavirus. N. Engl. J. Med. 349:508-509. [PubMed] [Google Scholar]

208. **Li, L., J. Wo, J. Shao, H. Zhu, N. Wu, M. Li, H. Yao, M. Hu, and R. H. Dennin.** 2003. SARS-coronavirus replicates in mononuclear cells of peripheral blood (PBMCs) from SARS patients. J. Clin. Virol. 28:239-244. [PubMed] [Google Scholar]

209. **Li, L. H., Y. L. Shi, P. Li, D. X. Xu, G. P. Wan, X. Q. Gu, X. L. Zhang, Q. J. Ma, and C. Cao.** 2003. Detection and analysis of SARS coronavirus-specific antibodies in sera from non-SARS children. Di Yi Jun Yi Da Xue Xue Bao 23:1085-1087. (In Chinese.) [PubMed] [Google Scholar]

210. **Li, Q., L. Wang, C. Dong, Y. Che, L. Jiang, L. Liu, H. Zhao, Y. Liao, Y. Sheng, S. Dong, and S. Ma.** 2005. The interaction of the SARS coronavirus non-structural protein 10 with the cellular oxido-reductase system causes an extensive cytopathic effect. J. Clin. Virol. 34:133-139. [PubMed] [Google Scholar]

211. **Li, S. S., C. W. Cheng, C. L. Fu, Y. H. Chan, M. P. Lee, J. W. Chan, and S. F. Yiu.** 2003. Left ventricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study. Circulation 108:1798-1803. [PubMed] [Google Scholar]

212. **Li, S. Y., C. Chen, H. Q. Zhang, H. Y. Guo, H. Wang, L. Wang, X. Zhang, S. N. Hua, J. Yu, P. G. Xiao, R. S. Li, and X. Tan.** 2005. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antivir. Res. 67:18-23. [PubMed] [Google Scholar]

213. **Li, T., Z. Qiu, L. Zhang, Y. Han, W. He, Z. Liu, X. Ma, H. Fan, W. Lu, J. Xie, H. Wang, G. Deng, and A. Wang.** 2004. Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. J. Infect. Dis. 189:648-651. [PubMed] [Google Scholar]

214. **Li, W., M. J. Moore, N. Vasilieva, J. Sui, S. K. Wong, M. A. Berne, M. Somasundaran, J. L. Sullivan, K. Luzuriaga, T. C. Greenough, H. Choe, and M. Farzan.** 2003. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426:450-454. [PubMed] [Google Scholar]

215. **Li, W., Z. Shi, M. Yu, W. Ren, C. Smith, J. H. Epstein, H. Wang, G. Crameri, Z. Hu, H. Zhang, J. Zhang, J. McEachern, H. Field, P. Daszak, B. T. Eaton, S. Zhang, and L. F. Wang.** 2005. Bats are natural reservoirs of SARS-like coronaviruses. Science 310:676-679. [PubMed] [Google Scholar]

216. **Li, W., C. Zhang, J. Sui, J. H. Kuhn, M. J. Moore, S. Luo, S. K. Wong, I. C. Huang, K. Xu, N. Vasilieva, A. Murakami, Y. He, W. A. Marasco, Y. Guan, H. Choe, and M. Farzan.** 2005. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J. 24:1634-1643. [PMC free article] [PubMed] [Google Scholar]

217. **Li, Y. Q., Z. L. Li, W. J. Zhao, R. X. Wen, Q. W. Meng, and Y. Zeng.** 2006. Synthesis of stilbene derivatives with inhibition of SARS coronavirus replication. Eur. J. Med. Chem. 41:1084-1089. [PubMed] [Google Scholar]

218. **Liang, G., Q. Chen, J. Xu, Y. Liu, W. Lim, J. S. Peiris, L. J. Anderson, L. Ruan, H. Li, B. Kan, B. Di, P. Cheng, K. H. Chan, D. D. Erdman, S. Gu, X. Yan, W. Liang, D. Zhou, L. Haynes, S. Duan, X. Zhang, H. Zheng, Y. Gao, S. Tong, D. Li, L. Fang, P. Qin, and W. Xu.** 2004. Laboratory diagnosis of four recent sporadic cases of community-acquired SARS, Guangdong Province, China. Emerg. Infect. Dis. 10:1774-1781. [PMC free article] [PubMed] [Google Scholar]

219. **Liang, L., C. He, M. Lei, S. Li, Y. Hao, H. Zhu, and Q. Duan.** 2005. Pathology of guinea pigs experimentally infected with a novel reovirus and coronavirus isolated from SARS patients. DNA Cell Biol. 24:485-490. [PubMed] [Google Scholar]

220. **Liao, Q. J., L. B. Ye, K. A. Timani, Y. C. Zeng, Y. L. She, L. Ye, and Z. H. Wu.** 2005. Activation of NF-kappaB by the full-length nucleocapsid protein of the SARS coronavirus. Acta Biochim. Biophys. Sin. (Shanghai) 37:607-612. [PubMed] [Google Scholar]

221. **Lim, P. L., A. Kurup, G. Gopalakrishna, K. P. Chan, C. W. Wong, L. C. Ng, S. Y. Se-Thoe, L. Oon, X. Bai, L. W. Stanton, Y. Ruan, L. D. Miller, V. B. Vega, L. James, P. L. Ooi, C. S. Kai, S. J. Olsen, B. Ang, and Y. S. Leo.** 2004. Laboratory-acquired severe acute respiratory syndrome. N. Engl. J. Med. 350:1740-1745. [PubMed] [Google Scholar]

222. **Lin, C. W., K. H. Lin, T. H. Hsieh, S. Y. Shiu, and J. Y. Li.** 2006. Severe acute respiratory syndrome coronavirus 3C-like protease-induced apoptosis. FEMS Immunol. Med. Microbiol. 46:375-380. [PubMed] [Google Scholar]

223. **Lin, M., H. K. Tseng, J. A. Trejaut, H. L. Lee, J. H. Loo, C. C. Chu, P. J. Chen, Y. W. Su, K. H. Lim, Z. U. Tsai, R. Y. Lin, R. S. Lin, and C. H. Huang.** 2003. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. BMC Med. Genet. 4:9. [PMC free article] [PubMed] [Google Scholar]

224. **Lindner, H. A., N. Fotouhi-Ardakani, V. Lytvyn, P. Lachance, T. Sulea, and R. Menard.** 2005. The papain-like protease from the severe acute respiratory syndrome coronavirus is a deubiquitinating enzyme. J. Virol. 79:15199-15208. [PMC free article] [PubMed] [Google Scholar]

225. **Lipsitch, M., T. Cohen, B. Cooper, J. M. Robins, S. Ma, L. James, G. Gopalakrishna, S. K. Chew, C. C. Tan, M. H. Samore, D. Fisman, and M. Murray.** 2003. Transmission dynamics and control of severe acute respiratory syndrome. Science 300:1966-1970. [PMC free article] [PubMed] [Google Scholar]

226. **Liu, I. J., P. J. Chen, S. H. Yeh, Y. P. Chiang, L. M. Huang, M. F. Chang, S. Y. Chen, P. C. Yang, S. C. Chang, and W. K. Wang.** 2005. Immunofluorescence assay for detection of the nucleocapsid antigen of the severe acute respiratory syndrome (SARS)-associated coronavirus in cells derived from throat wash samples of patients with SARS. J. Clin. Microbiol. 43:2444-2448. [PMC free article] [PubMed] [Google Scholar]

227. **Liu, S., G. Xiao, Y. Chen, Y. He, J. Niu, C. R. Escalante, H. Xiong, J. Farmar, A. K. Debnath, P. Tien, and S. Jiang.** 2004. Interaction between heptad repeat 1 and 2 regions in spike protein of SARS-associated coronavirus: implications for virus fusogenic mechanism and identification of fusion inhibitors. Lancet 363:938-947. [PubMed] [Google Scholar]

228. **Liu, Y. N., B. X. Fan, X. Q. Fang, B. X. Yu, and L. A. Chen.** 2003. The quantitative detection of anti-coronavirus antibody titer in medical personnel closely contacted with severe acute respiratory syndrome patients. Zhonghua Jie He He Hu Xi Za Zhi 26:583-585. (In Chinese.) [PubMed] [Google Scholar]

229. **Loon, S. C., S. C. Teoh, L. L. Oon, S. Y. Se-Thoe, A. E. Ling, Y. S. Leo, and H. N. Leong.** 2004. The severe acute respiratory syndrome coronavirus in tears. Br. J. Ophthalmol. 88:861-863. [PMC free article] [PubMed] [Google Scholar]

230. **Louie, L., A. E. Simor, S. Chong, K. Luinstra, A. Petrich, J. Mahony, M. Smieja, G. Johnson, F. Gharabaghi, R. Tellier, B. M. Willey, S. Poutanen, T. Mazzulli, G. Broukhanski, F. Jamieson, M. Louie, and S. Richardson.** 2006. Detection of severe acute respiratory syndrome coronavirus in stool specimens by commercially available real-time reverse transcriptase PCR assays. J. Clin. Microbiol. 44:4193-4196. [PMC free article] [PubMed] [Google Scholar]

231. **Loutfy, M. R., L. M. Blatt, K. A. Siminovitch, S. Ward, B. Wolff, H. Lho, D. H. Pham, H. Deif, E. A. LaMere, M. Chang, K. C. Kain, G. A. Farcas, P. Ferguson, M. Latchford, G. Levy, J. W. Dennis, E. K. Lai, and E. N. Fish.** 2003. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA 290:3222-3228. [PubMed] [Google Scholar]

232. **Lu, A., H. Zhang, X. Zhang, H. Wang, Q. Hu, L. Shen, B. S. Schaffhausen, W. Hou, and L. Li.** 2004. Attenuation of SARS coronavirus by a short hairpin RNA expression plasmid targeting RNA-dependent RNA polymerase. Virology 324:84-89. [PubMed] [Google Scholar]

233. **Lu, J. H., Z. M. Guo, W. Y. Han, G. L. Wang, D. M. Zhang, Y. F. Wang, S. Y. Sun, Q. H. Yang, H. Y. Zheng, B. L. Wong, and N. S. Zhong.** 2005. Preparation and development of equine hyperimmune globulin F(ab')2 against severe acute respiratory syndrome coronavirus. Acta Pharmacol. Sin. 26:1479-1484. [PubMed] [Google Scholar]

234. **Lu, W., B. J. Zheng, K. Xu, W. Schwarz, L. Du, C. K. Wong, J. Chen, S. Duan, V. Deubel, and B. Sun.** 2006. Severe acute respiratory syndrome-associated coronavirus 3a protein forms an ion channel and modulates virus release. Proc. Natl. Acad. Sci. USA 103:12540-12545. [PMC free article] [PubMed] [Google Scholar]

235. **Manopo, I., L. Lu, Q. He, L. L. Chee, S. W. Chan, and J. Kwang.** 2005. Evaluation of a safe and sensitive spike protein-based immunofluorescence assay for the detection of antibody responses to SARS-CoV. J. Immunol. Methods 296:37-44. [PubMed] [Google Scholar]

236. **Marra, M. A., S. J. Jones, C. R. Astell, R. A. Holt, A. Brooks-Wilson, Y. S. Butterfield, J. Khattra, J. K. Asano, S. A. Barber, S. Y. Chan, A. Cloutier, S. M. Coughlin, D. Freeman, N. Girn, O. L. Griffith, S. R. Leach, M. Mayo, H. McDonald, S. B. Montgomery, P. K. Pandoh, A. S. Petrescu, A. G. Robertson, J. E. Schein, A. Siddiqui, D. E. Smailus, J. M. Stott, G. S. Yang, F. Plummer, A. Andonov, H. Artsob, N. Bastien, K. Bernard, T. F. Booth, D. Bowness, M. Czub, M. Drebot, L. Fernando, R. Flick, M. Garbutt, M. Gray, A. Grolla, S. Jones, H. Feldmann, A. Meyers, A. Kabani, Y. Li, S. Normand, U. Stroher, G. A. Tipples, S. Tyler, R. Vogrig, D. Ward, B. Watson, R. C. Brunham, M. Krajden, M. Petric, D. M. Skowronski, C. Upton, and R. L. Roper.** 2003. The genome sequence of the SARS-associated coronavirus. Science 300:1399-1404. [PubMed] [Google Scholar]

237. **Martina, B. E., B. L. Haagmans, T. Kuiken, R. A. Fouchier, G. F. Rimmelzwaan, G. Van Amerongen, J. S. Peiris, W. Lim, and A. D. Osterbaus.** 2003. Virology: SARS virus infection of cats and ferrets. Nature 425:915. [PubMed] [Google Scholar]

238. **Maunder, R. G., W. J. Lancee, K. E. Balderson, J. P. Bennett, B. Borgundvaag, S. Evans, C. M. Fernandes, D. S. Goldbloom, M. Gupta, J. J. Hunter, L. M. Hall, L. M. Nagle, C. Pain, S. S. Peczeniuk, G. Raymond, N. Read, S. B. Rourke, R. J. Steinberg, T. E. Stewart, S. VanDeVelde-Coke, G. G. Veldhorst, and D. A. Wasylenki.** 2006. Long-term psychological

and occupational effects of providing hospital healthcare during SARS outbreak. Emerg. Infect. Dis. 12:1924-1932. [PMC free article] [PubMed] [Google Scholar]

239. **McAuliffe, J., L. Vogel, A. Roberts, G. Fahle, S. Fischer, W. J. Shieh, E. Butler, S. Zaki, M. St. Claire, B. Murphy, and K. Subbarao.** 2004. Replication of SARS coronavirus administered into the respiratory tract of African green, rhesus and cynomolgus monkeys. Virology 330:8-15. [PubMed] [Google Scholar]

240. **McCray, P. B., Jr., L. Pewe, C. Wohlford-Lenane, M. Hickey, L. Manzel, L. Shi, J. Netland, H. P. Jia, C. Halabi, C. D. Sigmund, D. K. Meyerholz, P. Kirby, D. C. Look, and S. Perlman.** 2007. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. J. Virol. 81:813-821. [PMC free article] [PubMed] [Google Scholar]

241. **Meier, C., A. R. Aricescu, R. Assenberg, R. T. Aplin, R. J. Gilbert, J. M. Grimes, and D. I. Stuart.** 2006. The crystal structure of ORF-9b, a lipid binding protein from the SARS coronavirus. Structure 14:1157-1165. [PubMed] [Google Scholar]

242. **Minskaia, E., T. Hertzig, A. E. Gorbalenya, V. Campanacci, C. Cambillau, B. Canard, and J. Ziebuhr.** 2006. Discovery of an RNA virus 3′→5′ exoribonuclease that is critically involved in coronavirus RNA synthesis. Proc. Natl. Acad. Sci. USA 103:5108-5113. [PMC free article] [PubMed] [Google Scholar]

243. **Morgenstern, B., M. Michaelis, P. C. Baer, H. W. Doerr, and J. Cinatl, Jr.** 2005. Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. Biochem. Biophys. Res. Commun. 326:905-908. [PubMed] [Google Scholar]

244. **Nagata, N., N. Iwata, H. Hasegawa, S. Fukushi, M. Yokoyama, A. Harashima, Y. Sato, M. Saijo, S. Morikawa, and T. Sata.** 2007. Participation of both host and virus factors in induction of severe acute respiratory syndrome (SARS) in F344 rats infected with SARS coronavirus. J. Virol. 81:1848-1857. [PMC free article] [PubMed] [Google Scholar]

245. **Nelson, C. A., A. Pekosz, C. A. Lee, M. S. Diamond, and D. H. Fremont.** 2005. Structure and intracellular targeting of the SARS-coronavirus Orf7a accessory protein. Structure 13:75-85. [PubMed] [Google Scholar]

246. **Neuman, B. W., D. A. Stein, A. D. Kroeker, M. J. Churchill, A. M. Kim, P. Kuhn, P. Dawson, H. M. Moulton, R. K. Bestwick, P. L. Iversen, and M. J. Buchmeier.** 2005. Inhibition, escape, and attenuated growth of severe acute respiratory syndrome coronavirus treated with antisense morpholino oligomers. J. Virol. 79:9665-9676. [PMC free article] [PubMed] [Google Scholar]

247. **Ng, C. K., J. W. Chan, T. L. Kwan, T. S. To, Y. H. Chan, F. Y. Ng, and T. Y. Mok.** 2004. Six montb radiological and physiological outcomes in severe acute respiratory syndrome (SARS) survivors. Thorax 59:889-891. [PMC free article] [PubMed] [Google Scholar]

248. **Ng, K. H., A. K. Wu, V. C. Cheng, B. S. Tang, C. Y. Chan, C. Y. Yung, S. H. Luk, T. W. Lee, L. Chow, and K. Y. Yuen.** 2005. Pulmonary artery thrombosis in a patient with severe acute respiratory syndrome. Postgrad. Med. J. 81:e3. [PMC free article] [PubMed] [Google Scholar]

249. **Ng, M. H., K. M. Lau, L. Li, S. H. Cheng, W. Y. Chan, P. K. Hui, B. Zee, C. B. Leung, and J. J. Sung.** 2004. Association of human-leukocyte-antigen class I (B*0703) and class II (DRB1*0301) genotypes with susceptibility and resistance to the development of severe acute respiratory syndrome. J. Infect. Dis. 190:515-518. [PubMed] [Google Scholar]

250. **Nicholls, J. M., L. L. Poon, K. C. Lee, W. F. Ng, S. T. Lai, C. Y. Leung, C. M. Chu, P. K. Hui, K. L. Mak, W. Lim, K. W. Yan, K. H. Chan, N. C. Tsang, Y. Guan, K. Y. Yuen, and J. S. Peiris.** 2003. Lung pathology of fatal severe acute respiratory syndrome. Lancet 361:1773-1778. [PubMed] [Google Scholar]

251. **Normile, D.** 2004. Infectious diseases. Mounting lab accidents raise SARS fears. Science 304:659-661. [PubMed] [Google Scholar]

252. **Normile, D.** 2004. Infectious diseases. Second lab accident fuels fears about SARS. Science 303:26. [PubMed] [Google Scholar]

253. **Okabayashi, T., H. Kariwa, S. Yokota, S. Iki, T. Indoh, N. Yokosawa, I. Takashima, H. Tsutsumi, and N. Fujii.** 2006. Cytokine regulation in SARS coronavirus infection compared to other respiratory virus infections. J. Med. Virol. 78:417-424. [PubMed] [Google Scholar]

254. **Olsen, S. J., H. L. Chang, T. Y. Cheung, A. F. Tang, T. L. Fisk, S. P. Ooi, H. W. Kuo, D. D. Jiang, K. T. Chen, J. Lando, K. H. Hsu, T. J. Chen, and S. F. Dowell.** 2003. Transmission of the severe acute respiratory syndrome on aircraft. N. Engl. J. Med. 349:2416-2422. [PubMed] [Google Scholar]

255. **Ong, K. C., A. W. Ng, L. S. Lee, G. Kaw, S. K. Kwek, M. K. Leow, and A. Earnest.** 2004. Pulmonary function and exercise capacity in survivors of severe acute respiratory syndrome. Eur. Respir. J. 24:436-442. [PubMed] [Google Scholar]

256. **Orellana, C.** 2004. Laboratory-acquired SARS raises worries on biosafety. Lancet Infect. Dis. 4:64. [PubMed] [Google Scholar]

257. **Paragas, J., L. M. Blatt, C. Hartmann, J. W. Huggins, and T. P. Endy.** 2005. Interferon alfacon1 is an inhibitor of SARS-corona virus in cell-based models. Antivir. Res. 66:99-102. [PubMed] [Google Scholar]

258. **Peiris, J. S., C. M. Chu, V. C. Cheng, K. S. Chan, I. F. Hung, L. L. Poon, K. I. Law, B. S. Tang, T. Y. Hon, C. S. Chan, K. H. Chan, J. S. Ng, B. J. Zheng, W. L. Ng, R. W. Lai, Y. Guan, and K. Y. Yuen.** 2003. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 361:1767-1772. [PubMed] [Google Scholar]

259. **Peiris, J. S., S. T. Lai, L. L. Poon, Y. Guan, L. Y. Yam, W. Lim, J. Nicholls, W. K. Yee, W. W. Yan, M. T. Cheung, V. C. Cheng, K. H. Chan, D. N. Tsang, R. W. Yung, T. K. Ng, and K. Y. Yuen.** 2003. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 361:1319-1325. [PubMed] [Google Scholar]

260. **Peiris, J. S., K. Y. Yuen, A. D. Osterhaus, and K. Stohr.** 2003. The severe acute respiratory syndrome. N. Engl. J. Med. 349:2431-2441. [PubMed] [Google Scholar]

261. **Peti, W., M. A. Johnson, T. Herrmann, B. W. Neuman, M. J. Buchmeier, M. Nelson, J. Joseph, R. Page, R. C. Stevens, P. Kuhn, and K. Wuthrich.** 2005. Structural genomics of the severe acute respiratory syndrome coronavirus: nuclear magnetic resonance structure of the protein nsP7. J. Virol. 79:12905-12913. [PMC free article] [PubMed] [Google Scholar]

262. **Pogrebnyak, N., M. Golovkin, V. Andrianov, S. Spitsin, Y. Smirnov, R. Egolf, and H. Koprowski.** 2005. Severe acute respiratory syndrome (SARS) S protein production in plants: development of recombinant vaccine. Proc. Natl. Acad. Sci. USA 102:9062-9067. [PMC free article] [PubMed] [Google Scholar]

263. **Poon, L. L., K. H. Chan, O. K. Wong, T. K. Cheung, I. Ng, B. Zheng, W. H. Seto, K. Y. Yuen, Y. Guan, and J. S. Peiris.** 2004. Detection of SARS coronavirus in patients with severe acute respiratory syndrome by conventional and real-time quantitative reverse transcription-PCR assays. Clin. Chem. 50:67-72. [PubMed] [Google Scholar]

264. **Poon, L. L., K. H. Chan, O. K. Wong, W. C. Yam, K. Y. Yuen, Y. Guan, Y. M. Lo, and J. S. Peiris.** 2003. Early diagnosis of SARS coronavirus infection by real time RT-PCR. J. Clin. Virol. 28:233-238. [PubMed] [Google Scholar]

265. **Poon, L. L., D. K. Chu, K. H. Chan, O. K. Wong, T. M. Ellis, Y. H. Leung, S. K. Lau, P. C. Woo, K. Y. Suen, K. Y. Yuen, Y. Guan, and J. S. Peiris.** 2005. Identification of a novel coronavirus in bats. J. Virol. 79:2001-2009. [PMC free article] [PubMed] [Google Scholar]

266. **Poon, L. L., B. W. Wong, K. H. Chan, C. S. Leung, K. Y. Yuen, Y. Guan, and J. S. Peiris.** 2004. A one step quantitative RT-PCR for detection of SARS coronavirus with an internal control for PCR inhibitors. J. Clin. Virol. 30:214-217. [PubMed] [Google Scholar]

267. **Poon, L. L., B. W. Wong, K. H. Chan, S. S. Ng, K. Y. Yuen, Y. Guan, and J. S. Peiris.** 2005. Evaluation of real-time reverse transcriptase PCR and real-time loop-mediated amplification assays for severe acute respiratory syndrome coronavirus detection. J. Clin. Microbiol. 43:3457-3459. [PMC free article] [PubMed] [Google Scholar]

268. **Poon, L. L., O. K. Wong, K. H. Chan, W. Luk, K. Y. Yuen, J. S. Peiris, and Y. Guan.** 2003. Rapid diagnosis of a coronavirus associated with severe acute respiratory syndrome (SARS). Clin. Chem. 49:953-955. [PubMed] [Google Scholar]

269. **Poon, P. M., C. K. Wong, K. P. Fung, C. Y. Fong, E. L. Wong, J. T. Lau, P. C. Leung, S. K. Tsui, D. C. Wan, M. M. Waye, S. W. Au, C. B. Lau, and C. W. Lam.** 2006. Immunomodulatory effects of a traditional Chinese medicine with potential antiviral activity: a self-control study. Am. J. Chin. Med. 34:13-21. [PubMed] [Google Scholar]

270. **Poutanen, S. M., D. E. Low, B. Henry, S. Finkelstein, D. Rose, K. Green, R. Tellier, R. Draker, D. Adachi, M. Ayers, A. K. Chan, D. M. Skowronski, I. Salit, A. E. Simor, A. S. Slutsky, P. W. Doyle, M. Krajden, M. Petric, R. C. Brunham, and A. J. McGeer.** 2003. Identification of severe acute respiratory syndrome in Canada. N. Engl. J. Med. 348:1995-2005. [PubMed] [Google Scholar]

271. **Putics, A., W. Filipowicz, J. Hall, A. E. Gorbalenya, and J. Ziebuhr.** 2005. ADP-ribose-1′′-monophosphatase: a conserved coronavirus enzyme that is dispensable for viral replication in tissue culture. J. Virol. 79:12721-12731. [PMC free article] [PubMed] [Google Scholar]

272. **Qin, C., J. Wang, Q. Wei, M. She, W. A. Marasco, H. Jiang, X. Tu, H. Zhu, L. Ren, H. Gao, L. Guo, L. Huang, R. Yang, Z. Cong, L. Guo, Y. Wang, Y. Liu, Y. Sun, S. Duan, J. Qu, L. Chen, W. Tong, L. Ruan, P. Liu, H. Zhang, J. Zhang, H. Zhang, D. Liu, Q. Liu, T. Hong, and W. He.** 2005. An animal model of SARS produced by infection of Macaca mulatta with SARS coronavirus. J. Pathol. 206:251-259. [PubMed] [Google Scholar]

273. **Qiu, M., J. Wang, H. Wang, Z. Chen, E. Dai, Z. Guo, X. Wang, X. Pang, B. Fan, J. Wen, J. Wang, and R. Yang.** 2005. Use of the COOH portion of the nucleocapsid protein in an antigen-capturing enzyme-linked immunosorbent assay for specific and sensitive detection of severe acute respiratory syndrome coronavirus. Clin. Diagn. Lab. Immunol. 12:474-476. [PMC free article] [PubMed] [Google Scholar]

274. **Qu, D., B. Zheng, X. Yao, Y. Guan, Z. H. Yuan, N. S. Zhong, L. W. Lu, J. P. Xie, and Y. M. Wen.** 2005. Intranasal immunization with inactivated SARS-CoV (SARS-associated coronavirus) induced local and serum antibodies in mice. Vaccine 23:924-931. [PubMed] [Google Scholar]

275. **Qu, X. X., P. Hao, X. J. Song, S. M. Jiang, Y. X. Liu, P. G. Wang, X. Rao, H. D. Song, S. Y. Wang, Y. Zuo, A. H. Zheng, M. Luo, H. L. Wang, F. Deng, H. Z. Wang, Z. H. Hu, M. X. Ding, G. P. Zhao, and H. K. Deng.** 2005. Identification of two critical amino acid residues of the severe acute respiratory syndrome coronavirus spike protein for its variation in zoonotic tropism transition via a double substitution strategy. J. Biol. Chem. 280:29588-29595. [PubMed] [Google Scholar]

276. **Rabenau, H. F., J. Cinatl, B. Morgenstern, G. Bauer, W. Preiser, and H. W. Doerr.** 2005. Stability and inactivation of SARS coronavirus. Med. Microbiol. Immunol. 194:1-6. [PubMed] [Google Scholar]

277. **Radun, D., M. Niedrig, A. Ammon, and K. Stark.** 2003. SARS: retrospective cohort study among German guests of the hotel 'M, ' Hong Kong Eur. Surveill. 8:228-230. [PubMed] [Google Scholar]

278. **Rainer, T. H., P. A. Cameron, D. Smit, K. L. Ong, A. N. Hung, D. C. Nin, A. T. Ahuja, L. C. Si, and J. J. Sung.** 2003. Evaluation of WHO criteria for identifying patients with severe acute respiratory syndrome out of hospital: prospective observational study. BMJ 326:1354-1358. [PMC free article] [PubMed] [Google Scholar]

279. **Ratia, K., K. S. Saikatendu, B. D. Santarsiero, N. Barretto, S. C. Baker, R. C. Stevens, and A. D. Mesecar.** 2006. Severe acute respiratory syndrome coronavirus papain-like protease: structure of a viral deubiquitinating enzyme. Proc. Natl. Acad. Sci. USA 103:5717-5722. [PMC free article] [PubMed] [Google Scholar]

280. **Reghunathan, R., M. Jayapal, L. Y. Hsu, H. H. Chng, D. Tai, B. P. Leung, and A. J. Melendez.** 2005. Expression profile of immune response genes in patients with severe acute respiratory syndrome. BMC Immunol. 6:2. [PMC free article] [PubMed] [Google Scholar]

281. **Reilley, B., M. Van Herp, D. Sermand, and N. Dentico.** 2003. SARS and Carlo Urbani. N. Engl. J. Med. 348:1951-1952. [PubMed] [Google Scholar]

282. **Ren, W., W. Li, M. Yu, P. Hao, Y. Zhang, P. Zhou, S. Zhang, G. Zhao, Y. Zhong, S. Wang, L. F. Wang, and Z. Shi.** 2006. Full-length genome sequences of two SARS-like coronaviruses in horseshoe bats and genetic variation analysis. J. Gen. Virol. 87:3355-3359. [PubMed] [Google Scholar]

283. **Rest, J. S., and D. P. Mindell.** 2003. SARS associated coronavirus has a recombinant polymerase and coronaviruses have a history of host-shifting. Infect. Genet. Evol. 3:219-225. [PubMed] [Google Scholar]

284. **Ricagno, S., M. P. Egloff, R. Ulferts, B. Coutard, D. Nurizzo, V. Campanacci, C. Cambillau, J. Ziebuhr, and B. Canard.** 2006. Crystal structure and mechanistic determinants of SARS coronavirus nonstructural protein 15 define an endoribonuclease family. Proc. Natl. Acad. Sci. USA 103:11892-11897. [PMC free article] [PubMed] [Google Scholar]

285. **Riley, S., C. Fraser, C. A. Donnelly, A. C. Ghani, L. J. Abu-Raddad, A. J. Hedley, G. M. Leung, L. M. Ho, T. H. Lam, T. Q. Tbach, P. Chau, K. P. Chan, S. V. Lo, P. Y. Leung, T. Tsang, W. Ho, K. H. Lee, E. M. Lau, N. M. Ferguson, and R. M. Anderson.** 2003. Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science 300:1961-1966. [PubMed] [Google Scholar]

286. **Roberts, A., D. Deming, C. D. Paddock, A. Cheng, B. Yount, L. Vogel, B. D. Herman, T. Sheahan, M. Heise, G. L. Genrich, S. R. Zaki, R. Baric, and K. Subbarao.** 2007. A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. PLoS Pathog. 3:e5. [PMC free article] [PubMed] [Google Scholar]

287. **Roberts, A., C. Paddock, L. Vogel, E. Butler, S. Zaki, and K. Subbarao.** 2005. Aged BALB/c mice as a model for increased severity of severe acute respiratory syndrome in elderly humans. J. Virol. 79:5833-5838. [PMC free article] [PubMed] [Google Scholar]

288. **Roberts, A., L. Vogel, J. Guarner, N. Hayes, B. Murphy, S. Zaki, and K. Subbarao.** 2005. Severe acute respiratory syndrome coronavirus infection of golden Syrian hamsters. J. Virol. 79:503-511. [PMC free article] [PubMed] [Google Scholar]

289. **Rockx, B., T. Sheahan, E. Donaldson, J. Harkema, A. Sims, M. Heise, R. Pickles, M. Cameron, D. Kelvin, and R. Baric.** 2007. Synthetic reconstruction of zoonotic and early human severe acute respiratory syndrome coronavirus isolates that produce fatal disease in aged mice. J. Virol. 81:7410-7423. [PMC free article] [PubMed] [Google Scholar]

290. **Rota, P. A., M. S. Oberste, S. S. Monroe, W. A. Nix, R. Campagnoli, J. P. Icenogle, S. Penaranda, B. Bankamp, K. Maher, M. H. Chen, S. Tong, A. Tamin, L. Lowe, M. Frace, J. L. DeRisi, Q. Chen, D. Wang, D. D. Erdman, T. C. Peret, C. Burns, T. G. Ksiazek, P. E. Rollin, A. Sanchez, S. Liffick, B. Holloway, J. Limor, K. McCaustland, M. Olsen-Rasmussen, R. Fouchier, S. Gunther, A. D. Osterhaus, C. Drosten, M. A. Pallansch, L. J. Anderson, and W. J. Bellini.** 2003. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science 300:1394-1399. [PubMed] [Google Scholar]

291. **Rowe, T., G. Gao, R. J. Hogan, R. G. Crystal, T. G. Voss, R. L. Grant, P. Bell, G. P. Kobinger, N. A. Wivel, and J. M. Wilson.** 2004. Macaque model for severe acute respiratory syndrome. J. Virol. 78:11401-11404. [PMC free article] [PubMed] [Google Scholar]

292. **Ruan, Y. J., C. L. Wei, A. L. Ee, V. B. Vega, H. Thoreau, S. T. Su, J. M. Chia, P. Ng, K. P. Chiu, L. Lim, T. Zhang, C. K. Peng, E. O. Lin, N. M. Lee, S. L. Yee, L. F. Ng, R. E. Chee, L. W. Stanton, P. M. Long, and E. T. Liu.** 2003. Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection. Lancet 361:1779-1785. [PubMed] [Google Scholar]

293. **Saijo, M., S. Morikawa, S. Fukushi, T. Mizutani, H. Hasegawa, N. Nagata, N. Iwata, and I. Kurane.** 2005. Inhibitory effect of mizoribine and ribavirin on the replication of severe acute respiratory syndrome (SARS)-associated coronavirus. Antivir. Res. 66:159-163. [PubMed] [Google Scholar]

294. **Saijo, M., T. Ogino, F. Taguchi, S. Fukushi, T. Mizutani, T. Notomi, H. Kanda, H. Minekawa, S. Matsuyama, H. T. Long, N. T. Hanh, I. Kurane, M. Tashiro, and S. Morikawa.** 2005. Recombinant nucleocapsid protein-based IgG enzyme-linked immunosorbent assay for the serological diagnosis of SARS. J. Virol. Methods 125:181-186. [PubMed] [Google Scholar]

295. **Sainz, B., Jr., E. C. Mossel, W. R. Gallaher, W. C. Wimley, C. J. Peters, R. B. Wilson, and R. F. Garry.** 2006. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) infectivity by peptides analogous to the viral spike protein. Virus Res. 120:146-155. [PMC free article] [PubMed] [Google Scholar]

296. **Seto, W. H., D. Tsang, R. W. Yung, T. Y. Ching, T. K. Ng, M. Ho, L. M. Ho, and J. S. Peiris.** 2003. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet 361:1519-1520. [PubMed] [Google Scholar]

297. **Shao, P. L., P. R. Hsueh, L. Y. Chang, C. Y. Lu, C. L. Kao, Y. P. Chiang, H. Y. Huang, F. Y. Huang, C. Y. Lee, L. J. Chang, T. C. Wu, and L. M. Huang.** 2005. Development of immunoglobulin G enzyme-linked immunosorbent assay for the serodiagnosis of severe acute respiratory syndrome. J. Biomed. Sci. 12:59-64. [PubMed] [Google Scholar]

298. **Shi, X., E. Gong, D. Gao, B. Zhang, J. Zheng, Z. Gao, Y. Zhong, W. Zou, B. Wu, W. Fang, S. Liao, S. Wang, Z. Xie, M. Lu, L. Hou, H. Zhong, H. Shao, N. Li, C. Liu, F. Pei, J. Yang, Y. Wang, Z. Han, X. Shi, Q. Zhang, J. You, X. Zhu, and J. Gu.** 2005. Severe acute respiratory syndrome associated coronavirus is detected in intestinal tissues of fatal cases. Am. J. Gastroenterol. 100:169-176. [PubMed] [Google Scholar]

299. **Shi, Y., Y. Yi, P. Li, T. Kuang, L. Li, M. Dong, Q. Ma, and C. Cao.** 2003. Diagnosis of severe acute respiratory syndrome (SARS) by detection of SARS coronavirus nucleocapsid antibodies in an antigen-capturing enzyme-linked immunosorbent assay. J. Clin. Microbiol. 41:5781-5782. [PMC free article] [PubMed] [Google Scholar]

300. **Simmons, G., D. N. Gosalia, A. J. Rennekamp, J. D. Reeves, S. L. Diamond, and P. Bates.** 2005. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc. Natl. Acad. Sci. USA 102:11876-11881. [PMC free article] [PubMed] [Google Scholar]

301. **Simmons, G., J. D. Reeves, A. J. Rennekamp, S. M. Amberg, A. J. Piefer, and P. Bates.** 2004. Characterization of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. Proc. Natl. Acad. Sci. USA 101:4240-4245. [PMC free article] [PubMed] [Google Scholar]

302. **Snijder, E. J., P. J. Bredenbeek, J. C. Dobbe, V. Thiel, J. Ziebuhr, L. L. Poon, Y. Guan, M. Rozanov, W. J. Spaan, and A. E. Gorbalenya.** 2003. Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineage. J. Mol. Biol. 331:991-1004. [PubMed] [Google Scholar]

303. **So, L. K., A. C. Lau, L. Y. Yam, T. M. Cheung, E. Poon, R. W. Yung, and K. Y. Yuen.** 2003. Development of a standard treatment protocol for severe acute respiratory syndrome. Lancet 361:1615-1617. [PubMed] [Google Scholar]

304. **Song, H. D., C. C. Tu, G. W. Zhang, S. Y. Wang, K. Zheng, L. C. Lei, Q. X. Chen, Y. W. Gao, H. Q. Zhou, H. Xiang, H. J. Zheng, S. W. Chern, F. Cheng, C. M. Pan, H. Xuan, S. J. Chen, H. M. Luo, D. H. Zhou, Y. F. Liu, J. F. He, P. Z. Qin, L. H. Li, Y. Q. Ren, W. J. Liang, Y. D. Yu, L. Anderson, M. Wang, R. H. Xu, X. W. Wu, H. Y. Zheng, J. D. Chen, G. Liang, Y. Gao, M. Liao, L. Fang, L. Y. Jiang, H. Li, F. Chen, B. Di, L. J. He, J. Y. Lin, S. Tong, X. Kong, L. Du, P. Hao, H. Tang, A. Bernini, X. J. Yu, O. Spiga, Z. M. Guo, H. Y. Pan, W. Z. He, J. C. Manuguerra, A. Fontanet, A. Danchin, N. Niccolai, Y. X. Li, C. I. Wu, and G. P. Zhao.** 2005. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc. Natl. Acad. Sci. USA 102:2430-2435. [PMC free article] [PubMed] [Google Scholar]

305. **Spiegel, M., A. Pichlmair, E. Muhlberger, O. Haller, and F. Weber.** 2004. The antiviral effect of interferon-beta against SARS-coronavirus is not mediated by MxA protein. J. Clin. Virol. 30:211-213. [PubMed] [Google Scholar]

306. **Stadler, K., A. Roberts, S. Becker, L. Vogel, M. Eickmann, L. Kolesnikova, H. D. Klenk, B. Murphy, R. Rappuoli, S. Abrignani, and K. Subbarao.** 2005. SARS vaccine protective in mice. Emerg. Infect. Dis. 11:1312-1314. [PMC free article] [PubMed] [Google Scholar]

307. **St. John, R. K., A. King, D. de Jong, M. Bodie-Collins, S. G. Squires, and T. W. Tam.** 2005. Border screening for SARS. Emerg. Infect. Dis. 11:6-10. [PMC free article] [PubMed] [Google Scholar]

308. **Stroher, U., A. DiCaro, Y. Li, J. E. Strong, F. Aoki, F. Plummer, S. M. Jones, and H. Feldmann.** 2004. Severe acute respiratory syndrome-related coronavirus is inhibited by interferon-alpha. J. Infect. Dis. 189:1164-1167. [PubMed] [Google Scholar]

309. **Su, D., Z. Lou, F. Sun, Y. Zhai, H. Yang, R. Zhang, A. Joachimiak, X. C. Zhang, M. Bartlam, and Z. Rao.** 2006. Dodecamer structure of severe acute respiratory syndrome coronavirus nonstructural protein nsp10. J. Virol. 80:7902-7908. [PMC free article] [PubMed] [Google Scholar]

310. **Su, T. P., T. C. Lien, C. Y. Yang, Y. L. Su, J. H. Wang, S. L. Tsai, and J. C. Yin.** 2007. Prevalence of psychiatric morbidity and psychological adaptation of the nurses in a structured SARS caring unit during outbreak: a prospective and periodic assessment study in Taiwan. J. Psychiatr. Res. 41:119-130. [PubMed] [Google Scholar]

311. **Subbarao, K., J. McAuliffe, L. Vogel, G. Fahle, S. Fischer, K. Tatti, M. Packard, W. J. Shieh, S. Zaki, and B. Murphy.** 2004. Prior infection and passive transfer of neutralizing antibody prevent replication of severe acute respiratory syndrome coronavirus in the respiratory tract of mice. J. Virol. 78:3572-3577. [PMC free article] [PubMed] [Google Scholar]

312. **Sui, J., W. Li, A. Murakami, A. Tamin, L. J. Matthews, S. K. Wong, M. J. Moore, A. S. Tallarico, M. Olurinde, H. Choe, L. J. Anderson, W. J. Bellini, M. Farzan, and W. A. Marasco.** 2004. Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. Proc. Natl. Acad. Sci. USA 101:2536-2541. [PMC free article] [PubMed] [Google Scholar]

313. **Sui, J., W. Li, A. Roberts, L. J. Matthews, A. Murakami, L. Vogel, S. K. Wong, K. Subbarao, M. Farzan, and W. A. Marasco.** 2005. Evaluation of human monoclonal antibody 80R for immunopropbylaxis of severe acute respiratory syndrome by an animal study, epitope mapping, and analysis of spike variants. J. Virol. 79:5900-5906. [PMC free article] [PubMed] [Google Scholar]

314. **Sung, J. J., A. Wu, G. M. Joynt, K. Y. Yuen, N. Lee, P. K. Chan, C. S. Cockram, A. T. Ahuja, L. M. Yu, V. W. Wong, and D. S. Hui.** 2004. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. Thorax 59:414-420. [PMC free article] [PubMed] [Google Scholar]

315. **Surjit, M., B. Liu, S. Jameel, V. T. Chow, and S. K. Lal.** 2004. The SARS coronavirus nucleocapsid protein induces actin reorganization and apoptosis in COS-1 cells in the absence of growth factors. Biochem. J. 383:13-18. [PMC free article] [PubMed] [Google Scholar]

316. **Sutton, G., E. Fry, L. Carter, S. Sainsbury, T. Walter, J. Nettleship, N. Berrow, R. Owens, R. Gilbert, A. Davidson, S. Siddell, L. L. Poon, J. Diprose, D. Alderton, M. Walsh, J. M. Grimes, and D. I. Stuart.** 2004. The nsp9 replicase protein of SARS-coronavirus, structure and functional insights. Structure 12:341-353. [PubMed] [Google Scholar]

317. **Takasuka, N., H. Fujii, Y. Takahashi, M. Kasai, S. Morikawa, S. Itamura, K. Ishii, M. Sakaguchi, K. Ohnishi, M. Ohshima, S. Hashimoto, T. Odagiri, M. Tashiro, H. Yoshikura, T. Takemori, and Y. Tsunetsugu-Yokota.** 2004. A subcutaneously injected UV-inactivated SARS coronavirus vaccine elicits systemic humoral immunity in mice. Int. Immunol. 16:1423-1430. [PubMed] [Google Scholar]

318. **Tan, E. L., E. E. Ooi, C. Y. Lin, H. C. Tan, A. E. Ling, B. Lim, and L. W. Stanton.** 2004. Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. Emerg. Infect. Dis. 10:581-586. [PMC free article] [PubMed] [Google Scholar]

319. **Tan, J., L. Mu, J. Huang, S. Yu, B. Chen, and J. Yin.** 2005. An initial investigation of the association between the SARS outbreak and weather: with the view of the environmental temperature and its variation. J. Epidemiol. Commun. Health 59:186-192. [PMC free article] [PubMed] [Google Scholar]

320. **Tan, Y. J., B. C. Fielding, P. Y. Goh, S. Shen, T. H. Tan, S. G. Lim, and W. Hong.** 2004. Overexpression of 7a, a protein specifically encoded by the severe acute respiratory syndrome coronavirus, induces apoptosis via a caspase-dependent pathway. J. Virol. 78:14043-14047. [PMC free article] [PubMed] [Google Scholar]

321. **Tan, Y. J., P. Y. Tham, D. Z. Chan, C. F. Chou, S. Shen, B. C. Fielding, T. H. Tan, S. G. Lim, and W. Hong.** 2005. The severe acute respiratory syndrome coronavirus 3a protein up-regulates expression of fibrinogen in lung epithelial cells. J. Virol. 79:10083-10087. [PMC free article] [PubMed] [Google Scholar]

322. **Tang, B. S., K. H. Chan, V. C. Cheng, P. C. Woo, S. K. Lau, C. C. Lam, T. L. Chan, A. K. Wu, I. F. Hung, S. Y. Leung, and K. Y. Yuen.** 2005. Comparative host gene transcription by microarray analysis early after infection of the Huh7 cell line by severe acute respiratory syndrome coronavirus and human coronavirus 229E. J. Virol. 79:6180-6193. [PMC free article] [PubMed] [Google Scholar]

323. **Tang, L., Q. Zhu, E. Qin, M. Yu, Z. Ding, H. Shi, X. Cheng, C. Wang, G. Chang, Q. Zhu, F. Fang, H. Chang, S. Li, X. Zhang, X. Chen, J. Yu, J. Wang, and Z. Chen.** 2004. Inactivated SARS-CoV vaccine prepared from whole virus induces a high level of neutralizing antibodies in BALB/c mice. DNA Cell Biol. 23:391-394. [PubMed] [Google Scholar]

324. **Tang, N. L., P. K. Chan, D. S. Hui, K. F. To, W. Zhang, F. K. Chan, J. J. Sung, and Y. M. Lo.** 2007. Lack of support for an association between CLEC4M homozygosity and protection against SARS coronavirus infection. Nat. Genet. 39:691-692, 694-696. [PubMed] [Google Scholar]

325. **Tang, N. L., P. K. Chan, C. K. Wong, K. F. To, A. K. Wu, Y. M. Sung, D. S. Hui, J. J. Sung, and C. W. Lam.** 2005. Early enhanced expression of interferon-inducible protein-10 (CXCL-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. Clin. Chem. 51:2333-2340. [PubMed] [Google Scholar]

326. **Tang, X. C., J. X. Zhang, S. Y. Zhang, P. Wang, X. H. Fan, L. F. Li, G. Li, B. Q. Dong, W. Liu, C. L. Cheung, K. M. Xu, W. J. Song, D. Vijaykrishna, L. L. Poon, J. S. Peiris, G. J. Smith, H. Chen, and Y. Guan.** 2006. Prevalence and genetic diversity of coronaviruses in bats from China. J. Virol. 80:7481-7490. [PMC free article] [PubMed] [Google Scholar]

327. **Tangudu, C., H. Olivares, J. Netland, S. Perlman, and T. Gallagher.** 2007. Severe acute respiratory syndrome coronavirus protein 6 accelerates murine coronavirus infections. J. Virol. 81:1220-1229. [PMC free article] [PubMed] [Google Scholar]

328. **Tanner, J. A., B. J. Zheng, J. Zhou, R. M. Watt, J. Q. Jiang, K. L. Wong, Y. P. Lin, L. Y. Lu, M. L. He, H. F. Kung, A. J. Kesel, and J. D. Huang.** 2005. The adamantane-derived bananins are potent inhibitors of the helicase activities and replication of SARS coronavirus. Chem. Biol. 12:303-311. [PubMed] [Google Scholar]

329. **ter Meulen, J., A. B. Bakker, E. N. van den Brink, G. J. Weverling, B. E. Martina, B. L. Haagmans, T. Kuiken, J. de Kruif, W. Preiser, W. Spaan, H. R. Gelderblom, J. Goudsmit, and A. D. Osterhaus.** 2004. Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. Lancet 363:2139-2141. [PubMed] [Google Scholar]

330. **Timani, K. A., L. Ye, L. Ye, Y. Zhu, Z. Wu, and Z. Gong.** 2004. Cloning, sequencing, expression, and purification of SARS-associated coronavirus nucleocapsid protein for serodiagnosis of SARS. J. Clin. Virol. 30:309-312. [PubMed] [Google Scholar]

331. **To, K. F., J. H. Tong, P. K. Chan, F. W. Au, S. S. Chim, K. C. Chan, J. L. Cheung, E. Y. Liu, G. M. Tse, A. W. Lo, Y. M. Lo, and H. K. Ng.** 2004. Tissue and cellular tropism of the coronavirus associated with severe acute respiratory syndrome: an in-situ bybridization study of fatal cases. J. Pathol. 202:157-163. [PubMed] [Google Scholar]

332. **Towler, P., B. Staker, S. G. Prasad, S. Menon, J. Tang, T. Parsons, D. Ryan, M. Fisher, D. Williams, N. A. Dales, M. A. Patane, and M. W. Pantoliano.** 2004. ACE2 X-ray structures reveal a large hinge-bending motion important for inhibitor binding and catalysis. J. Biol. Chem. 279:17996-18007. [PubMed] [Google Scholar]

333. **Traggiai, E., S. Becker, K. Subbarao, L. Kolesnikova, Y. Uematsu, M. R. Gismondo, B. R. Murphy, R. Rappuoli, and A. Lanzavecchia.** 2004. An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. Nat. Med. 10:871-875. [PubMed] [Google Scholar]

334. **Tripet, B., M. W. Howard, M. Jobling, R. K. Holmes, K. V. Holmes, and R. S. Hodges.** 2004. Structural characterization of the SARS-coronavirus spike S fusion protein core. J. Biol. Chem. 279:20836-20849. [PubMed] [Google Scholar]

335. **Tsai, L. K., S. T. Hsieh, C. C. Chao, Y. C. Chen, Y. H. Lin, S. C. Chang, and Y. C. Chang.** 2004. Neuromuscular disorders in severe acute respiratory syndrome. Arch. Neurol. 61:1669-1673. [PubMed] [Google Scholar]

336. **Tsang, K. W., P. L. Ho, G. C. Ooi, W. K. Yee, T. Wang, M. Chan-Yeung, W. K. Lam, W. H. Seto, L. Y. Yam, T. M. Cheung, P. C. Wong, B. Lam, M. S. Ip, J. Chan, K. Y. Yuen, and K. N. Lai.** 2003. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N. Engl. J. Med. 348:1977-1985. [PubMed] [Google Scholar]

337. **Tseng, C. T., C. Huang, P. Newman, N. Wang, K. Narayanan, D. M. Watts, S. Makino, M. M. Packard, S. R. Zaki, T. S. Chan, and C. J. Peters.** 2007. Severe acute respiratory syndrome coronavirus infection of mice transgenic for the human angiotensin-converting enzyme 2 virus receptor. J. Virol. 81:1162-1173. [PMC free article] [PubMed] [Google Scholar]

338. **Tu, C., G. Crameri, X. Kong, J. Chen, Y. Sun, M. Yu, H. Xiang, X. Xia, S. Liu, T. Ren, Y. Yu, B. T. Eaton, H. Xuan, and L. F. Wang.** 2004. Antibodies to SARS coronavirus in civets. Emerg. Infect. Dis. 10:2244-2248. [PMC free article] [PubMed] [Google Scholar]

339. **van der Hoek, L., K. Pyrc, M. F. Jebbink, W. Vermeulen-Oost, R. J. Berkhout, K. C. Wolthers, P. M. Wertheim-van Dillen, J. Kaandorp, J. Spaargaren, and B. Berkhout.** 2004. Identification of a new human coronavirus. Nat. Med. 10:368-373. [PubMed] [Google Scholar]

340. **Varia, M., S. Wilson, S. Sarwal, A. McGeer, E. Gournis, E. Galanis, and B. Henry.** 2003. Investigation of a nosocomial outbreak of severe acute respiratory syndrome (SARS) in Toronto, Canada. CMAJ 169:285-292. [PMC free article] [PubMed] [Google Scholar]

341. **Vincent, M. J., E. Bergeron, S. Benjannet, B. R. Erickson, P. E. Rollin, T. G. Ksiazek, N. G. Seidah, and S. T. Nichol.** 2005. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol. J. 2:69. [PMC free article] [PubMed] [Google Scholar]

342. **Vogt, T. M., M. A. Guerra, E. W. Flagg, T. G. Ksiazek, S. A. Lowther, and P. M. Arguin.** 2006. Risk of severe acute respiratory syndrome-associated coronavirus transmission aboard commercial aircraft. J. Travel Med. 13:268-272. [PubMed] [Google Scholar]

343. **von Grotthuss, M., L. S. Wyrwicz, and L. Rychlewski.** 2003. mRNA cap-1 methyltransferase in the SARS genome. Cell 113:701-702. [PubMed] [Google Scholar]

344. **Wang, C. H., C. Y. Liu, Y. L. Wan, C. L. Chou, K. H. Huang, H. C. Lin, S. M. Lin, T. Y. Lin, K. F. Chung, and H. P. Kuo.** 2005. Persistence of lung inflammation and lung cytokines with high-resolution CT abnormalities during recovery from SARS. Respir. Res. 6:42. [PMC free article] [PubMed] [Google Scholar]

345. **Wang, H., Y. Ding, X. Li, L. Yang, W. Zhang, and W. Kang.** 2003. Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. N. Engl. J. Med. 349:507-508. [PubMed] [Google Scholar]

346. **Wang, J. L., J. T. Wang, C. J. Yu, Y. C. Chen, P. R. Hsueh, C. H. Hsiao, C. L. Kao, S. C. Chang, and P. C. Yang.** 2003. Rhabdomyolysis associated with probable SARS. Am. J. Med. 115:421-422. [PubMed] [Google Scholar]

347. **Wang, M., M. Yan, H. Xu, W. Liang, B. Kan, B. Zheng, H. Chen, H. Zheng, Y. Xu, E. Zhang, H. Wang, J. Ye, G. Li, M. Li, Z. Cui, Y. F. Liu, R. T. Guo, X. N. Liu, L. H. Zhan, D. H. Zhou, A. Zhao, R. Hai, D. Yu, Y. Guan, and J. Xu.** 2005. SARS-CoV infection in a restaurant from palm civet. Emerg. Infect. Dis. 11:1860-1865. [PMC free article] [PubMed] [Google Scholar]

348. **Wang, S., T. H. Chou, P. V. Sakhatskyy, S. Huang, J. M. Lawrence, H. Cao, X. Huang, and S. Lu.** 2005. Identification of two neutralizing regions on the severe acute respiratory syndrome coronavirus spike glycoprotein produced from the mammalian expression system. J. Virol. 79:1906-1910. [PMC free article] [PubMed] [Google Scholar]

349. **Wang, W. K., S. Y. Chen, I. J. Liu, Y. C. Chen, H. L. Chen, C. F. Yang, P. J. Chen, S. H. Yeh, C. L. Kao, L. M. Huang, P. R. Hsueh, J. T. Wang, W. H. Sheng, C. T. Fang, C. C. Hung, S. M. Hsieh, C. P. Su, W. C. Chiang, J. Y. Yang, J. H. Lin, S. C. Hsieh, H. P. Hu, Y. P. Chiang, J. T. Wang, P. C. Yang, and S. C. Chang.** 2004. Detection of SARS-associated coronavirus in throat wash and saliva in early diagnosis. Emerg. Infect. Dis. 10:1213-1219. [PMC free article] [PubMed] [Google Scholar]

350. **Wang, Y. D., Y. Li, G. B. Xu, X. Y. Dong, X. A. Yang, Z. R. Feng, C. Tian, and W. F. Chen.** 2004. Detection of antibodies against SARS-CoV in serum from SARS-infected donors with ELISA and Western blot. Clin. Immunol. 113:145-150. [PubMed] [Google Scholar]

351. **Wang, Z., L. Ren, X. Zhao, T. Hung, A. Meng, J. Wang, and Y. G. Chen.** 2004. Inhibition of severe acute respiratory syndrome virus replication by small interfering RNAs in mammalian cells. J. Virol. 78:7523-7527. [PMC free article] [PubMed] [Google Scholar]

352. **Wang, Z. H., Y. Nong, J. T. Lin, Z. Cai, T. L. Zhou, L. Zhang, and G. Q. Li.** 2004. Covert infection of severe acute respiratory syndrome in health-care professionals and its relation to the workload and the type of work. Zhonghua Jie He He Hu Xi Za Zhi 27:151-154. (In Chinese.) [PubMed] [Google Scholar]

353. **Webster, R. G.** 2004. Wet markets—a continuing source of severe acute respiratory syndrome and influenza? Lancet 363:234-236. [PubMed] [Google Scholar]

354. **Wei, L., S. Sun, C. H. Xu, J. Zhang, Y. Xu, H. Zhu, S. C. Peh, C. Korteweg, M. A. McNutt, and J. Gu.** 2007. Pathology of the thyroid in severe acute respiratory syndrome. Hum. Pathol. 38:95-102. [PubMed] [Google Scholar]

355. **Weingartl, H., M. Czub, S. Czub, J. Neufeld, P. Marszal, J. Gren, G. Smith, S. Jones, R. Proulx, Y. Deschambault, E. Grudeski, A. Andonov, R. He, Y. Li, J. Copps, A. Grolla, D. Dick, J. Berry, S. Ganske, L. Manning, and J. Cao.** 2004. Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. J. Virol. 78:12672-12676. [PMC free article] [PubMed] [Google Scholar]

356. **Weingartl, H. M., J. Copps, M. A. Drebot, P. Marszal, G. Smith, J. Gren, M. Andova, J. Pasick, P. Kitching, and M. Czub.** 2004. Susceptibility of pigs and chickens to SARS coronavirus. Emerg. Infect. Dis. 10:179-184. [PMC free article] [PubMed] [Google Scholar]

357. **Wentworth, D. E., L. Gillim-Ross, N. Espina, and K. A. Bernard.** 2004. Mice susceptible to SARS coronavirus. Emerg. Infect. Dis. 10:1293-1296. [PMC free article] [PubMed] [Google Scholar]

358. **Wilder-Smith, A., N. I. Paton, and K. T. Goh.** 2003. Low risk of transmission of severe acute respiratory syndrome on airplanes: the Singapore experience. Trop. Med. Int. Health 8:1035-1037. [PubMed] [Google Scholar]

359. **Wilson, L., C. McKinlay, P. Gage, and G. Ewart.** 2004. SARS coronavirus E protein forms cation-selective ion channels. Virology 330:322-331. [PubMed] [Google Scholar]

360. **Wong, C. K., C. W. Lam, A. K. Wu, W. K. Ip, N. L. Lee, I. H. Chan, L. C. Lit, D. S. Hui, M. H. Chan, S. S. Chung, and J. J. Sung.** 2004. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin. Exp. Immunol. 136:95-103. [PMC free article] [PubMed] [Google Scholar]

361. **Wong, K. C., K. S. Leung, and M. Hui.** 2003. Severe acute respiratory syndrome (SARS) in a geriatric patient with a hip fracture. A case report. J. Bone Joint Surg. Am. 85-A:1339-1342. [PubMed] [Google Scholar]

362. **Wong, K. T., G. E. Antonio, D. S. Hui, N. Lee, E. H. Yuen, A. Wu, C. B. Leung, T. H. Rainer, P. Cameron, S. S. Chung, J. J. Sung, and A. T. Ahuja.** 2003. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 patients. Radiology 228:401-406. [PubMed] [Google Scholar]

363. **Wong, S., S. Lau, P. Woo, and K. Y. Yuen.** 2007. Bats as a continuing source of emerging infections in humans. Rev. Med. Virol. 17:67-91. [PubMed] [Google Scholar]

364. **Wong, S. F., K. M. Chow, T. N. Leung, W. F. Ng, T. K. Ng, C. C. Shek, P. C. Ng, P. W. Lam, L. C. Ho, W. W. To, S. T. Lai, W. W. Yan, and P. Y. Tan.** 2004. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am. J. Obstet. Gynecol. 191:292-297. [PubMed] [Google Scholar]

365. **Wong, S. K., W. Li, M. J. Moore, H. Choe, and M. Farzan.** 2004. A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. J. Biol. Chem. 279:3197-3201. [PubMed] [Google Scholar]

366. **Wong, V. W., D. Dai, A. K. Wu, and J. J. Sung.** 2003. Treatment of severe acute respiratory syndrome with convalescent plasma. Hong Kong Med. J. 9:199-201. [PubMed] [Google Scholar]

367. **Woo, P. C., S. K. Lau, C. M. Chu, K. H. Chan, H. W. Tsoi, Y. Huang, B. H. Wong, R. W. Poon, J. J. Cai, W. K. Luk, L. L. Poon, S. S. Wong, Y. Guan, J. S. Peiris, and K. Y. Yuen.** 2005. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J. Virol. 79:884-895. [PMC free article] [PubMed] [Google Scholar]

368. **Woo, P. C., S. K. Lau, K. S. Li, R. W. Poon, B. H. Wong, H. W. Tsoi, B. C. Yip, Y. Huang, K. H. Chan, and K. Y. Yuen.** 2006. Molecular diversity of coronaviruses in bats. Virology 351:180-187. [PubMed] [Google Scholar]

369. **Woo, P. C., S. K. Lau, H. W. Tsoi, K. H. Chan, B. H. Wong, X. Y. Che, V. K. Tam, S. C. Tam, V. C. Cheng, I. F. Hung, S. S. Wong, B. J. Zheng, Y. Guan, and K. Y. Yuen.** 2004. Relative rates of non-pneumonic SARS coronavirus infection and SARS coronavirus pneumonia. Lancet 363:841-845. [PubMed] [Google Scholar]

370. **Woo, P. C., S. K. Lau, H. W. Tsoi, Z. W. Chen, B. H. Wong, L. Zhang, J. K. Chan, L. P. Wong, W. He, C. Ma, K. H. Chan, D. D. Ho, and K. Y. Yuen.** 2005. SARS coronavirus spike polypeptide DNA vaccine priming with recombinant spike polypeptide from Escherichia coli as booster induces high titer of neutralizing antibody against SARS coronavirus. Vaccine 23:4959-4968. [PubMed] [Google Scholar]

371. **Woo, P. C., S. K. Lau, B. H. Wong, K. H. Chan, C. M. Chu, H. W. Tsoi, Y. Huang, J. S. Peiris, and K. Y. Yuen.** 2004. Longitudinal profile of immunoglobulin G (IgG), IgM, and IgA antibodies against the severe acute respiratory syndrome (SARS) coronavirus nucleocapsid protein in patients with pneumonia due to the SARS coronavirus. Clin. Diagn. Lab. Immunol. 11:665-668. [PMC free article] [PubMed] [Google Scholar]

372. **Woo, P. C., S. K. Lau, B. H. Wong, K. H. Chan, W. T. Hui, G. S. Kwan, J. S. Peiris, R. B. Couch, and K. Y. Yuen.** 2004. False-positive results in a recombinant severe acute respiratory syndrome-associated coronavirus (SARS-CoV) nucleocapsid enzyme-linked immunosorbent assay due to HCoV-OC43 and HCoV-229E rectified by Western blotting with recombinant SARS-CoV spike polypeptide. J. Clin. Microbiol. 42:5885-5888. [PMC free article] [PubMed] [Google Scholar]

373. **Woo, P. C., S. K. Lau, B. H. Wong, H. W. Tsoi, A. M. Fung, K. H. Chan, V. K. Tam, J. S. Peiris, and K. Y. Yuen.** 2004. Detection of specific antibodies to severe acute respiratory syndrome (SARS) coronavirus nucleocapsid protein for serodiagnosis of SARS coronavirus pneumonia. J. Clin. Microbiol. 42:2306-2309. [PMC free article] [PubMed] [Google Scholar]

374. **Woo, P. C., S. K. Lau, B. H. Wong, H. W. Tsoi, A. M. Fung, R. Y. Kao, K. H. Chan, J. S. Peiris, and K. Y. Yuen.** 2005. Differential sensitivities of severe acute respiratory syndrome (SARS) coronavirus spike polypeptide enzyme-linked immunosorbent assay (ELISA) and SARS coronavirus nucleocapsid protein ELISA for serodiagnosis of SARS coronavirus pneumonia. J. Clin. Microbiol. 43:3054-3058. [PMC free article] [PubMed] [Google Scholar]

375. **Woo, P. C., S. K. Lau, C. C. Yip, Y. Huang, H. W. Tsoi, K. H. Chan, and K. Y. Yuen.** 2006. Comparative analysis of 22 coronavirus HKU1 genomes reveals a novel genotype and evidence of natural recombination in coronavirus HKU1. J. Virol. 80:7136-7145. [PMC free article] [PubMed] [Google Scholar]

376. **Woo, P. C., S. K. Lau, and K. Y. Yuen.** 2006. Infectious diseases emerging from Chinese wet-markets: zoonotic origins of severe respiratory viral infections. Curr. Opin. Infect. Dis. 19:401-407. [PubMed] [Google Scholar]

377. **World Health Organization.** 2003. WHO issues consensus document on the epidemiology of SARS. Wkly. Epidemiol. Rec. 78:373-375. [PubMed] [Google Scholar]

378. **World Health Organization Multicentre Collaborative Network for Severe Acute Respiratory Syndrome Diagnosis.** 2003. A multicentre collaboration to investigate the cause of severe acute respiratory syndrome. Lancet 361:1730-1733. [PubMed] [Google Scholar]

379. **Wu, C. J., H. W. Huang, C. Y. Liu, C. F. Hong, and Y. L. Chan.** 2005. Inhibition of SARS-CoV replication by siRNA. Antivir. Res. 65:45-48. [PubMed] [Google Scholar]

380. **Wu, C. J., J. T. Jan, C. M. Chen, H. P. Hsieh, D. R. Hwang, H. W. Liu, C. Y. Liu, H. W. Huang, S. C. Chen, C. F. Hong, R. K. Lin, Y. S. Chao, and J. T. Hsu.** 2004. Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide. Antimicrob. Agents Chemother. 48:2693-2696. [PMC free article] [PubMed] [Google Scholar]

381. **Wu, C. Y., J. T. Jan, S. H. Ma, C. J. Kuo, H. F. Juan, Y. S. Cheng, H. H. Hsu, H. C. Huang, D. Wu, A. Brik, F. S. Liang, R. S. Liu, J. M. Fang, S. T. Chen, P. H. Liang, and C. H. Wong.** 2004. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc. Natl. Acad. Sci. USA 101:10012-10017. [PMC free article] [PubMed] [Google Scholar]

382. **Wu, D., C. Tu, C. Xin, H. Xuan, Q. Meng, Y. Liu, Y. Yu, Y. Guan, Y. Jiang, X. Yin, G. Crameri, M. Wang, C. Li, S. Liu, M. Liao, L. Feng, H. Xiang, J. Sun, J. Chen, Y. Sun, S. Gu, N. Liu, D. Fu, B. T. Eaton, L. F. Wang, and X. Kong.** 2005. Civets are equally susceptible to experimental infection by two different severe acute respiratory syndrome coronavirus isolates. J. Virol. 79:2620-2625. [PMC free article] [PubMed] [Google Scholar]

383. **Wu, E. B., and J. J. Sung.** 2003. Haemorrhagic-fever-like changes and normal chest radiograph in a doctor with SARS. Lancet 361:1520-1521. [PubMed] [Google Scholar]

384. **Wu, H. S., S. C. Chiu, T. C. Tseng, S. F. Lin, J. H. Lin, Y. H. Hsu, M. C. Wang, T. L. Lin, W. Z. Yang, T. L. Ferng, K. H. Huang, L. C. Hsu, L. L. Lee, J. Y. Yang, H. Y. Chen, S. P. Su, S. Y. Yang, S. Y. Lin, T. H. Lin, and I. S. Su.** 2004. Serologic and molecular biologic methods for SARS-associated coronavirus infection, Taiwan. Emerg. Infect. Dis. 10:304-310. [PMC free article] [PubMed] [Google Scholar]

385. **Wu, V. C., J. W. Huang, P. R. Hsueh, Y. F. Yang, H. B. Tsai, W. C. Kan, H. W. Chang, and K. D. Wu.** 2005. Renal hypouricemia is an ominous sign in patients with severe acute respiratory syndrome. Am. J. Kidney Dis. 45:88-95. [PubMed] [Google Scholar]

386. **Xiong, B., C. S. Gui, X. Y. Xu, C. Luo, J. Chen, H. B. Luo, L. L. Chen, G. W. Li, T. Sun, C. Y. Yu, L. D. Yue, W. H. Duan, J. K. Shen, L. Qin, T. L. Shi, Y. X. Li, K. X. Chen, X. M. Luo, X. Shen, J. H. Shen, and H. L. Jiang.** 2003. A 3D model of SARS-CoV 3CL proteinase and its inhibitors design by virtual screening. Acta Pharmacol. Sin. 24:497-504. [PubMed] [Google Scholar]

387. **Xu, H. F., M. Wang, Z. B. Zhang, X. Z. Zou, Y. Gao, X. N. Liu, E. J. Lu, B. Y. Pan, S. J. Wu, and S. Y. Yu.** 2004. An epidemiologic investigation on infection with severe acute respiratory syndrome coronavirus in wild animals traders in Guangzhou. Zhonghua Yu Fang Yi Xue Za Zhi 38:81-83. (In Chinese.) [PubMed] [Google Scholar]

388. **Xu, J., L. Qi, X. Chi, J. Yang, X. Wei, E. Gong, S. Peh, and J. Gu.** 2006. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol. Reprod. 74:410-416. [PubMed] [Google Scholar]

389. **Xu, J., S. Zhong, J. Liu, L. Li, Y. Li, X. Wu, Z. Li, P. Deng, J. Zhang, N. Zhong, Y. Ding, and Y. Jiang.** 2005. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. Clin. Infect. Dis. 41:1089-1096. [PubMed] [Google Scholar]

390. **Yam, W. C., K. H. Chan, K. H. Chow, L. L. Poon, H. Y. Lam, K. Y. Yuen, W. H. Seto, and J. S. Peiris.** 2005. Clinical evaluation of real-time PCR assays for rapid diagnosis of SARS coronavirus during outbreak and post-epidemic periods. J. Clin. Virol. 33:19-24. [PubMed] [Google Scholar]

391. **Yam, W. C., K. H. Chan, L. L. Poon, Y. Guan, K. Y. Yuen, W. H. Seto, and J. S. Peiris.** 2003. Evaluation of reverse transcription-PCR assays for rapid diagnosis of severe acute respiratory syndrome associated with a novel coronavirus. J. Clin. Microbiol. 41:4521-4524. [PMC free article] [PubMed] [Google Scholar]

392. **Yamamoto, N., R. Yang, Y. Yoshinaka, S. Amari, T. Nakano, J. Cinatl, H. Rabenau, H. W. Doerr, G. Hunsmann, A. Otaka, H. Tamamura, N. Fujii, and N. Yamamoto.** 2004. HIV protease inbibitor nelfinavir inhibits replication of SARS-associated coronavirus. Biochem. Biophys. Res. Commun. 318:719-725. [PubMed] [Google Scholar]

393. **Yan, X., Q. Hao, Y. Mu, K. A. Timani, L. Ye, Y. Zhu, and J. Wu.** 2006. Nucleocapsid protein of SARS-CoV activates the expression of cyclooxygenase-2 by binding directly to regulatory elements for nuclear factor-kappa B and CCAAT/enhancer binding protein. Int. J. Biochem. Cell Biol. 38:1417-1428. [PubMed] [Google Scholar]

394. **Yang, H., M. Yang, Y. Ding, Y. Liu, Z. Lou, Z. Zhou, L. Sun, L. Mo, S. Ye, H. Pang, G. F. Gao, K. Anand, M. Bartlam, R. Hilgenfeld, and Z. Rao.** 2003. The crystal structures of severe acute respiratory syndrome virus main protease and its complex with an inhibitor. Proc. Natl. Acad. Sci. USA 100:13190-13195. [PMC free article] [PubMed] [Google Scholar]

395. **Yang, L. T., H. Peng, Z. L. Zhu, G. Li, Z. T. Huang, Z. X. Zhao, R. A. Koup, R. T. Bailer, and C. Y. Wu.** 2006. Long-lived effector/central memory T-cell responses to severe acute respiratory syndrome coronavirus (SARS-CoV) S antigen in recovered SARS patients. Clin. Immunol. 120:171-178. [PubMed] [Google Scholar]

396. **Yang, S., S. J. Chen, M. F. Hsu, J. D. Wu, C. T. Tseng, Y. F. Liu, H. C. Chen, C. W. Kuo, C. S. Wu, L. W. Chang, W. C. Chen, S. Y. Liao, T. Y. Chang, H. H. Hung, H. L. Shr, C. Y. Liu, Y. A. Huang, L. Y. Chang, J. C. Hsu, C. J. Peters, A. H. Wang, and M. C. Hsu.** 2006. Synthesis, crystal structure, structure-activity relationships, and antiviral activity of a potent SARS coronavirus 3CL protease inhibitor. J. Med. Chem. 49:4971-4980. [PubMed] [Google Scholar]

397. **Yang, Y., Z. Xiong, S. Zhang, Y. Yan, J. Nguyen, B. Ng, H. Lu, J. Brendese, F. Yang, H. Wang, and X. F. Yang.** 2005. Bcl-xL inhibits T-cell apoptosis induced by expression of SARS coronavirus E protein in the absence of growth factors. Biochem. J. 392:135-143. [PMC free article] [PubMed] [Google Scholar]

398. **Yang, Z. Y., Y. Huang, L. Ganesh, K. Leung, W. P. Kong, O. Schwartz, K. Subbarao, and G. J. Nabel.** 2004. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN. J. Virol. 78:5642-5650. [PMC free article] [PubMed] [Google Scholar]

399. **Yang, Z. Y., W. P. Kong, Y. Huang, A. Roberts, B. R. Murphy, K. Subbarao, and G. J. Nabel.** 2004. A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. Nature 428:561-564. [PubMed] [Google Scholar]

400. **Yang, Z. Y., H. C. Werner, W. P. Kong, K. Leung, E. Traggiai, A. Lanzavecchia, and G. J. Nabel.** 2005. Evasion of antibody neutralization in emerging severe acute respiratory syndrome coronaviruses. Proc. Natl. Acad. Sci. USA 102:797-801. [PMC free article] [PubMed] [Google Scholar]

401. **Yeh, K. M., T. S. Chiueh, L. K. Siu, J. C. Lin, P. K. Chan, M. Y. Peng, H. L. Wan, J. H. Chen, B. S. Hu, C. L. Perng, J. J. Lu, and F. Y. Chang.** 2005. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J. Antimicrob. Chemother. 56:919-922. [PubMed] [Google Scholar]

402. **Yeh, S. H., H. Y. Wang, C. Y. Tsai, C. L. Kao, J. Y. Yang, H. W. Liu, I. J. Su, S. F. Tsai, D. S. Chen, and P. J. Chen.** 2004. Characterization of severe acute respiratory syndrome coronavirus genomes in Taiwan: molecular epidemiology and genome evolution. Proc. Natl. Acad. Sci. USA 101:2542-2547. [PMC free article] [PubMed] [Google Scholar]

403. **Yu, C. M., R. S. Wong, E. B. Wu, S. L. Kong, J. Wong, G. W. Yip, Y. O. Soo, M. L. Chiu, Y. S. Chan, D. Hui, N. Lee, A. Wu, C. B. Leung, and J. J. Sung.** 2006. Cardiovascular complications of severe acute respiratory syndrome. Postgrad. Med. J. 82:140-144. [PMC free article] [PubMed] [Google Scholar]

404. **Yu, F., M. Q. Le, S. Inoue, F. Hasebe, C. P. Mdel, S. Morikawa, and K. Morita.** 2007. Recombinant truncated nucleocapsid protein as antigen in a novel immunoglobulin M capture enzyme-linked immunosorbent assay for diagnosis of severe acute respiratory syndrome coronavirus infection. Clin. Vaccine Immunol. 14:146-149. [PMC free article] [PubMed] [Google Scholar]

405. **Yu, I. T., Y. Li, T. W. Wong, W. Tam, A. T. Chan, J. H. Lee, D. Y. Leung, and T. Ho.** 2004. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N. Engl. J. Med. 350:1731-1739. [PubMed] [Google Scholar]

406. **Yu, W. C., T. H. Tsang, W. L. Tong, T. K. Ng, W. Lim, H. C. Yeung, W. K. To, B. Lam, D. N. Tsang, T. O. Ho, S. T. Lai, and K. L. Tong.** 2004. Prevalence of subclinical infection by the SARS coronavirus among general practitioners in Hong Kong. Scand. J. Infect. Dis. 36:287-290. [PubMed] [Google Scholar]

407. **Yuan, K., L. Yi, J. Chen, X. Qu, T. Qing, X. Rao, P. Jiang, J. Hu, Z. Xiong, Y. Nie, X. Shi, W. Wang, C. Ling, X. Yin, K. Fan, L. Lai, M. Ding, and H. Deng.** 2004. Suppression of SARS-CoV entry by peptides corresponding to heptad regions on spike glycoprotein. Biochem. Biophys. Res. Commun. 319:746-752. [PubMed] [Google Scholar]

408. **Yuan, X., J. Wu, Y. Shan, Z. Yao, B. Dong, B. Chen, Z. Zhao, S. Wang, J. Chen, and Y. Cong.** 2006. SARS coronavirus 7a protein blocks cell cycle progression at G0/G1 phase via the cyclin D3/pRb pathway. Virology 346:74-85. [PubMed] [Google Scholar]

409. **Yuan, X., Z. Yao, Y. Shan, B. Chen, Z. Yang, J. Wu, Z. Zhao, J. Chen, and Y. Cong.** 2005. Nucleolar localization of non-structural protein 3b, a protein specifically encoded by the severe acute respiratory syndrome coronavirus. Virus Res. 114:70-79. [PubMed] [Google Scholar]

410. **Yudin, M. H., D. M. Steele, M. D. Sgro, S. E. Read, P. Kopplin, and K. A. Gough.** 2005. Severe acute respiratory syndrome in pregnancy. Obstet. Gynecol. 105:124-127. [PubMed] [Google Scholar]

411. **Yuen, K. Y., S. S. Wong, and J. S. Peiris.** 2007. The severe acute respiratory syndrome, p. 163-183. *In* I. W. Fong and K. Alibek (ed.), New and evolving infections of the 21st century, 1st ed. Springer Press, New York, NY.

412. **Zeng, F., K. Y. Chow, C. C. Hon, K. M. Law, C. W. Yip, K. H. Chan, J. S. Peiris, and F. C. Leung.** 2004. Characterization of humoral responses in mice immunized witb plasmid DNAs encoding SARS-CoV spike gene fragments. Biochem. Biophys. Res. Commun. 315:1134-1139. [PubMed] [Google Scholar]

413. **Zhai, J., T. Briese, E. Dai, X. Wang, X. Pang, Z. Du, H. Liu, J. Wang, H. Wang, Z. Guo, Z. Chen, L. Jiang, D. Zhou, Y. Han, O. Jabado, G. Palacios, W. I. Lipkin, and R. Tang.** 2004. Real-time polymerase chain reaction for detecting SARS coronavirus, Beijing, 2003. Emerg. Infect. Dis. 10:300-303. [PMC free article] [PubMed] [Google Scholar]

414. **Zhai, Y., F. Sun, X. Li, H. Pang, X. Xu, M. Bartlam, and Z. Rao.** 2005. Insights into SARS-CoV transcription and replication from the structure of the nsp7-nsp8 hexadecamer. Nat. Struct. Mol. Biol. 12:980-986. [PubMed] [Google Scholar]

415. **Zhang, H., G. Wang, J. Li, Y. Nie, X. Shi, G. Lian, W. Wang, X. Yin, Y. Zhao, X. Qu, M. Ding, and H. Deng.** 2004. Identification of an antigenic determinant on the S2 domain of the severe acute respiratory syndrome coronavirus spike glycoprotein capable of inducing neutralizing antibodies. J. Virol. 78:6938-6945. [PMC free article] [PubMed] [Google Scholar]

416. **Zhang, H., G. Zhou, L. Zhi, H. Yang, Y. Zhai, X. Dong, X. Zhang, X. Gao, Y. Zhu, and F. He.** 2005. Association between mannose-binding lectin gene polymorphisms and susceptibility to severe acute respiratory syndrome coronavirus infection. J. Infect. Dis. 192:1355-1361. [PubMed] [Google Scholar]

417. **Zhang, L., F. Zhang, W. Yu, T. He, J. Yu, C. E. Yi, L. Ba, W. Li, M. Farzan, Z. Chen, K. Y. Yuen, and D. Ho.** 2006. Antibody responses against SARS coronavirus are correlated with disease outcome of infected individuals. J. Med. Virol. 78:1-8. [PubMed] [Google Scholar]

418. **Zhang, R., Z. Guo, J. Lu, J. Meng, C. Zhou, X. Zhan, B. Huang, X. Yu, M. Huang, X. Pan, W. Ling, X. Chen, Z. Wan, H. Zheng, X. Yan, Y. Wang, Y. Ran, X. Liu, J. Ma, C. Wang, and B. Zhang.** 2003. Inhibiting severe acute respiratory syndrome-associated coronavirus by small interfering RNA. Chin. Med. J. 116:1262-1264. [PubMed] [Google Scholar]

419. **Zhang, Y., T. Li, L. Fu, C. Yu, Y. Li, X. Xu, Y. Wang, H. Ning, S. Zhang, W. Chen, L. A. Babiuk, and Z. Chang.** 2004. Silencing SARS-CoV Spike protein expression in cultured cells by RNA interference. FEBS Lett. 560:141-146. [PubMed] [Google Scholar]

420. **Zhang, Z., F. S. Wang, M. Zhao, J. C. Liu, D. P. Xu, L. Jin, J. M. Chen, M. Wang, and F. L. Chu.** 2004. Characterization of peripheral dendritic cell subsets and its implication in patients infected with severe acute respiratory syndrome. Zhonghua Yi Xue Za Zhi 84:22-26. (In Chinese.) [PubMed] [Google Scholar]

421. **Zhang, Z., Y. W. Xie, J. Hong, X. Zhang, S. Y. Kwok, X. Huang, S. W. Wong, and B. L. Wong.** 2005. Purification of severe acute respiratory syndrome hyperimmune globulins for intravenous injection from convalescent plasma. Transfusion 45:1160-1164. [PubMed] [Google Scholar]

422. **Zhao, G. P.** 2007. SARS molecular epidemiology: a Chinese fairy tale of controlling an emerging zoonotic disease in the genomics era. Philos. Trans. R. Soc. Lond. B 362:1063-1081. [PMC free article] [PubMed] [Google Scholar]

423. **Zhao, J., W. Wang, G. F. Wang, Y. Li, H. Zhuang, X. Xu, F. Ren, Z. Zhao, and X. M. Gao.** 2005. Development and evaluation of an enzyme-linked immunosorbent assay for detection of antibodies against the spike protein of SARS-coronavirus. J. Clin. Virol. 33:12-18. [PubMed] [Google Scholar]

424. **Zhao, P., J. Cao, L. J. Zhao, Z. L. Qin, J. S. Ke, W. Pan, H. Ren, J. G. Yu, and Z. T. Qi.** 2005. Immune responses against SARS-coronavirus nucleocapsid protein induced by DNA vaccine. Virology 331:128-135. [PubMed] [Google Scholar]

425. **Zhao, Z., F. Zhang, M. Xu, K. Huang, W. Zhong, W. Cai, Z. Yin, S. Huang, Z. Deng, M. Wei, J. Xiong, and P. M. Hawkey.** 2003. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. J. Med. Microbiol. 52:715-720. [PubMed] [Google Scholar]

426. **Zheng, B., M. L. He, K. L. Wong, C. T. Lum, L. L. Poon, Y. Peng, Y. Guan, M. C. Lin, and H. F. Kung.** 2004. Potent inhibition of SARS-associated coronavirus (SCOV) infection and replication by type I interferons (IFN-alpha/beta) but not by type II interferon (IFN-gamma). J. Interf. Cytok. Res. 24:388-390. [PubMed] [Google Scholar]

427. **Zheng, B. J., Y. Guan, M. L. Hez, H. Sun, L. Du, Y. Zheng, K. L. Wong, H. Chen, Y. Chen, L. Lu, J. A. Tanner, R. M. Watt, N. Niccolai, A. Bernini, O. Spiga, P. C. Woo, H. F. Kung, K. Y. Yuen, and J. D. Huang.** 2005. Synthetic peptides outside the spike protein heptad repeat regions as potent inhibitors of SARS-associated coronavirus. Antivir. Ther. 10:393-403. [PubMed] [Google Scholar]

428. **Zheng, B. J., Y. Guan, Q. Tang, C. Du, F. Y. Xie, M. L. He, K. W. Chan, K. L. Wong, E. Lader, M. C. Woodle, P. Y. Lu, B. Li, and N. Zhong.** 2004. Prophylactic and therapeutic effects of small interfering RNA targeting SARS-coronavirus. Antivir. Ther. 9:365-374. [PubMed] [Google Scholar]

429. **Zheng, B. J., K. H. Wong, J. Zhou, K. L. Wong, B. W. Young, L. W. Lu, and S. S. Lee.** 2004. SARS-related virus predating SARS outbreak, Hong Kong. Emerg. Infect. Dis. 10:176-178. [PMC free article] [PubMed] [Google Scholar]

430. **Zhi, L., G. Zhou, H. Zhang, Y. Zhai, H. Yang, F. Zhang, S. Wang, M. Wei, W. Cao, and F. He.** 2007. Lack of support for an association between CLEC4M homozygosity and protection against SARS coronavirus infection. Nat. Genet. 39:692-694, 694-696. [PubMed] [Google Scholar]

431. **Zhong, N. S., B. J. Zheng, Y. M. Li, Poon, Z. H. Xie, K. H. Chan, P. H. Li, S. Y. Tan, Q. Chang, J. P. Xie, X. Q. Liu, J. Xu, D. X. Li, K. Y. Yuen, J. S. Peiris, and Y. Guan.** 2003. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet 362:1353-1358. [PubMed] [Google Scholar]

432. **Zhu, J., G. Xiao, Y. Xu, F. Yuan, C. Zheng, Y. Liu, H. Yan, D. K. Cole, J. I. Bell, Z. Rao, P. Tien, and G. F. Gao.** 2004. Following the rule: formation of the 6-helix bundle of the fusion core from severe acute respiratory syndrome coronavirus spike protein and identification of potent peptide inhibitors. Biochem. Biophys. Res. Commun. 319:283-288. [PubMed] [Google Scholar]

433. **Zhu, M. S., Y. Pan, H. Q. Chen, Y. Shen, X. C. Wang, Y. J. Sun, and K. H. Tao.** 2004. Induction of SARS-nucleoprotein-specific immune response by use of DNA vaccine. Immunol. Lett. 92:237-243. [PubMed] [Google Scholar]

434. **Zhu, Z., S. Chakraborti, Y. He, A. Roberts, T. Sheahan, X. Xiao, L. E. Hensley, P. Prabakaran, B. Rockx, I. A. Sidorov, D. Corti, L. Vogel, Y. Feng, J. O. Kim, L. F. Wang, R. Baric, A. Lanzavecchia, K. M. Curtis, G. J. Nabel, K. Subbarao, S. Jiang, and D. S. Dimitrov.** 2007. Potent cross-reactive neutralization of SARS coronavirus isolates by human monoclonal antibodies. Proc. Natl. Acad. Sci. USA 104:12123-12128. [PMC free article] [PubMed] [Google Scholar]

From:	Hoffman, Corey (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BB09D03DB5A04C1DB3BC79621F80559E-HOFFMAN, CO <Corey.Hoffman@hhs.gov>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
CC:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Donis, Ruben (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=af00dcf720cb429f8e2accbe06ee32ff-Donis, Rube <Ruben.Donis@hhs.gov>; Oshansky, Christine (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7bd764440b44b06af644cdcd22e42d6-Oshansky, C <Christine.Oshansky@hhs.gov>; Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>
Subject:	Updated Green Folder
Date:	2020/04/07 17:42:01
Priority:	Normal
Type:	Note

Hello Rick,

Here are you green folder files for today.

I am resending since I received new numbers regarding HCQ/CQ from RQA. This file has been updated below and also in sharepoint.

These files are also available on SharePoint as well.

From the IMT

Please find the following attached and in your Sharepoint:

1. Report of current awards **(Word Document – Daily Report)**
2. List of planned awards – some may be beyond the next 7 days (see Date of Action column) **(Word Document – Daily Report)**
3. Daily budget report **(Excel – BARDA's COVID Obligations Report)**
4. List of communications packages and status **(Word Document – Daily Report)**

For your overview here are the following document

1. Daily Overview
2. Diagnostics with EUA
3. SNS HCQ/CQ Tracking
4. NRCC-SLB

Best,
Corey

FOUO/Procurement Sensitive/Company Confidential

Corey M. Hoffman, Ph.D.
Biologist
Radiological and Nuclear Countermeasures
Division of Chemical, Biological, Radiological, and Nuclear Countermeasures (CBRN)
Biomedical Advanced Research and Development Authority (BARDA)
Office of the Assistant Secretary for Preparedness and Response (ASPR)
Department of Health and Human Services
Office (202)730-8581

Sender:	Hoffman, Corey (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BB09D03DB5A04C1DB3BC79621F80559E-HOFFMAN, CO <Corey.Hoffman@hhs.gov>
Recipient:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Donis, Ruben (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=af00dcf720cb429f8e2accbe06ee32ff-Donis, Rube

	<Ruben.Donis@hhs.gov>; Oshansky, Christine (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7bd764440b44b06af644cdcd22e42d6-Oshansky, C <Christine.Oshansky@hhs.gov>; Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>
Sent Date:	2020/04/07 17:41:54
Delivered Date:	2020/04/07 17:42:01
Message Flags:	Unread

SNS Hydroxychloroquine/Chloroquine Requests

Requestor/State	Clinical Trial Material	Hydroxychloroquine/ Chloroquine	# of Pills*	Date
Cardinal Health		Hydroxychloroquine	3,081,600	Received on 04/07/2020
Amerisource		Hydroxychloroquine	3,216,000	Received on 04/07/2020
McKesson		Hydroxychloroquine	3,024,000	Received on 04/07/2020
Seminole Tribe of Florida		Hydroxychloroquine	9600	Received on 04/07/2020
North Carolina Division of Public Health		Hydroxychloroquine	998,400	Received 04/05/2020(993,600) Shipped 04/06/2020(4800)
Nevada Public Health & Human Services		Hydroxychloroquine	14,400	Received 04/06/2020
Mississippi Dept of Public Health		Hydroxychloroquine	24,000	Received 04/05/2020(14,400) Shipped 04/06/2020(9600)
California Dept of Public Health		Hydroxychloroquine	3,297,400	Received 04/06/2020
Henry Ford Hospital, Detriot MI	Yes	Hydroxychloroquine	81,600	Received 4/05/2020
US Virgin Islands		Hydroxychloroquine	19,200	Received 04/03/2020
California, LA County Public Health		Hydroxychloroquine	28,800	Received 04/03/2020
New York, NYS Dept of Corrections and Community Supervision Central Pharmacy		Hydroxychloroquine	139,200	Received 04/03/2020

*Calculations of pills and bottles/blister packs are made by RQA based on data provided by SNS for cases of product. These amounts are based on assumptions and may not be exact.

HQ: 242,880 Bottles* Remain: (100 pills/bottle)
CHQ: 3,952 Blister Packs* Remain: (250 pills/pack)

FOUO

COVID-19 PMO call (Paul Mango IOS)

02 MAR 2010 10:00 AM

Notes from Ruben

Brian Shuy and Sam Imbriale

BLUF – Detailed updates from across HHS. No Action items for BARDA.

Agenda item #2 Scientific priorities

BARDA/NIH

- BARDA - Rodney Wallace Diagnostics update
  - 11 companies with COVID assays in development
  - DOD has funded biofire
  - BARDA working with one of the companies – engage via OTA
  - Many companies reached out to BARDA EZBAA
  - 2/11 indicated what they don't want funding at this time (will continue development)
  - 3 additional companies in discussions with BARDA
  - In total, 4 companies with assays in development are in consideration
  - timeline to EUA is 2-4 months for these 4 companies
- BARDA - Robert Johnson
  - Therapeutics - Screening
  - Vaccine – develop non-clinical models
  - Therapeutics – Remdesivir clinical study (with NIH)
  - Question from Brian: Will send a DOE paper on modeling
  - RJ: BARDA received it from Chris Hassell - reviewed responded to Chris
- NIH report – H. Marston:
  - NIH interested in using the DOE method to screen protease inhibitors
  - VTEU – activating several sites in the coming days
  - DOD IDCRP to activate sites shortly
  - NIH sent team to Korea – activating 3 sites within 1 week to enroll patients
  - How can NIH move patients to sites ready to enroll patients in the Remdesivir Trial?

Agenda #4 HC system info collections

- Anita Patel
  - Manage patients with COVID and non-COVID
  - Insure HCW are safe
  - IPC guidance to be updated – infection control

    - PPE is one of the many actions for infection control.
    - Some areas WA CA FL – looking at HCW exposure and impact of HCW quarantines on patient care capacity
    - Pneumonias that last 14 days or longer – strain resources
- Sam: impact on smaller clinics
- Laura: PPE burn rate? What is the plan to conserve?
    - Anita: on the patient side – need to get a baseline on severity – median patient hospital stay
    - Hospitalization rate captured readily
    - Standards of care: stepping away from "crisis" and "alternative' standard

Agenda item #5

Nancy Messonier

- We are at a time in which case numbers are difficult
- State testing and reporting not synchronized
- This am – 91 cases in the US
- 45 from Diamond Princes Ship
- 43 identified by US surveillance
- 17 added yesterday
- 1 death in NY
- 1 death in WA
- Santa Clara CA – community transmission
- Seattle – community transmission
- Globally – China has the greatest # of cases - followed by S Korea Italy Iran
- What is the reason for the increase?
- In the US – both more testing and more transmission
- Globally – an explosion of cases (not a word to be used in public)
- CDC trying to move focus from numbers to more important actions
- Testing by states – their reporting is faster than CDC
- Transparency with media – need to have a sidebar discussion
- Work with NSC: Focus on actions other than case #s

Agenda Item #6. public sentiment

- Huge spike of social traffic on coronavirus terms – masks, respirators, sanitizer
- Twitter – volume of traffic in terms such as: CDC vaccine Azar and WHO warning
- Lots of coverage: Press conferences
- FEMA and CDC are working on understanding regional postings
- Volume of corona-related Social Media traffic
- CA NY TX and FL
- LA, DC, Chicago,

Agenda item #7. messaging

- Messages: 6 pm call
- Stakeholder call being scheduled –
- Woodbury – stakeholder outreach
- Governors – senior leaders
- Seniors: impact on services for this demographic
- Work with CMS CDC SAMSA – outreach to senior
- Tonight call – main topic is Vulnerable populations. Make sure we reach out to the right people: no new strategy.
- Working with CA and WA to be sure we have the right operational guidance: visitors in and out guidance
- ASPA – shared messages with WH for distribution on handwashing
- Surgeon General doing a video on handwashing

Agenda Item #8

- WP on supply chain for NSC
- Message:
- Course of action #1: strategy for buying more and making more masks
- Meeting tomorrow with NSC
- Course of action #2
- Prioritize HCW for accessing masks – divert from other users
- Course of action #3 conservation
- PREP act protection
- Course of action #4– comms with public
- Course of action #5: non-unanimous – block export via BPA
- Course of action #6 – meeting at 10:30 tomorrow with NSC – private sector engagement
- MFR talk to Kadlec on Wednesday – need to have
- Need to keep a tally of these COAs – what actions are

Agenda: #9 Modeling

- Diana and Matt Biggerstaff keeping things rolling:
- Matt Clay – all scenarios expired last Friday
- New scenario – completely unmitigated, not a prediction, don't share outside of this room
- Span the gamut of severity
- Lowered the low end of scenario like a bad seasonal flu
- Best guess scenario: it will change frequency
- CDC and NIH provided input for the model.
- Transmission – if unmitigated 60% infected (by serology)
- 200M infections – how many of these need care? ~95M
- Asympt rate: 50% (contentious)
- 11M of the 95M are seniors - 16% of those over age of 65 with symptoms admitted to hospital
- Hospitalizations – 2.7M (3% of 95M)
- Death: 225, 000 (190K of these are seniors) overall 0.25% from cases
- ~% of those in the hospital

- Will circulate a sheet with these figures
- **Brian: we need to understand what are the best mitigations**
- We have # hospital beds- how long until we run out of bed capacity?
- Jason --the main limitation is input data to do the model; need data
- Now working on modeling the impact of mitigation **– half day meeting on Wednesday**
- Potential action plan scenarios – school closings, etc
- What would be the best actions to mitigate?
- Work with AHA to increase bed capacity
- Supply chain actions
- Jason needs a list of potential actions

--

Meeting tomorrow – **actions:**

- DOE call today
- Sched new time for modeling on Wednesday
- Data collection plan from CDC
- Sentiment analysis
- ASPA CDC to figure out numbers on Website

COVID-19 BARDA Overview

Date: April 07, 2020

1. Diagnostics
    - Partnered with Hologic, DiaSorin, Qiagen, MesaBioTech, GenMark, Cepheid, Luminex (NxTag and Aries), Vela, OraSure and Nanomix to develop SARS-CoV-2 diagnostics
    - 28 Diagnostics with EUA
        - Luminex Aries received EUA 04/03/2020

2. Therapeutics
    - Shipments of Chloroquine/Hydroxychloroquine have left SNS for use under EUA
        i. 5 sites (US Virgins Islands, CA, MI, MO NY)
    - Emergent developing a plasma-derived Polyclonal Antibody-based COVID-19 Rx
    - Genentech Tocilizumab (α-IL-6R) clinical trial for COVID-19 targeting start early April
        i. 6 patients enrolled 04/05/2020
    - Regeneron adaptive phase 2/3 study of Sarilumab (α-IL-6R antibody) for COVID-19
        1. 51 sites activated (15 in NY, 5 in NJ, 4 in FL, 3 in MA, 2 in CA, GA, IL, PA, TX, WA, 1 each in CO, CT, DC, LA, MI, MN, OK, UT, VA)
        2. 838 Patients enrolled and dosed as of 04/05/2020
            a. Phase II – 463
            b. Phase III – 375
        3. DMC met 04/04/2020 study given safe to proceed
    - Regeneron has identified mAbs that neutralize SARs-CoV-2 virus in vitro
        i. Screening candidate mAbs for neutralizing activity and scaling up manufacturing
    - Janssen validation phase on going for high throughput screening

3. Vaccines
    - Sanofi Pasteur is pursuing a vaccine construct that is thought to be more stable.
        i. Award in process for development through Phase 1
    - Janssen preliminary non-clinical data in immunogenicity in mice
        1. 3 candidates identified, clinical trials expected early fall 2020

1) **BARDA Diagnostics**
    a) **14 White Papers submitted, reviews in progress.**
    b) **Current Diagnostic EUAs**
        i) 28 Diagnostics with (EUA):
            I. https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd
    c) **Cepheid**
        i) **No Update**
    d) **Cue**
        i) **No Update**
    e) **[PROCUREMENT SENSITIVE] EZ-BAA submissions**
            I. Hologic shipped 192,000 tests as of 04/06/2020
        ii) **DiaSorin Molecular**
            I. 88K tests shipped to US labs as of 04/06/2020
        iii) **MesaBioTech Point of care (hand-held device)**
            I. **No Update**
        iv) **Qiagen**
            I. **No update**
        v) **Genmark**
            I. **No Updates**
        vi) **Luminex Corp**
            I. **Luminex NxTAG-No Update**
            II. **Luminex Aries received EUA 04/03/2020**
        vii) **Vela Diagnostics**
            I. **LOD study completed, verification and validation in progress**
        viii) Nanomix kick off meeting in process of being scheduled
        ix) OraSure kick off meeting 04/08/2020
        x) **Pending EZ-BAA contract actions**
            I. **DiaSorin (Antibody)** waiting for signature from company
            II. **Hememics and** Inbios **(Antigen/Antibody): Stage 2 negotiations in process**
2) **BARDA Therapeutics**
    a) **Regeneron**
        i) **2019-nCoV specific mAb on track to have leads by end of April and production in August**
            1. **Screening leads for neutralizing activity and scaling up manufacturing**
        ii. **Regeneron adaptive phase 2/3 study of Sarilumab (α-IL-6R antibody) for COVID-19**
            1. 51 **sites activated (1S in NY, S in NJ, 4 in FL, 3 in MA, 2 in CA, GA, IL, PA, TX, WA, 1 each in CO, CT, DC, LA, MI, MN, OK, UT, VA)**
            2. 838 Patients enrolled and dosed as of 04/05/2020
                a. Phase II – 463

b. Phase III – 375

3. DMC met 04/04/2020 study given safe to proceed

b) Genentech IL-6R antibody (Tocilizumab) clinical trial in COVID-19 patients

i) 6 patients enrolled 04/05/2020

c) Antiviral screening

i) Discussions on steps to test hits (itraconazole) in non-clinicals models

d) SAb Biotherapeutics – Polyclonal antibody product

i) Clinical trial planned for late June/July

e) Grifols (HIG)

i) Targeting award week of 04/06/2020

f) Emergent

i) Possible submission of pre-IND submission to FDA week of 04/06/2020

3) BARDA Vaccines

a) SSA decision meeting one full proposal/two white papers convened 04/06/2020

b) Janssen Ad26 vaccine

i) 3 candidates identified, lead in process of being identified

ii) Targeting to start clinical trial early September

c) Sanofi Pasteur

i) AS03 supply purchase opportunity raised in GSK/BARDA discussion for SP

ii) SP indicated to FDA that they expect to enter Phase 1 study Sept/Oct 2020

d) Moderna

i) Project award on hold pending ASPR review

e) Merck SOW and draft contract modification submitted

4) Pfizer

a) Program and DCMA reviewed agreement position comments

S) BARDA Rapidly Deployable Technology

a) 2 EZ BAA in negotiations/1 EZ BAA awaiting Stage II proposal

i) Awards expected week of 04/06/2020

6) Sample Sharing Working Group

i) Launched campaign to rapidly secure convalescent serum in support of serological testing program.

ii) Will pursue 5 partnerships: Stanford, UMD, UCSD, Cantor Bioconnect, ICON

7) BARDA Clinical

a) NIAID ACTT Trial

i) Will be a 4 arm study investigating standard of care, remdesivir, baracitinib, combination of remdesivir, and baracitinib

b) Chloroquine/Hydroxychloroquine EUA

i) One million doses of chloroquine donated by Bayer arrived to the SNS

8) BARDA Non-clinical

a) 4 non-clinical kick off meetings scheduled

i) Battelle and Souther Research kick off meetings held 04/06/2020

ii) Kick of meetings for MRI Global and Lovelace scheduled 04/08/2020

iii) BARDA/NIAID nonclinical collaboration meeting scheduled for 04/07/2020

iv) Working to establish a repository with Fisher BioServices for the receipt of convalescent samples

9) BARDA RQA

a) Standing weekly meetings scheduled with CDER and CBER

b) Shipments of Chloroquine/Hydroxychloroquine have left SNS as of 04/03/02020

iii. 15 cases (1872 bottles) shipped to 5 sites (US Virgins Islands, CA, MI, MO, NY)

10) BARDA Manufacturing

a) Discussion with Seqirus regarding MF59 domestic manufacturing

Senior Leadership Brief COVID-19

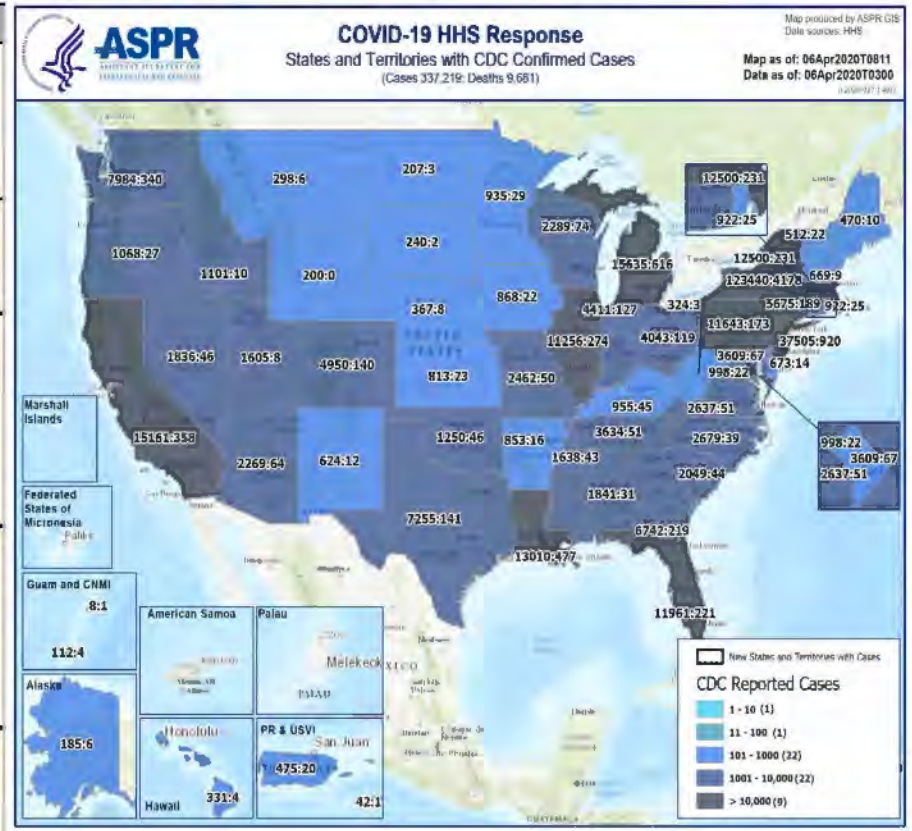
April 6, 2020 12:00 p.m. ET

For the most up to date COVID-19 data: https://geohealth.hhs.gov/arcgis/home/

Current Situation: FEMA is working with HHS to allocate and deliver key resources. FEMA continues to work with industry partners on producing, allocating and distributing PPE and ventilators, as quickly as possible; including expediting critical supplies from overseas to various US locations. FEMA is coordinating with USACE on the build-out of alternate care sites (ACS), with significant expansion capacity. FEMA Regional Administrators are coordinating closely with governors, tribal leaders, state emergency managers, and state public health officials to execute a whole of government response to fight the COVID-19 pandemic. On March 29, the president extended the nation's Slow the Spread campaign until April 30. **CDC Update:** CDC confirmed and presumptive U.S. cases of COVID-19: 337,219 (+26,251) across 50 states and D.C., Guam, PR, CNMI, and USVI; Deaths: 9,681 (+1939); Combined CDC and WHO reported global cases: 1,133,758 (+82,1230); global deaths: 62,784 (+5,799); Countries and areas with cases: 207 *(HHS Update, April 6, 2020, 8:04 a.m. ET)* **Testing:** 1,671,190 cumulative as of April 5 (includes samples tested by State/Local Public Health Laboratories, Commercial Laboratories, Hospital Laboratories, CDC, and VA)

Operational Task Forces

Medical Counter-Measure (MCM) Development	• Clinical trial to test antiviral remdesivir: 480 (+11) patients enrolled (700 target) *(MCM TF Update, April 6, 2020, 10:00 a.m. ET)* • Clinical trial requests for SNS chloroquine/hydroxychloroquine: 2 received, 1 fulfilled, and 1 pending review *(MCM TF Update, April 6, 2020, 10:00 a.m. ET)*
Health Care Resilience (HCR)	• Developed talking points for FEMA/HHS Regional Staff to explain the distinction between ACS and federal medical stations (FMS) *(HCR TF Update, April 5, 2020, 2:00 p.m. ET)*
Lab Diagnostics	• Met with diagnostics stakeholders (laboratories and manufacturers) and collected key information on testing capacity, ramp up capability, and current bottlenecks to inform strategy for the next phase of COVID-19 testing *(LD TF Update, April 6, 2020, 10:00 a.m. ET)* • Abbott is shipping its ID NOW rapid testing instruments and tests April 5, ETA to public health labs April 6-7 *(LD TF Update, April 6, 2020, 10:00 a.m. ET)*
Community Based Testing Sites (CBTS)	• 41 total sites: 26 operational, 4 anticipated, 3 closed, and 8 transitioned to state management; 64,662 (+4,279) tested cumulatively since March 23 *(CBTS TF Update, April 6, 2020, 10:00 a.m. ET)* • Negotiating modification of contracts to support case-by-case exceptions to April 10 transition date; assessing NJ and Houston, TX sites to identify barriers to transition; federal assistance to be extended for the NJ site through May 30 as needed *(CBTS TF Update, April 6, 2020, 10:00 a.m. ET)*
Supply Chain Stabilization	• 46 flights planned with 36 (-2) scheduled, and 10 (+2) complete; Airbridge Flight #9 landed in (b)(3):4 on April 5 at 10:40 p.m., exact cargo TBD; Flight #10 landed in (b)(3):42 on April 5 at 11:40 p.m., exact cargo TBD *(SC TF Update, April 6, 10:00 a.m. ET)*
Community Mitigation Measures	• Posted 2 updated guidance resources online: Social Distancing, Quarantine, and Isolation (containing new cloth face covering guidance) and Guidance for Building Water Systems *(CMM TF Update, April 6, 2020, 10:00 a.m. ET)*
Data and Analysis	• Data for 39 (+2) states/territories has been integrated into the HSS GeoHealth Common Operating Picture (COP) to support decision-making *(DA TF Update, April 6, 2020, 10:00 a.m. ET)* • Producing 30/60/90-day PPE requirement estimates for FEMA Region IV, ETD April 6 *(DA TF Update, April 6, 2020, 10:00 a.m. ET)*



Key Updates/Actions

All 50 states, the District of Columbia, 5 territories, and 21 tribal nations are working directly with FEMA under the nationwide emergency declaration for COVID-19

FEMA HQ: National Watch Center Steady State; NRCC Level I (6:00 a.m. ET to 12:00 a.m. ET); Level 1: Region I, IX; Level 2: Regions II, III, IV, V, VI, VII, VIII, X; COVID-19 Major Declarations: 50 (+3) (MS, NM, OK) *(FEMA Update, April 6, 2020, 1:07 a.m. ET)*

HHS: SOC at Level I (24/7) co-located with FEMA; CDC EOC activated, ACF OHSEPR at Level I *(FEMA National SITREP, March 21, 2020, 6:00 a.m. ET and HHS Update, March 20, 2020, 2:14 p.m. ET)*

Department of Homeland Security: 2,578 (+12) FEMA employees deployed to support COVID-19 Response; IMAT-A teams deployed to 26 states, territories, and DC; LNOs deployed to 37 states and territories *(FEMA Update, April 6, 2020, 8:54 a.m. ET)*

Health and Medical Lifeline

Public Health

Federal Assistance

- USACE received 25 (+3) mission assignments (MA): 3 national MAs, 2 EM Dec MAs (AZ, WI), and 8 MAs to design/build ACS in NY (8 [+3] sites), PA (5 sites), IL (4 sites), CA (3 sites), OR (3 sites), VA (3 sites), FL (2 sites), CO (2 sites), NM (2 [+1] sites), TN (1 site), ID (1 site), WA (1 site), NJ, MI, IA, KS, NV, and the Navajo Nation; 8 contracts awarded with a total projected bed capacity of 13,710 (+2,903); completed 828 (+72) out of 869 (+28) requested ACS assessments; 1,815 (+37) USACE personnel supporting *(ESF-3 Update, April 6, 2020, 9:54 a.m. ET)*
- United States Secret Service is alerting health care facilities nationwide about identified vulnerabilities in their networks that make them susceptible to ransomware and other network disruptions *(DHS Update, April 6, 2020, 8:54 a.m. ET)*

Medical Care

Hospital Capacity

- NYS: Governor issued Executive Order allowing graduating medical students to begin practicing now *(FEMA Region II Update, April 5, 2020, 11:00 a.m. ET)*
- NYC: Javits Center currently with 36 patients *(HHS Update, April 6, 2020, 10:16 a.m. ET)*
- NYC: USNS Comfort currently with 31 patients *(HHS Update, April 6, 2020, 10:16 a.m. ET)*
- NYC: Morgue space near 100% capacity; 85 refrigerated trucks en route to NYC to arrive by April 14 *(FEMA Region II Update, April 5, 2020, 4:10 p.m. ET)*
- NYS: NYS Department of Health Emergency Order mandates all medical facilities to expand capacity by 50%; 100% if possible; goal to increase to 110,000 total beds including 40,000 ICU *(FEMA Region II Update, April 5, 2020, 4:10 p.m. ET)*
- CA: USNS Mercy currently with 9/275 beds filled; 1/70 beds with ventilator filled; 3/80 ICU beds filled; 20 patients seen *(DoD Update, April 6, 2020, 8:16 a.m. ET)*

Other Domestic Lifelines

Safety & Security

- 40 states, D.C., 4 territories and 24 (+1) tribes issued shelter-in-place orders *(FEMA Tribal Advisor Update, April 5, 2020, 6:31 p.m. ET)*
- Since January 29, 42,594 U.S. Citizens and Lawful Permanent Residents (LPR) have been repatriated; 400 flights completed from 73 countries; 23,861 potential remaining to repatriate *(DHS Update, April 6, 2020, 8:54 a.m. ET)*

Food, Water, & Shelter

- Met with NBEOC and FEMA Supply Chain task force to sync PPE focus with their efforts; awaiting NRCC leadership dissemination of PPE process overview for inter-agency and private sector partners *(FSC TF Update, April 6, 2020, 10:00 a.m. ET)*

FEMA

Senior Leadership Brief COVID-19

April 6, 2020 12:00 p.m. ET

For the most up to date COVID-19 data: https://geohealth.hhs.gov/arcgis/home/

Title 32 Status by State

Total On Duty: 12544		T32 Approved: 25				T32 Requested: 23		
NGB Update, April 6, 2020, 12:00 p.m. ET								
State / Territory	On-Duty	Title 32 Request Status	State / Territory	On-Duty	Title 32 Request Status	State / Territory	On-Duty	Title 32 Request Status
AK	40	REQUESTED	KY	150	REQUESTED	OH	511	WH AUTHORIZED & APPROVED**
AL	71	N/A	LA	6	WH AUTHORIZED & APPROVED**	OK	1	REQUESTED
AR	53	REQUESTED	MA	774	WH AUTHORIZED & APPROVED**	OR	45	REQUESTED
AZ	701	REQUESTED	MD	105	WH AUTHORIZED & APPROVED**	PA	487	REQUESTED
CA	973	WH AUTHORIZED & APPROVED**	ME	10	REQUESTED	PR	520	WH AUTHORIZED & APPROVED**
CO	58	REQUESTED	MI	1	WH AUTHORIZED & APPROVED**	RI	708	WH AUTHORIZED & APPROVED**
CT	0	WH AUTHORIZED & APPROVED**	MN	7	REQUESTED	SC	243	REQUESTED
DC	170	WH AUTHORIZED & APPROVED**	MO	0	WH AUTHORIZED & APPROVED**	SD	3	N/A
DE	9	REQUESTED	MS	98	REQUESTED	TN	456	WH AUTHORIZED & APPROVED**
FL	63	WH AUTHORIZED & APPROVED**	MT	74	REQUESTED	TX	48	WH AUTHORIZED & APPROVED**
GA	1011	WH AUTHORIZED & APPROVED**	NC	226	REQUESTED	UT	0	N/A
GU	1	WH AUTHORIZED & APPROVED**	ND	26	REQUESTED	VA	72	REQUESTED
HI	185	WH AUTHORIZED & APPROVED**	NE	10	N/A	USVI	27	WH AUTHORIZED & APPROVED**
IA	150	REQUESTED	NH	58	WH AUTHORIZED & APPROVED**	VT	202	N/A
ID	52	REQUESTED	NJ	0	WH AUTHORIZED & APPROVED**	WA	0	WH AUTHORIZED & APPROVED**
IL	417	WH AUTHORIZED & APPROVED**	NM	133	WH AUTHORIZED & APPROVED**	WI	493	REQUESTED
IN	226	WH AUTHORIZED & APPROVED**	NV	103	REQUESTED	WV	298	REQUESTED
KS	50	REQUESTED	NY	2,419	WH AUTHORIZED & APPROVED**	WY	0	N/A
***Title 32 has been authorized and approved by the Secretary of Defense.*								

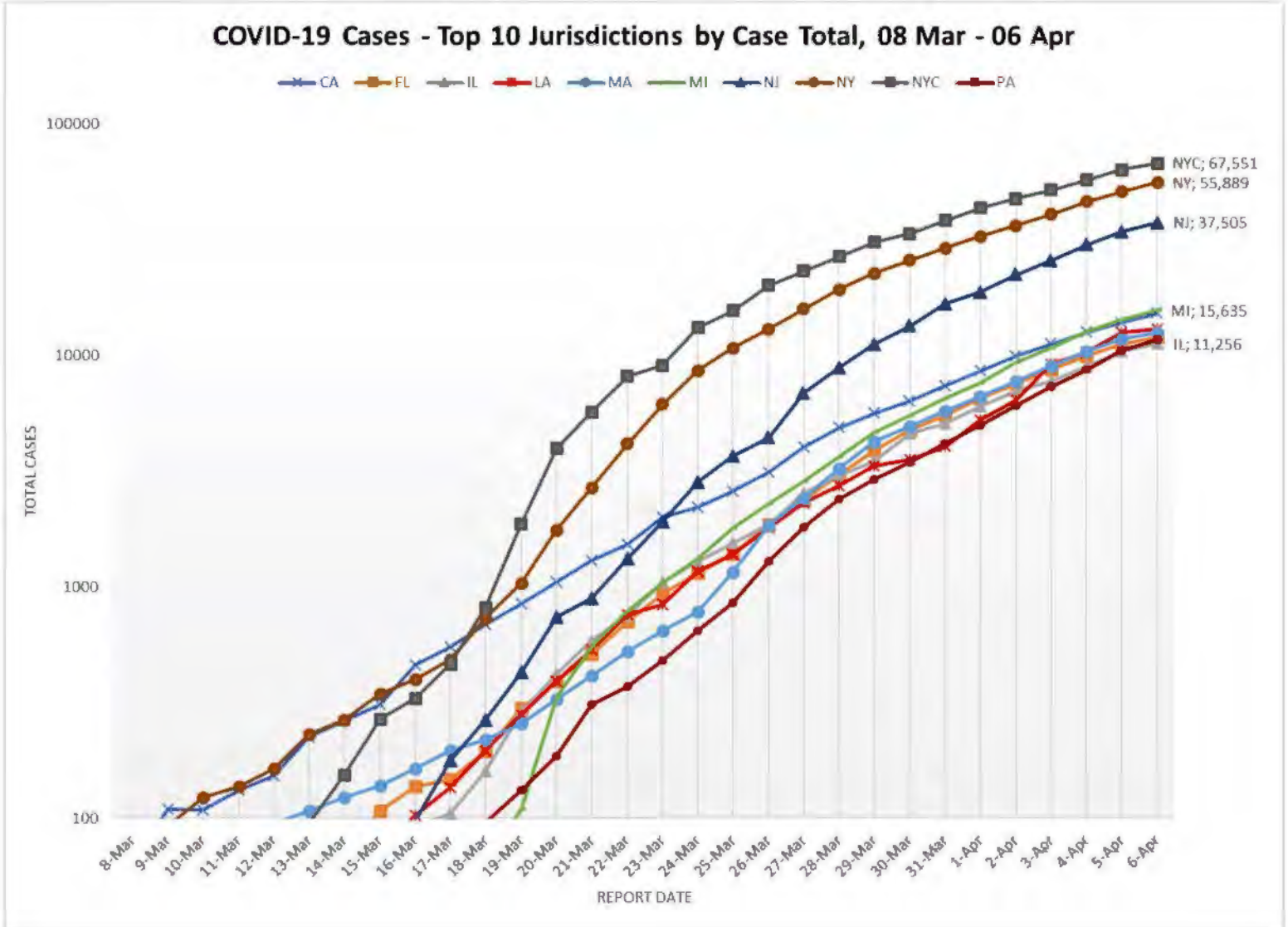
Ventilators

Region Number	Delivered	Processing	Total
⊟ 01	150		150
Connecticut	50		50
Massachusetts	100		100
⊟ 02	5450	300	5750
New Jersey	1050	300	1350
New York	2000		2000
New York City	2400		2400
⊟ 03	120		120
Maryland	120		120
⊟ 04	350		350
Florida	200		200
Georgia	150		150
⊟ 05	1150	150	1300
Chicago	150	150	300
Illinois	300		300
Michigan	700		700
⊟ 06	350		350
Louisiana	350		350
⊟ 09	170	30	200
Guam		30	30
LA County (CA)	170		170
⊟ 10	700		700
Alaska	60		60
Oregon	140		140
Washington	500		500
Total	8440	480	8920

SNS ventilators delivered or en route as of 10:00 a.m. on April 6

Product groups	Gloves			N95s			Surgical Gowns			Surgical Masks		
FEMA Region	In Transit	Delivered	Total	In Transit	Delivered	Total	In Transit	Delivered	Total	In Transit	Delivered	Total
⊟ II												
New York		1,499,298	**1,499,298**	3,413,380	2,609,420	**6,022,800**		301,639	**301,639**		2,536,890	**2,536,890**
⊟ IX												
California	184,258	1,637,164	**1,821,422**	582,950	1,026,670	**1,609,620**	25,688	386,329	**412,017**	143,511	3,644,498	**3,788,009**
⊟ V												
Michigan	368,514	250,416	**618,930**	120,900	190,160	**311,060**	51,375	70,328	**121,703**	287,022	452,996	**740,018**
⊟ VI												
Louisiana		483,464	**483,464**		208,322	**208,322**		83,633	**83,633**		494,800	**494,800**
⊟ X												
Washington		608,890	**608,890**		494,780	**494,780**		160,639	**160,639**		794,428	**794,428**

Table includes SNS and Logistics Supply Chain Management System as of April 5


COVID-19 Cases - Top 10 Jurisdictions by Case Total, 08 Mar - 06 Apr
CA
FL
IL
LA
MA
MI
NJ
NY
NYC
PA
100000
10000
1000
100
TOTAL CASES
NYC; 67,551
NY; 55,889
NJ; 37,505
MI; 15,635
IL; 11,256
8-Mar
9-Mar
10-Mar
11-Mar
12-Mar
13-Mar
14-Mar
15-Mar
16-Mar
17-Mar
18-Mar
19-Mar
20-Mar
21-Mar
22-Mar
23-Mar
24-Mar
25-Mar
26-Mar
27-Mar
28-Mar
29-Mar
30-Mar
31-Mar
1-Apr
2-Apr
3-Apr
4-Apr
5-Apr
6-Apr
REPORT DATE

COVID-19 HHS Response

CDC Confirmed Cases and Screening Airports

Total US Cases / Deaths: (337,219 / 9,681)*

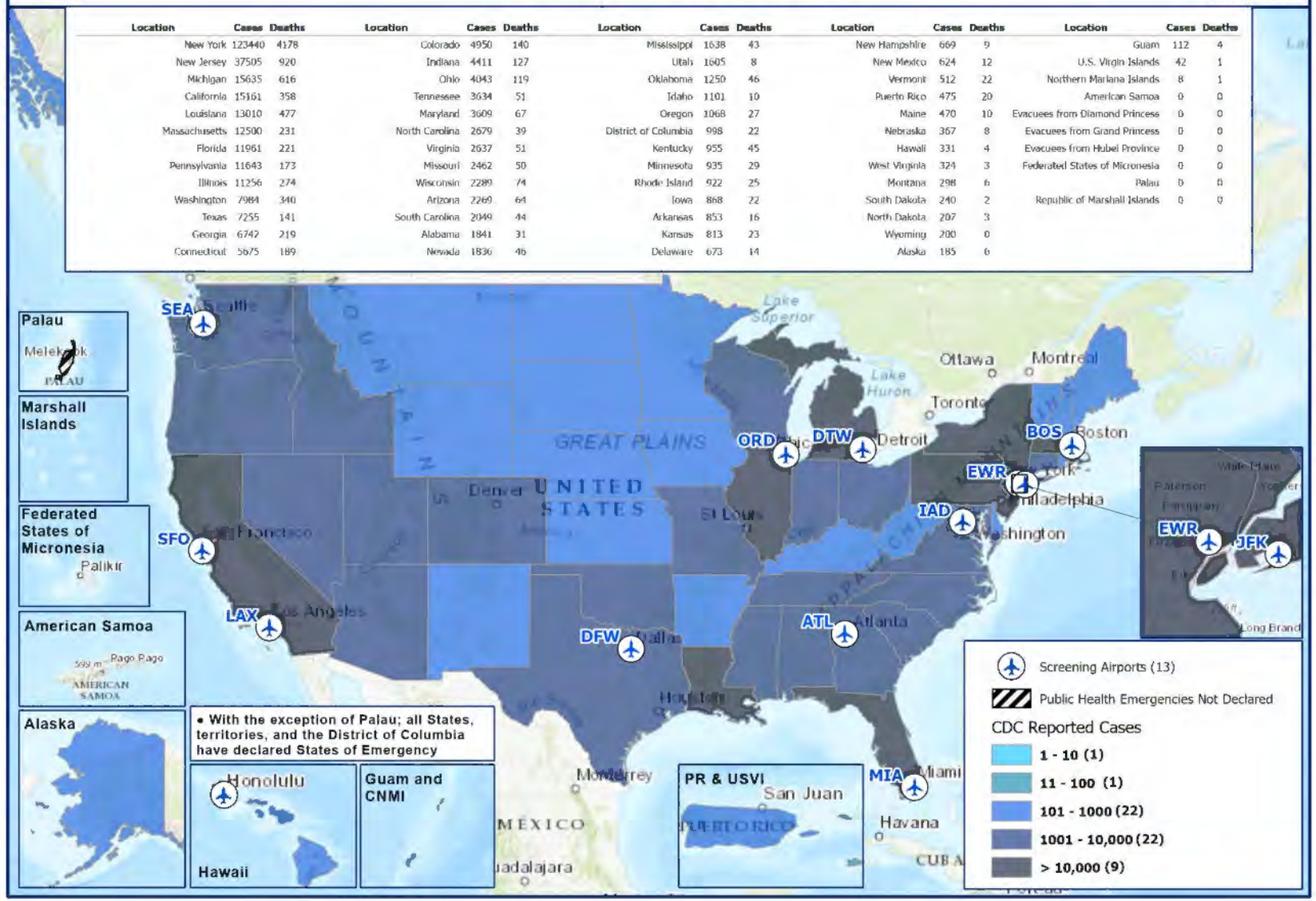
ASPR ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

Map produced by ASPR GIS
Data sources: HHS

Map as of: 06Apr2020T0813
Data as of: 06Apr2020T0300

(I 20200121 1 498)

Location	Cases	Deaths	Location	Cases	Deaths	Location	Cases	Deaths	Location	Cases	Deaths	Location	Cases	Deaths
New York	123440	4178	Colorado	4950	140	Mississippi	1638	43	New Hampshire	669	9	Guam	112	4
New Jersey	37505	920	Indiana	4411	127	Utah	1605	8	New Mexico	624	12	U.S. Virgin Islands	42	1
Michigan	15635	616	Ohio	4043	119	Oklahoma	1250	46	Vermont	512	22	Northern Mariana Islands	8	1
California	15161	358	Tennessee	3634	51	Idaho	1101	10	Puerto Rico	475	20	American Samoa	0	0
Louisiana	13010	477	Maryland	3609	67	Oregon	1068	27	Maine	470	10	Evacuees from Diamond Princess	0	0
Massachusetts	12500	231	North Carolina	2679	39	District of Columbia	998	22	Nebraska	367	8	Evacuees from Grand Princess	0	0
Florida	11961	221	Virginia	2637	51	Kentucky	955	45	Hawaii	331	4	Evacuees from Hubei Province	0	0
Pennsylvania	11643	173	Missouri	2462	50	Minnesota	935	29	West Virginia	324	3	Federated States of Micronesia	0	0
Illinois	11256	274	Wisconsin	2289	74	Rhode Island	922	25	Montana	298	6	Palau	0	0
Washington	7984	340	Arizona	2269	64	Iowa	868	22	South Dakota	240	2	Republic of Marshall Islands	0	0
Texas	7255	141	South Carolina	2049	44	Arkansas	853	16	North Dakota	207	3			
Georgia	6742	219	Alabama	1841	31	Kansas	813	23	Wyoming	200	0			
Connecticut	5675	189	Nevada	1836	46	Delaware	673	14	Alaska	185	6			



• With the exception of Palau; all States, territories, and the District of Columbia have declared States of Emergency

FEMA

Senior Leadership Brief COVID-19

April 6, 2020 12:00 p.m. ET

For the most up to date COVID-19 data: https://geohealth.hhs.gov/arcgis/home/

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

UNCLASSIFIED// FOR OFFICIAL USE ONLY

USG COVID-19 Response

USG Medical Resources and Force Laydown

Map produced by ASPR GIS
Data sources: CDC, DoD, HHS, FEMA, USACE

Map as of: 05Apr2020T2303

USG Total

Deployed Personnel: 16,492
- HHS Personnel: 527
- DoD Personnel: 15,965

Equipment / Supplies
- FMS 250 (31)
- FMS 50 (9)
- ASPR Rx (8)
- DoD Field Hospital (2)

ACS (41)
Total Beds: 19,494
- ASPR Beds: 7,950
- DoD Beds: 534
- USACE: 11,010

Ventilators (8,920)

USNS Medical Ship (2)

REGION X

Deployed Personnel: 1,204
- HHS Personnel: 219
- DoD Personnel: 985

Equipment / Supplies
- FMS 250 (1)
- FMS 50 (2)
- ASPR Rx (4)
- DoD Field Hospital (1)

ACS (2)
- Total Beds: 600
  - ASPR Beds: 350
  - DoD Beds: 250

Ventilators (700)

REGION IX

Deployed Personnel: 2,110
- HHS Personnel: 46
- DoD Personnel: 2,064

Equipment / Supplies
- FMS 250 (8)
- FMS 50 (5)

ACS (12)
- Total Beds: 2,250
  - ASPR Beds: 2,250

Ventilators (200)

USNS Mercy: 1,000 Beds

REGION VIII

Deployed Personnel: 8
- HHS Personnel: 8

REGION VI

Deployed Personnel: 853
- HHS Personnel: 4
- DoD Personnel: 849

Equipment / Supplies
- FMS 250 (3)
- FMS 50 (1)
- ASPR Rx (1)

ACS (4)
- Total Beds: 1,000
  - ASPR Beds: 800
  - USACE Beds: 200

Ventilators (350)

REGION V

Deployed Personnel: 1,507
- HHS Personnel: 68
- DoD Personnel: 1,439

Equipment / Supplies
- FMS 250 (4)

ACS (7)
- Total Beds: 5,650
  - ASPR Beds: 750
  - USACE Beds: 4,900

Ventilators (1,300)

REGION IV

Deployed Personnel: 1,787
- HHS Personnel: 25
- DoD Personnel: 1,762

Equipment / Supplies
- FMS 250 (1)

ACS (1)
- Total Beds: 250
  - ASPR Beds: 250

Ventilators (350)

REGION I

Deployed Personnel: 1,737
- DoD Personnel: 1,737

Equipment / Supplies
- FMS 250 (3)

ACS (1)
- ASPR Beds: 750

Ventilators (150)

REGION II

Deployed Personnel: 6,154
- HHS Personnel: 145
- DoD Personnel: 6,009

Equipment / Supplies
- FMS 250 (8)
- ASPR Rx (3)
- DoD Field Hospital (1)

ACS (11)
- Total Beds: 9,194
  - ASPR Beds: 2,000
  - DoD Beds: 284
  - USACE Beds: 5,910

Ventilators (5,750)

DoD Mortuary Affairs Team (1)

USNS Comfort: 1,000 Beds

REGION III

Deployed Personnel: 1,132
- HHS Personnel: 12
- DoD Personnel: 1,120

Equipment / Supplies
- FMS 250 (3)
- FMS 50 (1)

ACS (4)
- Total Beds: 800
  - ASPR Beds: 800

Ventilators (120)

HHS accepts donations of medicine to Strategic National Stockpile as possible treatments for COVID-19 patients

FDA issues emergency use authorization of both drugs

The U.S. Department of Health and Human Services (HHS) today accepted 30 million doses of hydroxychloroquine sulfate donated by Sandoz, the Novartis generics and biosimilars division, and X doses by Teva Pharmaceuticals, as well as three million doses of chloroquine phosphate donated by Bayer Pharmaceuticals for use in clinical trials and for possible treatment of patients hospitalized with COVID-19. The companies ramped up production to provide the medication.

Hydroxychloroquine sulfate and chloroquine phosphate are oral prescription drugs approved to treat malaria among other diseases. Although there are no currently approved treatments for COVID-19, both drugs have shown activity in laboratory studies against coronaviruses, including SARS-CoV-2 (the virus that causes COVID-19). Anecdotal reports or case series suggest that these drugs may offer some benefit in the treatment of COVID-19 patients.

"President Trump is taking every possible step to protect Americans from the coronavirus and provide them with hope," said HHS Secretary Alex Azar. "Scientists in America and around the world have identified a number of potential therapeutics for COVID-19, including chloroquine and hydroxychloroquine. The President's bold leadership and the hard work of FDA and HHS's Assistant Secretary for Preparedness and Response have succeeded in securing this large donation of potential treatments. We'll continue working around the clock to get American patients access to therapeutics that may help them battle COVID-19, while building more evidence around which options have proven effectiveness."

Commented [KE(1]: Recommended edit now that HHS is accepting donations of two drugs from two companies

HHS' Office of the Assistant Secretary for Preparedness and Response (ASPR) worked with the Department of State, the Department of Homeland Security, and the companies to receive the donated shipments.

The U.S. Food and Drug Administration (FDA) reviewed the donated products and then issued an Emergency Use Authorization (EUA) to allow the hydroxychloroquine sulfate and chloroquine phosphate products to be donated to the Strategic National Stockpile and distributed to states for doctors to provide patients hospitalized with COVID-19 when a clinical trial is not available or feasible.

The EUA includes a fact sheet that provides important information for health care providers and patients about using chloroquine phosphate and hydroxychloroquine sulfate in treating COVID-19.

The National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, and the Biomedical Advanced Research and Development Authority (BARDA), part of ASPR, will collaborate with a network of hospitals on clinical trials of the drugs.

Commented [KE(2]: BARDA, NIAID, please confirm whether this is the case.

In addition, the Strategic National Stockpile, managed by ASPR, will work with Federal Emergency Management Agency (FEMA) to ship donated doses to states. The SNS does not regularly stock either drug.

The FDA also is working with manufacturers of chloroquine and hydroxychloroquine to increase production to ensure these drugs also remain available for patients dependent on them for treatment of malaria, lupus and rheumatoid arthritis. Some states and retail pharmacies also have taken action to preserve the supply of these and other drugs.

HHS continues to work across the U.S. government, including with the Department of Defense, to review potential products from public and private sectors to identify promising candidates that could detect, protect against, or treat COVID-19 for development and use.

The FDA has the regulatory emergency use authority to facilitate access to unapproved medical countermeasures (MCMs) or unapproved uses of approved MCMs needed to prepare for and respond to chemical, biological, radiological and nuclear threats.

A product may be considered for an EUA if the FDA determines that, among other criteria, the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product, and there are no adequate, approved, available alternatives. Emergency access to a medical product under an EUA is separate from use of a medical product under an investigational drug application.

In addition to accepting and distributing the donated chloroquine, HHS is funding clinical trials of two drugs, Kevzara and remdesivir, and is supporting the development of multiple potential therapeutic treatments, vaccines, and diagnostic tests for COVID-19. In addition, the FDA has issued emergency use authorization for multiple diagnostics and personal protective equipment for the COVID-19 response. HHS continues to seek partners for COVID-19 medical countermeasures, and offers multiple ways to submit proposals for potential products or technologies.

Sandoz, Teva, and Bayer are the latest companies stepping up to strengthen the U.S. response to COVID-19. Companies interested in donating goods or services should contact fema-nrcc-iagsupv@fema.dhs.gov or visit https://www.fema.gov/coronavirus/how-to-help.

About HHS, ASPR, and FDA

HHS works to enhance and protect the health and well-being of all Americans, providing for effective health and human services and fostering advances in medicine, public health, and social services. The mission of ASPR is to save lives and protect Americans from 21st century health security threats, and within ASPR, the Strategic National Stockpile represents the nation's largest stockpile of life-saving pharmaceuticals and medical supplies for use in supplementing state and local supplies in a public health emergency. The FDA protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

###

Edits: MFelberbaum, OMA, 3/25/20

cleared by: R. Roberts, J. Farley, D. Ashley, J. Corrigan, P. Cavazzoni. 3/26/20

Edits: MFelberbaum, OMA, 3/25/20

EVERCORE ISI
Equity Research – Biotech, Pharma, Spec Pharma

Umer Raffat
umer.raffat@evercoreisi.com
W 212-888-3905 | C (b)(6)

COVID-19 DRUGS & VACCINES

NEW clinical efficacy data

Mar 2020

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Yesterday, we got clinical data from 2 clinical trials of antivirals for COVID-19

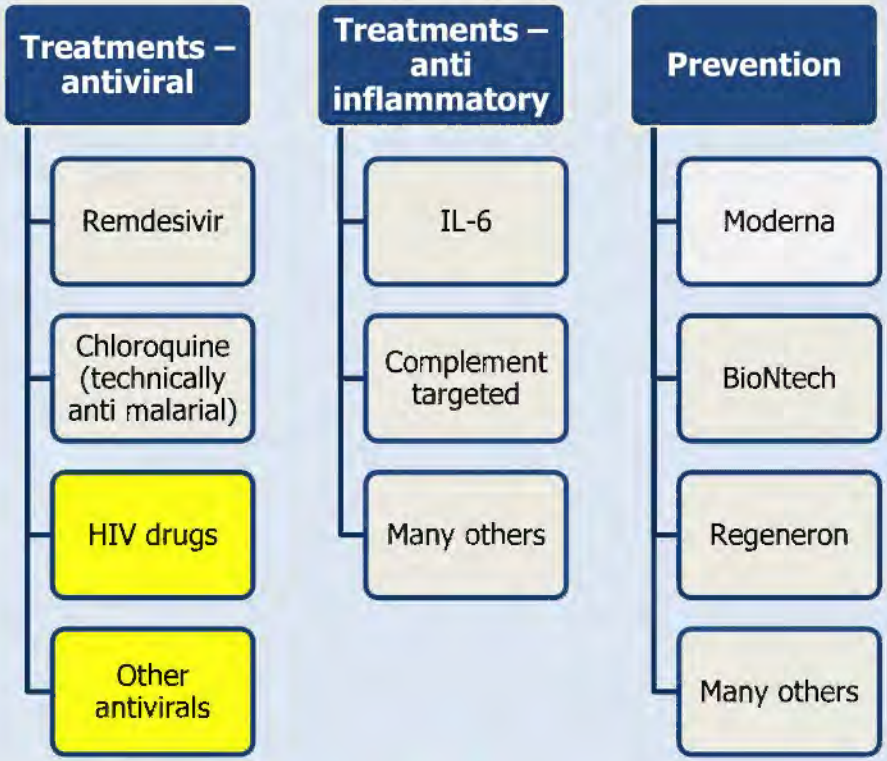
- Again, these are not random case reports
- These are proper trials
- Specifically, we data from 2 trials yesterday:

	LPV vs placebo	LPV vs favipravir
Type of drug	HIV med	HIV med vs antiviral
Total # patients in trial	199	80
Trial location	China	China
Outcome	Overall, LPV didn't work ... but in a subgroup it did	Favipravir looked better than LPV
Published where?	Top medical journal (New England Journal of Medicine)	Less known Chinese journal

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Since there are SO many COVID-19 treatments, let's make we group up the different drugs in 3 broad categories:



The trials that reported yesterday are in these yellow cells

****email me if you'd like to see our full compilation of all treatments/vaccines in development – our excel file has ~130 rows at this point!**

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Agenda

- First trial that read out yesterday: HIV med
- Second trial that read out yesterday: favipravir vs HIV med
- When is Gilead remdesivir data due? And what can we learn from yesterday's trials?
- When is first vaccine data due? (Moderna)
- Manufacturing capacity for Gilead and Moderna

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

The most highlighted clinical data yesterday had a bad headline:

The New York Times

A Promising Treatment for Coronavirus Fails

Researchers had hoped that antiviral drugs would help patients, but a new study from China said that one antiviral drug combination didn't work.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

CONCLUSIONS

In hospitalized adult patients with severe Covid-19, no benefit was observed with l navir–ritonavir treatment beyond standard care. Future trials in patients with se illness may help to confirm or exclude the possibility of a treatment benefit. (Fun by Major Projects of National Science and Technology on New Drug Creation Development and others; Chinese Clinical Trial Register number, ChiCTR20000293

Sources: Company statements, Conference Presentations, FDA, Publicly Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Hang on – was the HIV med (LPV) truly a failure for COVID-19???

Table S1. Outcomes in the modified intention-to-treat population.

Characteristics	Total (N = 196)	Lopinavir/ritonavir (N = 96)*	Standard Care (N = 100)	Difference†
TTCI	16.0 (15.0, 17.0)	15.0 (13.0, 17.0)	16.0 (15.0, 18.0)	1.39 (1.00,1.91)†
Day 28 mortality	41 (20.9)	16 (16.7)	25 (25.0)	-8.3 (-19.6, 3.0)
Early (≤12 days of symptom onset)	19 (21.6)	6 (15.0)	13 (27.1)	-12.0 (-28.8, 4.7)
Late (> 12 days of symptom onset)	22 (20.4)	10 (17.9)	12 (23.1)	-5.2 (-20.4, 10.0)

- In patients that took LPV relatively early, there was a survival trend: **28-day mortality = 15% on LPV vs 27% on placebo**
- I really wonder what the efficacy looked like in the data cut for patients who initiated <9 days from symptom onset

In antiviral setting, it is NOT about the overall trial result … all that matters is being able to identify the time point post-infection until which you can initiate an antiviral and expect efficacy

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

… and the paper also said this: (about patients who started early)

mentary Appendix). In the intention-to-treat population, lopinavir–ritonavir treatment within 12 days after the onset of symptoms was associated with shorter time to clinical improvement (hazard ratio, 1.25; 95% CI, 1.77 to 2.05), but later treatment with lopinavir–ritonavir was not (hazard ratio, 1.30; 95% CI, 0.84 to 1.99) (Fig. S2A and S2B). No significant differences were observed

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

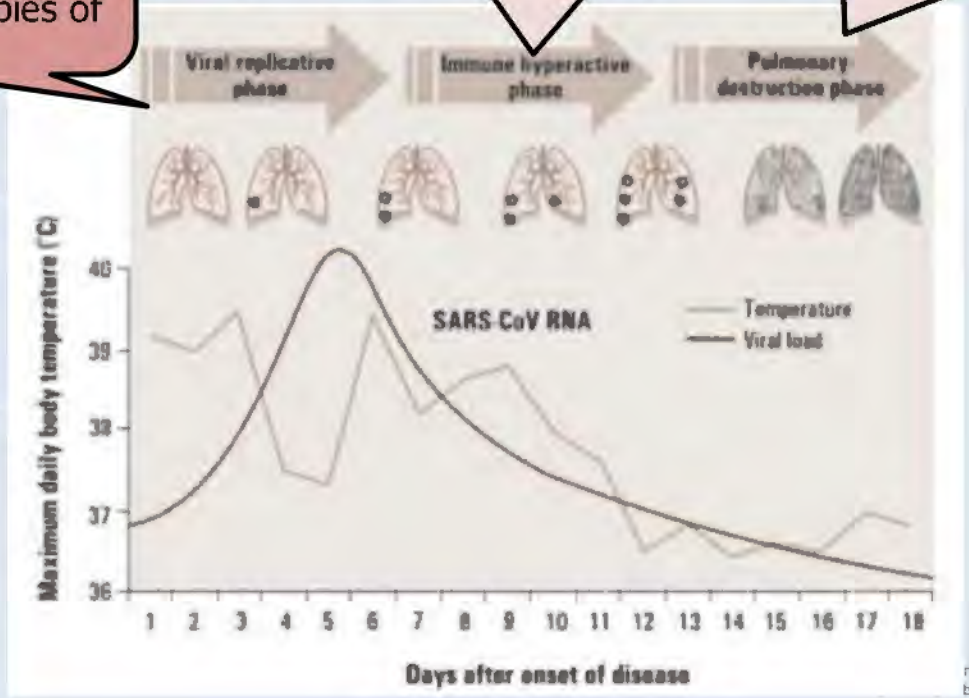
The reason I am focused on patients who started early is because an antiviral needs to be taken in Stage 1: viral replication phase

Stage 1: virus infects human, and takes over human machinery to start making countless copies of itself

Stage 2: in response to the countless virus floating around the body, immune system kicks in

Stage 3: if the infected human is generally healthy, immune response will overcome the virus … if human has weak immune system, virus can overwhelm

Antiviral needs to be given in this phase … this is CRITICAL to success in these trials



nference Presentations, FDA, Youtube, bmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Have you ever taken Tamiflu for flu?
It's a great case study … efficacy looks best when taken as early as possible

Treatment
Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

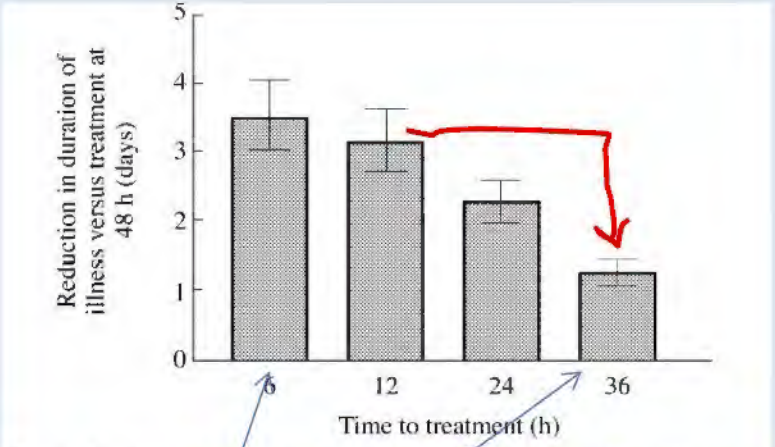


Figure 2. The reduction in days of illness duration with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population). The data are median and 95% CI.

- Notice Tamiflu's **impact on reduction in disease duration is highest when taken within 6-12 hours from symptoms**
- Data above is from a study in ambulatory adults

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Agenda

- First trial that read out yesterday: HIV med
- Second trial that read out yesterday: favipravir vs HIV med
- When is Gilead remdesivir data due? And what can we learn from yesterday's trials?
- When is first vaccine data due? (Moderna)
- Manufacturing capacity for Gilead and Moderna

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Next, there was a second trial reported yesterday … and favipravir beat LPV

Article

Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study

Qingxian Cai, Minghui Yang, Dongjing Liu, Jun Chen, Dan Shu, Junxia Xia, Xuejiao Liao, Yuanbo Gu, Qiue Cai, Yang Yang, Chenguang Shen, Xiaohe Li, Ling Peng, Deliang Huang, Jing Zhang, Shurong Zhang, Fuxiang Wang, Jiaye Liu, Li Chen, Shuyan Chen, Zhaoqin Wang, Zheng Zhang, Ruiyuan Cao, Wu Zhong, Yingxia Liu, Lei Liu

the two groups. For the 35 patients enrolled in the FPV arm and the 45 patients in the control arm, all baseline characteristics were comparable between the two arms. A shorter viral clearance time was found for the FPV arm versus the control arm (median (interquartile range, IQR), 4 (2.5–9) d versus 11 (8–13) d, $P < 0.001$). The FPV arm also showed significant improvement in chest imaging compared with the control arm, with an improvement rate of 91.43% versus 62.22% ($P = 0.004$). After adjustment for potential confounders, the FPV arm also showed a significantly higher improvement rate in chest imaging. Multivariable Cox regression showed that FPV was independently associated with faster viral clearance. In addition, fewer adverse reactions were found in the FPV arm than in the control arm. In this open-label nonrandomized control study, FPV showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance; if causal, these results should be important information for establishing standard treatment guidelines to combat the SARS-CoV-2 infection.

Key issue with this trial: it was not randomized …

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Favipravir had better time to viral clearance:

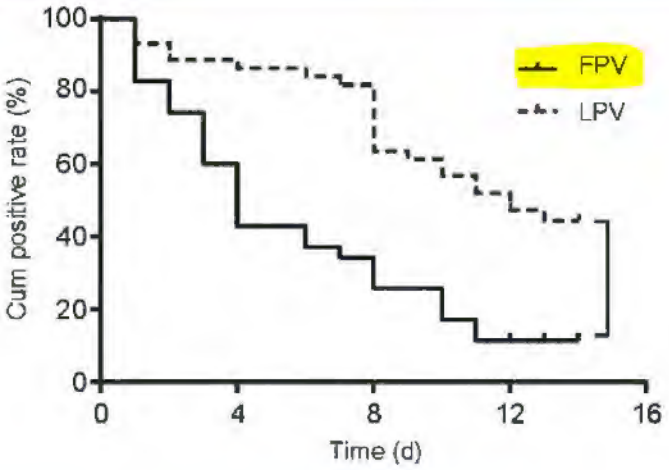
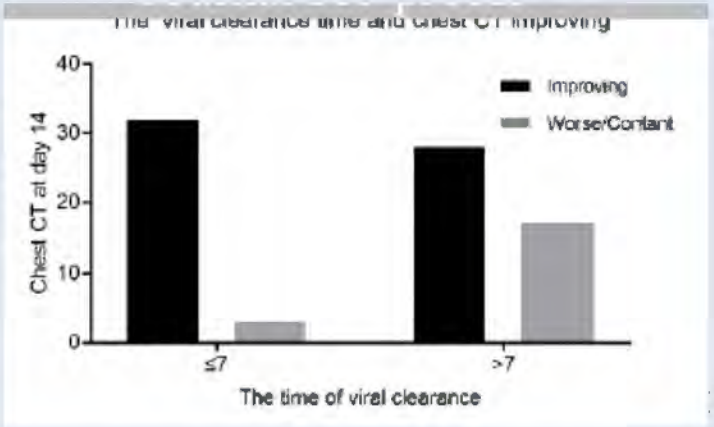


Fig 3. Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy ($P < 0.001$).

And faster viral clearance correlated with better chest CT scan >>



Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

… and favipravir also improved chest CT scans more than LPV:

Table 2
Chest CT changes in patients with COVID-19 after treatment.

Chest CT changes	COVID-19 patients ($N = 80$)		
	FPV ($N = 35$)	LPV/RTV ($N = 45$)	P value
Day 4 after treatment			
Improve	8 (22.86%)	8 (17.78%)	
Worse	9 (25.71%)	15 (33.33%)	
Constant	18 (51.43%)	22 (48.89%)	0.42
Day 9 after treatment[a]			
Improve	18 (56.25%)	16 (35.55%)	
Worse	8 (25.00%)	16 (35.55%)	
Constant	6 (18.75%)	13 (28.90%)	0.11
Day 14 after treatment			
Improve	32 (91.43%)	28 (62.22%)	
Worse	1 (3.23%)	9 (20.00%)	
Constant	2 (6.45%)	8 (17.78%)	0.004

[a] For three patients in the FPV arm, the lung CT scan on Days 6–9 after medication was not carried out.

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, Facebook, Court documents

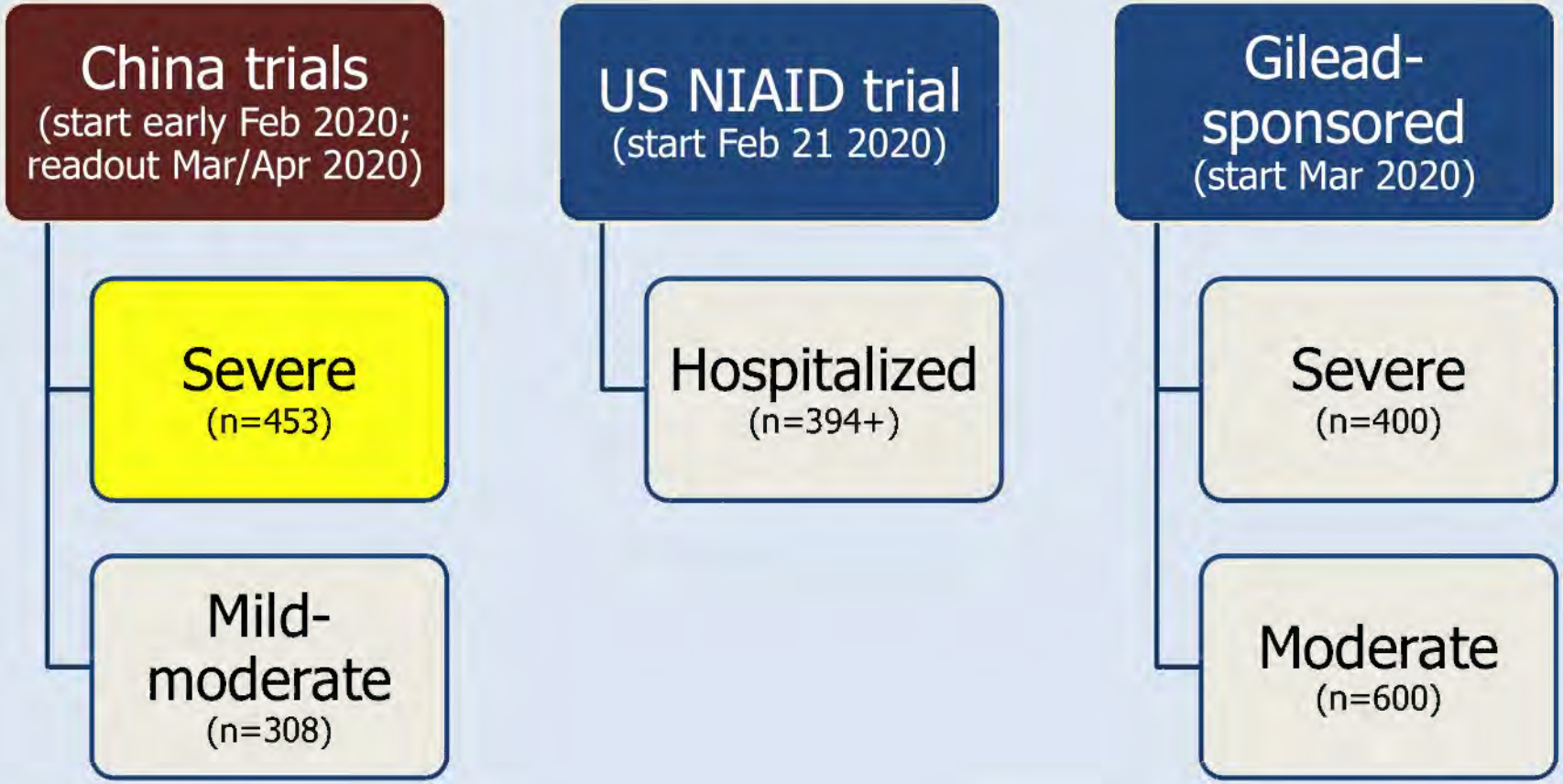
Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Agenda

- First trial that read out yesterday: HIV med
- Second trial that read out yesterday: favipravir vs HIV med
- When is Gilead remdesivir data due? And what can we learn from yesterday's trials?
- When is first vaccine data due? (Moderna)
- Manufacturing capacity for Gilead and Moderna

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Next key data readout (coming shortly) is the highly anticipated severe trial of Gilead's remdesivir for COVID-19:



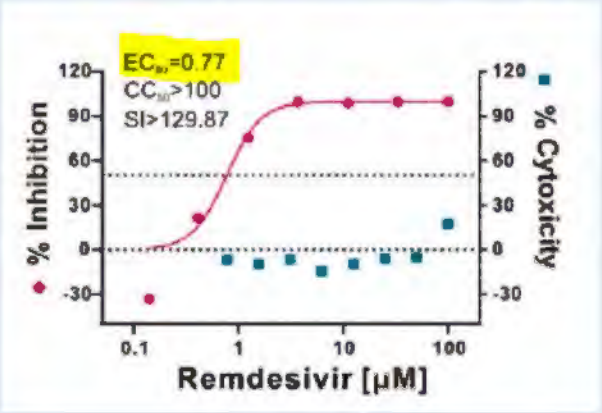
Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

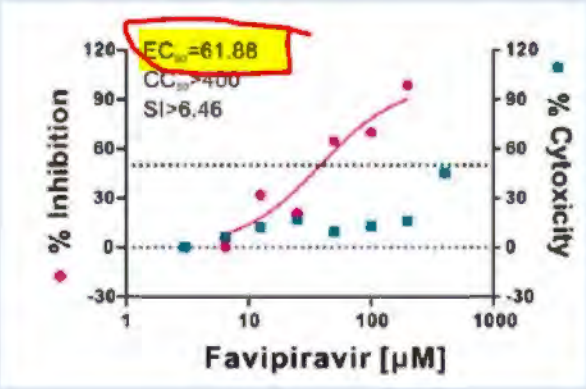
Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Remdesivir is FAR more potent than LPV and favipravir

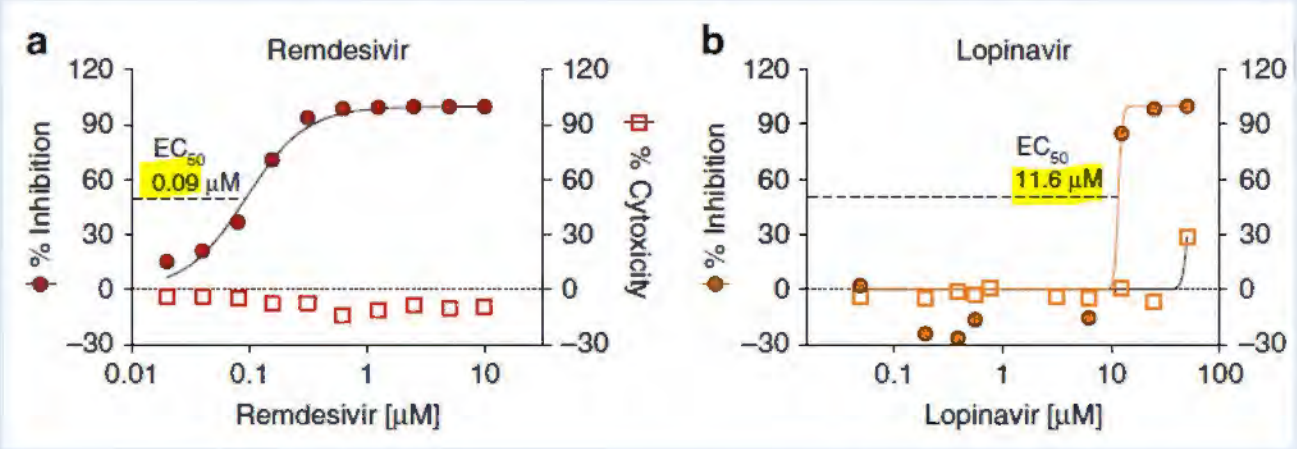
(the lower the EC50, the stronger the antiviral effect)

- In COVID-19 model:





- In a coronavirus MERS model:



Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, Facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

But let's keep some caveats in mind when reading across from the new clinical trials over to remdesivir

- Favipravir trial capped enrollment at <7 days from disease onset. This is KEY for any antiviral. Recall remdesivir severe trial is letting patients up to 12 days from symptom onset

- Favipravir trial did NOT allow pts with oxygen saturation <93%. That is exactly the type of patients which are in the "severe" trial for remdesivir (<94% oxygen saturation).

- Finally, favipravir trial allowed aerosolized IFN. We don't know for sure if EVERY patient in remdesivir trial will also get that.

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, Facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Agenda

- First trial that read out yesterday: HIV med
- Second trial that read out yesterday: favipravir vs HIV med
- When is Gilead remdesivir data due? And what can we learn from yesterday's trials?
- When is first vaccine data due? (Moderna)
- Manufacturing capacity for Gilead and Moderna

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

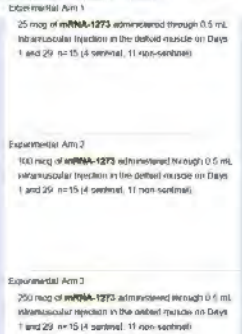
One last thing, on vaccine front, I expect a date update as early as May timeframe:

Moderna may disclose early immune response

- First 4 patients got low dose already … and there may be some early immunogenicity data by May in my opinion

Study Design

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	45 participants
Allocation:	Non-Randomized
Intervention Model:	Sequential Assignment
Masking:	None (Open Label)
Primary Purpose:	Prevention
Official Title:	Phase I, Open-Label, Dose-Ra 2019-nCoV Vaccine (**mRNA-1**
Actual Study Start Date :	March 3, 2020
Estimated Primary Completion Date :	June 1, 2021
Estimated Study Completion Date :	June 1, 2021



Primary Outcome Measures :

1. Frequency of solicited local reactogenicity adverse events (AEs) [Time Frame: Through 7 days post-vaccination]
2. Frequency of any medically-attended adverse events (MAAEs) [Time Frame: Day 1 to Day 394]
3. Frequency of any new-onset chronic medical conditions (NOCMCs) [Time Frame: Day 1 to Day 394]
4. Frequency of any serious adverse events (SAEs) [Time Frame: Day 1 to Day 394]
5. Frequency of any unsolicited adverse events (AEs) [Time Frame: Through 28 days post-vaccination]
6. Frequency of solicited systemic reactogenicity adverse events (AEs) [Time Frame: Through 7 days post-vaccination]
7. Grade of any unsolicited adverse events (AEs) [Time Frame: Through 28 days post-vaccination]
8. Grade of solicited local reactogenicity adverse events (AEs) [Time Frame: Through 7 days post-vaccination]
9. Grade of solicited systemic reactogenicity adverse events (AEs) [Time Frame: Through 7 days post-vaccination]

Secondary Outcome Measures :

1. Geometric mean fold rise (GMFR) in IgG titer from baseline [Time Frame: Day 1 to Day 57]
2. Geometric mean titer (GMT) of antibody [Time Frame: Day 57]
3. Percentage of subjects who seroconverted [Time Frame: Day 1 to Day 57]

   Seroconversion is defined as a 4-fold change in antibody titer from baseline

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Agenda

- First trial that read out yesterday: HIV med
- Second trial that read out yesterday: favipravir vs HIV med
- When is Gilead remdesivir data due? And what can we learn from yesterday's trials?
- When is first vaccine data due? (Moderna)
- Manufacturing capacity for Gilead and Moderna

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Gilead's most recent comment on manufacturing capacity suggest they should have reasonable capacity shortly:

- My question to Gilead: **Do you believe Gilead can supply something in the range of 500,000 patients worth of remdesivir if that's needed by the summer or fall?**

Daniel O'Day
Chairman & Chief Executive Officer, Gilead Sciences, Inc.

A

Yeah, Umer, Thank you. Thanks a lot, Merdad, for that. Umer, I just would emphasize what Merdad said on remdesivir. I think there are a variety of different scenarios depending on moderate, severe, depending on the clinical data. So, what we're doing is we're creating as much optionality in our supply chain as we can. And those trigger points will allow us to determine the demand. Right now, the demand is really unknown as are many things about coronavirus. But rest assured that we're doing everything possible not only with our own supply chain, but within our partners' supply chain around the globe to ramp up when we get to those trigger points. So, more soon on that and it will be driven by clinical data need. But we have teams of people that are preparing for this should we be able to contribute to the human need.

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Meanwhile, keep in mind Chinese mftr's also attempting to make remdesivir on their own (but their capacity disclosures have been misleading)

- 3 Chinese companies claim to have mft capacity for Remdesivir API, needing GILD authorization to mft – BUT **NOT COMMERCIAL SUPPLY CAPACITY**; ALL received Criticism Notice for misleading/unclear/incomplete statement
  - Borui: on 2/11, claimed can produce API, testing formulation; BUT on 3/1, got Shanghai Exchange criticism notice for unclear statement, have not shown capacity for commercial supply
  - Hainan Haiyao: by 2/15, claim to have mft 1st mid-size batch, 3.5M dose/y capacity (50, 100 mL), API purity >99%; but got Shenzhen Exchange criticism notice for misleading statement
  - Keben Pharma (Wuchan Zhongda): by 2/6, start a program to mft 10M dose/y within 2 years; but got Shanghai Exchange criticism notice for incomplete info disclosure

- Qilu, k

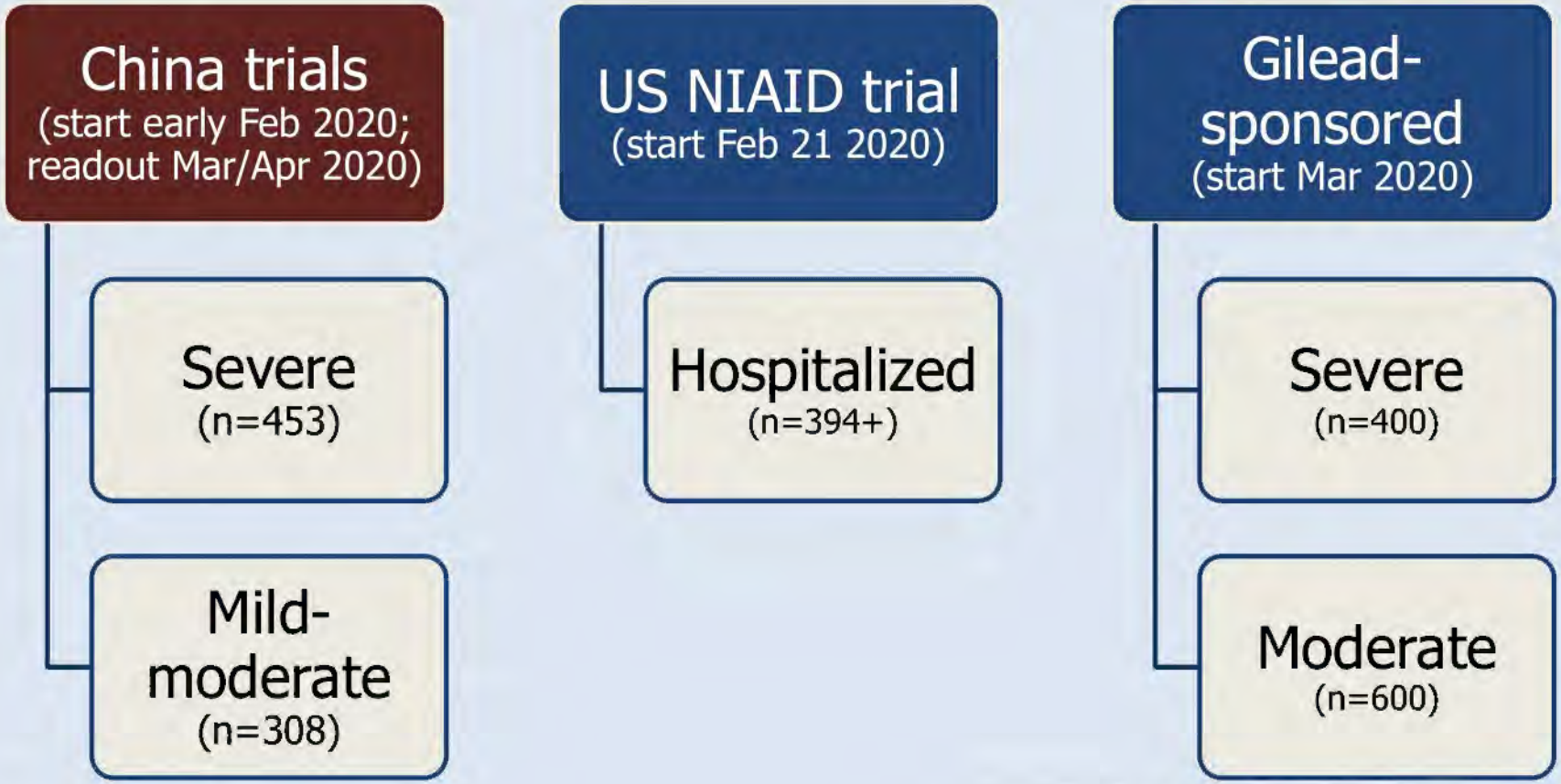
证券代码	证券简称	监管类型	处理事由	涉及对象	处理日期
688166	博瑞生药	通报批评	关于对博瑞生物医药（苏州）股份有限公司时任董事会秘书王应鹏予以通报批评的决定	董秘	2020-03-01
688166	博瑞生药	监管关注	关于对博瑞生物医药（苏州）股份有限公司予以监管关注的决定	上市公司	2020-03-01
600704	物产中大	通报批评	关于对物产中大集团股份有限公司及时任董事会秘书张浩予以通报批评的决定	上市公司 董秘	2020-03-01

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

https://www.hotbak.net/key/%E7%91%9E%E5%BE%B7%E8%A5%BF%E9%9F%A6%E6%9C%89%E4%BA%94%E5%AE%B6%E5%85%AC%E5%8F%B8%E7%

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Ultimately, don't forget Gilead barely took ~4-6 weeks to make drug available for ~1600 active arm patients across these trials already



Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

Moderna's vaccine manufacturing capacity:
Is it 10M or 100M doses?
(to be clear, each patient may need 2-3 doses)

CMV vials already produced for phase 2 trial

- Same lyophilized image intended for phase 3
- Norwood site can produce mRNA and LNP for phase 3
- Norwood site can support commercial launch (FFF to be done at CMO)
- Potential for >10+ million doses/year from Norwood

Slide 47

moderna

Feedback on call: could make 10M doses during this summer (again, during entire summer)

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, Facebook, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

TIMESTAMP

(Article 3(1)e and Article 7 of MAR)

Time of dissemination: March 19 2020 09:33 AM ET

ANALYST CERTIFICATION

The analysts, Umer Raffat, primarily responsible for the preparation of this research report attest to the following: (1) that the views and opinions rendered in this research report reflect his or her personal views about the subject companies or issuers; and (2) that no part of the research analyst's compensation was, is, or will be directly related to the specific recommendations or views in this research report.

DISCLOSURES

This report is approved and/or distributed by Evercore Group L.L.C. ("Evercore Group"), a U.S. licensed broker-dealer regulated by the Financial Industry Regulatory Authority ("FINRA"), and Evercore ISI International Limited ("ISI UK"), which is authorised and regulated in the United Kingdom by the Financial Conduct Authority. The institutional sales, trading and research businesses of Evercore Group and ISI UK collectively operate under the global marketing brand name Evercore ISI ("Evercore ISI"). Both Evercore Group and ISI UK are subsidiaries of Evercore Inc. ("Evercore"). The trademarks, logos and service marks shown on this report are registered trademarks of Evercore.

The analysts and associates responsible for preparing this report receive compensation based on various factors, including Evercore's Partners' total revenues, a portion of which is generated by affiliated investment banking transactions. Evercore ISI seeks to update its research as appropriate, but various regulations may prevent this from happening in certain instances. Aside from certain industry reports published on a periodic basis, the large majority of reports are published at irregular intervals as appropriate in the analyst's judgment.

Evercore ISI generally prohibits analysts, associates and members of their households from maintaining a financial interest in the securities of any company in the analyst's area of coverage. Any exception to this policy requires specific approval by a member of our Compliance Department. Such ownership is subject to compliance with applicable regulations and disclosure. Evercore ISI also prohibits analysts, associates and members of their households from serving as an officer, director, advisory board member or employee of any company that the analyst covers.

This report may include a Tactical Call, which describes a near-term event or catalyst affecting the subject company or the market overall and which is expected to have a short-term price impact on the equity shares of the subject company. This Tactical Call is separate from the analyst's long-term recommendation (Outperform, In Line or Underperform) that reflects a stock's forward 12-month expected return, is not a formal rating and may differ from the target prices and recommendations reflected in the analyst's long-term view.

Applicable current disclosures regarding the subject companies covered in this report are available at the offices of Evercore ISI, and can be obtained by writing to Evercore Group L.L.C., Attn. Compliance, 666 Fifth Avenue, 11th Floor, New York, NY 10103.

Evercore and its affiliates, and / or their respective directors, officers, members and employees, may have, or have had, interests or qualified holdings on issuers mentioned in this report. Evercore and its affiliates may have, or have had, business relationships with the companies mentioned in this report.

Additional information on securities or financial instruments mentioned in this report is available upon request.

Ratings Definitions

Current Ratings Definition

Evercore ISI's recommendations are based on a stock's total forecasted return over the next 12 months. Total forecasted return is equal to the expected percentage price return plus gross dividend yield. We divide our stocks under coverage into three primary ratings categories, with the following return guidelines:

Outperform- the total forecasted return is expected to be greater than the expected total return of the analyst's coverage universe
In Line- the total forecasted return is expected to be in line with the expected total return of the analyst's universe
Underperform- the total forecasted return is expected to be less than the expected total return of the analyst's universe
Coverage Suspended- the rating and target price have been removed pursuant to Evercore ISI policy when Evercore is acting in an advisory capacity in a merger or strategic transaction involving this company and in certain other circumstances.*
Rating Suspended- Evercore ISI has suspended the rating and target price for this stock because there is not sufficient fundamental basis for determining, or there are legal, regulatory or policy constraints around publishing, a rating or target price. The previous rating and target price, if any, are no longer in effect for this company and should not be relied upon.*

*Prior to October 10, 2015, the "Coverage Suspended" and "Rating Suspended" categories were included in the category "Suspended."

FINRA requires that members who use a ratings system with terms other than "Buy," "Hold/Neutral" and "Sell" to equate their own ratings to these categories. For this purpose, and in the Evercore ISI ratings distribution below, our Outperform, In Line, and Underperform ratings can be equated to Buy, Hold and Sell, respectively.

Historical Ratings Definitions

Prior to March 2, 2017, Evercore ISI's recommendations were based on a stock's total forecasted return over the next 12 months:

Buy- the total forecasted return is expected to be greater than 10%
Hold- the total forecasted return is expected to be greater than or equal to 0% and less than or equal to 10%
Sell -the total forecasted return is expected to be less than 0%

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

On October 31, 2014, Evercore acquired International Strategy & Investment Group LLC ("ISI Group") and ISI UK (the "Acquisition") and transferred Evercore Group's research, sales and trading businesses to ISI Group. On December 31, 2015, the combined research, sales and trading businesses were transferred back to Evercore Group in an internal reorganization. Since the Acquisition, the combined research, sales and trading businesses have operated under the global marketing brand name Evercore ISI.

ISI Group and ISI UK:

Prior to October 10, 2014, the ratings system of ISI Group and ISI UK which was based on a 12-month risk adjusted total return:

Strong Buy- Return > 20%
Buy- Return 10% to 20%
Neutral - Return 0% to 10%
Cautious- Return -10% to 0%
Sell- Return< -10%

For disclosure purposes, ISI Group and ISI UK ratings were viewed as follows: Strong Buy and Buy equate to Buy, Neutral equates to Hold, and Cautious and Sell equate to Sell.

Evercore Group:

Prior to October 10, 2014, the rating system of Evercore Group was based on a stock's expected total return relative to the analyst's coverage universe over the following 12 months. Stocks under coverage were divided into three categories:

Overweight- the stock is expected to outperform the average total return of the analyst's coverage universe over the next 12 months.
Equal-Weight- the stock is expected to perform in line with the average total return of the analyst's coverage universe over the next 12 months.
Underweight -the stock is expected to underperform the average total return of the analyst's coverage universe over the next 12 months.
Suspended- the company rating, target price and earnings estimates have been temporarily suspended.

For disclosure purposes, Evercore Group's prior "Overweight," "Equal-Weight" and "Underweight" ratings were viewed as "Buy," "Hold" and "Sell," respectively.

Ratings Definitions for Portfolio-Based Coverage

Evercore ISI utilizes an alternate rating system for companies covered by analysts who use a model portfolio-based approach to determine a company's investment recommendation. Covered companies are included or not included as holdings in the analyst's Model Portfolio, and have the following ratings:

Long- the stock is a positive holding in the model portfolio; the total forecasted return is expected to be greater than 0%.
Short- the stock is a negative holding in the model portfolio; the total forecasted return is expected to be less than 0%.
No Position- the stock is not included in the model portfolio.
Coverage Suspended- the rating and target price have been removed pursuant to Evercore ISI policy when Evercore is acting in an advisory capacity in a merger or strategic transaction involving this company, and in certain other circumstances; a stock in the model portfolio is removed.
Rating Suspended - Evercore ISI has suspended the rating and/or target price for this stock because there is not sufficient fundamental basis for determining, or there are legal, regulatory or policy constraints around publishing, a rating or target price. The previous rating and target price, if any, are no longer in effect for this company and should not be relied upon; a stock in the model portfolio is removed.

Stocks included in the model portfolio will be weighted from 0 to 100% for Long and 0 to -100% for Short. A stock's weight in the portfolio reflects the analyst's degree of conviction in the stock's rating relative to other stocks in the portfolio. The model portfolio may also include a cash component. At any given time the aggregate weight of the stocks included in the portfolio and the cash component must equal 100%.

Stocks assigned ratings under the alternative model portfolio-based coverage system cannot also be rated by Evercore ISI's Current Ratings definitions of Outperform, In Line and Underperform.

FINRA requires that members who use a ratings system with terms other than "Buy," "Hold/Neutral" and "Sell," to equate their own ratings to these categories. For this purpose, and in the Evercore ISI ratings distribution below, our Long, No Position and Short ratings can be equated to Buy, Hold and Sell respectively.

Evercore ISI rating (as of 03/19/2020)

Coverage Universe			Investment Banking Services I Past 12 Months		
Ratings	Count	Pct.	Ratings	Count	Pct.
Buy	381	50	Buy	93	24
Hold	296	38	Hold	44	15
Sell	55	7	Sell	7	13
Coverage Suspended	24	3	Coverage Suspended	8	33
Rating Suspended	13	2	Rating Suspended	2	15

Issuer-Specific Disclosures (as of March 19, 2020)

Price Charts

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C (b)(6)

GENERAL DISCLOSURES

This report is approved and/or distributed by Evercore Group L.L.C. ("Evercore Group"), a U.S. licensed broker-dealer regulated by the Financial Industry Regulatory Authority ("FINRA") and by International Strategy & Investment Group (UK) Limited ("ISI UK"), which is authorised and regulated in the United Kingdom by the Financial Conduct Authority. The institutional sales, trading and research businesses of Evercore Group and ISI UK collectively operate under the global marketing brand name Evercore ISI ("Evercore ISI"). Both Evercore Group and ISI UK are subsidiaries of Evercore Inc. ("Evercore"). The trademarks, logos and service marks shown on this report are registered trademarks of Evercore Inc.

This report is provided for informational purposes only. It is not to be construed as an offer to buy or sell or a solicitation of an offer to buy or sell any financial instruments or to participate in any particular trading strategy in any jurisdiction. The information and opinions in this report were prepared by employees of affiliates of Evercore. The information herein is believed by Evercore ISI to be reliable and has been obtained from public sources believed to be reliable, but Evercore ISI makes no representation as to the accuracy or completeness of such information. Opinions, estimates and projections in this report constitute the current judgment of the author as of the date of this report. They do not necessarily reflect the opinions of Evercore or its affiliates and are subject to change without notice. In addition, opinions, estimates and projections in this report may differ from or be contrary to those expressed by other business areas or groups of Evercore and its affiliates. Evercore ISI has no obligation to update, modify or amend this report or to otherwise notify a reader thereof in the event that any matter stated herein, or any opinion, projection, forecast or estimate set forth herein, changes or subsequently becomes inaccurate. Facts and views in Evercore ISI research reports and notes have not been reviewed by, and may not reflect information known to, professionals in other Evercore affiliates or business areas, including investment banking personnel.

Evercore ISI does not provide individually tailored investment advice in research reports. This report has been prepared without regard to the particular investments and circumstances of the recipient. The financial instruments discussed in this report may not suitable for all investors and investors must make their own investment decisions using their own independent advisors as they believe necessary and based upon their specific financial situations and investment objectives. Securities and other financial instruments discussed in this report, or recommended or offered by Evercore ISI, are not insured by the Federal Deposit Insurance Corporation and are not deposits of or other obligations of any insured depository institution. If a financial instrument is denominated in a currency other than an investor's currency, a change in exchange rates may adversely affect the price or value of, or the income derived from the financial instrument, and such investor effectively assumes such currency risk. In addition, income from an investment may fluctuate and the price or value of financial instruments described in this report, either directly or indirectly, may rise or fall. Estimates of future performance are based on assumptions that may not be realized. Furthermore, past performance is not necessarily indicative of future performance.

Evercore ISI salespeople, traders and other professionals may provide oral or written market commentary or trading strategies to our clients that reflect opinions that are contrary to the opinions expressed in this research. Our asset management affiliates and investing businesses may make investment decisions that are inconsistent with the recommendations or views expressed in this research.

Electronic research is simultaneously available to all clients. This report is provided to Evercore ISI clients and may not be redistributed, retransmitted or disclosed, in whole or in part, or in any form or manner, without the express written consent of Evercore ISI. Receipt and review of this research report constitutes your agreement not to redistribute, retransmit, or disclose to others the contents, opinions, conclusion or information contained in this report (including any investment recommendations, estimates or target prices) without first obtaining express permission from Evercore ISI.

This report is not intended for distribution to, or use by any person or entity in any jurisdiction or country where such distribution or use would be contrary to local law or regulation.

For investors in the UK: In making this report available, Evercore makes no recommendation to buy, sell or otherwise deal in any securities or investments whatsoever and you should neither rely or act upon, directly or indirectly, any of the information contained in this report in respect of any such investment activity. This report is being directed at or distributed to, (a) persons who fall within the definition of Investment Professionals (set out in Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the "Order")); (b) persons falling within the definition of high net worth companies, unincorporated associations, etc. (set out in Article 49(2) of the Order); (c) other persons to whom it may otherwise lawfully be communicated (all such persons together being referred to as "relevant persons"). This report must not be acted on or relied on by persons who are not relevant persons.

Applicable current disclosures regarding the subject companies covered in this report are available at the offices of Evercore ISI, and can be obtained by writing to Evercore Group L.L.C., Attn. Compliance, 666 Fifth Avenue, 11th Floor, New York, NY 10103.

In compliance with the European Securities and Markets Authority's Market Abuse Regulation, a list of all Evercore ISI recommendations disseminated in the preceding 12 months for the subject companies herein, may be found at the following site: https://evercoreisi.mediasterling.com/disclosure.

Sources: Company documents, Conference Presentations, FDA, Youtube, Evercore ISI Estimates, Twitter, Pubmed, facebook, Court documents

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: MSF: MSF response on COVID-19 drugs pricing study by Andrew Hill et al.
Date: 2020/04/10 14:48:33
Priority: Normal
Type: Note

10 April 2020

MSF response on COVID-19 drugs pricing study by Andrew Hill et al.

COVID-19

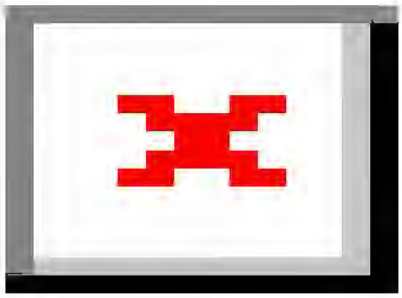
"Literally every single person on earth is susceptible to this pandemic—now is not the time for price gouging and pandemic profiteering."

Thumbnail

Jessica Burry
Pharmacist
MSF Access Campaign

Geneva, 10 April 2020 – Andrew Hill et al. published a study today on 'Minimum costs to manufacture new treatments for COVID-19' in the Journal of Virus Eradication. The study analyses the cost of production of several promising drugs (remdesivir, favipiravir, hydroxychloroquine, chloroquine, tocilizumab, azithromycin, lopinavir/ritonavir, sofosbuvir/daclatasvir, and pirfenidone) that are currently in clinical trials globally with results expected to be available from May 2020 onwards. The study shows that a full treatment course for COVID-19 (ranging between 10 and 28 days) could be priced between US$0.30 and $31. Most of the drugs being trialed for COVID-19 are repurposed drugs (existing drugs being investigated for new medical indications) and off-patent, yet several of them are currently priced far higher than this study shows their price could be.

Médecins Sans Frontières/Doctors Without Borders (MSF) welcomes this important pricing study highlighting that potential medicines for the treatment of COVID-19 could be made available to all at affordable prices during this pandemic.

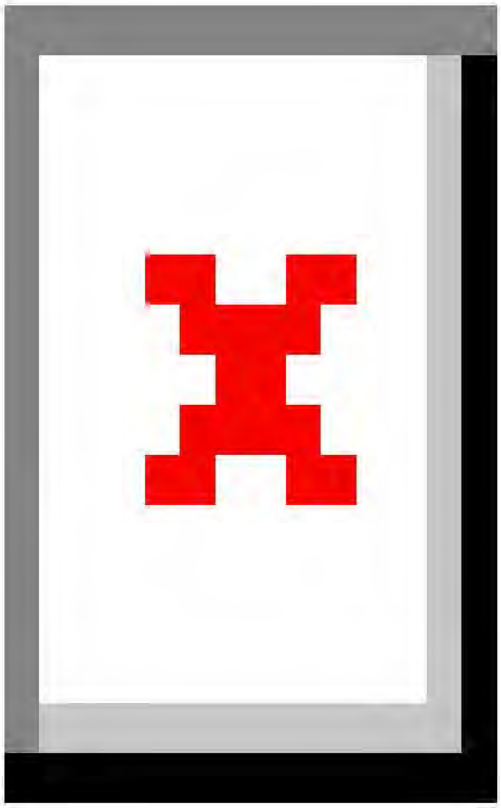


Andrew Hill et al. study on the cost of production of potential treatments

Minimum costs to manufacture new treatments for COVID-19

Jessica Burry, Pharmacist, MSF Access Campaign

"This pricing study shows clearly that potential **medicines to treat COVID-19 are not at all expensive to produce** and could be priced such that anyone who needs treatment should be able to access it. **Several of the treatments being trialed for COVID-19 are currently priced much higher than these estimates show they should be.** Literally every single person on earth is susceptible to this pandemic—now is not the time for price gouging and pandemic profiteering. Patents and monopolies will only result in limited supply and unnecessarily high prices. Rationing drugs because of high prices and limited supply will only serve to prolong the pandemic. What good is a lifesaving drug if you can't afford it?"



Open letter: Civil society urges Gilead to take immediate action to ensure access to potential COVID-19 treatment

Letter |

30 March 2020

COVID-19

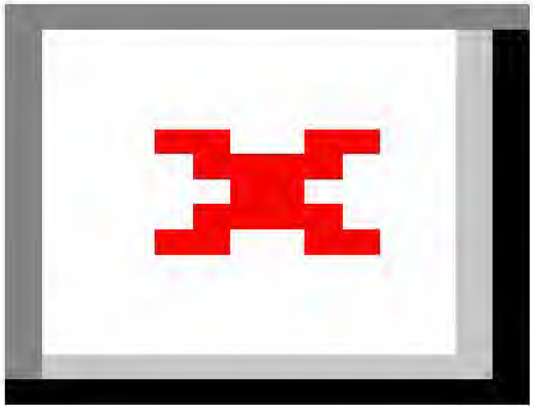
Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/10 14:48:01
Delivered Date:	2020/04/10 14:48:33
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: NYT: Coronavirus Ravages 7 Members of a Single Family, Killing 3
Date: 2020/03/18 23:16:52
Priority: Normal
Type: Note

Coronavirus Ravages 7 Members of a Single Family, Killing 3

The matriarch of the large New Jersey family died Wednesday night without ever knowing that her two oldest children had died before her.



Grace Fusco, center, and her 11 children in a family photo.
By Tracey Tully

- • March 18, 2020Updated 10:58 p.m. ET

• • Grace Fusco — mother of 11, grandmother of 27 — would sit in the same pew at church each Sunday, surrounded by nearly a dozen members of her sprawling Italian-American family. Sunday dinners drew an even larger crowd to her home in central New Jersey.

Now, her close-knit clan is united anew by unspeakable grief: Mrs. Fusco, 73, died on Wednesday night after contracting the coronavirus — hours after her son died from the virus and five days after her daughter's death, a relative said.

Four other children who contracted coronavirus remain hospitalized, three of them in critical condition, the relative, Roseann Paradiso Fodera, said.

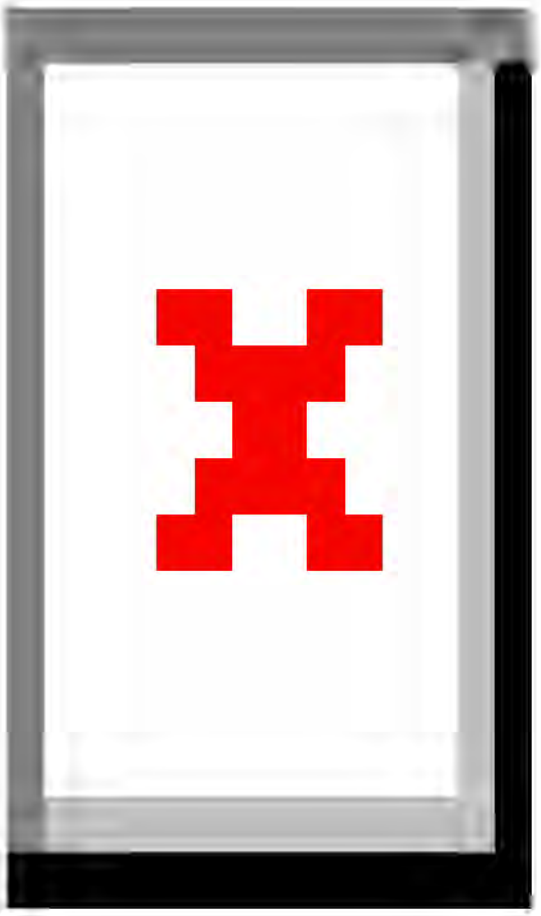
Mrs. Fusco's eldest child, Rita Fusco-Jackson, 55, of Freehold, N.J., died Friday; after her death, the family learned she had contracted the virus. Her eldest son, Carmine Fusco, of Bath, Pa., died on Wednesday, said Ms. Paradiso Fodera, the family's lawyer who is Mrs. Fusco's cousin and is serving as a spokeswoman.

Mrs. Fusco, of Freehold, died after spending Wednesday "gravely ill" and breathing with help from a ventilator, unaware that her two oldest children had died, Ms. Paradiso Fodera said.

Nearly 20 other relatives are quarantined at their homes, praying in isolated solitude, unable to mourn their deep collective loss together.

"If they're not on a respirator, they're quarantined," Ms. Paradiso Fodera said.

"It is so pitiful," she added. "They can't even mourn the way you would."



Ms. Fusco, with her son, Carmine Fusco, who died on Wednesday after contracting coronavirus. She died hours later.

As of Wednesday afternoon, five New Jersey residents had died after contracting the virus, which has infected at least 427 people statewide. Nationwide, at least 7,047 people across every state, plus Washington, D.C., and three U.S. territories, have tested positive for coronavirus, and at least 121 have died, according to a New York Times database.

But the virus's devastating toll on a single family is considered as rare as it is perplexing.

"They're young and they don't have any underlying conditions," Ms. Paradiso Fodero said.

Mrs. Fusco and four of her children were being treated at CentraState Medical Center in Freehold, about an hour south of Manhattan, relatives said. Mr. Fusco died at a Pennsylvania hospital near his home, Ms. Paradiso Fodera said.

The family has deep ties to the horse-racing industry near Freehold Raceway. Some trained horses. Others raced them. The children's father, Vincenzo L. Fusco, did both, according to his obituary.

A person who had contact with a man who died in New Jersey on March 10, becoming the state's first coronavirus-related fatality, had attended a recent Fusco family gathering, the state's health commissioner, Judith M. Persichilli, has said.

The first New Jersey man to die has been identified by a close friend and the harness track where he worked, Yonkers Raceway, as John Brennan.

Ms. Paradiso Fodera said the gathering was a routine Tuesday dinner.

"A party to most people was a regular dinner to them," she said before counting names on a family tree that listed 27 grandchildren.

The gathering is believed to be the source of the virus, and information about the number of people infected there led to a new intensity in Ms. Persichilli's warnings over the weekend against even small get-togethers with friends or relatives.

"I cannot emphasize enough how important it is to take personal responsibility and to avoid even small gatherings," Ms. Persichilli said during a press briefing on Sunday.

Dr. James Matera, chief medical officer of CentraState Medical Center, said he had discussed the uniqueness of treating so many members of the same family with the state's health commissioner and officials at the Centers for Disease Control and Prevention.

He said officials are in the process of evaluating the patients' medical histories to look for clues about why the disease might have progressed so rapidly, and been so potent.

"I don't know if it's a strain thing," Dr. Matera said. "I would consider these particular people to be unusual."

Ms. Fusco-Jackson died a day before her test for coronavirus came back positive on Saturday evening. Her relatives are urging officials at CentraState or the C.D.C. to conduct an autopsy to learn more about how the virus killed Ms. Fusco-Jackson. She had been in good health, they said, and taught religious education classes at the Roman Catholic church where many members of the large extended family worshiped, St. Robert Bellarmine in Freehold.

Ms. Fusco-Jackson, a mother of three, also sang in the choir, coordinated parish weddings and volunteered in the church's gardening club, the pastor, Msgr. Sam Sirianni, said.

She had attended a retreat for students preparing for the sacrament of confirmation on Feb. 29, but her contact with participants was minimal, the church said on Facebook.

"I can't tell you enough about her," Monsignor Sirianni said on Wednesday in an interview. "She was always willing to assist and to lead."

The family was among the founding members of the church, he added.

"Until this virus came, they were still the family that would gather for Sunday dinner," Monsignor Sirianni said. "If grandma was there, everybody came."

The church has since been deep-cleaned, and Monsignor Sirianni, like all members of the parish staff, is operating under quarantine based on possible exposure.
"It means I turn to the Lord even more," Monsignor Sirianni said. "What came to mind last week was. 'Lord save your people.' And that's been one of my mantras when I go to pray."
He said he was struggling to come to terms with being unable to visit the sick at CentraState.
In addition to those who have tested positive for coronavirus at CentraState, a midsize hospital that operates as a nonprofit, 27 community members who have been tested for the virus but are awaiting results are hospitalized under observation, Dr. Matera said on Wednesday.
He said the lengthy turnaround time for test results leaves patients in the dark and burdens the hospital's limited resources. Patients who might ultimately test negative for coronavirus, and be healthy enough to leave the hospital, are instead being kept in isolation.
If tests were returned more quickly, more patients could be discharged.
"That opens up beds," Dr. Matera said. "It lowers the anxiety of the staff."
Ms. Fusco-Jackson's relatives also believe that speedier test results could have made a difference in her care.
"They didn't treat her as a confirmed case because everything is so delayed," Ms. Paradiso Fodera said. "It's a big bureaucracy. The testing result time is important."

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/18 23:16:37
Delivered Date:	2020/03/18 23:16:52
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: HHS accepts donations of medicine to Strategic National Stockpile as possible treatments for COVID-19 patients
Date: 2020/03/29 21:22:59
Priority: Normal
Type: Note

FOR IMMEDIATE RELEASE
March 29, 2020
Contact: ASPR Press Office
202-205-8117
asprmedia@hhs.gov

HHS accepts donations of medicine to Strategic National Stockpile as possible treatments for COVID-19 patients

FDA issues emergency use authorization for donated hydroxychloroquine sulfate, chloroquine phosphate

The U.S. Department of Health and Human Services (HHS) today accepted 30 million doses of hydroxychloroquine sulfate donated by Sandoz, the Novartis generics and biosimilars division, and one million doses of chloroquine phosphate donated by Bayer Pharmaceuticals, for possible use in treating patients hospitalized with COVID-19 or for use in clinical trials. These and other companies may donate additional doses, and companies have ramped up production to provide additional supplies of the medication to the commercial market.

"President Trump is taking every possible step to protect Americans from the coronavirus and provide them with hope," said HHS Secretary Alex Azar. "Scientists in America and around the world have identified multiple potential therapeutics for COVID-19, including chloroquine and hydroxychloroquine. The President's bold leadership and the hard work of FDA and HHS's Assistant Secretary for Preparedness and Response have succeeded in securing this large donation of medicine. We'll continue working around the clock to get American patients access to therapeutics that may help them battle COVID-19, while building the evidence to evaluate which options are effective."

HHS' Office of the Assistant Secretary for Preparedness and Response (ASPR) worked with colleagues within HHS, the companies, the Department of State, and the Department of Homeland Security to secure the donated shipments. Given the importance of understanding the efficacy of these medications for the treatment and prevention of COVID-19, federal agencies, such as the National Institutes of Health and ASPR's Biomedical Advanced Research and Development Authority (BARDA), are working together to plan clinical trials.

The U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to BARDA to allow hydroxychloroquine sulfate and chloroquine phosphate products donated to the Strategic National Stockpile (SNS) to be distributed and prescribed by doctors to hospitalized teen and adult patients with COVID-19, as appropriate, when a clinical trial is not available or feasible.

The EUA requires that fact sheets that provide important information about using chloroquine phosphate and hydroxychloroquine sulfate in treating COVID-19 be made available to health care providers and patients, including the known risks and drug interactions.

The SNS, managed by ASPR, will work with the Federal Emergency Management Agency (FEMA) to ship donated doses to states. The SNS does not regularly stock either drug.

Hydroxychloroquine sulfate and chloroquine phosphate are oral prescription drugs approved to treat malaria and other diseases. Although there are no currently approved treatments for COVID-19, both drugs have shown activity in laboratory studies against coronaviruses, including SARS-CoV-2 (the virus that causes COVID-19). Anecdotal reports suggest that these drugs may offer some benefit in the treatment of hospitalized COVID-19 patients. Clinical trials are needed to provide scientific evidence that these treatments are effective.

When the Secretary of Health and Human Services declares that issuance of an EUA is appropriate, the FDA has the regulatory emergency use authority to facilitate access to unapproved medical countermeasures or unapproved uses of approved medical countermeasures needed to prepare for and respond to chemical, biological, radiological and nuclear threats.

An EUA may be issued if the FDA determines that, among other criteria, the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product, and there are no adequate, approved, available alternatives. Emergency access to a medical product under an EUA is separate from use of a medical product under an investigational drug application.

The FDA has issued an EUA for multiple diagnostics, for several other medical devices such as respiratory devices and a system for decontaminating them to allow for their reuse, and ventilators and ventilator equipment for the COVID-19 response. This is the first EUA for a drug related to the COVID-19 response.

Sandoz and Bayer are the latest companies stepping up to strengthen the U.S. response to COVID-19, and ASPR is working with additional companies willing to donate doses of hydroxychloroquine and chloroquine. Companies interested in donating goods or services should contact fema-nrcc-iagsupv@fema.dhs.gov or visit https://www.fema.gov/coronavirus/how-to-help.

Use of the donated medications is expected to help ease supply pressures for the drug, and the FDA is also working with manufacturers of chloroquine and hydroxychloroquine to increase production to ensure these drugs also remain available for patients dependent on them for treatment of malaria, lupus and rheumatoid arthritis. Some states and retail pharmacies also have taken action to preserve the supply of these and other drugs for these patients.

In addition to accepting and distributing the donated medicines, HHS is funding clinical trials of two drugs, Kevzara (sarilumab) and remdesivir, and is supporting the earlier development of multiple potential therapeutic treatments, vaccines, and diagnostic tests for COVID-19.

HHS continues to seek partners for COVID-19 medical countermeasures, and offers multiple ways to submit proposals for potential products or technologies.

About HHS, ASPR, and FDA

HHS works to enhance and protect the health and well-being of all Americans, providing for effective health and human services and fostering advances in medicine, public health, and social services. The mission of ASPR is to save lives and protect Americans from 21st century health security threats, and within ASPR, the Strategic National Stockpile represents the nation's largest stockpile of life-saving pharmaceuticals and medical supplies for use in supplementing state and local supplies in a public health emergency. The FDA protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

###

Note: All HHS press releases, fact sheets and other news materials are available at https://www.hhs.gov/news.

Like HHS on Facebook - exit disclaimer icon , follow HHS on Twitter @HHSgov - exit disclaimer icon ,

and sign up for HHS Email Updates.
Last revised: March 29, 2020

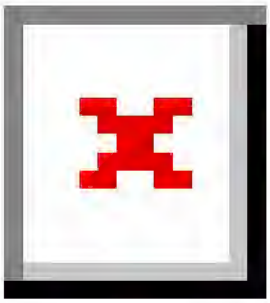
Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/29 21:22:49
Delivered Date:	2020/03/29 21:22:59

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: CIDRAP: Trump says FDA on fast track to approve COVID-19 drugs
Date: 2020/03/20 12:21:07
Priority: Normal
Type: Note

Trump says FDA on fast track to approve COVID-19 drugs

Stephanie Soucheray | News Reporter | CIDRAP News
|
Mar 19, 2020



Woman taking white pill

fizkes / iStock

Today during the daily White House Coronavirus Task Force meeting, President Trump said he was pushing the Food and Drug Administration (FDA) to eliminate barriers to using the antimalarial drug, hydroxychloroquine, to treat COVID-19 infections.

"It's been around for a long time, so we know if things don't go as planned it's not going to kill anybody," Trump said of the drug, which is also used to treat arthritis symptoms in some patients. An unpublished, small, non-randomized trial based on French COVID-19 patients shows the drug has promise against the virus.

FDA chief more cautious

But FDA Commissioner Steve Hahn, MD, struck a more cautious tone during the press conference. He said he did not know how effective the treatment would be, and urged caution when looking at therapeutics for the novel coronavirus.

"Let me make one thing clear. The FDA's responsibility to the American people is to ensure that products are safe and effective," said Hahn. Of using hydroxychloroquine, Hahn said, "We want to do that in the setting of a clinical trial, a large, pragmatic clinical trial to actually gather that information."

But Trump said red tape surrounding therapies for coronavirus would be cut dramatically in the coming days.

"Therapies are something we can move on much faster [than a vaccine]," said Trump, who also said the FDA would be allowing the compassionate use of remdesivir, an antiviral originally used for Ebola treatment that's been studied in Chinese coronavirus patients. Last month, theNational Institutes of Health launched a trial of remdesivir in COVID-19 patients at the University of Nebraska Medical Center (UNMC) in Omaha.

Trump also said he was directing the FDA to look at treatments being used in Europe and Japan, and extrapolate good results in those regions to American patients.

Hahn said the FDA would look into "convalescent plasma" taken from recovered COVID-19 patients as a possible treatment, based on antibody therapy.

Amesh Adalja, MD, of the Johns Hopkins University Center for Health Security, said hydroxychloroquine has been well-studied, and has both antiviral and anti-inflammatory properties.

"It's an important tool we have to study and make sure we get good data on good coronavirus patients and what the impact is," he told CIDRAP News. But he cautioned that there is limited availability of the drug, and many patients with rheumatoid arthritis rely on it. He also worried the sudden interest in the drug could cause supply chain issues.

New York's case count, and testing, soars

Trump also said he spoke with New York Governor Andrew Cuomo last night about hydroxychloroquine, and said the governor was excited to try the medication. New York has been one of the hardest hit states, but also one of the states that's effectively ramped up testing.

Overnight, Cuomo tweeted that the state tested 7,500 samples for coronavirus, finding 1,769 new positive cases. The state's total is now 4,152, including 2,469 cases in New York City alone.

"Remember: We know that as more people are tested we will find more cases," Cuomo cautioned on Twitter. Today Cuomo also signed an executive order mandating that 75% of the non-essential workforce must work from home.

By early afternoon the US case count had surged past 10,000 cases to 11,274 cases, per the Johns Hopkins University tracker. White House Coronavirus Response Coordinator, Deborah Birx, MD, said that about 50% of US cases are in 10 counties, primarily in Washington, California, and New York. Yesterday, health officials in King County, Washington—the first US county to be hit hard with the coronavirus—warned that rapid widespread community transmission could happen.

Washington state has reported 1,026 cases and 68 deaths, according to the *New York Times* coronavirus tracker. Thirty-five of those deaths occured in patients or visitors to the Life Care Center, a long-term care facility in Kirkland, Washington.

There have been 169 deaths total in the United States.

Two Congressmen have COVID-19

Yesterday two lawmakers, Reps. Mario Diaz-Balart (R-Fla.) and Ben McAdams (D-Utah), said they both tested positive for COVID-19 and were in self-quarantine, becoming the first members of Congress to test positive for the coronavirus. The Washington Post reported at least three additional members of Congress would be self-quarantining because they had been in close contact with Diaz-Balart and McAdams.

Meanwhile, the State Department this afternoon announced a level 4 travel advisory, urging all Americans abroad to return home immediately or be prepared to remain abroad indefinitely. Americans were also instructed to avoid all international travel.

A level 4 warning is the highest given by the department.

Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/20 12:20:44
Delivered Date:	2020/03/20 12:21:07
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Bloomberg: Two-Thirds of Severe Covid-19 Cases Improved on Gilead Drug (2)
Date: 2020/04/11 14:22:38
Priority: Normal
Type: Note

Two-Thirds of Severe Covid-19 Cases Improved on Gilead Drug (2)

April 11, 2020, 9:17 AM

- • Patients got experimental drug on a compassionate use basis
- • Definitive evidence of safety will require clinical trials

Gilead Sciences Inc.'s experimental drug for patients with severe Covid-19 infections showed promise in an early analysis, raising tentative hope that the first treatment for the novel virus may be on the horizon.

The report published in the New England Journal of Medicine tracked 53 people in the U.S., Europe and Canada who needed respiratory support, with about half receiving mechanical ventilation and four on a heart-lung by-pass machine. Eight additional patients were left out of the analysis: one due to a dosing error and seven because no information was available on how they fared.

All received remdesivir for up to 10 days on a compassionate use basis, a program that allows people to use unapproved medicines when no other treatment options are available. Over 18 days, 68% of the patients improved, with 17 of the 30 patients on mechanical ventilation being able to get off the breathing device. Almost half of the patients studied were ultimately discharged, while 13% died. Mortality was highest among those who were on a ventilator, with 18% of them dying.

"We cannot draw definitive conclusions from these data, but the observations from this group of hospitalized patients who received remdesivir are hopeful," said lead author Jonathan Grein, director of hospital epidemiology at Cedars-Sinai Medical Center in Los Angeles, in a statement from Gilead. The Foster City, California-based company provided the medication and also helped analyze the results.

Some scientists have expressed skepticism with regard to the results.

"The data from this paper are almost uninterpretable," Stephen Evans, a professor of pharmacoepidemiology at the London School of Hygiene &Tropical Medicine, said in an emailed statement. "There is some evidence suggesting efficacy, but we simply do not know what would have happened to these patients had they not been given the drug."

Several large scale clinical trials are underway to evaluate the benefit of remdesivir for Covid-19, the disease caused by the novel coronavirus that has infected more than 1.65 million people worldwide and killed 100,000. One that was conducted in China could report results this month. Another, sponsored by the U.S. National Institutes of Health, has enrolled patients rapidly as the virus spread throughout the U.S. It could also report results in the coming weeks. Gilead itself is sponsoring an additional two trials.

'Answers Are Needed'

"In studying remdesivir, the question is not just whether it is safe and effective against Covid-19, but in which patients it shows activity, how long should they receive treatment and at what stage of their disease would treatment be most beneficial," said Daniel O'Day, Gilead's chairman and chief executive

officer. "Many answers are needed, which is why we need multiple types of studies involving many types of patients."

Some of these answers will emerge in the coming weeks with the release of initial data from the various clinical trials, O'Day said Friday in an open letter sent via email.

There are currently no treatments proven to work specifically against the coronavirus infection. Gilead has provided the medicine to more than 1,800 patients on a compassionate use basis.

Cheap to Make

If it's shown to be safe and effective for treating Covid-19, the medication is estimated to cost about $9 a treatment to make, said Andrew Hill, a senior visiting research fellow in the pharmacology department at Liverpool University, and colleagues in a study Friday.

As an intravenous infusion, there would be additional costs to administer remdesivir, which are likely to exceed the estimated manufacturing, the authors said.

Potential Coronavirus Drugs May Cost as Little as $1, Study Says

Results of controlled studies of remdesivir are highly anticipated because they will be some of the first rigorous large-scale studies completed on potential anti-coronavirus drugs.

President Donald Trump and others have touted the potential of hydroxychloroquine, an old malaria and lupus drug, for treating Covid-19. But that drug hasn't yet been carefully studied in a large trial to see if it prevents severe complications. Most of the excitement stems from relentless social media promotion of a tiny French study whose methodology has been heavily criticized by many U.S. medical experts.

Remdesivir, a broad-spectrum antiviral, is viewed by researchers and doctors as one of the most promising agents against Covid-19 to enter human trials to date. In lab studies conducted prior to the Covid-19 outbreak on numerous compounds, researchers at the University of North Carolina and Vanderbilt University found the drug had potent activity against against a wide variety of coronaviruses similar to the new coronavirus.

Tested for Ebola

Because it had already been tested in patients with Ebola, where it was shown to be safe but ineffective, researchers were able to quickly begin studying it human trials when the Covid-19 pandemic hit.

Read More: Apple, Google Bring Covid-19 Contact-Tracing to 3 Billion People

About one in four patients on the medicine experienced severe side effects, including multiple-organ dysfunction syndrome, septic shock, acute kidney injury and low blood pressure. Another 23% showed signs of liver damage on laboratory tests. Four patients had to stop receiving infusions of the drug entirely.

Remdesivir was considered to be the most promising therapeutic candidate based on its broad antiviral spectrum, and existing data based on human and animal studies, a World Health Organization panel said in January. The medication was developed initially for Ebola and studied in patients in Eastern Congo.

If it works well, one issue will be whether there is enough of a supply of the drug, especially if the epidemic is still raging. Gilead has been working all-out to bolster supply of the hard-to-make medicine. It said earlier this month that it hopes to to have 500,000 treatment courses by October, and more than 1 million by year-end. Production time has also been accelerated to six months from one year.

(Updates with comment from scientist in sixth paragraph)

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/11 14:22:24
Delivered Date:	2020/04/11 14:22:38
Message Flags:	Unread

From:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject:	Medscape: COVID-19: More Hydroxychloroquine Data From France, More Questions
Date:	2020/03/31 10:42:11
Priority:	Normal
Type:	Note

www.medscape.com

COVID-19: More Hydroxychloroquine Data From France, More Questions

Véronique Duqueroy
March 30, 2020

Editor's note: Find the latest COVID-19 news and guidance in Medscape's Coronavirus Resource Center.

A controversial study led by Didier Raoult, MD, PhD, on the combination of hydroxychloroquine and azithromycin in patients with COVID-19 was published on March 20, as reported by *Medscape Medical News*. The latest results from the same Marseille team, which involve 80 patients, were reported on March 27.

The investigators report a significant reduction in the viral load (83% patients had negative results on quantitative polymerase chain reaction testing at day 7, and 93% had negative results on day 8). There was a "clinical improvement compared to the natural progression." One death occurred, and three patients were transferred to intensive care units.

If the data seem encouraging, the lack of a control arm in the study leaves clinicians perplexed, however.

Medscape French Edition spoke to Benjamin Davido, MD, an infectious disease specialist at Raymond-Poincaré Hospital in Garches, Paris, about the implications of these new results.

What do you think about the new results presented by Prof Raoult's team? Do they confirm the effectiveness of hydroxychloroquine?

These results are complementary [to the original results] but don't offer any new information or new statistical evidence. They are absolutely superimposable and say overall that, between 5 and 7 days [of treatment], very few patients shed the virus. But that is not the question that everyone is asking.

Even if we don't necessarily have to conduct a randomized study, we should at least compare the treatment, either against another therapy — which could be hydroxychloroquine monotherapy, or just standard of care. It needed an authentic control arm.

To recruit 80 patients so quickly, the researchers probably took people with essentially ambulatory forms of the disease (there was a call for screening in the south of France) — therefore, by definition, less severe cases.

But to describe such a population of patients as going home and say, "There were very few hospitalizations and it is going well," does not in any way prove that the treatment reduces hospitalizations.

The argument for not having a control arm in this study was that it would be unethical. What do you think?

I agree with this argument when it comes to patients presenting with risk factors or who are starting to develop pneumonia.
But I don't think this is the case at the beginning of the illness. Of course, you don't want to wait to have severe disease or for the patient to be in intensive care to start treatment. In these cases, it is indeed very difficult to find a control arm.
In the ongoing Discovery trial, which involves more than 3000 patients in Europe, including 800 in France, the patients have severe disease, and there are five treatment arms. Moreover, hydroxychloroquine is given without azithromycin. What do you think of this?
I think it's a mistake. It will not answer the question of the effectiveness of hydroxychloroquine in COVID-19, especially as they're not studying azithromycin in a situation where the compound seems necessary for the effectiveness of the treatment.
In addition, Discovery reinforces the notion of studying *Kaletra* [lopinavir/ritonavir, AbbVie] again, while Chinese researchers have shown that it does not work, the argument being that Kaletra was given too late. Therefore, if we make the same mistakes from a methodological point of view, we will end up with negative results.
What should have been done in the Marseille study?
The question is, Are there more or fewer hospitalizations when we treat a homogeneous population straight away?
The answer could be very clear, as a control already exists! They are the patients that flow into our hospitals every day — ironically, these 80 patients [in the latest results, presented March 27] could be among the 80% who had a form similar to nasopharyngitis and resolved.
In this illness, we know that there are 80% spontaneous recoveries and 20% so-called severe forms. Therefore, with 80 patients, we are very underpowered. The cohort is too small for a disease in which 80% of the evolution is benign.
It would take 1000 patients, and then, even without a control arm, we would have an answer.
On March 26, Didier Raoult's team also announced having already treated 700 patients with hydroxychloroquine, with only one death. Therefore, if this cohort increases significantly in Marseille and we see that, on the map, there are fewer issues with patient flow and saturation in Marseille and that there are fewer patients in intensive care, you will have to wonder about the effect of hydroxychloroquine.
We will find out very quickly. If it really works and they treat all the patients presenting at Timone Hospital, we will soon have the answer. It will be a real-life study....
What are the other studies on hydroxychloroquine that could give us answers?
There was a Chinese study that did not show a difference in effectiveness between hydroxychloroquine and placebo, but that was, again, conducted in only around 20 patients. This cohort is too small and tells us nothing; it cannot show anything. We must wait for the results of larger trials being conducted in China.
It surprises me that, today, we still do not have Italian data on the use of chloroquine-type drugs...perhaps because they have a care pathway that means there is no outpatient treatment and that they arrive already with severe disease. The Italian recommendations nevertheless indicate the use of hydroxychloroquine.
I also wonder about the lack of studies of cohorts where, in retrospect, we could have followed people previously treated with hydroxychloroquine for chronic diseases (eg, rheumatoid arthritis, lupus, etc). Or we could identify all those patients on the health insurance system who had prescriptions.
That is how we discovered the AIDS epidemic in San Francisco: there was an increase in the number of prescriptions for *Bactrim* [trimethoprim/sulfamethoxazole] that corresponded to a population subtype (homosexual), and we realized that it was for a disease that resembled pneumocystosis. We discovered that via the drug!

If hydroxychloroquine is effective, it is enough to look at people who took it before the epidemic and see how they fared. And there, we do not need a control arm. This could give us some direction. The March 26 decree of the new Véran Law states that community pharmacies can dispense to patients with a previous prescription, so we can find these individuals.

Do you think that the lack of, or difficulty in setting up, studies on hydroxychloroquine in France is linked to decisions that are more political than scientific?

Perhaps the contaminated blood scandal still casts a shadow in France, and there is a great deal of anxiety over the fact that we are already in a crisis and we do not want a second one. I can understand that.

However, just a week ago, access to this drug (and others with market approval that have been on the market for several years) was blocked in hospital central pharmacies, while we are the medical specialists with the authorization! It was unacceptable.

It was sorted out 48 hours ago: hydroxychloroquine is now available in the hospital, and to my knowledge, we no longer have a problem obtaining it.

It took time to alleviate doubts over the major health risks with this drug. [Officials] seemed almost like amateurs in their hesitation; I think they lacked foresight. We have forgotten that the treatment advocated by Prof Didier Raoult is not chloroquine but rather hydroxychloroquine, and we know that the adverse effects are less [with hydroxychloroquine] than with chloroquine.

You yourself have treated patients with chloroquine, despite the risk for toxicity highlighted by some....

Initially, when we first started treating patients, we thought of chloroquine because we did not have data on hydroxychloroquine, only Chinese data with chloroquine. We therefore prescribed chloroquine several days before prescribing hydroxychloroquine.

The question of the toxicity of chloroquine was not unjustified, but I think we took far too much time to decide on the toxicity of hydroxychloroquine. Is [the latter] political? I don't know. It was widely publicized, which amazes me for a drug that is already available.

On the other hand, everyone was talking at the same time about the toxicity of NSAIDs.... One has the impression it was to create a diversion. I think there were double standards at play and a scapegoat was needed to gain some time and ask questions.

What is sure is that it is probably not for financial reasons, as hydroxychloroquine costs nothing. That's to say there were probably pharmaceutical issues at stake for possible competitors of hydroxychloroquine; I do not want to get into this debate, and it doesn't matter, as long as we have an answer.

Today, the only thing we have advanced on is the "safety" of hydroxychloroquine, the low risk to the general population.... On the other hand, we have still not made any progress on the evidence of efficacy compared with other treatments.

Personally, I really believe in hydroxychloroquine. It would nevertheless be a shame to think we had found the fountain of youth and realize, in 4 weeks, that we have the same number of deaths. That is the problem. I hope that we will soon have solid data so we do not waste time focusing solely on hydroxychloroquine.

What are the other avenues of research that grab your attention?

The Discovery trial will probably give an answer on remdesivir [GS-5734, Gilead], which is a direct antiviral and could be interesting. But there are other studies being conducted currently in China.

There is also favipiravir [T-705, *Avigan*, Toyama Chemical], which is an anti-influenza drug used in Japan, which could explain, in part, the control of the epidemic in that country. There are effects in vitro on coronavirus. But it is not at all studied in France at the moment. Therefore, we should not focus exclusively on hydroxychloroquine; we must keep a close eye on other molecules, in particular the "old" drugs, like this antiviral.

The study was supported by the Institut Hospitalo-Universitaire (IHU) Méditerranée Infection, the National Research Agency, under the Investissements d'avenir program, Région Provence Alpes Côte d'Azur, and European funding FEDER PRIMI. The authors have disclosed no relevenant financial relationships..
A preprint version of the study is available online.
Translated and adapted from Medscape's French edition.
Follow Medscape on Facebook, Twitter, Instagram, and YouTube.

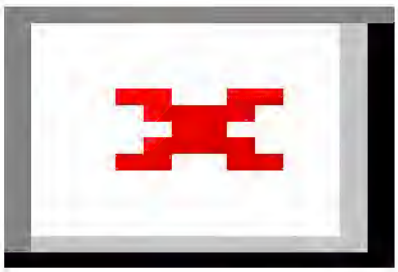
Cite this: COVID-19: More Hydroxychloroquine Data From France, More Questions - *Medscape* - Mar 30, 2020.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/31 10:41:12
Delivered Date:	2020/03/31 10:42:11
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Wash Times: Trump meets with COVID-19 survivors, an overlooked group
Date: 2020/04/15 11:24:25
Priority: Normal
Type: Note

Trump meets with COVID-19 survivors, an overlooked group

Michigan state legislator praises Trump for pushing malaria drug: 'I wouldn't be here today'
Follow Us Top of Form



President Donald Trump listens during a meeting with people that have recovered from COVID-19, in the Cabinet Room of the White House, Tuesday, April 14, 2020, in Washington. (AP Photo/Evan Vucci)

President Donald Trump listens during a meeting with people that have recovered from COVID-19, in the Cabinet Room of the White House, Tuesday, April 14, 2020, in Washington. (AP Photo/Evan Vucci)
more > Print
By Tom Howell Jr. - The Washington Times - Tuesday, April 14, 2020
President Trump on Tuesday met coronavirus survivors who counted their blessings and thanked the president for pushing an investigational drug for the virus, though scientists say it could be a tough road to full recovery for many patients who make it through a nasty bout of the new disease.
Even the people with success stories who trekked to the White House said they weren't fully fit, with one former NFL player complaining of diminished lung capacity and one Arkansas woman saying she tested negative five days ago but is still only "85%" well.
"Stay away from me, please," Mr. Trump said to laughter in the Cabinet Room.

Much of the public focus on COVID-19 has been on the awful death toll and the frantic scramble to test for the virus and provide acute care. But 465,000 people have officially recovered from COVID-19 worldwide, including more than 45,000 in the U.S., according to a Johns Hopkins University tracker.

For these survivors, there's the upside of full or partial immunity to future infection. Yet patients who have made it out alive are writing op-eds and Twitter posts that suggest the road back to health is a rocky one fraught with breathing problems, anxiety and a struggle to regain their senses of smell and taste.

The pandemic could cause lifelong problems for those were vulnerable from the start.

"It's not fun being in an intensive care unit. You lose muscle mass," said Dr. William Schaffner, an infectious disease specialist at Vanderbilt University. "There are people, particularly older people or those who are particularly frail, who may not ever make it back to that same level of function of daily living in our society."

While COVID-19 is new, the disease can lead to a well-documented condition known as acute respiratory distress syndrome (ARDS).

"We know a lot about the outcomes from that particular syndrome, which can be caused by COVID-19," said Dr. Russell Buhr, a pulmonary and critical care doctor at UCLA Health. "We know the long-term survival from that can be lower."

About 3% to 10% of COVID-19 patients appear to develop the syndrome, as the virus causes a profound immune response resulting in damaging inflammation. Typically about half of those who develop ARDS from any cause survive, but those people often require longer hospital stays or supplemental oxygen or even become candidates for lung transplants.

It's not just the lungs, either. Viral infections can attack muscle cells in the heart, resulting in damaging inflammation.

A recent study of blood tests among 34 patients in Wuhan, China, where the pandemic started, found evidence that the new coronavirus attacks the liver, muscles, the gastrointestinal tract and lymph nodes. Even among patients who survived, were discharged and tested negative twice, there were signs that certain physiological measures had "failed to return to normal" compared to healthy volunteers in the study.

"This finding indicates that these discharged patients, regardless of the severity of their previous symptoms, had not been fully recovered from the disease in the aspect of metabolism," particularly liver function.

The authors said those patients will "still need better nutrition and care that would be very helpful for their faster and full recovery from the disease."

The new coronavirus has genetic similarities to the Severe Acute Respiratory Syndrome (SARS) outbreak that devastated parts of Asia in 2002-2003. Experts say the research may offer clues to the post-COVID-19 world.

A study from 2009 found that nearly a quarter of former SARS patients had problems with lung capacity well after they got sick.

"Exercise capacity and health status were markedly lower than the general population at one year after illness onset," according to the Research Fund for the Control of Infectious Diseases in Hong Kong.

COVID-19 survivors' struggle to get back to 100% will be a factor that business owners and policymakers will confront as they try to get life back to normal.

"It's not as simple as just trying to get people back to work quickly. You have to account for people who've gotten sick. Trying to get them back to work is going to be a challenge, too," Dr. Buhr said.

A recent New York Times op-ed by Fiona Lowenstein — a writer, producer and yoga teacher — says that's already a problem for those locked in the unseen struggle to recover.

"Some of the young people in my online support group are struggling to get more time off from work — they are, after all, supposedly recovered," she wrote. "Almost all are experiencing mental health

problems, including severe anxiety, panic attacks and depression, as they struggle to understand what's next for them. In addition to the physical symptoms that still keep me up at night, I have frequent nightmares in which I am once again gasping for breath."
She wrote that the news "is filled with uplifting stories of patients who have survived COVID-19 — including my own — but rarely do these narratives cover the long and jagged road to recovery that follows."
Mr. Trump asked his guests Tuesday whether they felt back up to speed and, while many did, ex-NFL tight end Mark Campbell said he's still about "95%."
"The only thing is my lung capacity isn't quite where it was," Mr. Campbell said, saying it is harder to go for a jog.
Mr. Campbell and Democratic state Rep. Karen Whitsett of Michigan both said they recovered after taking hydroxychloroquine, a malaria drug that Mr. Trump has promoted as a potential game-changer in the COVID-19 fight.
"Had you not brought this to the forefront ... I wouldn't be here today to even have this conversation with you and talk about the needs of Detroit and talk about the people who really need this," Mrs. Whitsett said.
Mr. Trump, who won Michigan in 2016 and is hoping to nab the state in November, joked there may be a political upside to the legislator's story.
"I don't see her voting for Sleepy Joe Biden," Mr. Trump said.
Medical experts have said they would like to see more clinical trials of the drug to understand its impact on COVID-19 and possible side effects before declaring it a success story.
Hydroxychloroquine is part of a long list of investigation drugs being used across the country. Mr. Trump also has cited one by Gilead Sciences, remdesivir, as a promising treatment to get patients out of the hospital and back to full health.
"There's a lot of science happening right now," Dr. Buhr said. "A lot of studies on treatment and outcomes and we're going to know a lot more a few months from now, just like we know a lot more now than we did in January."

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/15 11:24:02
Delivered Date:	2020/04/15 11:24:25
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Subject: Ann Intern Med: A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19 Free

Date: 2020/03/30 17:42:24

Priority: Normal

Type: Note

Ideas and Opinions |30 March 2020

A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19 Free

Alfred H.J. Kim, MD, PhD*; Jeffrey A. Sparks, MD, MMSc*; Jean W. Liew, MD; Michael S. Putman, MD; Francis Berenbaum, MD, PhD; Ali Duarte-Garcia, MD, MS; Elizabeth R. Graef, DO; Peter Korsten, MD; Sebastian E. Sattui, MD; Emily Sirotich, BSc; Manuel F. Ugarte-Gil, MD, MSc; Kate Webb, MBBCh, PhD; Rebecca Grainger, MBChB, PhD; for the COVID-19 Global Rheumatology Alliance†
Article, Author, and Disclosure Information

The coronavirus disease 2019 (COVID-19) pandemic has placed the scientific and research communities under extraordinary pressure, to which they have responded with exceptional vigor and speed. This desire to quickly find safe and effective treatments may also lead to relaxed standards of data generation and interpretation, which may have undesirable downstream effects. The recent publication of a study evaluating hydroxychloroquine (HCQ) in COVID-19 is a useful test case, highlighting the challenges of conducting research during a pandemic.

A scientific rationale existed for investigating HCQ in COVID-19. Preclinical data suggested that the antimalarials HCQ and chloroquine have in vitro antiviral activity against severe acute respiratory syndrome–coronavirus 2 (SARS–CoV-2) (1–3). Antimalarials are also inexpensive, are widely available, and have an acceptable short-term safety profile. In a nonrandomized study, Gautret and colleagues (4) reported a higher frequency of SARS–CoV-2 clearance from the nasopharynx after 6 days of treatment with HCQ, plus azithromycin (AZM) if deemed necessary, versus an untreated control group (14 of 20 patients [70%] vs. 2 of 16 patients [13%]; P <0.001). Given the urgency of the situation, some limitations of this study may be acceptable, including the small sample size, use of an unvalidated surrogate end point, and lack of randomization or blinding. However, other methodological flaws also noted by others (5) may affect the validity of the findings, even in the current setting, where an efficacious treatment is desperately needed.

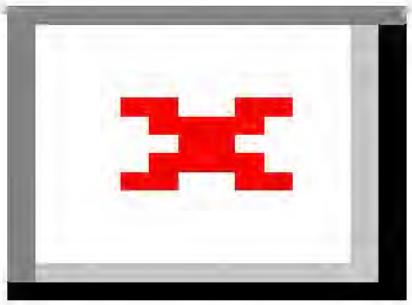
First, potentially substantial confounders may explain the findings. The HCQ + AZM treatment group was recruited from a single center. Instead of excluding patients who declined treatment, the researchers assigned them to the control group. The remainder of the control group was recruited from other centers that could not contribute to the treatment group. This introduces the potential for baseline

confounding and different treatment regimens at different institutions. In addition, patients in the HCQ + AZM group had lower viral loads at the time of treatment initiation compared with the control and HCQ groups, and so may have been at a later phase of infection. All patients who received HCQ + AZM had a SARS–CoV-2 baseline cycle threshold (Ct) greater than 22 on polymerase chain reaction (PCR). Of the 5 patients receiving HCQ who had a baseline Ct of 22 or less on PCR (that is, higher viral burden), 4 still had detectable virus at day 6. Of the 9 patients with a baseline Ct greater than 22 on PCR, only 2 had detectable virus at day 6. Thus, another explanation is that the baseline viral load, not therapy with HCQ + AZM, affects viral load at day 6.

This problem may have been further exacerbated by issues with data measurement and imputation. Sites other than Marseille did not perform daily PCR testing, creating gaps in PCR data for control group patients that were later imputed with values from other days. Consequently, 75% (12 of 16 patients) of the control group lacked at least 1 PCR result, including 44% (7 of 16 patients) who were not tested on at least 4 of the 7 possible days. In the HCQ + AZM group, only 20% (4 of 20 patients) were missing at least 1 PCR result and none were missing more than 2. In the control group, 38% of the PCR data were imputed versus only 5% in the treatment group.

Second, the handling of patients who were lost to follow-up also raises serious questions about scientific validity. Only 20 of 26 patients in the treatment group were included in the analysis despite meeting baseline eligibility criteria. Six patients were excluded because day 6 PCR data were missing, owing to early treatment cessation due to nausea (n = 1), hospital discharge (n = 1), intensive care unit transfer (n = 3), and death (n = 1). Therefore, patients who had the most serious and clinically relevant outcomes, including intensive care unit transfer and death, were excluded from analysis. These patients had treatment failure and should have been analyzed as such. We strongly agree with others that adequate follow-up of patients with relevant outcomes should be attempted (6).

Despite the study's substantial limitations, a simplification and probable overinterpretation of these findings was rapidly disseminated by the lay press and amplified on social media, ultimately endorsed by many government and institutional leaders. Public interest in HCQ rapidly grew (Figure). The study's findings were extrapolated to include the use of HCQ to prevent COVID-19 infection or as postexposure prophylaxis, indications for which there are currently no direct supporting data. Despite promising in vitro data for influenza (7, 8), HCQ failed to prevent infection in a randomized, placebo-controlled, double-blind trial (9). Efforts to understand the clinical efficacy of HCQ as postexposure prophylaxis are under way (https://clinicaltrials.gov/ct2/show/NCT04308668), which should yield important insight into this issue.



Global Google Trends search patterns for "hydroxychloroquine," "chloroquine," and "hydroxychloroquine shortage," 16 to 22 March 2020.
The spike on 17 March corresponded with the publication of Gautret and colleagues' report (4). The second spike on 20 March 20 followed the U.S. presidential press conference in which hydroxychloroquine was described as a treatment of coronavirus disease 2019.
A major consequence has been an inadequate supply of HCQ for patients in whom efficacy is established. Hydroxychloroquine is an essential treatment of rheumatoid arthritis and of systemic lupus erythematosus, reducing flares and preventing organ damage in the latter disease (10). Pharmacies have reported shortages of antimalarials (www.washingtonpost.com/business/2020/03/20/hospitals-doctors-are-wiping-out-supplies-an-unproven-coronavirus-treatment), and patients with rheumatic diseases have had difficulty obtaining prescription refills. Several major medical organizations released a joint statement regarding the HCQ shortage (https://protect2.fireeye.com/url?k=ca4e597a-961b5069-ca4e6845-0cc47adb5650-0050b206f3dc7e2a&u=http://www.lupus.org/s3fs-public/pdf/Joint-Statement-on-HCQ-LFA-ACR-AADA-AF.pdf), warning of possible dire consequences for patients with rheumatic diseases.

Hydroxychloroquine shortages could place these patients at risk for severe and even life-threatening flares; some may require hospitalization when hospitals are already at capacity. Until reliable evidence is generated and adequate supply chains have been put in place, rational use of HCQ in patients with COVID-19 must be emphasized, such as use in investigational studies.
In critical situations, large randomized controlled trials are not always feasible or ethical, and critically ill patients may need to be treated empirically during times of uncertainty. However, it is our responsibility as clinicians, researchers, and patient partners to promote proper and rigorous interpretation of results, particularly in our interactions with the nonscientific community. We must consider the societal implications of published work in these unprecedented times.

There is enough rationale to justify the continued investigation of the efficacy and safety of HCQ in hospitalized patients with COVID-19. It is critical to reiterate that although viral clearance is important, clinical outcomes are much more relevant to patients. There currently are no data to recommend the use of HCQ as prophylaxis for COVID-19, although we eagerly await data from trials under way. Thus, we

discourage its off-label use until justified and supply is bolstered. The HCQ shortage not only will limit availability to patients with COVID-19 if efficacy is truly established but also represents a real risk to patients with rheumatic diseases who depend on HCQ for their survival.

Appendix: Steering Committee and Regional Leaders of the COVID-19 Global Rheumatology Alliance

For more information on the alliance, including contact details of the steering committee and regional leaders, visit https://protect2.fireeye.com/url?k=7f06b42a-2353bd39-7f068515-0cc47adb5650-b3741d159ccbe6e2&u=https://rheum-covid.org/about.

Current Steering Committee

Philip Robinson, MBChB, PhD, FRACP, MAICD (*Chair, Governance, Policy*); Jinoos Yazdany, MD, MPH (*Vice-Chair, Real-world Data Infrastructure, Registry and IRB/Ethics*); Paul Sufka, MD (*Technology and Marketing Lead*); Rebecca Grainger, MBChB (Dstn), BMedSci (Dstn) MIsntD, CHIA, FRACP, FACHI, PhD (*Literature Review Co-Leod*); Zach Wallace, MD, MSc (*Literature Review Co-Lead*); Organizational Liaison and Media); Emily Sirotich (*Patient Engagement Lead*); Jean Liew, MD (Administrative Lead); Jonathan Hausmann, MD (*Patient Registries Collaboration Lead*); Pedro Machado, MD (*European Lead*).

Current Regional Leads

Australia: David Liew
Brazil: Claudia Marques
Canada: Diane LaCaille, Sindhu Johnson, Keshini Devakandan, Carter Thorne
China: Mengtao Li
France: Francis Berenbaum
Germany: Johannes Knitza, Peter Korsten
Ireland: Richard Conway
Latvia: Bulina Inita
Mexico: Erick Adrian Zamora Tehozol
New Zealand: Rebecca Grainger
Peru: Manuel Ugarte-Gil
Saudi Arabia: Ibrahim Almaghlouth
South Africa: Kate Webb
United Kingdom: Taryn Youngstein, Pedro Machado, Richard Beesley, Kimme Hyrich
United States: Adam Kilian, Maria Danila, Isabelle Amigues, Eugenia Chock, Michael Putman, Laura Lewandowski, Jon Hausmann, Maximilian Konig, Beth Wallace, Reema Syed, Sebastian Sattui, Arundathi Jayatilleke, Jean Liew, Namrata Singh, Aarat Patel, Katherine Wysham, Alí Duarte, Marc Nolan

References

1. • **Liu J, Cao R, Xu M, et al.** Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16. [PMID: 32194981] doi:10.1038/s41421-020-0156-0
2. • **Wang M, Cao R, Zhang L, et al.** Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro [Letter]. Cell Res. 2020;30:269-271. [PMID: 32020029] doi:10.1038/s41422-020-0282-0
3. • **Yao X, Ye F, Zhang M, et al.** In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020. [PMID: 32150618] doi:10.1093/cid/ciaa237
4. • **Gautret P, Lagier JC, Parola P, et al.** Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020:105949. [PMID: 32205204] doi:10.1016/j.ijantimicag.2020.105949

5. • **Dahly D, Gates S, Morris T.** Statistical review of hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label nonrandomized clinical trial. Preprint. Posted online 23 March 2020. Zenodo. doi:10.5281/zenodo.3725560
6. • **Cortegiani A, Ingoglia G, Ippolito M, et al.** A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020. [PMID: 32173110] doi:10.1016/j.jcrc.2020.03.005
7. • **Di Trani L, Savarino A, Campitelli L, et al.** Different pH requirements are associated with divergent inhibitory effects of chloroquine on human and avian influenza A viruses. Virol J. 2007;4:39. [PMID: 17477867]
8. • **Ooi EE, Chew JS, Loh JP, et al.** In vitro inhibition of human influenza A virus replication by chloroquine. Virol J. 2006;3:39. [PMID: 16729896]
9. • **Paton NI, Lee L, Xu Y, et al.** Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. Lancet Infect Dis. 2011;11:677-83. [PMID: 21550310] doi:10.1016/51473-3099(11)70065-2
10. • **Fava A, Petri M.** Systemic lupus erythematosus: Diagnosis and clinical management. J Autoimmun. 2019;96:1-13. [PMID: 30448290] doi:10.1016/j.jaut.2018.11.001

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/30 17:42:06
Delivered Date:	2020/03/30 17:42:24
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Bloomberg Law: Hundreds of Corona Patients Allowed to Try Gilead's Ebola Drug
Date: 2020/03/10 18:14:32
Priority: Normal
Type: Note

Hundreds of Corona Patients Allowed to Try Gilead's Ebola Drug

March 10, 2020, 4:34 PM
Jeannie Baumann
Reporter

- Repurposed Ebola antiviral furthest along in drug development for Covid-19
- Many in Washington state among those treated, CDC chief says

Hundreds of coronavirus patients have been treated with Gilead's experimental Ebola treatment under an FDA program to allow access to unapproved drugs.

Gilead Sciences, Inc. expects to know by April whether a clinical trial in China testing the antiviral drug remdesivir can effectively treat patients infected with the virus that causes Covid-19. But company spokesperson Ryan McKeel said Tuesday it's already "provided remdesivir on a compassionate use basis to treat several hundred patients with confirmed, severe COVID-19 infection in the United States, Europe and Japan."

Expanded access, also known as compassionate use, allows patients with life-threatening conditions who have run out of options to try experimental therapies outside of a clinical trial. The Food and Drug Administration must approve all expanded access requests, which it does more than 99% of the time, but the company is never required to provide the experimental drug.

A number of people in Washington state have been treated with remdesivir through the compassionate use program, CDC Director Robert Redfield told a House appropriations panel during a hearing on Tuesday. Twenty-three of the 28 deaths in the U.S. that are linked to Covid-19 outbreak have occurred in Washington state.

"For people that are very sick, and we have a number that are very sick, there is an experimental drug called remdesivir that's available right now in compassionate use. This country has used it," Redfield said in response to a question form Rep. Bonnie Watson Coleman (D-N.J.).

The Department of Health and Human Services announced last week it provided remdesivir to severely ill patients in Japan as part of a collaboration with the U.S. Public Health Service Commissioned Corps; the U.S. Embassy in Japan; the Japanese Ministry of Health, Labour and Welfare; and Gilead Sciences Inc.

Remdesivir has shown promise in animal studies as a possible treatment for Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which are caused by other coronaviruses.

Other companies such as AbbVie Inc. are pursuing cornoavirus therapies. But Gilead's remdesivir is furthest along in the drug development pipeline, Anthony S. Fauci told, director of the National Institute of Allergy and Infectious Diseases, told a Senate panel March 3.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/10 18:14:14
Delivered Date:	2020/03/10 18:14:32
Message Flags:	Unread

From:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject:	bioRxiv+medRxiv: 66 Results for full text or abstract or title "coronavirus" (match whole all) and posted between "02 Apr, 2020 and 03 Apr, 2020" https://bit.ly/2V1yvIS
Date:	2020/04/03 15:02:58
Priority:	Normal
Type:	Note

- • If long-term suppression is not possible, how do we minimize mortality for COVID-19 and other emerging infectious disease outbreaks?
  Andreas Handel, Joel Miller, Yang Ge, Isaac Chun-Hai Fung
  medRxiv 2020.03.13.20034892; doi: https://doi.org/10.1101/2020.03.13.20034892

- • Reply to Gautret et al. 2020: A Bayesian reanalysis of the effects of hydroxychloroquine and azithromycin on viral carriage in patients with COVID-19
  Oliver J Hulme, Eric-Jan Wagenmakers, Per Damkier, Christoffer Fugl Madelung, Hartwig Roman Siebner, Jannik Helweg-Larsen, Quentin Gronau, Thomas Lars Benfield, Kristoffer H Madsen
  medRxiv 2020.03.31.20048777; doi: https://doi.org/10.1101/2020.03.31.20048777

- • Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK
  Christopher I Jarvis, Kevin Van Zandvoort, Amy Gimma, Kiesha Prem, CMMID COVID-19 working group, Petra Klepac, G James Rubin, W John Edmunds
  medRxiv 2020.03.31.20049023; doi: https://doi.org/10.1101/2020.03.31.20049023

- • In silico approach for designing of a multi-epitope based vaccine against novel Coronavirus (SARS-COV-2)
  Ratnadeep Saha, Burra VLS Prasad
  bioRxiv 2020.03.31.017459; doi: https://doi.org/10.1101/2020.03.31.017459

- • Projected ICU and Mortuary load due to COVID-19 in Sydney
  Andrew Francis, Yi Guo, Paul Hurley, Oliver Obst, Laurence A. F. Park, Mark Tanaka, Russell Thomson, Rosalind Wang
  medRxiv 2020.03.31.20049312; doi: https://doi.org/10.1101/2020.03.31.20049312

- • SEIR and Regression Model based COVID-19 outbreak predictions in India
  Rajan Gupta, Gaurav Pandey, Poonam Chaudhary, Saibal Kumar Pal
  medRxiv 2020.04.01.20049825; doi: https://doi.org/10.1101/2020.04.01.20049825

- • Japanese citizens' behavioral changes and preparedness against COVID-19: How effective is Japan's approach of self-restraint?
  Kaori Muto, Isamu Yamamoto, Miwako Nagasu, Mikihito Tanaka, Koji Wada
  medRxiv 2020.03.31.20048876; doi: https://doi.org/10.1101/2020.03.31.20048876

- • Evaluating features of scientific conferences: A call for improvements

Sarvenaz Sarabipour, Benjamin Schwessinger, Fiona N Mumoki, Aneth D Mwakilili, Aziz Khan, Humberto J Debat, Pablo Saez, Samantha Seah, Tomislav Mestrovic
bioRxiv 2020.04.02.022079; doi: https://doi.org/10.1101/2020.04.02.022079

- • Meteorological factors correlate with transmission of 2019-nCoV: Proof of incidence of novel coronavirus pneumonia in Hubei Province, China
Jianfeng Li, Linyuan Zhang, Zhihua Ren, Caihong Xing, Peihuan Qiao, Bing Chang
medRxiv 2020.04.01.20050526; doi: https://doi.org/10.1101/2020.04.01.20050526

- • Knowledge and Beliefs towards Universal Safety Precautions to flatten the curve during Novel Coronavirus Disease (nCOVID-19) Pandemic among general Public in India: Explorations from a National Perspective
Sai Krishna Gudi, Krishna Undela, Rajesh Venkataraman, Uday Venkat Mateti, Manik Chhabra, Sanath Nyamagoud, Komal Krishna Tiwari
medRxiv 2020.03.31.20047126; doi: https://protect2.fireeye.com/url?k=f5d072b2-a9857b62-f5d0438d-0cc47a6a52de-d6c20f64f13d1a50&u=https://doi.org/10.1101/2020.03.31.20047126

- • Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support
Giuseppe Gritti, Federico Raimondi, Diego Ripamonti, Ivano Riva, Francesco Landi, Leonardo Alborghetti, Marco Frigeni, Marianna Damiani, Caterina Micò, Stefano Fagiuoli, Roberto Cosentini, Ferdinando Luca Lorini, Fabrizio Fabretti, Jonathan Morgan, Benjamin M.J. Owens, Karan Kanhai, Jim Cowburn, Marco Rizzi, Fabiano Di Marco, Alessandro Rambaldi
medRxiv 2020.04.01.20048561; doi: https://protect2.fireeye.com/url?k=2b6ef2f6-773bfb26-2b6ec3c9-0cc47a6a52de-d40448543d0672ae&u=https://doi.org/10.1101/2020.04.01.20048561

- • Structural basis to design multi-epitope vaccines against Novel Coronavirus 19 (COVID19) infection, the ongoing pandemic emergency: an in silico approach
Sukrit Srivastava, Sonia Verma, Mohit Kamthania, Rupinder Kaur, Ruchi Kiran Badyal, Ajay Kumar Saxena, Ho-Joon Shin, Kailash Pandey, Michael Kolbe
bioRxiv 2020.04.01.019299; doi: https://protect2.fireeye.com/url?k=7d0d9358-21589a88-7d0da267-0cc47a6a52de-b25c54d50f55181e&u=https://doi.org/10.1101/2020.04.01.019299

- • The Spike Protein S1 Subunit of SARS-CoV-2 Contains an LxxIxE-like Motif that is Known to Recruit the Host PP2A-B56 Phosphatase
Halim Maaroufi
bioRxiv 2020.04.01.020941; doi: https://protect2.fireeye.com/url?k=8da0ef0b-d1f5e6db-8da0de34-0cc47a6a52de-6384763561cae9f8&u=https://doi.org/10.1101/2020.04.01.020941

- • Using ILI surveillance to estimate state-specific case detection rates and forecast SARS-CoV-2 spread in the United States
Justin D Silverman, Alex D Washburne
medRxiv 2020.04.01.20050542; doi: https://protect2.fireeye.com/url?k=c8864e10-94d347c0-c8867f2f-0cc47a6a52de-307866af64c89d63&u=https://doi.org/10.1101/2020.04.01.20050542

- • The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin

Ehud Chorin, Matthew Dai, Eric Shulman, Lailt Wadhwani, Roi Bar Cohen, Chirag Barbhaiya, Anthony Aizer, Douglas Holmes, Scott Bernstein, Michael Soinelli, David S Park, Larry Chinitz, Lior Jankelosn
medRxiv 2020.04.02.20047050; doi: https://protect2.fireeye.com/url?k=13e278f9-4fb77129-13e249c6-0cc47a6a52de-5a1856b4cf36bbd6&u=https://doi.org/10.1101/2020.04.02.20047050

- • Spatial variability in the risk of death from COVID-19 in Italy, 2020
Kenji Mizumoto, Sushma Dahal, Gerardo Chowell
medRxiv 2020.04.01.20049668; doi: https://protect2.fireeye.com/url?k=5af8cab6-06adc366-5af8fb89-0cc47a6a52de-68d3e599685dc2ce&u=https://doi.org/10.1101/2020.04.01.20049668

- • Harmonizing heterogeneous endpoints in COVID-19 trials without loss of information - an essential step to facilitate decision making
Maja von Cube, Marlon Grodd, Martin Wolkewitz, Derek Hazard, Jerome Lambert
medRxiv 2020.03.31.20049007; doi: https://protect2.fireeye.com/url?k=12187a44-4e4d7394-12184b7b-0cc47a6a52de-a1182d2bf4f370b4&u=https://doi.org/10.1101/2020.03.31.20049007

- • Reporting the life tracks of confirmed cases can effective prevent and control the COVID-19 outbreak in China
Jie Zhang, Tianjing Wang, Jiaqi Wang, Jingjing Chen, Hongwei Yan, Lin Sun
medRxiv 2020.04.01.20050450; doi: https://protect2.fireeye.com/url?k=32f7fa85-6ea2f355-32f7cbba-0cc47a6a52de-d62a76475a7dcd84&u=https://doi.org/10.1101/2020.04.01.20050450

- • A flexible load sharing system and implementation to anticipate and organise transfers based on ICU demand in the context of COVID-19 pandemic
Lucas Lacasa, Robert Challen, Ellen Brooks-Pollock, Leon Danon
medRxiv 2020.03.31.20049239; doi: https://protect2.fireeye.com/url?k=d653aa1c-8a06a3cc-d6539b23-0cc47a6a52de-10ec5876625e8b4c&u=https://doi.org/10.1101/2020.03.31.20049239

- • Evaluation of the Anticipated Burden of COVID-19 on Hospital-Based Healthcare Services Across the United States
Rohan Khera, Snigdha Jain, Zhenqiu Lin, Joseph S. Ross, Harlan Krumholz
medRxiv 2020.04.01.20050492; doi: https://protect2.fireeye.com/url?k=8eb1d678-d2e4dfa8-8eb1e747-0cc47a6a52de-5695d15873529062&u=https://doi.org/10.1101/2020.04.01.20050492

- • Interleukin-6 in COVID-19: A Systematic Review and Meta-Analysis
Eric Anthony Coomes, Hourmazd Haghbayan
medRxiv 2020.03.30.20048058; doi: https://protect2.fireeye.com/url?k=c25d39b4-9e083064-c25d088b-0cc47a6a52de-edfbf265e798180d&u=https://doi.org/10.1101/2020.03.30.20048058

- • Modelling the COVID-19 epidemics in Brasil: Parametric identification and public health measures influence
Renato Machado Cotta, Carolina Palma Naveira-Cotta, pierre magal
medRxiv 2020.03.31.20049130; doi: https://protect2.fireeye.com/url?k=a2a15648-fef45f98-a2a16777-0cc47a6a52de-9eafc70f33858787&u=https://doi.org/10.1101/2020.03.31.20049130

- • Analysis of adaptive immune cell populations and phenotypes in the patients infected by SARS-CoV-2
  Xiaofeng Yang, Tongxin Dai, Xiaobo Zhou, Hongbo Qian, Rui Guo, Lei Lei, Xingzhe Zhang, Dan Zhang, Lin Shi, Yanbin Cheng, Yaling Guo, Jinsong Hu, Baojun Zhang
  medRxiv 2020.03.23.20040675; doi: https://protect2.fireeye.com/url?k=55218500-09748cd0-5521b43f-0cc47a6a52de-44cf1ef9672db59e&u=https://doi.org/10.1101/2020.03.23.20040675

- • Clinical features, Diagnosis, and Treatment of COVID-19: A systematic review of case reports and case series
  Azin Tahvildari, Mahta Arbabi, Yeganeh Farsi, Parnian Jamshidi, Saba Hasanzadeh, Tess Moore Calcagno, Mohammad Javad Nasiri, Mehdi Mirsaeidi
  medRxiv 2020.03.28.20046151; doi: https://protect2.fireeye.com/url?k=1dd900d4-418c0904-1dd931eb-0cc47a6a52de-e5e6632597d155aa&u=https://doi.org/10.1101/2020.03.28.20046151

- • Parametric analysis of early data on COVID-19 expansion in selected European countries
  Martin Spousta
  medRxiv 2020.03.31.20049155; doi: https://protect2.fireeye.com/url?k=930ce6d4-cf59ef04-930cd7eb-0cc47a6a52de-7dbb21c51435b6c5&u=https://doi.org/10.1101/2020.03.31.20049155

- • Globalized low-income countries may experience higher COVID-19 mortality rates
  Rodolfo Jaffe, Mabel Patricia Ortiz Vera, Klaus Jaffe
  medRxiv 2020.03.31.20049122; doi: https://protect2.fireeye.com/url?k=2fdefb81-738bf251-2fdecabe-0cc47a6a52de-b5db3294c0935761&u=https://doi.org/10.1101/2020.03.31.20049122

- • Simple model for Covid-19 epidemics - back-casting in China and forecasting in the US
  Slav W Hermanowicz
  medRxiv 2020.03.31.20049486; doi: https://protect2.fireeye.com/url?k=3471c91a-6824c0ca-3471f825-0cc47a6a52de-c74c3b1e8d6fea83&u=https://doi.org/10.1101/2020.03.31.20049486

- • COVID-19 infection during pregnancy: a systematic review to summarize possible symptoms, treatments, and pregnancy outcomes
  Md. Mostaured Ali Khan, Md Nuruzzaman Khan, Md. Golam Mustagir, Juwel Rana, Md. Rajwanul Haque, Md. Mosfequr Rahman
  medRxiv 2020.03.31.20049304; doi: https://protect2.fireeye.com/url?k=8c40aa26-d015a3f6-8c409b19-0cc47a6a52de-39e8cb8f9c5c090a&u=https://doi.org/10.1101/2020.03.31.20049304

- • Intervention Serology and Interaction Substitution: Modeling the Role of 'Shield Immunity' in Reducing COVID-19 Epidemic Spread
  Joshua S Weitz, Stephen J Beckett, Ashley R Coenen, David Demory, Marian Dominguez-Mirazo, Jonathan Dushoff, Chung-Yin Leung, Guanlin Li, Andreea Magalie, Sang Woo Park, Rogelio Rodriguez-Gonzalez, Shashwat Shivam, Conan Zhao
  medRxiv 2020.04.01.20049767; doi: https://protect2.fireeye.com/url?k=c433160f-98661fdf-c4332730-0cc47a6a52de-97f9cee2c80f5f9d&u=https://doi.org/10.1101/2020.04.01.20049767

- • Perceptions and behavioural responses of the general public during the COVID-19 pandemic: A cross-sectional survey of UK Adults

Christina J Atchison, Leigh Bowman, Charlotte Vrinten, Rozlyn Redd, Philippa Pristera, Jeffrey W Eaton, Helen Ward
medRxiv 2020.04.01.20050039; doi: https://protect2.fireeye.com/url?k=e13656b1-bd635f61-e136678e-0cc47a6a52de-757ad56c8d0f7b36&u=https://doi.org/10.1101/2020.04.01.20050039

- • The Effectiveness of Targeted Quarantine for Minimising Impact of COVID-19
Alastair D Jamieson-Lane, Eric Cytrnbaum
medRxiv 2020.04.01.20049692; doi: https://protect2.fireeye.com/url?k=1f5962ca-430c6b1a-1f5953f5-0cc47a6a52de-72a4581b7649492c&u=https://doi.org/10.1101/2020.04.01.20049692

- • A Deep Learning Algorithm for Automated Cardiac Murmur Detection Via a Digital Stethoscope Platform
John S Chorba, Avi M Shapiro, Le Le, John Maidens, John Prince, Steve Pham, Mia M Kanzawa, Daniel N Barbosa, Brent E White, Jason Paek, Sophie G Fuller, Grant W Stalker, Sara A Bravo, Dina Jean, Subramaniam Venkatraman, Patrick M McCarthy, James D Thomas
medRxiv 2020.04.01.20050518; doi: https://protect2.fireeye.com/url?k=a5e28a87-f9b78357-a5e2bbb8-0cc47a6a52de-6c3d3d33f53fefe3&u=https://doi.org/10.1101/2020.04.01.20050518

- • Clinical Manifestations of Children with COVID-19: a Systematic Review
Tiago Henrique de Souza, Jose Antonio Nadal, Roberto Jose Negrao Nogueira, Ricardo Mendes Pereira, Marcelo Barciela Brandao
medRxiv 2020.04.01.20049833; doi: https://protect2.fireeye.com/url?k=025f7c1f-5e0a75cf-025f4d20-0cc47a6a52de-08fc8c6e8dd7dadc&u=https://doi.org/10.1101/2020.04.01.20049833

- • Remdesivir inhibits renal fibrosis in obstructed kidneys
Ming wu, Lin Xu, Bo Tan, Di Huang, Meijie Yuan, Chaoyang Ye
bioRxiv 2020.04.01.019943; doi: https://protect2.fireeye.com/url?k=222bc94b-7e7ec09b-222bf874-0cc47a6a52de-1e75ff83f2df0265&u=https://doi.org/10.1101/2020.04.01.019943

- • Monocyte-derived Prostaglandin E2 inhibits antigen-specific cutaneous immunity during ageing
Emma S Chambers, Milica Vukmanovic-Stejic, Barbara B Shih, Hugh Trahir, Priya Subramanian, Oliver P Devine, James Glanville, Derek Gilroy, Malcolm Rustin, Tom C Freeman, Neil A Mabbott, Arne N Akbar
bioRxiv 2020.04.02.020081; doi: https://protect2.fireeye.com/url?k=30513011-6c0439c1-3051012e-0cc47a6a52de-e753906e9853e5ba&u=https://doi.org/10.1101/2020.04.02.020081

- • Deducing the N- and O- glycosylation profile of the spike protein of novel coronavirus SARS-CoV-2
Asif Shajahan, Nitin T Supekar, Anne S Gleinich, Parastoo Azadi
bioRxiv 2020.04.01.020966; doi: https://protect2.fireeye.com/url?k=d0c3c734-8c96cee4-d0c3f60b-0cc47a6a52de-3283ec366e95f4da&u=https://doi.org/10.1101/2020.04.01.020966

- • SARS-CoV-2 neutralizing serum antibodies in cats: a serological investigation
Qiang Zhang, Huajun Zhang, Kun Huang, Yong Yang, Xianfeng Hui, Jindong Gao, Xinglin He, Chengfei Li, Wenxiao Gong, Yufei Zhang, Cheng Peng, Xiaoxiao Gao, Huanchun Chen, Zhong Zou, Zhengli Shi, Meilin Jin

bioRxiv 2020.04.01.021196; doi: https://protect2.fireeye.com/url?k=82fea82b-deaba1fb-82fe9914-0cc47a6a52de-01d26f4cf53972ae&u=https://doi.org/10.1101/2020.04.01.021196

- • The protein expression profile of ACE2 in human tissues
  Feria Hikmet, Loren Mear, Mathias Uhlen, Cecilia Lindskog
  bioRxiv 2020.03.31.016048; doi: https://protect2.fireeye.com/url?k=d224a996-8e71a046-d22498a9-0cc47a6a52de-3894967f9615dec1&u=https://doi.org/10.1101/2020.03.31.016048

- • Prospects for detecting early warning signals in discrete event sequence data: application to epidemiological incidence data.
  Emma Southall, Louise Dyson, Michael Tildesley
  bioRxiv 2020.04.02.021576; doi: https://protect2.fireeye.com/url?k=d2d180a3-8e848973-d2d1b19c-0cc47a6a52de-8808c8e2ef35763e&u=https://doi.org/10.1101/2020.04.02.021576

- • Structural analysis of SARS-CoV-2 and prediction of the human interactome
  Andrea Vandelli, Michele Monti, Edoardo Milanetti, Riccardo Delli Ponti, Gian Gaetano Tartaglia
  bioRxiv 2020.03.28.013789; doi: https://protect2.fireeye.com/url?k=cfcf7f55-939a7685-cfcf4e6a-0cc47a6a52de-5fa0e2ea1707023d&u=https://doi.org/10.1101/2020.03.28.013789

- • A SARS-CoV-2 Vaccination Strategy Focused on Population-Scale Immunity
  Mark Yarmarkovich, John M Warrington, Alvin Farrel, John M Maris
  bioRxiv 2020.03.31.018978; doi: https://protect2.fireeye.com/url?k=5756cd89-0b03c459-5756fcb6-0cc47a6a52de-d944e00d7cd8cd12&u=https://doi.org/10.1101/2020.03.31.018978

- • Insights into The Codon Usage Bias of 13 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Isolates from Different Geo-locations
  Ali Mostafa Anwar, Saif M. Khodary
  bioRxiv 2020.04.01.019463; doi: https://protect2.fireeye.com/url?k=3773c8db-6b26c10b-3773f9e4-0cc47a6a52de-fac6d032caf9122a&u=https://doi.org/10.1101/2020.04.01.019463

- • deepMINE - Natural Language Processing based Automatic Literature Mining and Research Summarization for Early Stage Comprehension in Pandemic Situations specifically for COVID-19
  Bhrugesh Pravinchandra Joshi, Vishvajit D Bakrola, Parth Shah, Ramar Krishnamurthy
  bioRxiv 2020.03.30.014555; doi: https://protect2.fireeye.com/url?k=e4cdaff7-b898a627-e4cd9ec8-0cc47a6a52de-9c291f7e02760f4b&u=https://doi.org/10.1101/2020.03.30.014555

- • SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium
  Leon Fodoulian, Joel Tuberosa, Daniel Rossier, Basile Landis, Alan Carleton, Ivan Rodriguez
  bioRxiv 2020.03.31.013268; doi: https://protect2.fireeye.com/url?k=77155094-2b405944-771561ab-0cc47a6a52de-e60f19590c929afc&u=https://doi.org/10.1101/2020.03.31.013268

- • Variable Macro X Domain of SARS-CoV-2 Retains the Ability to Bind ADP-ribose
  David Frick, Rajdeep S Virdi, Nemanja Vuksanovic, Narayan Dahal, Nicholas R Silvaggi
  bioRxiv 2020.03.31.014639; doi: https://protect2.fireeye.com/url?k=908972d4-ccdc7b04-908943eb-0cc47a6a52de-628f995d50a36718&u=https://doi.org/10.1101/2020.03.31.014639

- • Characterization and treatment of SARS-CoV-2 in nasal and bronchial human airway epithelia

Andres Pizzorno, Blandine Padey, Thomas Julien, Sophie Trouillet-Assant, Aurelien Traversier, Elisabeth Errazuriz-Cerda, Julien Fouret, Julia Dubois, Alexandre Gaymard, Xavier Lescure, Victoria Duliere, Pauline Brun, Samuel Constant, Julien Poissy, Bruno Lina, Yazdan Yazdanpanah, Olivier Terrier, Manuel Rosa-Calatrava
bioRxiv 2020.03.31.017889; doi: https://protect2.fireeye.com/url?k=cd046dc1-91516411-cd045cfe-0cc47a6a52de-15269d848ebe5e29&u=https://doi.org/10.1101/2020.03.31.017889

- • Identification of a common deletion in the spike protein of SARS-CoV-2
Zhe Liu, Huanying Zheng, Runyu Yuan, Mingyue Li, Huifang Lin, Jingju Peng, Qianlin Xiong, Jiufeng Sun, Baisheng Li, Jie Wu, Changwen Ke, Ruben J.G. Hulswit, Thomas A. Bowden, Andrew Rambaut, Oliver G Pybus, Nick Loman, Jing Lu
bioRxiv 2020.03.31.015941; doi: https://protect2.fireeye.com/url?k=b1cf72e8-ed9a7b38-b1cf43d7-0cc47a6a52de-7f84a2a48a1297fc&u=https://doi.org/10.1101/2020.03.31.015941

- • Virus-host interactome and proteomic survey of PMBCs from COVID-19 patients reveal potential virulence factors influencing SARS-CoV-2 pathogenesis
Qiming Liang, Jingjiao Li, Mingquan Guo, Xiaoxu Tian, Chengrong Liu, Xin Wang, Xing Yang, Ping Wu, Zixuan Xiao, Yafei Qu, Yue Yin, Joyce Fu, Zhaoqin Zhu, Zhenshan Liu, Chao Peng, Tongyu Zhu
bioRxiv 2020.03.31.019216; doi: https://protect2.fireeye.com/url?k=eeffcd44-b2aac494-eefffc7b-0cc47a6a52de-b224667808506c07&u=https://doi.org/10.1101/2020.03.31.019216

- • Comparative genomics suggests limited variability and similar evolutionary patterns between major clades of SARS-Cov-2
Matteo Chiara, David Stephen Horner, Graziano Pesole
bioRxiv 2020.03.30.016790; doi: https://protect2.fireeye.com/url?k=5cd51703-00801ed3-5cd5263c-0cc47a6a52de-d7efc10d0b450715&u=https://doi.org/10.1101/2020.03.30.016790

- • Covid-19 Outbreak Progression in Italian Regions: Approaching the Peak by March 29th
COSIMO DISTANTE, PRISCO PISCITELLI, ALESSANDRO MIANI
medRxiv 2020.03.30.20043612; doi: https://protect2.fireeye.com/url?k=435d2899-1f082149-435d19a6-0cc47a6a52de-ea06de04fa2abc25&u=https://doi.org/10.1101/2020.03.30.20043612

- • Forecasting COVID-19 impact in India using pandemic waves Nonlinear Growth Models
Pavan Kumar, Ram Kumar Singh, Chintan Nanda, Himangshu Kalita, Shashikanta Patairiya, Yagya Datt Sharma, Meenu Rani, Akshaya Srikanth Bhagavathula
medRxiv 2020.03.30.20047803; doi: https://protect2.fireeye.com/url?k=5e1e0c83-024b0553-5e1e3dbc-0cc47a6a52de-92d22674b4d61e4b&u=https://doi.org/10.1101/2020.03.30.20047803

- • Population based estimates of comorbidities affecting risk for complications from COVID-19 in the US
Mary L Adams, David L Katz, Joseph Grandpre
medRxiv 2020.03.30.20043919; doi: https://protect2.fireeye.com/url?k=217d76ad-7d287f7d-217d4792-0cc47a6a52de-52a094739110020c&u=https://doi.org/10.1101/2020.03.30.20043919

- • Growth rate and acceleration analysis of the COVID-19 pandemic reveals the effect of public health measures in real time

Yuri Tani Utsunomiya, Adam Taiti Harth Utsunomiya, Rafaela Beatriz Pintor Torrecilha, Silvana Cassia Paulan, Marco Milanesi, Jose Fernando Garcia
medRxiv 2020.03.30.20047688; doi: https://protect2.fireeye.com/url?k=6388d460-3fddddb0-6388e55f-0cc47a6a52de-7aaafcb27fd66ae1&u=https://doi.org/10.1101/2020.03.30.20047688

- • Clinical features and outcomes of 2019 novel coronavirus-infected patients with high plasma BNP levels
youbin liu, Dehui Liu, Huafeng Song, Chunlin chen, Mingfang lv, Xing pei, Zhongwei Hu, Zhihui Qin, Jinglong Li
medRxiv 2020.03.31.20047142; doi: https://protect2.fireeye.com/url?k=221f35a7-7e4a3c77-221f0498-0cc47a6a52de-4509d4e1e012ba0e&u=https://doi.org/10.1101/2020.03.31.20047142

- • Flattening the curve is not enough, we need to squash it. An explainer using a simple model
Emma S McBryde, Michael T Meehan, James M Trauer
medRxiv 2020.03.30.20048009; doi: https://protect2.fireeye.com/url?k=2dae26af-71fb2f7f-2dae1790-0cc47a6a52de-6af58433f1b13d6e&u=https://doi.org/10.1101/2020.03.30.20048009

- • Research on the Influence of Information Diffusion on the Transmission of the Novel Coronavirus (COVID-19)
Lin Shanlang, Ma Chao, Lin Ruofei, Huang Junpei, Xu Ruohan, Yuan Aini
medRxiv 2020.03.31.20048439; doi: https://protect2.fireeye.com/url?k=18b6fcc4-44e3f514-18b6cdfb-0cc47a6a52de-66d4764b084bf203&u=https://doi.org/10.1101/2020.03.31.20048439

- • *ACE2* and *TMPRSS2* variants and expression as candidates to sex and country differences in COVID-19 severity in Italy
Rosanna Asselta, Elvezia Maria Paraboschi, Alberto Mantovani, Stefano Duga
medRxiv 2020.03.30.20047878; doi: https://protect2.fireeye.com/url?k=6f4219d5-33171005-6f4228ea-0cc47a6a52de-56b08c8003080e8d&u=https://doi.org/10.1101/2020.03.30.20047878

- • Ambient nitrogen dioxide pollution and spread ability of COVID-19 in Chinese cities
Ye Yao, Jinhua Pan, Zhixi Liu, Xia Meng, Weidong Wang, Haidong Kan, Weibing Wang
medRxiv 2020.03.31.20048595; doi: https://protect2.fireeye.com/url?k=0aedd627-56b8dff7-0aede718-0cc47a6a52de-46d4164e7c413dba&u=https://doi.org/10.1101/2020.03.31.20048595

- • Monitoring trends and differences in COVID-19 case fatality rates using decomposition methods: Contributions of age structure and age-specific fatality
Christian Dudel, Tim Riffe, Enrique Acosta, Alyson A. van Raalte, Mikko Myrskyla
medRxiv 2020.03.31.20048397; doi: https://protect2.fireeye.com/url?k=b630974e-ea659e9e-b630a671-0cc47a6a52de-f2ff9d319ec5aecf&u=https://doi.org/10.1101/2020.03.31.20048397

- • Blood glucose levels in elderly subjects with type 2 diabetes during COVID-19 outbreak: a retrospective study in a single center
Ting Xue, Qianwen Li, Qiongyao Zhang, Wei Lin, Junping Wen, Li Li, Gang Chen
medRxiv 2020.03.31.20048579; doi: https://protect2.fireeye.com/url?k=fbd51f42-a7801692-fbd52e7d-0cc47a6a52de-d801e127da09bdfb&u=https://doi.org/10.1101/2020.03.31.20048579

- • A Gaussian model for the time development of the Sars-Cov-2 corona pandemic disease. Predictions for Germany made on March 30, 2020

Reinhard Schlickeiser, Frank Schlickeiser
medRxiv 2020.03.31.20048942; doi: https://protect2.fireeye.com/url?k=0558a6e3-590daf33-055897dc-0cc47a6a52de-0f3ac48f8d77bb6b&u=https://doi.org/10.1101/2020.03.31.20048942

- • Importance of suppression and mitigation measures in managing COVID-19 outbreaks
Michael E. Hochberg
medRxiv 2020.03.31.20048835; doi: https://protect2.fireeye.com/url?k=ab28ce76-f77dc7a6-ab28ff49-0cc47a6a52de-2ad0a63636bd64bc&u=https://doi.org/10.1101/2020.03.31.20048835

- • Differences in power-law growth over time and indicators of COVID-19 pandemic progression worldwide
Jack Merrin
medRxiv 2020.03.31.20048827; doi: https://protect2.fireeye.com/url?k=9c1753ca-c0425a1a-9c1762f5-0cc47a6a52de-afe70aefca2e4678&u=https://doi.org/10.1101/2020.03.31.20048827

- • Knowledge and behaviors toward COVID-19 among U.S. residents during the early days of the pandemic
John M. Clements
medRxiv 2020.03.31.20048967; doi: https://protect2.fireeye.com/url?k=8dd16707-d1846ed7-8dd15638-0cc47a6a52de-d6c15b2acc1ced20&u=https://doi.org/10.1101/2020.03.31.20048967

- • VPTMdb: a viral post-translational modification database
Yujia Xiang, Quan Zou, Lilin Zhao
bioRxiv 2020.04.01.019562; doi: https://protect2.fireeye.com/url?k=77f569df-2ba0600f-77f558e0-0cc47a6a52de-67529df029cc9083&u=https://doi.org/10.1101/2020.04.01.019562

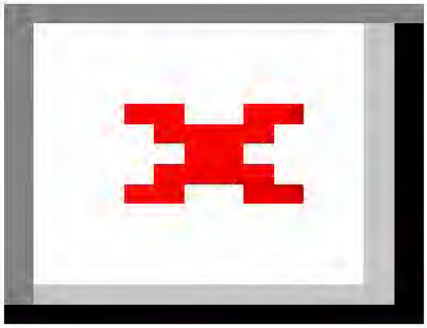
- • Sickness behaviour reduces network centrality in wild vampire bats
Simon P Ripperger, Sebastian Stockmaier, Gerald G Carter
bioRxiv 2020.03.30.015545; doi: https://protect2.fireeye.com/url?k=efc6833c-b3938aec-efc6b203-0cc47a6a52de-6a13693c1c1bea3d&u=https://doi.org/10.1101/2020.03.30.015545

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/03 15:02:25
Delivered Date:	2020/04/03 15:02:58
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: FiercePharma: AbbVie's HIV drug Kaletra stumbles in COVID-19 trial, but one analyst begs to differ
Date: 2020/03/19 11:59:33
Priority: Normal
Type: Note

AbbVie's HIV drug Kaletra stumbles in COVID-19 trial, but one analyst begs to differ

by
Angus Liu |
Mar 19, 2020 10:59am



Coronavirus

AbbVie's HIV combo med Kaletra (Aluvia) failed in a Chinese clinical trial of COVID-19, a study published in The New England Journal of Medicine shows. (Gettys)

Without an approved drug to tackle the novel coronavirus, scientists and biopharma companies are busy looking to repurpose existing therapies. One of the earliest efforts in that direction seems to have hit a snag—but at least one analyst refuses to call it a dead end.

AbbVie's HIV med Kaletra (Aluvia), a combination of antiviral drugs lopinavir and ritonavir, failed across the board in a 199-patient clinical trial. It didn't top standard of care at improving clinical symptoms, extending lifespan or cutting viral shedding in patients hospitalized with severe COVID-19, results from a study published Wednesday in The New England Journal of Medicine show.

Physicians at China's Jin Yin-tan Hospital in the city of Wuhan—which was until recently the epicenter of the outbreak—therefore concluded that Kaletra doesn't offer additional benefits over standard care in COVID-19. But Evercore ISI analyst Umer Raffat begs to disagree.

Basically, the team shouldn't look at overall results from the study, Raffat argued in a Wednesday note to clients.

Because it was one of the earliest clinical trials of COVID-19—the first patients enrolled on Jan. 18, just a week after SARS-CoV-2 had been identified and sequenced—little was known about the virus. And the patients had already been showing symptoms for about two weeks when they entered the study.

That's "very long," Raffat said, noting that Roche's flu drug Tamiflu needs to be initiated less than two days from symptom onset.

Because nobody knows when a patient's SARS-CoV-2 viral load peaks, the study should have focused on "identifying the time point up until which an antiviral may work," he said.

In fact, if we zero in on patients that received Kaletra earlier, a clearer mortality benefit shows up. According to the study, the death rate in Kaletra patients was 15.0% at day 28, versus 27.1% among placebo patients, provided therapy started within 12 days of symptoms starting, Raffat noted. When all modified intention-to-treat patients are analyzed, the difference narrowed to 16.7% versus 25.0%.

"Honestly, I want to see a further sub-cut of this data ... perhaps for patients that initiated [Kaletra] less than eight days from symptom onset," Raffat said.

In a separate editorial that ran alongside the study, infectious disease specialists Lindsey Baden, director of clinical research at Brigham and Women's Hospital; and NEJM Editor-in-Chief Eric Rubin also looked for silver linings.

Though they called the results "disappointing," Baden and Rubin pointed to the fact that the team chose a challenging population to study, because the patients recruited were already late in the disease course and already had major tissue damage. "Even highly active antibacterial agents have limited efficacy in advanced bacterial pneumonia," they wrote.

To put it into perspective, as of Thursday, China has reported 81,263 infections of the novel coronavirus, with 3,250 deaths. That translates into an overall mortality rate of 4%, far lower than the double-digit percentages seen in the Kaletra trial.

But perhaps the more worrisome data lies in Kaletra's inability to cut viral load, which is important because the drug is meant to directly target the virus rather than merely relieving symptoms. At day 28, SARS-CoV-2 RNA was still detected in 40.7% of the patients on Kaletra.

RELATED: Roche launches clinical trial of COVID-19 pneumonia hopeful Actemra after backing from China

Lopinavir and ritonavir inhibit protease, an enzyme HIV and coronaviruses use to replicate. The combo first attracted interest after a pulmonary and critical care physician dispatched to Wuhan said Kaletra had healed his disease. China's National Health Commission soon added the med to its COVID-19 clinical guidance and has kept it there in all its subsequent updates.

Earlier this month, AbbVie said it's collaborating with health authorities, including the U.S. FDA, to determine Kaletra's antiviral activity in COVID-19 patients, as well as efficacy and safety.

Other drugs recommended by the Chinese guidance include an influenza med called Arbidol (umifenovir) that's not approved in Western countries, the standard malaria drug chloroquine, as well as old antiviral ribavirin and interferon-alpha, among others.

Chinese scientists and Gilead Sciences are also examining the latter's antiviral drug remdesivir, which has so far shown the most promise against the novel coronavirus.

Bin Cao, the lead author of the Kaletra study, is also leading the Chinese clinical study on remdesivir—and that has Evercore ISI's Raffat concerned that the overall remdesivir trial may be presented the same way.

"We should look specifically for patients that initiated remdesivir fast enough," he argued. "[T]he entire purpose of [the] trial is to define that dosing window."

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/19 11:59:20
Delivered Date:	2020/03/19 11:59:33
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: KHN Morning Briefing, Monday, Apr 6 2020
Date: 2020/04/06 12:14:57
Priority: Normal
Type: Note

KHN Morning Briefing

Summaries of health policy coverage from major news organizations
Monday, Apr 6 2020 UPDATED 9:22 AM

From Kaiser Health News - Latest Stories:

Kaiser Health News Original Stories

'You Pray That You Got The Drug.' Ailing Couple Gambles On Trial For COVID-19 Cure
Josie and George Taylor of Everett, Washington, are two of the first people in the U.S. to recover from novel coronavirus infections after joining a clinical trial for the antiviral drug remdesivir. (JoNel Aleccia, 4/6)

Mysterious Heart Damage, Not Just Lung Troubles, Befalling COVID-19 Patients
Most of the attention in the COVID-19 pandemic has been on how the virus affects the lungs. But evidence shows that up to 1 in 5 infected patients have signs of heart damage and many are dying due to heart problems. (Markian Hawryluk, 4/6)

Trump Administration Uses Wartime Powers To Be First In Line On Medical Supplies
As states scour the world for masks and other protective medical equipment, the federal government has repeatedly invoked a little-known clause in the Defense Production Act to step to the front of the line for sought-after health supplies. (Christina Jewett and Lauren Weber, 4/3)

'Staying Away From Grandma' Isn't An Option In Multigenerational Homes
About 1 in 5 U.S. residents live in multigenerational households. Many of those have three or more generations all under one roof. While the living arrangement has financial and emotional benefits, those families face a unique set of challenges as COVID-19 continues to spread. (Cara Anthony, 4/6)

Long-Standing Racial And Income Disparities Seen Creeping Into COVID-19 Care
Many health officials around the nation have not released data on the ethnic and racial demographics of people tested for the new coronavirus. But public health experts said the anecdotes are adding up, and they fear the response to the pandemic will result in predictable health care disparities. (Blake Farmer, Nashville Public Radio, 4/6)

'You've Been Served': Wisconsin Hospitals Sued Patients Even During Pandemic
Wisconsin hospitals had filed at least 104 lawsuits in small claims court since the state declared a public health emergency March 12. Most now say they are suspending the cases; one hospital has dismissed them after a reporter's calls. (Bram Sable-Smith, Wisconsin Public Radio, 4/3)

As Coronavirus Spreads, Workers Could Lean On ACA Coverage Protection
KHN's Julie Rovner discusses the role of the Affordable Care Act in helping to provide coverage to people affected by the virus' economic repercussions. (4/3)

Political Cartoon: 'Passing the Buck?'
Kaiser Health News provides a fresh take on health policy developments with "Political Cartoon: 'Passing the Buck?'" by Ann Telnaes.

Here's today's health policy haiku:
IT'S NOT ALWAYS THAT SIMPLE

Staying away from
Grandma isn't an option
For some families.
- Anonymous

Summaries Of The News:

Federal Response

Political, Institutional Failures Undermined U.S. Response In Early Phase Of Outbreak: What Happened In Those Key 70 Days?

The Washington Post investigates government and White House actions during the first two months of the year when top officials knew about the threat but the country failed to rise to meet it. And AP looks at how that critical time was squandered in terms of stocking up on equipment. Meanwhile, health care was already a losing issue for President Donald Trump and Republicans, and this pandemic highlights that vulnerability.

The Washington Post: Denial And Dysfunction Plagued U.S. Government As Coronavirus Raged By the time Donald Trump proclaimed himself a wartime president — and the coronavirus the enemy — the United States was already on course to see more of its people die than in the wars of Korea, Vietnam, Afghanistan and Iraq combined. The country has adopted an array of wartime measures never employed collectively in U.S. history — banning incoming travelers from two continents, bringing commerce to a near-halt, enlisting industry to make emergency medical gear, and confining 230 million Americans to their homes in a desperate bid to survive an attack by an unseen adversary. (Abutaleb, Dawsey, Nakashima and Miller, 4/4)

The Associated Press: U.S. 'Wasted' Months Before Preparing For Virus Pandemic After the first alarms sounded in early January that an outbreak of a novel coronavirus in China might ignite a global pandemic, the Trump administration squandered nearly two months that could have been used to bolster the federal stockpile of critically needed medical supplies and equipment. A review of federal purchasing contracts by The Associated Press shows federal agencies largely waited until mid-March to begin placing bulk orders of N95 respirator masks, mechanical ventilators and other equipment needed by front-line health care workers. (Biesecker, 4/6)

The Associated Press: Lost Time: How Coronavirus Spread While Supply Orders Lagged An Associated Press review has found that the Trump administration squandered precious months before bolstering the federal stockpile of urgently needed medical supplies and equipment. (4/6)

NBC News: Two Months In, Trump's Coronavirus Response Creates More Chaos More than two months into what President Donald Trump calls a "war" against COVID-19, his administration's efforts to combat the deadly disease, along with its disastrous effects on the U.S. economy, are often creating more problems than they solve. Bidding wars for lifesaving equipment, a power struggle between Trump's son-in-law and the vice president, political gamesmanship, the centralization of authority and decentralization of accountability, and the creation of new government programs while standing bureaucracies are ignored have all contributed to chaos within the political, economic and health care systems. (Allen, 4/5)

The Associated Press: Trump Sees Limits Of Presidency In Avoiding Blame For Virus President Donald Trump is confronting the most dangerous crisis a U.S. leader has faced this century as the coronavirus spreads and a once-vibrant economy falters. As the turmoil deepens, the choices he makes in the critical weeks ahead will shape his reelection prospects, legacy and the character of the nation. The early fallout is sobering. In the White House's best-case scenario, more than 100,000 Americans will die and millions more will be sickened. At least 10 million have already lost their jobs, and some economists warn it could be years before they find work again. (Peoples, Colvin and Miller, 4/6)

NBC News: 'His Achilles' Heel': Coronavirus Crisis Highlights Trump's Lack Of Health Care Plan Health care was already a vulnerability for President Donald Trump before the coronavirus pandemic hit. Now his lack of a plan to fix the system is coming under a new microscope as the crisis costs many Americans their coverage and overwhelms providers. (Kapur, 4/6)

Politico: Trump Tries On A Fourth Chief Of Staff In The Middle Of A Devastating Crisis President Donald Trump's fourth chief of staff relinquished a safe seat in Congress and agreed to join the White House in early March, when the unemployment rate sat at a historic low and Trump's team appeared confident about his reelection. A month later, Mark Meadows is now presiding over vastly different West Wing, which is under siege like never before due to the coronavirus pandemic. The administration still lacks the ability to widely test Americans for the virus. (Cook and Zanona, 4/6)

Top Health Officials Say Americans Should Brace For Tragedy This Week On Par With Pearl Harbor, 9/11 Even as President Donald Trump offered a more optimistic stance, his officials warned that this week will be tough for Americans. "This is going to be the hardest and the saddest week of most Americans' lives, quite frankly," said Surgeon General Jerome Adams. Meanwhile, experts fear that the number of confirmed cases in the country--which has exceeded 330,000--is only a fraction of the cases out there.

The Associated Press: Trump Tempers Officials' Grave Assessments With Optimism The U.S. surgeon general says that Americans should brace for levels of tragedy reminiscent of the Sept. 11 attacks and the bombing of Pearl Harbor, while the nation's infectious disease chief warned that the new coronavirus may never be completely eradicated from the globe. Those were some of the most grim assessments yet for the immediate future and beyond. But hours later, President Donald Trump and Vice President Mike Pence tried to strike more optimistic tones, suggesting that hard weeks ahead could mean beginning to turn a corner. (Weissert and Freking, 4/6)

Reuters: U.S. Faces 'Really Bad' Week As Coronavirus Deaths Spike The United States is entering what a senior official warned on Sunday would be the "hardest" week of the coronavirus crisis as the death toll mounted, but some saw glimmers of hope from a slight slowing of fatalities in hard-hit New York. New York, the epicenter of the U.S. coronavirus outbreak, reported on Sunday that for the first time in a week, deaths had fallen slightly from the day before. But there were still nearly 600 new fatalities and more than 7,300 new cases in the state. (Trotta and Alper, 4/5)

Reuters: Trump Hopes Virus Leveling-Off In Hot Spots; Advisers Take Tempered View New York, the hardest-hit state, reported on Sunday that for the first time in a week, deaths had fallen slightly from the day before, but there were still nearly 600 new fatalities and more than 7,300 new cases. "Maybe that's a good sign," Trump told reporters at a White House briefing, referring to the drop in fatalities in New York.While Trump cited those numbers as an indication that Americans were starting to see "light at the end of the tunnel", Anthony Fauci, a member of Trump's coronavirus task force, said it took weeks for efforts like social-distancing and stay-at-home orders to slow the virus' spread. (Alper and Spetalnick, 4/5)

The Washington Post: Americans Warned Of 'Pearl Harbor Moment' As Trump Tells Parts Of The Nation To Brace For 'Peak' Fauci, when asked if dire predictions were at odds with the promise of light at the tunnel's end, said a peak suggests a possible turning point in the path of the virus but "doesn't take away from the fact that tomorrow or the next day is going to look really bad." The dead in the United States already number more than 9,500, triple the toll of the terrorist attacks that brought the nation low on Sept. 11, 2001. U.S. Surgeon General Jerome M. Adams reached back further to find an analogue for the sense of national alarm, as the country surpassed 333,000 known cases. He said the coming days could bring catastrophe comparable to the attack that drew the United States into World War II in 1941. (Stanley-Becker, Gregg and Booth, 4/5)

The Wall Street Journal: U.S. Expects Coronavirus Peak In Some Cities Next Week As Global Toll Climbs Modeling shows New York, Detroit and New Orleans—and areas around those cities—will likely reach the peak of their outbreaks in the next six to seven days, White House coronavirus response coordinator

Deborah Birx said Saturday evening. "The next two weeks are extraordinarily important," Dr. Birx said at a White House news briefing. "This is the moment to do everything that you can on the presidential guidelines. This is the moment to not be going to the grocery store, not going to the pharmacy, but doing everything you can to keep your family and your friends safe." (Restuccia, Korn and Honan, 4/4)

CNN: Fauci: US Is 'Struggling' To Get Coronavirus Under Control And To Say Otherwise Would Be Wrong The nation's top infectious disease expert said Sunday that the United States is "struggling" to get the coronavirus crisis under control and that to say otherwise "would be a false statement." Dr. Anthony Fauci warned Americans in an interview on CBS that "it is going to be a bad week" ahead as there is an escalation in cases, but that "within a week" or so the number of cases should start to flatten out. (Robertson and Cole, 4/5)

ABC News: Trump Discusses Opening The Country As Coronavirus Peak Approaches The president discussed a Saturday morning call he had with commissioners of most of the major sports to discuss the effects of coronavirus to the industry, emphasizing that he wants fans "back in the arena" as soon as they can be. "You know, they want to see basketball and baseball and football and hockey. They want to see their sports. They want to go out onto the golf courses and breathe nice clean, beautiful fresh air," Trump said. "No, I can't tell you a date, but I think it's going to be sooner rather than later." (Stoddart, 4/4)

The New York Times: Official Counts Understate The U.S. Coronavirus Death Toll A coroner in Indiana wanted to know if the coronavirus had killed a man in early March, but said that her health department denied a test. Paramedics in New York City say that many patients who died at home were never tested for the coronavirus, even if they showed telltale signs of infection. In Virginia, a funeral director prepared the remains of three people after health workers cautioned her that they each had tested positive for the coronavirus. But only one of the three had the virus noted on the death certificate. Across the United States, even as coronavirus deaths are being recorded in terrifying numbers — many hundreds each day — the true death toll is likely much higher. (Kliff and Bosman, 4/5)

The Washington Post: Coronavirus Death Toll: Americans Are Almost Certainly Dying Of Covid-19 But Being Left Out Of The Official Count The fast-spreading novel coronavirus is almost certainly killing Americans who are not included in the nation's growing death toll, according to public health experts and government officials involved in the tally. The U.S. Centers for Disease Control and Prevention counts only deaths in which the presence of the coronavirus is confirmed in a laboratory test. "We know that it is an underestimation," agency spokeswoman Kristen Nordlund said. (Brown, Reinhard and Davis, 4/5)

Politico: CDC Begins Blood Tests To Find Undetected Coronavirus Cases The CDC has started conducting antibody tests to help determine how many people have been infected with the coronavirus — including those who never developed symptoms, an agency spokesperson confirmed. The test analyzes antibodies in a person's blood to detect if they have been exposed to the coronavirus. identifying people who have recovered from infection and likely have some degree of protection from reinfection is a possible key to opening back up the country's workforce. (Roubein, 4/4)

In other news about top health officials —

The Washington Post: Fauci And Birx Worked Together On AIDS. Now They're Partners In Fighting The Coronavirus. Anthony Fauci and Deborah Birx walked side-by-side in the 1980s on hospital rounds, watching young men die of a mysterious disease that had no cure. The disease was so deadly that when Birx lost a large amount of blood giving birth in 1983 at the hospital where she worked, she screamed at the physician not to give her a transfusion, concerned tainted blood might come from men with the mysterious disease. (Kranish, 4/5)

CNN: Dr. Anthony Fauci Said He Tested Negative For Coronavirus Saturday The nation's top infectious disease expert said he tested negative for coronavirus Saturday when asked why he wasn't wearing a face mask as the pandemic spreads across the nation. "There are a couple of reasons. One of them is

part of the, in fact the major reason to wear a face mask is to protect you from infecting you," Dr. Anthony Fauci said Sunday at a news conference with the White House coronavirus task force. "I had my test yesterday and it's negative." (Carvajal and Kelly, 4/5)

The Hill: Scott Gottlieb Becomes Key Voice Warning Trump, GOP On Coronavirus Scott Gottlieb has seen his national profile grow amid the coronavirus outbreak as the former Food and Drug Administration commissioner becomes a leading voice from outside the administration on how to tackle the worst health epidemic the country may ever have faced. Gottlieb, a 47-year-old physician, has become a regular presence on cable news shows, and his Twitter account is widely followed by journalists, health policy experts and politicians. (Chalfant, 4/5)

Captain Of Aircraft Carrier Who Was Fired After Sounding Outbreak Alarm Tests Positive For COVID-19 Capt. Brett Crozier was relieved of duty after a memo he wrote about his concerns for the crew of aircraft carrier USS Theodore Roosevelt went public. Top administration officials say they stand by the decision, despite harsh criticism. Some worry that a pattern of such actions could have a chilling effect for those who are concerned about soldiers' health and well being.

The New York Times: He Led A Top Navy Ship. Now He Sits In Quarantine, Fired And Infected. For days, he fended off fears that the contagion would spread unchecked through his crew. Then last week, the captain of the aircraft carrier Theodore Roosevelt, who had appealed to his superiors for help, was fired. By Sunday, friends said, he had come down with the coronavirus himself. The military has long adhered to a rigid chain of command and tolerated no dissent expressed outside official channels. Capt. Brett E. Crozier, the skipper of the aircraft carrier, knew he was up against those imperatives when he asked for help for nearly 5,000 crew members trapped in a petri dish of a warship in the middle of a pandemic. (Schmitt and Ismay, 4/5)

Politico: 'How We Hold Leaders Accountable': Esper Defends Firing Of Navy Captain Who Raised Coronavirus Alarm Defense Secretary Mark Esper on Sunday defended the firing of the Navy captain who sounded the alarm about a coronavirus outbreak aboard an aircraft carrier, characterizing the commanding officer's ouster as an "example of how we hold leaders accountable." On CNN's "State of the Union," Esper said acting Navy Secretary Thomas Modly "made a very tough decision" Thursday to relieve Capt. Brett Crozier of command of the USS Theodore Roosevelt, but the Pentagon chief added that it was a decision he supported. (Forgey, 4/5)

The Wall Street Journal: Trump Backs Dismissal Of USS Roosevelt Captain President Trump said he agreed with the Navy's decision to fire Capt. Brett Crozier, the commanding officer of the USS Theodore Roosevelt, after a memo in which the captain pleaded for help with a coronavirus outbreak at sea leaked to the media. The president said Saturday that it was inappropriate for Capt. Crozier to write the four-page memo in which he demanded that superiors allow him to take the carrier to the port in Guam to offload sailors stricken with Covid-19, the pneumonialike disease caused by the virus. As of Saturday, *155 of the ship's sailors had tested positive.* (Restuccia, 4/5)

ProPublica: It's Hardly Shocking The Navy Fired A Commander For Warning Of Coronavirus Threat. It's Part Of A Pattern. Navy experts believe that the cumulative effects of the service's decisions over the past several years to punish those who speak out will result in silencing sailors with legitimate concerns about their health and safety. "This may have the effect of chilling the responses of other commanding officers because it will be perceived, fairly or not, as a shoot the messenger scenario," said James Stavridis, a retired admiral and former head of the United States Naval Institute, who called for an investigation into the circumstances surrounding the dismissal. (Miller and Rose, 4/4)

The Wall Street Journal: Aboard The USS Roosevelt, Sailors Braced For The Worst The visit to Vietnam in early March was intended as a historic milestone and a symbol of far-reaching U.S. aims in the Pacific, marking 25 years of diplomatic relations with a rare port call by an American aircraft carrier that had been months in the planning. But as the USS Theodore Roosevelt headed back out to sea, sailors and officers realized they faced danger aboard the ship. Crew members soon began suffering from an

outbreak of Covid-19 that spread rapidly, plunging the Roosevelt and the Navy into a crisis that now holds implications for U.S. military readiness. (Kesling and Youssef, 4/5)

The Washington Post: Biden Says It Was 'Close To Criminal' For Navy To Oust Captain Who Warned Of Coronavirus Outbreak On Aircraft Carrier Former vice president Joe Biden on Sunday sharply criticized the dismissal of Capt. Brett Crozier, who was removed from his post as commander of the USS Theodore Roosevelt after speaking up in a leaked letter to his superiors about the handling of a coronavirus outbreak aboard the vessel. "I think it's close to criminal, the way they're dealing with this guy. ... The idea that this man stood up and said what had to be said, got it out that his troops, his Navy personnel, were in danger, in danger — look how many have the virus," Biden said in an interview on ABC News's "This Week." (Sonmez and DeBonis, 4/5)

The Wall Street Journal: Ships Are Moving, But Exhausted Sailors Are Stuck At Sea Under Coronavirus Restrictions Oceangoing shipping companies, already hit by crumbling demand and fractured supply chains from the coronavirus pandemic, are facing another problem on their vessels. Thousands of seafarers can't travel to man ships, leaving growing numbers of crews around the world exhausted and facing illness at sea. (Paris, 4/5)

Preparedness

'This Is Ludicrous': Governors Frustrated With Lack Of National Ventilator Distribution Strategy States have been forced to compete with each other to get ventilators and other medical supplies after the federal government put most of the onus on the governors to acquire equipment. While some governors try to avoid being too critical of the Trump administration, others expressed their frustration. "To say, 'we're a backup' — I mean, the surgeon general alluded to Pearl Harbor," said Washington Gov. Jay Inslee. "Can you imagine if Franklin Delano Roosevelt said, 'I'll be right behind you, Connecticut. Good luck building those battleships'?"

The New York Times: Amid Warnings Of A Coronavirus 'Pearl Harbor,' Governors Walk A Fine Line As the surgeon general told the nation to brace for "our Pearl Harbor moment" of cascading coronavirus deaths this week, several governors said on Sunday that their states were in urgent need of federal help and complained that they had been left to compete for critical equipment in the absence of a consistent strategy and coordination from the Trump administration. Some clearly walked a delicate path, criticizing what they saw as an erratic, inadequate federal response, while also trying to avoid alienating the White House as states vie with one another for resources both from Washington and on the market that can mean the difference between life and death. (Rojas and Swales, 4/5)

The Wall Street Journal: New York Races To Get Coronavirus Supplies Before Cases Peak New York City scrambled on Sunday to get more hospital equipment as it faced the possibility of running out of ventilators in the next few days. As New York state prepared for an apex of coronavirus cases, Mayor Bill de Blasio said about 4,000 patients were intubated as of Sunday and the city expected nearly 1,000 more intubations in the coming days. The city needs 1,000 to 1,500 more ventilators to avoid running out by Tuesday or Wednesday, the mayor said. The city had originally expected to run out on Sunday. (Calfas and Ansari, 4/5)

The Wall Street Journal: Coronavirus Cases Rise Sharply, As U.S. Braces For Most Challenging Days Ahead "Everyone says federal stockpile, federal stockpile. There's not enough in the federal stockpile to take care of New York, and Illinois, and Texas, and Florida, and California," said Mr. Cuomo, a Democrat. The Chinese government helped facilitate a donation of 1,000 ventilators, as well as a large supply of masks, that arrived in New York City on Saturday. And New York was expecting a shipment of 140 ventilators from Oregon. "New York needs more ventilators, and we are answering their call for help," Democratic Oregon Gov. Kate Brown said in a tweet, explaining that her state was in a better position now. (Ansari, Michaels and Calfas, 4/6)

Politico: Trump Administration Tells States To Step Up As Governors Plead For Aid Republican and Democratic governors alike pushed back, saying the Trump administration had failed to mount the kind

of national coordinated response needed to address the crisis and that shortages of tests, ventilators and protective equipment for physicians persisted. "This is ludicrous," said Gov. Jay Inslee of Washington, a Democrat. "The surgeon general referred to Pearl Harbor. Can you imagine if Franklin Delano Roosevelt said, 'We'll be right behind you, Connecticut. Good luck building those battleships?'" (McCaskill and Ollstein, 4/5)

The Hill: Feds Send Ventilators To Coronavirus Hot Spots Around Country President Trump announced Sunday that the federal government is sending several hundred additional ventilators to states hit hard by the coronavirus outbreak. Trump during a White House briefing said that over the last 24 hours, the federal government has delivered an additional 500 ventilators to New Jersey, which is among the hardest-hit states. He said it also has sent 200 ventilators to Louisiana and 300 to Michigan. Another 600 have gone to Illinois, he said, while Massachusetts will be getting 100. (Sullivan, 4/5)

WBUR: N.J. Governor Wants More Ventilators From Stockpile: 'We Need The Feds To Step Up' With cases of COVID-19 surging and medical supplies rapidly dwindling, New Jersey Gov. Phil Murphy is calling on federal officials to scale up aid efforts for the state, saying, "It feels like we entered this war, and it is a war, with less ammunition than we needed." New Jersey has reported more than 25,500 cases of the coronavirus and more than 500 deaths — second only to New York. The crush of cases pushed Murphy to take dramatic action on Thursday by granting the state police the authority to commandeer medical supplies and equipment from private companies. (Breslow, 4/3)

CNN: New York Surgeon Writes Haunting Letter About Rationing Care For Patients Who Don't Have The Coronavirus In a haunting letter to his friends and colleagues, a Columbia University surgeon describes how coronavirus has forced doctors to ration care for very sick patients who don't have the virus, but still need medical procedures. "We have had to make decisions that I personally have never had to contemplate before," wrote Dr. Emile Bacha, director of the pediatric and congenital cardiac surgery at Columbia University Irving Medical Center. "We have had to ration care and make decisions about who is considered an urgent or emergent case." (Cohen, Bonifield and Nigam, 4/5)

CNN: As Coronavirus Cases Grow, Hospitals Adopt A System To Rank Patients For Treatment With the peak of Covid-19 infections still ahead and medical supplies still scarce, hospitals and physicians are gearing up for a nearly impossible challenge: deciding who gets a life-saving ventilator and who doesn't. "Physicians who work in parts of the world that don't have adequate resources have had to make decisions like this maybe even on a routine basis, but physicians in the United States have never faced anything like this before," said Dr. Robert Truog, director of the Center for Bioethics at Harvard Medical School. "It is going to be extremely difficult." (de Puy Kamp, Devine and Griffin, (4/3)

CNN: Alibaba Billionaire And Brooklyn Nets Owner Joe Tsai Donates Millions Of Supplies To New York Joe Tsai, the billionaire co-founder of Chinese ecommerce giant Alibaba, and his wife Clara Wu Tsai, have donated 2.6 million masks, 170,000 goggles and 2000 ventilators to New York — the US epicenter of the coronavirus pandemic. The supplies were split into two shipments. The first arrived on Thursday at Newark Liberty International Airport, while the second arrived on Saturday at John F. Kennedy International Airport. (Alesci and Liao, 4/4)

The Hill: Momentum Grows To Change Medical Supply Chain From China Calls are growing for the U.S. to reduce its dependence on China for key medicines and supplies as Americans face widespread shortages in the midst of the coronavirus pandemic. While the U.S. supply chain's heavy reliance on Beijing for medical manufacturing has been glaringly apparent for roughly two decades, both lawmakers and administration officials say the virus has exposed just how vulnerable the country is as it leans on China and other nations to help provide the tools necessary to combat the pathogen. (Beavers, 4/5)

Meanwhile, a website change reveals Jared Kushner's sway over the federal response —

ABC News: After Kushner Says 'It's Our Stockpile,' HHS Website Changed To Echo His Comments On Federal Crisis Role It was a telling moment in the rising tensions between the Trump White House and

state governors desperate for medical equipment to deal with the exploding coronavirus crisis. At Thursday's briefing on how the government is responding, Trump's senior adviser and son-in-law Jared Kushner scolded states for not building up their own stockpiles, saying that the "the notion of the federal stockpile was it's supposed to be our stockpile, it's not supposed to be states' stockpiles that they then use." (Gittleson, 4/3)

Politico: Strategic National Stockpile Description Altered Online After Kushner's Remarks The official government webpage for the Strategic National Stockpile was altered Friday to seemingly reflect a controversial description of the emergency repository that White House adviser Jared Kushner offered at a news conference Thursday evening. According to a brief online summary on the Department of Health and Human Services website, the stockpile's role "is to supplement state and local supplies during public health emergencies. Many states have products stockpiled, as well." (Forgey, 4/3)

In other news about the governors' response efforts —

The Associated Press: Governors Seize Spotlight Amid States' Coronavirus Response Across America, as families stuck in their homes anxious and isolated by the new coronavirus, a new daily ritual is taking shape: tuning into the governor's afternoon press briefing. Residents sequestered under a stay-at-home order in Ohio seem to hang on Republican Gov. Mike DeWine's every word, sharing his latest orders among friends via text message and on social media and following along with a drinking game — "Wine with DeWine." Signature T-shirts and tumblers are available online. (Smyth and Ronayne, 4/6)

The Washington Post: Unafraid To Call Out Trump, Hogan Emerges As Lead GOP Voice For Urgent Action On Pandemic Maryland Gov. Larry Hogan (R) phoned his favorite country radio station the other day and made a confession. He can't listen anymore. The coronavirus pandemic consumes his every waking moment. The host seemed unsurprised. "Do you ever get tired of being interviewed?" she asked. "Because I'm seeing you everywhere." (Cox, Dawsey and Wiggins, 4/5)

The Washington Post: Maryland Gov. Hogan Issues Emergency Order For Nursing Homes, D.C. Shutters Waterfront Market As Region Continues Coronavirus Fight The Washington region's battle with the novel coronavirus intensified Sunday, as the number of confirmed cases soared to more than 7,000 and Maryland Gov. Larry Hogan (R) issued an emergency order requiring nursing home staff to wear protective gear and segregate infected patients to halt the spread of the disease following outbreaks in the state's long-term care facilities. (Shapira, Chason, Nirappil and Natanson, 4/5)

The Associated Press: Governors Plead For Food Stamp Flexibility Amid Pandemic Yvonne Knight, who has respiratory problems that make her especially vulnerable in the coronavirus pandemic, can't buy groceries online with her food stamps — even though each trip to the store is now a risky endeavor. Going out to buy food terrifies the 38-year-old woman with cerebral palsy, but she is one of millions of people who receive food aid through the federal Supplemental Nutrition Assistance Program that can't be used in flexible ways. (Galvan and Khalil, 4/6)

When It Comes To Testing Shortages, Necessity Is Proving To Be The Mother Of Invention

As diagnostic testing continues to pick up speed, shortages of some supplies and a backlog of samples push hospitals, academic medical centers and labs to create their own patchwork solutions.

The Wall Street Journal: Shortage Of Test Components Forces Labs To Beg, Borrow And Improvise Facing looming shortages of supplies needed to conduct coronavirus tests, some laboratories are taking matters into their own hands. Labs at places such as New York University and Stanford University are starting to make their own chemical mixtures because they can't buy enough. A high-school lab in Tennessee managed to set up testing operations, with two science teachers leading the charge to reduce turnaround time in their area. And Northwell Health, a hospital network in New York, said it is making its own 3-D printed swabs to take samples from patients' throats or noses. (Abbott, 4/5)

NPR: Coronavirus Testing Woes Continue To Plague U.S. One of the nation's most important medical testing companies has acknowledged that it has a backlog of at least 115,000 coronavirus tests, which helps explain why so many desperate doctors and patients haven't been able to get tested. Quest

Diagnostics of Secaucus, N.J., says the backlog occurred because a company lab in San Juan Capistrano, Calif., where the company's coronavirus testing started, got overwhelmed when testing started to ramp up. (Stein, 4/3)

In Global Cutthroat Competition To Acquire Protective Gear For Health Workers, U.S. Is Making Enemies With Its Tactics

"It's 'Lord of the Flies: PPE Edition'," said Jeremy Konyndyk, a former U.S. official who specializes in disaster response. "We need some global solidarity, and instead we have global competition." In other news on health care workers: staff shortages, tales from the front lines, rationing gear, and more.

Politico: 'Lord Of The Flies: PPE Edition': U.S. Cast As Culprit In Global Scrum Over Coronavirus Supplies The coronavirus pandemic is pushing countries around the world into a cutthroat competition for medical resources — and the United States is being cast as a leading villain. President Donald Trump's administration stands accused of effectively hijacking shipments of masks and additional crucial supplies meant for other countries, including U.S. allies, and strong-arming private firms to prioritize America over other parts of the world. (Toosi, 4/3)

NBC News: Government Watchdog: Hospitals Face Severe Shortages Of Medical Gear, Confusing Guidance From Government Hospitals across the country face dire shortages of vital medical equipment amid the coronavirus outbreak — including testing kits and thermometers — and fear they can't ensure the safety of health care workers needed to treat patients with COVID-19, according to an internal government watchdog report released Monday. The alarming findings, based on interviews conducted from March 23 to March 27, represent the first government assessment of how the country's hospitals are coping with the outbreak and confirm previous media reports and warnings from health workers that the medical system is under unprecedented strain. (Strickler, Rappleye, De Luce and Dilanian, 4/6)

Kaiser Health News: Trump Administration Uses Wartime Powers To Be First In Line On Medical Supplies The Trump administration quietly invoked the Defense Production Act to force medical suppliers in Texas and Colorado to sell to it first — ahead of states, hospitals or foreign countries. It took this action more than a week before it announced Thursday that it would use the little-known aspect of the law to force 3M to fill its contract to the U.S. first. Firms face fines or jail time if they don't comply.The Cold War-era law gives federal officials the power to edge out the competition and force contractors to provide supplies to them before filling orders for other customers. (Jewett and Weber, 4/3)

WBUR: Health Care Workers Push Back Against Rationing Of Protective Equipment The Massachusetts Nurses Association, where Wright is a union leader, says Mercy is one of several medical facilities in the state that have recently adopted concerning policies. In statements released on Thursday, the union described it as part of a chaotic response to the COVID-19 pandemic at two large hospital networks: Trinity Health, which operates Mercy, and Steward Health Care, which operates Carney Hospital and eight other facilities in the state. The policies have left nurses confused and worried for their own health and that of their patients, union leaders say. (Chen, 4/3)

Modern Healthcare: Protective Equipment Shortage Spurs Grassroots Solutions More than 2,500 healthcare providers have requested protective gear for their employees via Project N95, one of the latest volunteer-based efforts to mitigate equipment shortages spurred by COVID-19.Project N95 aims to connect healthcare facilities, manufacturers and distributors to arm frontline workers with personal protective equipment like N95 respirators, which are in short supply. As of March 24, around 1,700 healthcare institutions requested more than 70 million units of PPE via the website. That has grown to nearly 2,550 facilities and more than 341 million units. (Kacik, 4/3)

NBC News: Staff At NYC Hospital Where Nurse Died Will Finally Get Coronavirus Tests A New York hospital where some staffers said they could not get coronavirus tests even after a nurse died of the disease it causes has told workers that starting Tuesday it will provide tests to all employees who have developed symptoms consistent with COVID-19, according to an email obtained by NBC News. "Starting on Tuesday, April 7, if you develop symptoms consistent with COVID-19, we would like to test you for

this viral infection using the PCR test with a nasopharyngeal swab within a few days of the onset of your symptoms," said the email Saturday from Senior Vice President Vicki R. LoPachin to all staffers of the New York City area's Mount Sinai hospital network. "This will provide guidance to you and to Employee Health Services regarding your clinical status and return to work." (Saliba and Rappleye, 4/5)

KQED: Most In-Home Caregivers Receive Low Pay And No Protective Gear The United Domestic Workers AFSCME local 3930 union represents (UDW) 117 thousand workers in 21 counties and helps negotiate these contracts. According to the union, IHHS providers make on average $13.43 an hour and only 9% get employee-sponsored healthcare. IHHS providers have been hit hard and are in a similar difficult position as other domestic workers. Like house cleaners and child care providers, a majority of IHHS workers are hired individually by the person receiving care. They're classified as contractors, so they do not have access to traditional unemployment benefits. (Harnett, 4/4)

The Washington Post: A Chicago Anesthesiologist's Account Of Treating Coronavirus/Covid-19 Patients, One Of The Pandemic's Most Dangerous Jobs "It's a powerless feeling, watching someone die": An anesthesiologist on the frontline of coronavirus outbreak. (4/5)

The New York Times: With Virus Surge, Dermatologists And Orthopedists Are Drafted For The E.R. One of the largest hospital networks in New York has given its doctors an ultimatum: either help deal with the coronavirus crush, or stay home without pay. At other hospitals, too, all hands are being called to deck. Neurosurgeons and cardiologists, orthopedic, dermatology and plastic surgery residents — all have been pulled into emergency rooms and intensive care wards. Receptionists who normally deal with billing are also being told they will be reassigned, to emergency rooms to help screen Covid-19 patients. (Sengupta, 4/3)

And some tips for DIY masks that won't exacerbate shortage for workers —

The New York Times: What's The Best Material For A Mask For Coronavirus? While a simple face covering can reduce the spread of coronavirus by blocking outgoing germs from coughs or sneezes of an infected person, experts say there is more variation in how much homemade masks might protect the wearer from incoming germs, depending on the fit and quality of the material used. Scientists around the country have taken it upon themselves to identify everyday materials that do a better job of filtering microscopic particles. In recent tests, HEPA furnace filters scored well, as did vacuum cleaner bags, layers of 600-count pillowcases and fabric similar to flannel pajamas. Stacked coffee filters had medium scores. Scarves and bandanna material had the lowest scores, but still captured a small percentage of particles. (Parker-Pope, 4/5)

The New York Times: Facebook Hampers Do-It-Yourself Mask Efforts As health workers on the front lines of the coronavirus pandemic plead for personal protective equipment, volunteer efforts to create hand-sewn masks and deliver them to medical professionals have quickly sprung up across the internet. But those efforts were hampered by Facebook's automated content moderation systems over the past week, according to sewing organizers who have used the social network to coordinate donation campaigns. (Isaac, 4/5)

Army Of Workers In Amazon Warehouses Voice Concerns About Workplace Safety

Amazon's inconsistent response to the epidemic has unsettled many of the 400,000 workers helping to fill orders that have soared at least 50% for groceries. Infections have occurred in at least 50 of its 500 warehouses. Other supply chain news is on protections for grocery store workers and wasted food, as well.

The New York Times: Gaps In Amazon's Coronavirus Response Fuel Warehouse Workers' Demands

Jonathan Bailey, a 30-year-old Amazon warehouse employee in Queens, has a system for protecting himself from the coronavirus at work. He wears a medical mask with a bandanna tied over it. When he returns to the apartment he shares with his wife, he dumps his mask, work gloves, neon green Amazon safety vest and other clothes into a plastic trash bag. He's not certain it really works, but he figures it's better than nothing. "We're very careful," Mr. Bailey said. "We're in the epicenter of it all." As millions

of Americans heed government orders to hunker down, ordering food and medicines and books and puzzle boards for home delivery, many of Amazon's 400,000 warehouse workers have stayed on the job, fulfilling the crushing demands of a country suddenly working and learning from home. (Weise and Conger, 4/5)

The Associated Press: Grocery Workers Are Key During The Virus. And They're Afraid Every day, grocery workers are restocking toilet paper, eggs, produce and canned goods as fast as the items fly off the shelves. They disinfect keypads, freezer handles and checkout counters as hundreds of people weave around them, sometimes standing too close for comfort amid the coronavirus pandemic. Some work for hours behind clear plastic barriers installed at checkout counters, bulwarks against sudden sneezes or coughs that can propel germs. (Vertuno, 4/6)

Politico: Food Goes To Waste Amid Coronavirus Crisis The coronavirus pandemic is leading the food industry and regulators to change policies as they grapple with empty shelves, a glut of fresh produce and milk, and sudden shifts in consumer buying habits. The problem isn't a shortage of food and commodities. If anything, food waste is becoming a bigger issue as traditionally big, bulk buyers — like college dorms and restaurant chains — suddenly stop receiving deliveries. As a result, millions of gallons of milk are being dumped, and farmers have no alternative but to turn fresh vegetables into mulch. (Behsudi and McCrimmon, 4/5)

Science And Innovations

Flouting Advice From Experts In His Own Administration, Trump Again Touts Malaria Drug's Potential Although the malaria drug has shown promising results, the studies so far have been far too small to offer a true look at the treatment's potential. President Donald Trump, though, continues to push for its use, despite a shortage for patients who use the medication for other illnesses. Meanwhile, patients rush to get into clinical trials for experimental drugs.

The New York Times: Ignoring Expert Opinion, Trump Again Promotes Use Of Hydroxychloroquine President Trump doubled down Sunday on his push for the use of an anti-malarial drug against the coronavirus, issuing medical advice that goes well beyond scant evidence of the drug's effectiveness as well as the advice of doctors and public health experts. Mr. Trump's recommendation of hydroxychloroquine, for the second day in a row at a White House briefing, was a striking example of his brazen willingness to distort and outright defy expert opinion and scientific evidence when it does not suit his agenda. (Crowley, Thomas and Haberman, 4/5)

The Associated Press Fact Check: Trump Pitches Drug Not Approved For Coronavirus President Donald Trump is pitching a medicine for COVID-19 sufferers that science has not concluded is effective or safe for their use. "Take it," he said of the drug. For people sick with the coronavirus, he said Sunday, "It can help them but it's not going to hurt them." In fact, it may or may not help some people, and it may or may not hurt them. His straight-ahead advocacy of hydroxychloroquine, a malaria drug, is the latest and one of the most consequential examples of Trump and public-health authorities not being on the same page in the pandemic. (Yen, Tucker and Woodward, 4/6)

The Washington Post: Giuliani, A Familiar Voice In Trump's Ear, Promotes Experimental Coronavirus Treatments Rudolph W. Giuliani, who was in the center of the impeachment storm earlier this year as an unpaid private attorney for President Trump, has cast himself in a new role: as personal science adviser to a president eager to find ways to short-circuit the coronavirus pandemic. In one-on-one phone calls with Trump, Giuliani said, he has been touting the use of an anti-malarial drug combination that has shown some early promise in treating covid-19, the disease the novel coronavirus causes, but whose effectiveness has not yet been proved. (Helderman, Dawsey and Swaine, 4/5)

The Wall Street Journal: States Try Reducing Malaria-Drug Hoarding Amid Unproven Coronavirus Benefit States across the U.S. are taking steps to prevent hoarding of decades-old antimalarial drugs for treatment of the new coronavirus, an effort to preserve supplies for other patients who rely on the medicines to remedy ailments such as lupus and arthritis. At least 20 states late last month began

implementing emergency restrictions or guidelines to ease pressure on the supply of hydroxychloroquine and chloroquine for the autoimmune patients. Some states are limiting prescription sizes or asking pharmacists to make sure a patient tested positive for the coronavirus. (Hopkins, 4/5)

The Wall Street Journal: Gilead Accelerates Production Of Experimental Coronavirus Drug Gilead Sciences Inc. GILD 1.60% has ramped up production of its experimental coronavirus drug, which has seen overwhelming demand amid a surge in cases around the world. The drugmaker said Saturday that it now has 1.5 million individual doses of its drug remdesivir on hand, an amount that could be enough to supply more than 140,000 patients. Gilead, which won't charge for the supply, is making the drug available through clinical trials and special programs that allow doctors and hospitals to apply for access. (Wilde Mathews and Rockoff, 4/4)

The Associated Press: Patients Rush To Join Studies Testing Drug For Coronavirus The new coronavirus made Dr. Jag Singh a patient at his own hospital. His alarm grew as he saw an X-ray of his pneumonia-choked lungs and colleagues asked his wishes about life support while wheeling him into Massachusetts General's intensive care unit. When they offered him a chance to help test remdesivir, an experimental drug that's shown promise against some other coronaviruses, "it did not even cross my mind once to say 'no,'" said Singh, a heart specialist. Coronavirus patients around the world have been rushing to join remdesivir studies that opened in hospitals in the last few weeks. (Marchione, 4/6)

Kaiser Health News: 'You Pray That You Got The Drug.' Ailing Couple Gambles On Trial For COVID-19 Cure For 10 days last month, they lay in side-by-side isolation units in a Seattle-area hospital, tethered to oxygen and struggling to breathe as the coronavirus ravaged their lungs. After nearly 52 years of marriage, that was the hardest thing: being apart in this moment, too weak to care for each other, each alone with their anxiety and anguish. "I worried about my husband a lot," recalled Josie Taylor, 74, who fell ill a few days before George, 76. "Yes, I was concerned about me, but I was more concerned about what was going to happen to him." (Aleccia, 4/6)

CNN: Trump Doubles Down On Unproven Drug Hydroxychloroquine To Treat And Prevent Coronavirus President Donald Trump on Sunday again doubled down on an unproven therapy for the novel coronavirus: hydroxychloroquine. Without citing evidence, he said it's a "great" and "powerful" anti-malaria drug "and there are signs that it works on this, some very strong signs. "For people without heart problems, Trump recommended combining hydroxychloroquine with azithromycin, a common antibiotic. He said azithromycin "will kill certain things that you don't want living within your body." (Azad, Yu and Robertson, 4/6)

The Hill: Trump Promotes Use Of Drug For Coronavirus: 'I'm Not A Doctor. But I Have Common Sense' President Trump on Sunday forcefully touted the use of hydroxychloroquine as a potential means to combat or even prevent the onset of symptoms from the coronavirus, wading further into a medical debate that has put him at odds with some of his top health experts. Trump said the government has stockpiled 29 million pills of the drug, which is also used to treat lupus. For a second consecutive day, he suggested even those without coronavirus symptoms might consider taking the drug despite limited evidence about its efficacy in treating the virus. (Samuels, 4/5)

Bill Gates To Build Factories For 7 Leading Vaccines To Help Accelerate Long Journey From Development To Public Use

"Even though we'll end up picking at most two of them, we're going to fund factories for all seven, just so that we don't waste time in serially saying which vaccine works and then building the factory," Bill Gates said. The strategy means billions of dollars will be wasted, but Gates said the loss would be worth it in the long run.

The Wall Street Journal: Bill Gates To Spend Billions On Coronavirus Vaccine Development Microsoft Corp. co-founder Bill Gates said his foundation will spend billions of dollars to fund the construction of factories for the most promising efforts to develop a vaccine to combat the novel coronavirus. Mr. Gates, a billionaire philanthropist who is one the richest people in the world, said the Bill and Melinda

Gates Foundation will work with seven makers of a possible vaccine to build these factories. Mr. Gates, who announced the efforts in an appearance on "The Daily Show With Trevor Noah" Thursday, acknowledged that billions of dollars would be wasted on vaccines that won't pan out. (Calfas, 4/5)
Meanwhile —
The New York Times: Can An Old Vaccine Stop The New Coronavirus? A vaccine that was developed a hundred years ago to fight the tuberculosis scourge in Europe is now being tested against the coronavirus by scientists eager to find a quick way to protect health care workers, among others. The Bacillus Calmette-Guerin vaccine is still widely used in the developing world, where scientists have found that it does more than prevent TB. The vaccine prevents infant deaths from a variety of causes, and sharply reduces the incidence of respiratory infections. The vaccine seems to "train" the immune system to recognize and respond to a variety of infections, including viruses, bacteria and parasites, experts say. (Rabin, 4/3)
Stat: This Tiny Federal Agency Was Built To Respond To A Crisis Like Coronavirus. Now That It's Here, Is BARDA Ready? It seems like an agency tailor-made for a crisis like the coronavirus pandemic. The Biomedical Advanced Research and Development Authority, or BARDA, was created to invest in drug development projects that private industry wouldn't touch, such as anthrax vaccines and therapies for Ebola, Zika, or swine flu. Lawmakers were so confident that BARDA could help scientists develop a coronavirus vaccine, therapy, or even a diagnostic test that Congress has showered the agency with a $3.5 billion boost in funding, more than tripling its total budget. But consultants and experts in biotech and in academia told STAT they had serious concerns about BARDA's preparedness to absorb the massive new workload it will take to identify targets for a coronavirus vaccine or therapy. (Florko, 4/6)
In The Era Of Coronavirus, Scientists Are The New Rock Stars
After a long period of popular backlash against experts and expertise, people are turning to scientists for hope. Dr. Anthony Fauci's rise in popularity is just one example of many around the world. In other science and innovation news: a look at how one patient survived, the mysterious heart damage that comes with the disease, and the hope hidden in survivors' blood.
The New York Times: The Rising Heroes Of The Coronavirus Era? Nations' Top Scientists If it weren't the age of social distancing, people would stop them on the street to take selfies. Instead, they get adoring messages on social media. Others appear on television daily. The new celebrities emerging across Europe as the coronavirus burns a deadly path through the continent are not actors or singers or politicians. Instead, they are epidemiologists and virologists who have become household names after spending most of their lives in virtual anonymity. (Stevis-Gridneff, 4/5)
The New York Times: How New Jersey's First Coronavirus Patient Survived On the evening of March 4, James Cai, a 32-year-old physician assistant, was languishing on a cot, isolated in a small, windowless room on the emergency-room floor of Hackensack University Medical Center, when the television news caught his attention. Before that moment, Cai had been in a strange medical limbo, starting midday on March 2, when he left a medical conference in Times Square because he had a bad cough. Instead of heading to his home in Lower Manhattan, he texted his wife that he was going to spend the night at his mom's place in New Jersey. His mother was out of town, and if he had the flu, he could spare his wife and their daughter, a cheerful 21-month-old who clung to him when he was home, the risk of catching whatever it was. That was Cai: cautious, a worrier, overprotective, the kind of medical professional who liked to rule out the worst-case scenarios first. (Dominus, 4/5)
Kaiser Health News: Mysterious Heart Damage, Not Just Lung Troubles, Befalling COVID-19 Patients
While the focus of the COVID-19 pandemic has been on respiratory problems and securing enough ventilators, doctors on the front lines are grappling with a new medical mystery. In addition to lung damage, many COVID-19 patients are also developing heart problems — and dying of cardiac arrest. As more data comes in from China and Italy, as well as Washington state and New York, more cardiac experts are coming to believe the COVID-19 virus can infect the heart muscle. (Hawryluk, 4/6)

CNN: He Recovered From The Coronavirus And Now His Plasma Donation Could Save The Lives Of Others A California man who was diagnosed with the coronavirus and recovered has donated his plasma to help others fighting the potentially deadly virus. On March 6, Jason Garcia noticed he had a mild cough and some congestion. The 36-year-old aerospace engineer from Escondido, California, didn't think that much of it. But later while on a work trip, he noticed a headache had begun accompanying his cough. (Silverman, 4/6)

Capitol Watch

Special Committee To Oversee Stimulus Spending Will Be 'Forward-Looking,' Clyburn Says

While some Democrats want the special committee to investigate the Trump administration's early missteps, top House leaders said it will be focused on "the here and now." House Majority Whip Jim Clyburn will head the panel. Meanwhile, Democrats and Republicans are already clashing over a potential fourth coronavirus package.

Politico: Clyburn: House Coronavirus Panel 'Will Be Forward-Looking,' Not Review Trump's Early Response House Majority Whip Jim Clyburn said on Sunday that a new congressional panel intended to oversee the distribution of coronavirus relief funds "will be forward-looking" and not probe President Donald Trump's widely criticized initial response to the ongoing public health crisis. "My understanding is that this committee will be forward-looking," Clyburn told CNN's "State of the Union." (Forgey, 4/5)

Modern Healthcare: White House Floated Limited Surprise Billing Proposal In COVID-19 Talks The White House proposed a simple ban on surprise medical billing that left out controversial arbitration and payment benchmarking mechanisms during negotiations on Congress' third COVID-19 relief package, three sources familiar with the talks said. All surprise billing measures were ultimately left out of the final economic stimulus package after fierce lobbying by healthcare providers. Reports of patients being balance billed for services related to COVID-19 are already emerging. The White House declined to comment. (Cohrs, 4/3)

The Hill: Pelosi, McConnell Clash Over Next Coronavirus Bill Speaker Nancy Pelosi (D-Calif.) and Senate Majority Leader Mitch McConnell (R-Ky.) are publicly at odds over a potential fourth coronavirus package. The two leaders, whose public relationship has been tense in recent weeks, are taking different tactics on follow-up legislation and sparring through the media on next steps to address the devastating economic and health effects of the pandemic. The mixed messaging, which comes as lawmakers are out of town until at least April 20, underscores the looming challenge of keeping the congressional response to the coronavirus bipartisan. The first three bills passed with overwhelming support on both sides of the aisle. (Carney, 4/5)

Economic Toll

Four Benchmarks That Can Help States Decide When To Re-Open Include Heavy Testing And Contact Tracing

Experts weigh on when the country will know it can start to re-open. But a foundational piece of that is testing, an area where the United States has repeatedly fallen short. In other news on the economy: stimulus package distribution, sick leave, mounting debt, and more.

The New York Times: U.S. Is Nowhere Close To Reopening The Economy, Experts Say How long can we keep this up? It is still very early in the U.S. effort to snuff a lethal pandemic by shutting down much of the economy. But there is a growing question — from workers, the White House, corporate boardrooms and small businesses on the brink — that hangs over what is essentially a war effort against a virus that has already killed more than 9,000 Americans. There is no good answer yet, in part because we don't even have the data needed to formulate one. (Tankersley, 4/6)

The New York Times: How Will We Know When It's Time To Reopen The Nation? Everyone wants to know when we are going to be able to leave our homes and reopen the United States. That's the wrong way to frame it. The better question is: "How will we know when to reopen the country?" Any date that

is currently being thrown around is just a guess. It's pulled out of the air. To this point, Americans have been reacting, often too late, and rarely with data. (Carroll, 4/6)

Stat: The 'Certified Recovered' From Covid-19 Could Lead The Economic Recovery Re-opening a nightclub in New York seems crazy at this point, as that's just the kind of setting in which Covid-19 can spread like wildfire. But it wouldn't be crazy if all of the workers and patrons had previously had Covid-19 and recovered from it. (Edlin and Nesbitt, 4/6)

The Washington Post: Americans Hit By Economic Shocks As Confusion, Stumbles Undermine Trump's Stimulus Effort The Trump administration has stumbled in its initial push to implement the $2 trillion coronavirus aid package, with confusion and fear mounting among small businesses, workers and the newly unemployed since the bill was signed into law late last month. Small-business owners have reported delays in getting approved for loans without which they will close their doors, while others say they have been denied altogether by their lenders and do not understand why. (Stein, 4/5)

The New York Times: Coronavirus And Paid Sick Leave: A Quarantined Uber Driver's Quest Zachary Frenette likes working as an Uber driver in Phoenix. He is a top-rated driver who often chats with his customers on their trips. During the outbreak of the coronavirus last month, business began to slow. Then, a possible exposure to the virus prompted Mr. Frenette, 29, to quarantine himself. Off the roads and worried about making his rent on time, he turned to Uber for help. (Fortin, 4/4)

The New York Times: Millennials, Burdened With Debt, Are Now Facing Their First Economic Crisis The last time a serious economic downturn hit in 2008, Evan Schade was in high school and the crisis seemed like a news event that happened to other people. This time, as the coronavirus has brought the economy to its knees, it has become a personal affair. When nonessential businesses were closed last month in Kansas City, Mo., where he lives, Mr. Schade, 26, lost his job at a carpet store and almost all of the shifts in his second job at a coffee shop. His girlfriend, Kaitlyn Gardner, 23, was laid off from a different coffee shop. (Popper, 4/6)

NBC News: Falling Through The Cracks: Many Americans Won't Get Coronavirus Checks For millions of Americans awaiting coronavirus cash, help is not on the way. Although the $2 trillion stimulus bill passed last month includes payments of up to $1,200 for everyone who makes less than the limit, many Americans will fall through the cracks. That includes most college kids, immigrants without Social Security numbers and some disabled adults. (Lederman, 4/6)

ABC News: Hobby Lobby Closes Its Stores After Defying Coronavirus Stay-At-Home Orders Hobby Lobby finally closed all of its stores in the U.S. after the craft supplies company received backlash for staying open in at least one state amid the novel coronavirus pandemic. Nearly all of the store employees will be furloughed, as well as a large portion of corporate and distribution employees, according to a statement from the company. (Torres, 4/4)

CIDRAP: What Can Firms Do Now In The Midst Of A Pandemic? While US business owners may feel anxious or unsure amid the COVID-19 pandemic, they should resist institutional paralysis and use this time to prioritize operations, protect the health and mental wellbeing of employees, and plan for recovery, experts say. "Businesses can prioritize the services they provide if they are short-staffed or do not have all the supplies needed and identify alternative suppliers, if feasible," said Lisa Koonin, DrPH, MN, MPH, senior advisor to the US Centers for Disease Control and Prevention's (CDC's) pandemic response team and founder of Health Preparedness Partners in Atlanta. She said that planning for COVID-19 is "very similar" to planning for an influenza pandemic. (Van Beusekom, 4/3)

Modern Healthcare: Outpatient Care Gets Walloped By COVID-19 In March Job Losses Dentists' offices, physicians' offices, home health providers and other outpatient healthcare sectors shouldered the brunt of healthcare's steep job losses in March as the novel coronavirus ravaged the economy and forced businesses to shed workers. The healthcare industry shed 42,500 jobs last month. The ambulatory sector, which typically captures most of the industry's job gains, in March comprised a whopping 96% of

the losses, according to preliminary data from the U.S. Bureau of Labor Statistics, released Friday. Hospitals added a modest 200 jobs. (Bannow, 4/3)

Elections

Republicans Were Counting On An 'America Vs. Socialism' Dichotomy For 2020. Then Came The Pandemic.

The coronavirus is unending political plans on both sides, but has hit Republicans particularly hard as more and more Americans turn to the government for help. Meanwhile, Democrats refocus their message to point to how quickly the economic success voters attribute to President Donald Trump has been wiped out. And Wisconsin mayors call on state officials to postpone Tuesday's primary.

The New York Times: Politics Through The Looking Glass: Virus Scrambles The Left-Right Lines The 2020 edition of the Conservative Political Action Conference in Oxon Hill, Md., in February offered a theme-park version of what was to be President Trump's re-election message: Under the banner of "America vs. Socialism," the convention featured anti-Marx branded popcorn, an RV emblazed with the words "Socialism Takes Capitalism Creates" and a children's book promoting personal freedom and private-property rights. Speeches included tirades against big government and "Medicare for all." (Rutenberg, 4/5)

The New York Times: Progressives Built An Organizing Juggernaut For 2020. Then The Virus Hit. When it became clear last month that former Vice President Joseph R. Biden Jr. would almost certainly win the Democratic nomination, many of the progressive Democrats who supported other presidential candidates were disappointed but not deterred. They quickly shifted their electoral focus to candidates lower on the ballot. The plan was straightforward: They would donate to a slew of insurgent congressional candidates, and a stable of grass-roots groups would be ready and waiting to organize for the general election and beyond. (Herndon and Philbrick, 4/5)

Politico: Dems Find A Rallying Cry: Trump Tanked The Economy For most of the presidential campaign, the economy looked like the one thing that could overcome Donald Trump's stubbornly low approval ratings and carry him to a second term. Even many Democrats acknowledged they had no cohesive economic message of their own. But now that the coronavirus has laid waste to the surging stock market and low unemployment, Democrats are discovering another obstacle — framing a coherent economic argument that all the party's factions can rally around. (Siders and Schneider, 4/6)

The Hill: Campaigns Face Attack Ad Dilemma Amid Coronavirus Crisis A volley of political advertisements attacking the government's responses to the coronavirus pandemic has some strategists worried that going negative at a time of crisis will backfire. Most of the ads have so far come from Democrats and have been sharply critical of President Trump's delayed response to the outbreak. (Greenwood, Manchester and Brufke, 4/5)

Politico: 'It's A Sh-- Sandwich': Republicans Rage As Florida Becomes A Nightmare For Trump The staggering unemployment exploding on President Donald Trump's watch would worry any incumbent running for reelection, but troubles in Florida are injecting an added dose of fear into a jittery GOP. Already anxious about Trump's chances in the nation's biggest swing state, Republicans now are dealing with thousands of unemployed workers unable to navigate the Florida system to apply for help. And the blowback is directed straight at Trump's top allies in the state, Gov. Ron DeSantis and Sen. Rick Scott. (Fineout and Caputo, 4/3)

Reuters: Citing Coronavirus, Wisconsin Mayors Urge Postponement Of Tuesday's Election Nine Wisconsin mayors, including those representing the state's five largest cities, on Sunday urged the state's top public health official to postpone Tuesday's primary election due to the coronavirus pandemic. The mayors of Milwaukee, Madison, Green Bay and six others asked Wisconsin Health Services Secretary Andrea Palm in a letter to use emergency powers under the state constitution to postpone in-person voting and avoid "putting hundreds of thousands of citizens at risk." (Ax, 4/6)

The Washington Post: Wisconsin Legislature Comes Under Fire For 'Unconscionable' Decision To Hold Primary Amid Coronavirus Pandemic Two members of the Wisconsin Elections Commission on Sunday denounced the Republican-led legislature for moving forward with the state's primary this Tuesday, warning that the move will put the lives of Wisconsin residents at risk amid the spiraling coronavirus pandemic. The two commissioners — Ann S. Jacobs and Mark L. Thomsen, both Democratic appointees — voiced their concerns in a letter to state House Speaker Robin Vos (R) and state Senate Republican leader Scott L. Fitzgerald. (Sonmez, 4/5)

The Wall Street Journal: Supreme Court To Weigh In On Wisconsin's Absentee Ballots The Supreme Court was poised Sunday to decide whether Wisconsin voters would have an extra six days to submit absentee ballots to compensate for the disruption imposed by the coronavirus pandemic on Tuesday's in-person primary election. While more than a dozen other states postponed spring election dates to avoid conflicting with public-health orders to minimize crowds and public gatherings, Wisconsin decided to proceed with its April 7 primary. (Bravin and Corse, 4/5)

ProPublica: Who Has Emergency Authority Over Elections? Nobody's Quite Sure. In each of the past seven years, Massachusetts Secretary of State William Galvin has sought authority to revamp or reschedule elections in case of emergency. Every time, the legislature has blocked him. These rebuffs had repercussions in Westborough, a Boston suburb that was set to hold its town election last month. As COVID-19 cases rose across the state, the governor shut down gatherings of more than 25 people two days before ballots were to be cast, making it illegal for voters to congregate at the local polling place, a senior center, on election day, March 17. (Huseman, 4/6)

Health Law

First Pandemic Since Health Law Was Instituted Will Put It Through The Wringer

A pandemic-created recession is expected to test the health law like it's never been tested before. Meanwhile, President Donald Trump's decision not to create a special enrollment session surprised even his own advisers.

NBC News: Obamacare's Health Care Protections Face First True Test In Coronavirus Crisis The Affordable Care Act turned 10 last month and is credited with helping 20 million more Americans get health insurance than before the law was enacted. But the coronavirus pandemic could be the first true test of how well "Obamacare" works at preventing significant coverage loss, experts say. For people stricken with COVID-19, the disease caused by the coronavirus, coverage through the ACA could mean the difference between financial stability and bankruptcy that could cause lingering hardship long after the pandemic ends, industry experts say. (Stenson, 4/5)

Politico: How Trump Surprised His Own Team By Ruling Out Obamacare As the coronavirus ran rampant and record jobless numbers piled up, the nation's health insurers last week readied for a major announcement: The Trump administration was reopening Obamacare enrollment to millions of newly uninsured Americans. It was an announcement that never came. (Cancryn, Cook and Luthi, 4/3)

Kaiser Health News: As Coronavirus Spreads, Workers Could Lean On ACA Coverage Protection Concerns about health care during the coronavirus pandemic are raising the profile of the federal Affordable Care Act, which can help those who have lost their jobs with an option to get insurance. Julie Rovner, Kaiser Health News' chief Washington correspondent, talked to WBUR's "Here &Now" host Jeremy Hobson on Friday about efforts to get the federal government to let people have a special enrollment period for coverage plans sold on the ACA marketplaces, as well as the effect massive job layoffs will have on Medicaid. (4/3)

WBUR: Medicare For All Coronavirus Patients? But Who Exactly Qualifies? Millions of people who have lost their jobs in recent weeks also face the prospect of losing health coverage. Democrats have called on the Trump administration to open a special enrollment period for those people to sign up for health coverage under Obamacare. Instead, Secretary of Health and Human Services Alex Azar said health care

providers will be reimbursed for COVID-19 care "at Medicare rates," and they will be forbidden from billing patients for services directly on top of that. (Charles, 4/3)

Public Health And Education

Tragedy In Nursing Homes: Consequence Of Failed Testing, Shortage Of Protective Gear For Workers Nationally, at least 400 long-term care facilities have at least one resident infected, but Politico reports that's likely an undercount for an industry that has a tough time getting equipment and is slow to respond to change. Just last week, CMS recommended nursing homes separate those with Covid-19 from those who don't have the infection, but without adequate testing that proves difficult to do. Nursing home news is from Massachusetts, Florida, Rhode Island, Washington, Texas and Georgia, as well.

Politico: How Public Health Failed Nursing Homes The unfolding tragedy in American nursing homes, where patients are dying in clusters, is another consequence of the coronavirus testing debacle. While America wasn't looking, family visitors, staff and other health professionals unknowingly brought the virus into long-term care facilities, spreading it among the population least likely to withstand it. On top of that, the shortages of protective gear for health workers exacerbated the situation because nursing homes, hospices and other outpatient settings have a tough time getting scarce equipment like masks and gowns, provider groups said. (Kenen, Roubein and Luthi, 4/6)

WBUR: Nursing Home Advocates Call For More Funds, Tests And Protective Equipment In the past week, dozens of Massachusetts nursing home residents have tested positive for COVID-19, and at least 20 have died from the disease. Now, an industry group that represents hundreds of senior care facilities around the state says their members are facing a major a shortage of staffing, funds, and personal protective equipment like masks and gowns. (Ma, 4/5)

ABC News: Cut Off From Loved Ones In Nursing Care, Families Are Left Fearing The Unknown Jenn Hubbert was working from home on March 17 when her husband called out to her from across the house. "He was watching TV when he realized the breaking news was about my mother's nursing facility," said Hubbert, a real estate agent in Florida. "The first death from coronavirus had been reported, and I didn't even know there was a case there. I was in disbelief." (Mosk, Romero, Pecorin and Freger, 4/6)

Boston Globe: Residents And Families Angry And Helpless As Coronavirus Overwhelms Nursing Homes COVID-19 has ripped through many of the state's 800 or so nursing homes and assisted living facilities with astonishing speed. At Charlwell, three staffers told the Globe they believe the virus contributed to 21 deaths in less than two weeks, although not all of those people were tested. When the mail arrived Friday, there were 20 greeting cards for patients who had recently died. (Weisman and Krantz, 4/4)

Boston Globe: Half The Rhode Islanders Who Have Died From The Coronavirus Lived In Nursing Homes As Governor Gina M. Raimondo announced her daily tally of coronavirus cases and deaths Friday, she pointed out a disturbing fact: Half of the Rhode Islanders who have died lived in nursing homes, and 21 percent of the positive test results have been among staff and residents of those homes.And that daily tally was grim: 54 more cases, two more deaths, both women in their 70s. (Milkovits, 4/3)

Houston Chronicle: More Than 80 Residents Of Texas City Nursing Home Test Positive For New Coronavirus Samuel Quinn didn't find out his mother had coronavirus until after he visited her at a Texas City nursing home Friday morning. Quinn said he was given a mask and gown upon entering The Resort at Texas City, a 135-bed long-term care facility, and asked nurses if his mother, Peggy Smith, had tested positive for the virus. They said she had not. (Powell and Lewis, 4/3)

Atlanta Journal-Constitution: State Provides First Accounting Of Outbreaks In Senior Care Facilities Georgia Friday evening made public the names of 47 nursing homes and other senior care facilities that have had coronavirus outbreaks, providing the public with the most complete accounting to date of the

virus's spread in facilities for the elderly since the first reported case became public on March 16. The list of facilities identified by the Georgia Department of Public Health reflects known outbreaks as of Wednesday afternoon. By Friday afternoon, the total number of senior communities that had residents who tested positive for COVID-19 had climbed to 60, underscoring how rapidly the disease is spreading in facilities that serve thousands of the state's most vulnerable adults. (Schrade and Teegardin, 4/3)

Governments, Advocates Race For Ways To Protect Victims Of Domestic Abuse Amid Stay-At-Home Orders

"It's almost like a petri dish for violence to increase within families," says Barbara Paradiso, director of the Center on Domestic Violence at the University of Colorado Denver. In other public health news: the voice behind the hotlines, the environmental impact of the outbreak, a changing world view, how LGBTQ youth are impacted, and more.

The Wall Street Journal: As Coronavirus Piles Pressure On Families, Domestic Violence Concerns Surge

Authorities and women's groups are racing to find ways to protect women against domestic abuse as the coronavirus pandemic confines families to their homes. In much of Europe, officials are quickly deploying new programs, as a surge in abuse reports around a region that has been locked down for weeks presages what could be a similar increase in the U.S. In some parts of the U.S., women's groups say they have already seen an increase in domestic violence calls, as stress, isolation and the financial pressure of lost jobs and income threaten to take a heavy toll on some women and children. (Bisserbe and Lmobardi, 4/5)

ABC News: Answering The Call: Working A Coronavirus Hotline In a time of so much uncertainty, no one has all the answers, but COVID-19 hotlines across the country have assembled to try to answer some of the thousands of questions Americans are pondering right now. While hotlines cannot provide clinical advice as a doctor can, the staff can still answer questions regarding novel coronavirus testing, symptoms and prevention. (Krall, 4/6)

The Wall Street Journal: How Environmental Movement Plans To Leverage The Coronavirus Pandemic

One hopeful development arising from the coronavirus pandemic: Global air quality is improving dramatically as the outbreak sends many countries into lockdown, climate scientists say. The improvement comes as demand for fossil fuels plummeted with flights grounded, factories and offices closed and people confined to their homes. (McFarlane, 4/6)

The Wall Street Journal: Coronavirus Lockdowns Clear The Air, But The Green Effect Could Be Fleeting

The Los Angeles smog has lifted, water in Venice's canals has cleared and China's factory emissions have fallen so dramatically the change can be seen from space. International travel restrictions and city lockdowns designed to slow the spread of coronavirus have led to swift and sometimes surprising environmental benefits. The long-term implications are unclear but many climate scientists now expect greenhouse gas emissions to fall for the first time since the financial crisis more than a decade ago, when they dropped by 7%. (Condie, 4/5)

The Associated Press: After Virus, How Will Americans' View Of The World Change? A thick thread of the American experience has always been to hold the rest of the world at arm's length, whether in economics, technology or cultural exchange. The truth is, this nation has always been a bit of an island, a place where multilingualism, or even holding a passport, is less common than in many other lands. Now, the notion of a virus that came from a distant "elsewhere" stands to carve deeper grooves into that landscape. (Anthony, 4/6)

The New York Times: Periods Don't Stop For Pandemics, So She Brings Pads To Women In Need Dana Marlowe was preparing her family's home for quarantine, stocking up on food and school supplies, when she received an unexpected phone call: Would she trade a box of tampons for 36 homemade matzo balls? Her friend making the request was desperate. She had scoured all the pharmacies in her neighborhood for tampons and pads, but the shelves were picked clean. For Marlowe, who runs the

nonprofit I Support the Girls, which collects donations of feminine hygiene products and bras for shelters, prisons and people in need, the plea set off alarm bells. (Goldberg, 4/5)

NBC News: Coronavirus Pandemic A Perfect Storm For LGBTQ Homeless Youth Finding a secure place to live has not been easy for Nez Marquez, 23, who has experienced homelessness for the past five years. Born in Mexico and raised in New York, he left home at 18 because his family did not accept his gender identity and sexual orientation, he said. Marquez is staying at Sylvia's Place, an emergency shelter for LGBTQ young adults on the bottom floor of a Manhattan church. (Kuhr, 4/5)

NBC News: 'Awful And Beautiful': Saying Goodbye To Coronavirus Victims Without A Funeral Lorena Borjas dedicated her life to helping others as an activist for the transgender community in New York City, bailing people out of jail, fighting against transphobia and championing the rights of human trafficking victims. But when she died this week from COVID-19, the people who loved her the most could not come together to mourn her. (Lozano, 4/5)

Boston Globe: A Scramble To Continue Care For People With Addiction Amid Deep Fears For The Most Vulnerable Such encounters, now permitted under regulations newly loosened for the coronavirus crisis, have become routine for Taylor, as the pandemic transforms addiction care in ways never seen before. In a matter of days — in some cases literally overnight — services for people with addiction in Massachusetts have morphed from office visits to phone calls, from meeting rooms to laptops, from drop-in centers to street outreach. (Freyer, 4/3)

Milwaukee Journal Sentinel: Farmworkers At Risk For Coronavirus Also Don't Have Access To Doctors While picking strawberries in Florida the past few weeks, migrant worker Angelica Martinez often crouched only 3 feet away from her co-workers, shuffling along the narrow rows of plants. That's half the minimum distance experts say people should keep from one another to avoid catching or passing on the coronavirus. But on the farm, Martinez said, the virus gripping the nation did not prompt improvements in basic worker protection. No one trained them to fight the virus' spread, she said, and her employer never offered health insurance or paid sick leave. (Perez, 4/5)

Kaiser Health News: 'Staying Away From Grandma' Isn't An Option In Multigenerational Homes The Walker family never thought having an age range of 3 to 96 under the same roof would be risky. That was before the coronavirus pandemic. Wilma Walker's now nonagenarian mom moved into her daughter and son-in-law's home about 15 years ago. Their party of three turned into a household of six when the Walkers' now 30-year-old daughter, Andre'a Walker-Nimrod, moved back in with her young son and a daughter on the way. (Anthony, 4/6)

The New York Times: The Coronavirus Inflicts Its Own Kind Of Terror The coronavirus has created its own form of terror. It has upended daily life, paralyzed the economy and divided people one from another. It has engendered fear of the stranger, of the unknown and unseen. It has emptied streets, restaurants and cafes. It has instilled a nearly universal agoraphobia. It has stopped air travel and closed borders. It has sown death in the thousands and filled hospitals with wartime surges, turning them into triage wards. People gird for the grocery store in mask and gloves, as if they were going into battle. (Erlanger, 4/6)

The New York Times: Coronavirus Scammers: Another Thing To Fear The white banner with images of red crosses had been hastily erected in front of two pop-up tents at a convenience store parking lot in central Louisville, Ky. "Covid-19 testing here," it read. A clutch of workers in white hazmat suits swabbed the mouths of drivers, who had each forked over $240 to learn whether they had been infected with the coronavirus. "I have managed hospitals for years," a man in charge told journalists and skeptical community activists at the scene on Wednesday. "We are doing things the right way." (LaFraniere and Hamby, 4/5)

A Disproportionate Number Of African-Americans Are Dying, But The U.S. Has Been Silent On Race Data "COVID is just unmasking the deep disinvestment in our communities, the historical injustices and the impact of residential segregation," said Dr. Camara Jones, a family physician. Jones said the outbreak

reflects similar outcomes for African-Americans in terms of disproportionately high rates of maternal death, low levels of access to medical care and higher rates of asthma. But without data, any efforts to address the disparities are undermined.

ProPublica: Early Data Shows African Americans Have Contracted And Died Of Coronavirus At An Alarming Rate The coronavirus entered Milwaukee from a white, affluent suburb. Then it took root in the city's black community and erupted. As public health officials watched cases rise in March, too many in the community shrugged off warnings. Rumors and conspiracy theories proliferated on social media, pushing the bogus idea that black people are somehow immune to the disease. And much of the initial focus was on international travel, so those who knew no one returning from Asia or Europe were quick to dismiss the risk. (Johnson and Buford, 4/3)

Milwaukee Journal Sentinel: African Americans In Milwaukee Hit Hard By Coronavirus Death arrived in Milwaukee two weeks ago, carried by an invisible enemy. In three days, the novel coronavirus known as COVID-19 claimed three lives: all African American men in their 50s and 60s with underlying health conditions. Since then, the losses have continued to mount. Of the 25 people confirmed to have died from complications of COVID-19 in Milwaukee County as of late Friday morning, 20 have been African American, two have been Latino and three have been white. (Spicuzza, Luthern and Dirr, 4/3)

Kaiser Health News: Long-Standing Racial And Income Disparities Seen Creeping Into COVID-19 Care The new coronavirus doesn't discriminate. But physicians in public health and on the front lines said they already can see the emergence of familiar patterns of racial and economic bias in the response to the pandemic. In one analysis, it appears doctors may be less likely to refer African Americans for testing when they show up for care with signs of infection. (Farmer, 4/6)

Meanwhile, a look at how other demographics are playing a role —

CNN: Why The Coronavirus Kills Some Young People When 30-year-old Ben Luderer started to feel sick, he wasn't that surprised. Just a few days earlier, his wife, Brandy, had tested positive for coronavirus, but there wasn't much to it... For Ben, however, his symptoms quickly became more severe. He had more shortness of breath, and by the last Friday in March, he told Brandy it was time to go to the emergency room. (Gupta, 4/6)

GMA: Healthy 18-Year-Old Speaks Out After Contracting COVID-19: 'It Can Happen To Anyone' An 18-year-old student who said he tested positive for the novel coronavirus wants the world to know that regardless of age, the respiratory illness does not discriminate. Dimitri Mitchell, a freshman at Kirkwood Community College in Cedar Rapids, Iowa, has had no prior health complications and began showing symptoms for COVID-19 on March 13... "It's the most sick I've ever been and I told my mom I felt like I was hit by a truck," he said. (Pelletiere, 4/6)

The Washington Post: All Across The United States, The Coronavirus Is Killing More Men Than Women, Data Show As New York City erupts in coronavirus infections and deaths, Kaedrea Jackson has noticed something peculiar during her shifts inside the emergency department at Mount Sinai Morningside hospital. "It seems there are more men coming in with really severe illness," said Jackson, an emergency physician. "In general, I've seen more male patients. And when they do come in, they are at a sicker state." (Mooney, Kaplan and Dennis, 4/4)

The New York Times: Does Covid-19 Hit Women And Men Differently? U.S. Isn't Keeping Track As the novel coronavirus sweeps the world, sickening hundreds of thousands of people and killing at least 50,000 individuals to date, scientists have learned more and more about it. We know that older adults — aged 60 and above — are at greater risk of dying from it. And, based on data from China, Italy and South Korea, we also know that men seem to have higher fatality rates. But in the U.S., where ramped-up testing is churning out reams of data by the minute, there's one thing we're not monitoring: the sex breakdown. How many women are infected versus men? Are men and women equally likely to get infected? What is the fatality rate for each sex? Are symptoms exactly alike for men and women? (Gupta, 4/3)

South Bend Tribune: Details On COVID-19 Cases Often Scant; Officials Point To Privacy Laws As the number of COVID-19 infections climbs throughout the Midwest and the rest of the nation, state and county health officials are typically releasing broad information and statistics on infections, despite a hunger from residents for more details on the spread of the virus in their communities, or even their neighborhoods. (Sheckler, 4/6)

From The States

Southern States Late To Social Distancing Dealt With Strained Health Resources Even Before Pandemic Experts worry that states in the South that only recently issued stay-at-home orders will be hit hard next. With rural hospital and health systems already stretched thin, it could be especially devastating. Hospital news comes out of California, New York, New Jersey, Wisconsin, Illinois and Michigan, as well.

Politico: Virus Hot Spots In South Poised For Disproportionate Suffering St. John the Baptist Parish, just southeast of Baton Rouge, La., has a population of just over 43,000 — and the highest per capita coronavirus mortality rate in the nation. Frantic local officials instituted an overnight curfew just this week and are begging residents to stay home. But in largely rural Southern states like Louisiana — where social distancing has been spotty, widespread testing is unavailable and hospitals are poorer and farther apart — the response may be coming too late to avoid a public health crisis as bad as the one now engulfing New York. (Goldberg and Ollstein, 4/3)

ABC News: With Coronavirus Apex Still To Come, Some US Hospitals Reeling From Capacity Crunch Already told to boost patient capacity by as much as 100%, many hospitals in New York state, the nation's top hot zone for the coronavirus, reached overcapacity on Sunday, Gov. Andrew Cuomo said... As the coronavirus crisis sweeps across the nation, hospitals administrators say their medical personnel are struggling to keep up with a flood of infected patients -- and the apex of the pandemic could still be days and possibly weeks away. (Hutchinson and Margolin, 4/5)

The Wall Street Journal: Coronavirus Crisis Puts Bankrupt Hospitals Back In Demand From small-town Vermont to Los Angeles, local governments are commandeering shut-down hospitals to add space amid the coronavirus pandemic—a trend that could revamp the market for health-care facilities. Just months ago, St. Vincent Medical Center in Los Angeles and Astria Regional Medical Center in Yakima, Wash., were closed, unable to bring in enough revenue to stay afloat. Both are poised to reopen with the help of state funds and, in the case of St. Vincent, $135 million from the family foundation of Patrick Soon-Shiong, the billionaire owner of the Los Angeles Times. (Brickley, 4/6)

NBC News: What Does It Take To Convert A Hotel Bedroom Into A COVID-19 Care Room? As hospitals around the country prepare for an increased number of coronavirus patients and potential bed shortages, local officials seek hotel rooms and dorms as alternative housing for coronavirus patients with less severe symptoms... But how do you turn a hotel room into a health care room? The first step is understanding that the coronavirus is primarily spread by respiratory droplets. (Garcia-Hodges, 4/5)

Modern Healthcare: Home Healthcare Agency To Take COVID-19 Referrals From Hospitals The Visiting Nurse Service of New York is accepting COVID-19 referrals from local hospitals. The goal is to offset some of the burden. The approach comes with challenges, however."We want to do everything possible to alleviate the strain on the New York metro area's hospital system," said Michael Bernstein, executive vice president and chief administrative officer at VNSNY. (Henderson, 4/2)

CNN: Trump On USNS Comfort: 'If We Need It For The Virus, We'll Use It For That' President Donald Trump said Sunday night that the USNS Comfort, docked in New York, could be used for coronavirus patients if needed. "That was not supposed to be for the virus at all and under circumstances. It looks like more and more we'll be using it for that," Trump told reporters at a coronavirus task force briefing at the White House. "The ship is ready and if we need it for the virus, we'll use it for that." The USNS Comfort had originally been designated as a space for non-coronavirus patients to alleviate the pressure from New York hospitals. (Robertson, 4/5)

The New York Times: Chinese-Americans, Facing Abuse, Unite To Aid Hospitals In Coronavirus Battle Dr. Peter Lee, an emergency room doctor from Montville, N.J., was close to an emotional breakdown by the time he took to WeChat, the social media app, last month. He was under siege on all fronts. At work, he was constantly dodging exposure to the coronavirus. At home, he was worried about infecting his pregnant wife and young daughters. And in his everyday life, he was suddenly navigating a new bias against Chinese-Americans. (La Gorce, 4/5)

Kaiser Health News: 'You've Been Served': Wisconsin Hospitals Sued Patients Even During Pandemic When her doorbell rang Sunday night, Blanche Jordan was just starting a new Game of Thrones puzzle on her living room floor. Jordan, 39, is a breast-cancer survivor who is taking social distancing seriously, so she put on a mask before opening the door. A woman handed Jordan a paper and said: "You've been served." (Sable-Smith, 4/3)

Modern Healthcare: Chicago Adding Another Field Hospital As COVID-19 Cases And Deaths Soar A new field hospital is being planned for Chicago to address an expected surge in patients as COVID-19 spreads. In addition to McCormick Place, one of the nation's largest convention centers, which is being turned into a makeshift hospital by the Army Corps of Engineers, a not-for-profit that provides relief during disasters intends to establish at least one mobile field hospital in Chicago. (Goldberg, 4/3)

Crain's Detroit Business: Blue Cross Blue Shield Of Michigan Paying Employees To Volunteer At Field Hospital Blue Cross Blue Shield of Michigan is offering to pay the salaries and benefits of employees with medical training who volunteer to work in the coronavirus field hospital being constructed inside TCF Center in downtown Detroit. Michigan's largest health insurance company sent employees a memo Wednesday announcing the plan to grant full paid leaves of absence to any employee with a background in nursing or medicine to help the state staff the 1,000-bed hospital the U.S. Army Corps of Engineers is constructing. (Livengood, 4/3)

Panel Of California Judges Rules Against Mass Release Of State Inmates, For Now News is on how the prison systems in California, Alabama, Louisiana, Wisconsin and Massachusetts are handling the virus outbreak crisis.

Politico: Judges Balk At Mass Release Of California Prisoners Over Virus Danger A panel of federal judges has rebuffed a bid to order a mass release of California prison inmates in an effort to reduce the danger posed by the coronavirus. The three-judge panel did not rule out the possibility that lawyers for inmates could eventually win a court-ordered reduction in the state's prison population of roughly 120,000 to allow more social distancing, especially for elderly prisoners and those with pre-existing medical conditions. Proponents of slashing California's prison rolls took their request to three judges who, in 2009, ordered the state not to exceed 137.5% of the intended capacity of its prisons. (Gerstein, 4/5)

ABC News: 'We Need Help': Inmates Describe Prison System Unprepared For Coronavirus Some inmates at Alabama state prison facilities asking for help amid the novel coronavirus pandemic highlighted what they described as broader threats inside the U.S. prison system. "It's fixin' to be a mass grave site," one prisoner said in exclusive footage obtained by ABC News. (Doherty and Cannon, 4/5)

NBC News: 1st Federal Inmate To Die Of Coronavirus Wrote Heartbreaking Letter To Judge In the months before the coronavirus infiltrated the U.S., a 49-year-old inmate began drafting a letter inside the walls of a federal prison in Louisiana. The man, Patrick Jones, had been locked up for nearly 13 years on a nonviolent drug charge. He hadn't seen his youngest son, then 16, since the boy was a toddler. (Schapiro, 4/5)

New Orleans Times-Picayune: Attorney General Barr Orders Shift To Home Confinement At Coronavirus-Plagued Louisiana Prison With the coronavirus cases skyrocketing at the Federal Correctional Institution at Oakdale, U.S. Attorney General William Barr ordered the Bureau of Prisons to give highest priority to the Louisiana prison complex, where five inmates have died and more than a dozen others remain hospitalized. (Rechdahl, 4/4)

Milwaukee Journal Sentinel: Coronavirus Found In Wisconsin Prisons Where Spread Is Hard To Avoid
Two weeks after Gov. Tony Evers ordered Wisconsinites to stay at home and avoid close contact with people outside their own households, the first Wisconsin prisoner has tested positive for coronavirus. Of about 23,000 inmates in Wisconsin's prisons, 66 have been tested, according to corrections spokeswoman Anna Neal.Forty-two of those tests came back negative. The department continues to wait on the results of the other 23. (Barton, 4/4)
WBUR: Mass. High Court Rules Some Prisoners Will Be Eligible For Release Due To COVID-19 The Massachusetts Supreme Judicial Court has ruled that some prisoners can be released from state jails and prisons in an effort to stem the spread of COVID-19. The 45-page ruling says pre-trial detainees not charged with certain violent offenses and those held on technical probation and parole violations are eligible for hearings to determine if they can be released. The ruling does not affect those who have been sentenced. (Becker, 4/3)
Boston's Mayor Asks Residents To Wear A Cloth Mask, Advises Curfew; Shelters For Homeless Close In 17 States
Media outlets report on news from Massachusetts, California, District of Columbia, New York, Texas, Louisiana, Illinois, Florida, Michigan, Kansas and New Jersey, as well.
Boston Globe: Walsh Recommends Curfew For Boston, Asks All To Wear Masks Outside Home Mayor Martin J. Walsh on Sunday said he is asking everyone in Boston to observe a curfew and to wear masks when they are outside their homes, as the number of COVID-19 cases in the city and the state rises toward a peak that could test the region's public health infrastructure in coming days. Walsh said the recommended curfew will be in place between 9 p.m. and 6 a.m. starting Monday and running at least through May 4. (Rosen, 4/5)
Boston Globe: State's Largest Construction Union Calls For A Monday Walkout Over Coronavirus Concerns Members of the region's largest construction workers union are set to walk off the job Monday over mounting worries about coronavirus safety at building sites. The North Atlantic States Regional Council of Carpenters is directing its roughly 10,000 members in Massachusetts to stop working, effective Monday, saying it's essentially impossible to keep construction sites safe from the spread of COVID-19. (Logan, 4/3)
Boston Globe: 24 More Coronavirus-Related Deaths, More Than 1,300 New Confirmed Cases In Mass.; Hospital Executive Pledges Salary To Lowest-Paid Workers The state reported two dozen additional deaths attributed to the coronavirus Saturday, as the numbers of residents in long-term care facilities infected with the disease continued to grow, and the federal government prepared to send more ventilators to Massachusetts. While front-line health care workers face the growing numbers of patients with COVID-19, the disease caused by the coronavirus, some are stepping up. (Hilliard, 4/4)
Boston Globe: Homeless Facing 'A Disaster For Families' On any given night, roughly 3,700 families, or about 12,000 people, are without homes across Massachusetts. Most are living in shelters — temporary apartments or dorm-style rooms. Now, with the state plunged into a deep freeze to halt the coronavirus, these homeless families are struggling to secure basic necessities. Crowded facilities make social distancing nearly impossible. Food pantries are desperately strained, and with schools shut down and people out of work, homeless families are pinned down in rooms that are not their own, facing weeks that threaten to stretch into months of uncertainty. (Gay and Greenberg, 4/3)
Boston Globe: Amid Pandemic, State Moving Infected And Non-Infected Alike From Chelsea Soldiers' Home Amid a deadly cluster of coronavirus cases, state officials have begun transferring veterans out the Chelsea Soldiers' Home, including those who aren't infected but are at high risk — a move that has all but emptied the facility of confirmed cases, officials said Friday. The decision comes as officials are also grappling with another outbreak at the state Soldiers' Home in Holyoke, where they have launched an investigation into how several deaths went unreported for days and at least 15 veterans have died

after contracting the virus. Officials there plan to move as many of 20 veterans who've tested negative to a local hospital. (Stout, 4/3)

Boston Globe: Marijuana Companies Are Making Hand Sanitizer To Donate To Local Hospitals Revolutionary Clinics, one of the state's largest cannabis providers, recently completed the first 100-gallon batch of hand sanitizer produced at its Fitchburg facility, and had it packaged and ready to be donated to local hospitals on Monday. The delivery is part of a larger movement within the state's cannabis industry, which kicked into gear after John Hillier, a board member of the Commonwealth Dispensary Association (CDA), brought the feasibility of the project to the association's attention. (Slane, 4/3)

Stateline: Some Shelters Shutter To Protect Homeless, Staff Like Harbor House, other homeless shelters around the country are being pushed to the brink by the pandemic. Even in the best of times, some 568,000 people live in shelters, on the streets or in a car. And now, shelters in at least 17 states plus Washington, D.C., have been forced to close, suspend services or otherwise limit their operations, according to the National Low Income Housing Coalition. (Wiltz, 4/6)

ProPublica: 'Dead On Arrival': A N.Y. Fire Chief's COVID Journal Simon Ressner is a battalion chief with the Fire Department of New York based in central Brooklyn. Twenty-five years ago, the department, nicknamed New York's 8ravest, took on the added role and responsibility of responding to emergency medical calls. Today, firefighters make some 300,000 runs a year. Last week, we asked Ressner, 60, to keep an informal diary of his latest 24-hour shift, a tour of duty that began at 9 a.m. on Friday, April 3. (4/5)

The Wall Street Journal: Texas Gets Double Punch From Coronavirus And Oil Shock. 'There's No Avoiding This One.' Texas had one of the best economic records of any U.S. state after the 2008 financial crisis. In this crisis, it faces the prospect of a deep and prolonged downturn. The Lone Star State is exposed to many of the pandemic and shutdown's economic ill consequences, with three cities—Austin, Houston and Dallas—home to an abundance of service-sector jobs, especially at risk. A downturn in the oil industry and other businesses big in Texas, including airlines and ports, will likely amplify its pain. Industry analysts expect the oil downturn to outlast the current viral outbreak. (Eaton and Hilsenrath, 4/5)

Houston Chronicle: Feds Could Cut 25% Of Houston's FEMA Funding For Coronavirus Test Sites Federal authorities are expected to slash 25 percent of Houston's funding to administer the city's coronavirus testing sites and relocate six site workers. Mayor Sylvester Turner and U.S. Rep. Al Green, D-Houston, both warned about the cuts at press conferences Sunday. (Wu and Deam, 4/5)

New Orleans Times-Picayune: Louisiana Unions Irate As Texas Workers Brought In For Coronavirus Convention Center Jobs Some local union leaders are angered that dozens of workers have been brought in from Texas to help convert the Ernest N. Morial Convention Center into a medical facility to deal with the coronavirus crisis, at a time when hundreds of their members are out of work. The order to convert the convention center into a facility to provide up to 3,000 beds for spillover COVID-19 patients was made by Governor John Bel Edwards two weeks ago. (McAuley, 4/4)

New Orleans Times-Picayune: 'I've Never Seen This': Because Of Coronavirus, Makeshift Morgues Set Up In Metro New Orleans Coroners offices and funeral homes throughout the New Orleans area are scrambling to store bodies and hold funeral services as deaths from the novel coronavirus continue to mount. State officials on Sunday reported the biggest daily jump in deaths from the relentless pandemic, with fatalities rising by 68 to 477. (Hassell and Stole, 4/5)

New Orleans Times-Picayune: Louisiana Nursing Homes With Coronavirus Clusters Won't Be ID'd Anymore, Officials Say The state announced Friday that 60 residents of nursing homes and other long-term senior care facilities have died of the novel coronavirus, but in a reversal of previous practice said it would no longer publish a list of such facilities identified as clusters of the contagion. Instead, the state

Department of Health said it would begin publishing a tally of homes where there are confirmed cases, residents who had tested positive and the number who have died. (Roberts III, 4/3)

The Hill: Tiger At Bronx Zoo Tests Positive For Coronavirus A tiger at the Bronx Zoo in New York City has tested positive for the coronavirus, while several other animals are being monitored for similar symptoms. In a press release, the Wildlife Conservation Society (WCS), which operates the zoo, said that the animals were likely infected by an asymptomatic carrier of the disease. It's the first known case of the virus being detected in an animal in the U.S. as well as the first confirmed case in a tiger anywhere in the world. (Bowden, 4/5)

The Wall Street Journal: Tourist Towns Say, 'Please Stay Away,' During Coronavirus Lockdowns Resort towns rely on visitors as their economic lifeblood, but as the new coronavirus pandemic rages, many are asking nonresidents to stay away. More than 12,000 residents of Cape Cod, Mass., signed a petition this week asking authorities to turn away visitors and nonresident homeowners from the two bridges that are the only access points to the Boston-area summertime playland. (Barrett, 4/6)

The Washington Post: Coronavirus Creates Conflict For Churches, Where Gatherings Can Be Dangerous But Also Provide Solace Pastor Dan Ostring promised parishioners that, as Christians began marking their holiest week on this Palm Sunday, the Rivers of Living Water Church would be open for the fellowship, song and sermon that they have always celebrated together. He kept his public pledge, despite receiving hate mail all week warning that he would "burn in hell" if he opened the cross-covered doors of his tiny church. A few miles away, across the wide American River, a church more than 100 times larger than Ostring's was shuttered late last month after scores of parishioners and a senior pastor tested positive for the novel coronavirus. (Wilson, Boorstein, Hernandez and Rozsa, 4/5)

KQED: California Coronavirus Testing Backlog Cut By Two-Thirds California has cut its COVID-19 testing backlog by more than two-thirds, Gov. Gavin Newsom announced Saturday, but has still managed to test less than one half of 1% of the state's nearly 40 million residents. (Beam and Nguyen, 4/5)

Detroit Free Press: Michigan GOP And Dems Divided Over Extending Whitmer's Emergency Order Michigan's state of emergency should be extended until May 1 — not for the 70 days requested by Gov. Gretchen Whitmer, House Speaker Lee Chatfield said in a Saturday letter. The shorter extension, which Chatfield, R-Levering, wants to vote on during a legislative session planned for Tuesday at the Capitol in Lansing, "will allow the governor to continue her important work while still giving local residents hope that they will have a real plan presented to them sooner than the end of June." (Egan and Gray, 4/5)

WBUR: Kansas Gov. Says Federal Government Had A 'Late Start' On Stockpiling Medical Supplies Senior adviser Jared Kushner sparked backlash at a Thursday press conference for saying the national stockpile of medical supplies does not belong to the states. Now, governors are pushing back. One of them is Kansas Gov. Laura Kelly, whose state has only seen 620 cases but is preparing for more. (Hobson, 4/3)

The New York Times: Coronavirus In NJ: The Nurse Was Holding Up. Then Her 3 Close Relatives Were Brought In Twelve doctors at her hospital and the chief executive were sickened with the coronavirus. A colleague had died. Patients as young as 19 were being placed on ventilators. But Michele Acito, the director of nursing at Holy Name Medical Center, in the hardest-hit town in New Jersey's hardest-hit county, felt like she was holding up.Then her mother-in-law, sister-in-law and brother-in-law arrived. (Tully, 4/5)

Health IT

Tech Companies Team Up With Health Groups For Pandemic Response Hackathons Technology companies come together to focus on solutions to a wide range of problems created by the pandemic, Modern Healthcare reports. Last weekend, several thousand developers met over Zoom and via Slack at a Datavant event that touched on public health information-sharing, epidemiology, keeping health workers safe and social impact. More tech news looks at Quil's efforts to help patients find trustworthy information, the lowering of telemedicine barriers, and timely funding for digital startups.

Modern Healthcare: Hackathons Challenge Developers To Tackle COVID-19 With Tech Health groups and technology companies are teaming up to challenge developers to apply their skills to problems linked with the novel coronavirus. Datavant last weekend hosted more than 2,000 engineers, software developers, data scientists and other technology folks to develop tools that help those in the health sector better understand or mitigate the spread of COVID-19. It was part of the healthcare data company's hackathon event, which it called the Pandemic Response Hackathon. (Cohen, 4/3)

Stat: The Covid-19 Pandemic Forces Comcast's Health Tech Startup To Adapt When telecom giant Comcast and health insurer Independence Blue Cross teamed up to found Quil in 2018, the health tech company's goal was clear: give people simple, step-by-step guidance to help them navigate big health events, from pregnancies to hip replacements. But today, the joint venture finds itself in a very different place, as the coronavirus pandemic has forced physicians to put off routine appointments and postpone elective surgeries. Everyday health care is, in some ways, being put on hold — and startups like Quil are racing to adapt. (Brodwin, 4/6)

Modern Healthcare: Telemedicine Regulatory Barriers Continue To Drop For COVID-19 For years, telemedicine advocates have pushed to make it easier for patients to access care remotely. Many, but not all, of the barriers they had been fighting fell last month as lawmakers and government officials rushed to make telemedicine more available in the wake of the novel coronavirus. Telemedicine has been cited as a promising avenue to reduce the spread of COVID-19, letting patients receive care at home without visiting a crowded emergency department, and minimizing the need for providers to use personal protective equipment that is in short supply. (Cohen, 4/3)

Stat: Digital Health Startups Scored A Critical Cash Infusion At The Start Of This Year As much of the world prepares for the possibility of a coronavirus-driven recession, a new report suggests that some digital health startups scored a critical infusion of cash just in the nick of time. Rock Health — a digital-health-focused venture fund — released a report Monday showing that startups in its portfolio raised a record-breaking $3.1 billion from investors between January 1 and March 31, 2020. The funding, which took place over roughly 100 deals, is more than double the total first quarter funding seen in any previous year. (Brodwin, 4/6)

Global Watch

UK Prime Minister Boris Johnson Hospitalized; Queen Issues Address To Nation: 'Better Days Will Return' British Prime Minister Boris Johnson is reportedly doing well and undergoing routine tests after he was hospitalized with COVID-19. Queen Elizabeth II took the rare step of addressing her nation just before the news was released.

The New York Times: Boris Johnson Hospitalized As Queen Urges British Resolve In Face Of Epidemic Prime Minister Boris Johnson was hospitalized on Sunday evening after 10 days of battling the coronavirus, unnerving a country that had gathered to watch Queen Elizabeth II rally fellow Britons to confront the pandemic and reassure them that when the crisis finally ebbed, "we will meet again. "The British government said that Mr. Johnson would be undergoing tests and that he would continue to carry out his duties. But the uncertainty generated by his persistent illness underscored the sense of crisis that led the queen to address the country in a rare televised speech that evoked the darkest days of World War II. (Landler, 4/5)

The Associated Press: UK Prime Minister Boris Johnson Hospitalized With Virus In a message Friday, a flushed and red-eyed Johnson said he said he was feeling better but still had a fever. The virus causes mild to moderate symptoms in most people, but for some, especially older adults and the infirm, it can cause pneumonia and lead to death. U.S. President Donald Trump offered encouragement to Johnson as he opened a White House briefing on the pandemic Sunday. "All Americans are praying for him," Trump said. (Lawless, 4/6)

Reuters: British PM Johnson Still In Hospital With Persistent Coronavirus Symptoms The prime minister is doing well and will undergo routine tests on Monday but will continue to lead the government,

Housing Secretary Robert Jenrick said. "He'll stay in hospital as long as he needs to do that, but I've heard that he's doing well and I very much look forward to him being back in Number 10 as soon as possible," Jenrick said. (Faulconbridge, James and Piper, 4/6)

The Washington Post: Britain's Queen Elizabeth Addresses Coronavirus; Boris Johnson To Hospital The news of his hospitalization broke an hour after the queen broadcast her prerecorded message to the United Kingdom and Commonwealth — only the fifth such speech in her 68-year reign. "We should take comfort that while we may have more still to endure, better days will return," she said. "We will be with our friends again, we will be with our families again, we will meet again." (Booth, 4/5)

The Wall Street Journal: U.K. Prime Minister Boris Johnson Hospitalized For Coronavirus Tests The monarch, in a prerecorded address from Windsor Castle, thanked health care workers and focused on the difficulties of being isolated from loved ones. She cited a radio address she made as Princess Elizabeth, along with her sister, Princess Margaret, 80 years ago, as children were being evacuated from cities to avoid bombing attacks. "We, as children, spoke from here at Windsor to children who had been evacuated from their homes and sent away for their own safety. Today, once again, many will feel a painful sense of separation from their loved ones. But now, as then, we know, deep down, that it is the right thing to do," she said. (Fidler, 4/5)

Politico: British Health Secretary: Follow Coronavirus Rules Or We'll Ban Outdoor Exercise U.K. Health Secretary Matt Hancock warned that the government will ban people from leaving their homes to exercise if too many people flout social distancing rules. "If you don't want us to have to take the step to ban exercise of all forms outside of your own home, then you've got to follow the rules," he told the BBC's Andrew Marr Show on Sunday. (Wax, 4/5)

Global Health Watch: China Tries To Control Death Toll Narrative; Italy Starts Talking About How To Re-Open

China and Italy continue to cope with the fallout from massive coronavirus outbreaks, while experts look to Germany to examine how that nation has, so far, avoided one.

The New York Times: China Pushes For Quiet Burials As Coronavirus Death Toll Is Questioned Liu Pei'en held the small wooden box that contained his father's remains. Only two months ago, he had helplessly clutched his father's frail hand as the elderly man took his last breath, and the pain was still raw. He wept. But there was little time, or space, for Mr. Liu to grieve. He said officials in the central Chinese city of Wuhan had insisted on accompanying him to the funeral home and were waiting anxiously nearby. Later, they followed him to the cemetery where they watched him bury his father, he said. Mr. Liu saw one of his minders taking photos of the funeral, which was over in 20 minutes. (Qin and Li, 4/3)

Reuters: China Sees Rise In Asymptomatic Coronavirus Cases Mainland China reported 39 new coronavirus cases as of Sunday, up from 30 a day earlier, and the number of asymptomatic cases also surged, as Beijing continued to struggle to extinguish the outbreak despite drastic containment efforts. (Zhang and Munroe, 4/5)

The New York Times: In Italy, Going Back To Work May Depend On Having The Right Antibodies There is a growing sense in Italy that the worst may have passed. The weeks of locking down the country, center of the world's deadliest coronavirus outbreak, may be starting to pay off, as officials announced this week that the numbers of new infections had plateaued. That glimmer of hope has turned the conversation to the daunting challenge of when and how to reopen without setting off another cataclysmic wave of contagion. To do so, Italian health officials and some politicians have focused on an idea that might once have been relegated to the realm of dystopian novels and science fiction films. (Horowitz, 4/4)

The New York Times: Italy's Virus Shutdown Came Too Late. What Happens Now? Italy underestimated the spread of the virus at first. These maps show why the country's nationwide lockdown came too late to contain it. (McCann, Popovich and Wu, 4/5)

The New York Times: A German Exception? Why The Country's Coronavirus Death Rate Is Low They call them corona taxis: Medics outfitted in protective gear, driving around the empty streets of Heidelberg to check on patients who are at home, five or six days into being sick with the coronavirus. They take a blood test, looking for signs that a patient is about to go into a steep decline. They might suggest hospitalization, even to a patient who has only mild symptoms; the chances of surviving that decline are vastly improved by being in a hospital when it begins. (Bennhold, 4/4)

Pharmaceuticals

Failed Search For Alzheimer's Drugs: Hypothesis About Amyloid Plaques Likely Reason Why
A new understanding of the disease is emerging, researchers and advocates say, and that treatment will have to be individualized instead of relying on a single drug. Industry news is also on cancer treatments.

The Washington Post: Alzheimer's Treatments And Cures: A Frustrating Trail Of Failures In February, pharmaceutical companies Roche and Eli Lilly announced that two experimental drugs they had developed for Alzheimer's disease had failed in clinical trials. Roche's drug, gantenerumab, and Eli Lilly's solanezumab joined more than 100 other potential Alzheimer's drugs that have flopped, including aducanumab, a much-heralded drug from Biogen. In March 2019, Biogen announced that it had halted two clinical trials of the drug early after an interim analysis showed they weren't working, but the company has since changed course, saying it intends to seek approval from the Food and Drug Administration based on a new analysis of the data. (Aschwanden, 4/4)

Stat: The Latest Failure In Alzheimer's Casts Doubt On Biogen's Ostensible Success The prevailing theory of how to treat Alzheimer's disease endured its 1,001st cut on Thursday, as results from a lengthy clinical trial showed that reducing toxic plaques in the brain had no effect on slowing cognitive decline. While the disappointing result is only the latest in a metronomic series of failures, it could have implications for the drug industry's only ostensible success: a plaque-targeting treatment from Biogen soon to undergo Food and Drug Administration review. (Garde, 4/2)

Stat: On Immunotherapy, We've Mastered The Foothills But The Summit Lies Ahead The Nobel Prize-winning discovery of immune checkpoint inhibitors has changed how cancer is treated. These drugs "unblock" the immune system's normally protective pathways that prevent T cells from overreacting and potentially harming healthy cells. Immune checkpoint inhibitors work by "uninhibiting" a cancer patient's T cells to attack his or her tumor. (Davis and Flechtner, 4/6)

Editorials And Opinions

Perspectives: Certain Governors' Inactions Threaten Entire Country's Health; Why Are Unqualified People In Charge Of U.S. Response?
Editorial pages focus on these pandemic issues and others.

The Washington Post: Foot-Dragging GOP Governors Are Imperiling The Whole Country President Trump likens the struggle against the pandemic to a war that will yield a colossal toll in human lives, but refuses to urge states uniformly to issue stay-at-home orders. The president's equivocations have produced an uncoordinated jumble of policy subverted by foot-dragging governors who treat the coronavirus less as a national emergency and more as a political annoyance. They are guilty of an abdication of leadership whose consequences will be measured in body bags. (4/4)

Bloomberg: To Beat The Global Pandemic, Empower Local Leaders While many Americans are watching the daily news conferences by President Donald Trump and some governors, the action behind the scenes is being led by the elected officials who are closest to the public, and who are directly managing the crisis in their communities: mayors.As we listen to public health experts, including doctors Anthony Fauci and Deborah Birx, we should also be listening to America's mayors, who are best positioned to identify problems as they arise and act swiftly to address them — if they have the resources and authority to do so. (Michael R. Bloomberg, 4/5)

NBC News: Trump Enables Jared Kushner's Coronavirus Task Force, Revealing The Dangers Of Nepotism
According to President Donald Trump, Vice President Mike Pence is in charge of America's response to

the coronavirus crisis. This choice was, in itself, controversial since Pence has no real experience in this area and his one attempt at dealing with a public health problem as governor of Indiana turned out very poorly. But what many Americans don't know is that an equally unqualified if apparently even more loyal Trump adherent is secretly running his own coronavirus task force, leaving a series of ethics issues in wake. (Jordan Libowitz, 4/6)

The New York Times: The Real Tragedy Of Not Having Enough Covid-19 Tests President Trump said last week that he hadn't "heard about testing in weeks." But right now — let's face it — tests are being rationed in many parts of the country. Of course, the seriously ill and essential front-line personnel like doctors, nurses and policemen require and deserve to go to the front of the line for testing.But there are hundreds of thousands more people who should have been tested at this point, if more tests were available. Testing them would have vastly changed their behavior, their self-care at home, and (perhaps most importantly) our understanding of Covid-19, so that when it flares locally we would know how to respond in a more nuanced way, rather than shutting society down. As of this writing I know nearly a dozen people who are "presumed Covid." None of them were tested, because they were not sick enough to be admitted to a hospital — though all were quite symptomatic. (Elisabeth Rosenthal, 4/6)

Los Angeles Times: Queen Elizabeth Nails Her Coronavirus Speech Britain's Queen Elizabeth on Sunday joined the chorus of world figures weighing in on the COVID-19 pandemic. In a rare televised speech, she offered no bluster, no drama, no scolding reminder that only six feet of distance stand between you and possible death. Nor were there any of the claims of accomplishment and ascriptions of blame that have become a staple on these shores. Instead, she offered comfort, gratitude to her nation's health workers, a belief that life will go back to normal, and this simple poetic coda:"We will meet again." (Carla Hall, 4/5)

The New York Times: Has Anyone Found Trump's Soul? Anyone? Do you remember President George W. Bush's remarks at Ground Zero in Manhattan after the Sept. 11 terrorist attacks? I can still hear him speaking of national grief and national pride. This was before all the awful judgment calls and fatal mistakes, and it doesn't excuse them. But it mattered, because it reassured us that our country's leader was navigating some of the same emotional currents that we were. Do you remember President Barack Obama's news conference after the school shooting in Newtown, Conn., that left 28 people, including 20 children, dead? I do. (Frank Bruni, 4/6)

CNN: Stelter: Federal Response To Pandemic Is A 9/11-Level Failure There's a lot of revisionist history being written right now. Lots of digging of the so-called memory hole. Pro-Trump media outlets are trying to bury the Trump White House's failures to fully protect the country from this pandemic. They're trying with all their might to shift the blame to mayors and governors. (Brian Stelter, 4/6)

The Washington Post: In Singapore, A Quarantine Offers Surprising Lessons The rest of the time, I will be alone, confined to the 230-square-foot hotel room the Singapore government has ordered me not to leave for two weeks. I do not have the coronavirus — not as far as I can tell. But I am part of the government's new initiative to combat a recent uptick in coronavirus cases, which was announced the day before I boarded the last Singapore Airlines flight from New York to Singapore for some time on March 25. (Cheryl Lu-Lien Tan, 4/3)

St. Louis Post Dispatch: Health And Financial Catastrophe Looms, But Trump Won't Ease Obamacare Access For 10 years now, Republicans have been trying to kill the Affordable Care Act, former President Barack Obama's program extending health care coverage to millions of uninsured Americans. ... It was difficult to imagine this obsessive GOP campaign to deny health coverage to vulnerable Americans sinking any lower, but now it has: The White House is refusing calls to reopen the Obamacare exchanges outside their normal operating dates, which could ease the health and financial woes of millions of people whose lives have been upended by the coronavirus pandemic without having to set up a new government program. (4/4)

St. Louis Post Dispatch: Lowered Auto Emissions Standards Threaten Americans' Health — And The Planet's Even as America battles a virus that attacks the lungs, the Trump administration is pressing ahead with an environmental sabotage campaign that would ultimately make it harder for all Americans to breathe. The administration on Tuesday finalized its plan to weaken Obama-era automobile emissions standards — rolling them back to a point that even some automobile makers say is too far — in a move that promises to worsen air pollution and global warming in years to come.The administration says the move will save money for consumers, and has even suggested it could save lives. The first claim is highly debatable, the second, ridiculous. This unnecessary and irresponsible step backward will cost lives. (4/5)
Viewpoints: FDA Needs To Step Up Pace For COVID-19 Treatments; Pros, Cons Of Wearing Masks Opinion writers weigh in on these health care issues stemming from the pandemic and others.
The Wall Street Journal: Bet Big On Treatments For Coronavirus Some imagine that the coronavirus will run its tragic course in the spring, with the direst results avoided by intense social-distancing and other mitigation efforts, and then our lives can more or less return to normal in the summer. But that isn't realistic. Even if new cases start to stall in the summer heat, the virus will return in the fall, and so will fresh risk of large outbreaks and even a new epidemic. People will still be reluctant to crowd into stores, restaurants or arenas. Schools may remain closed. The public's fears won't relent simply because there are fewer new cases. We'll be running an 80% economy. (Scott Gottlieb, 4/5)
The New York Times: Healthcare Workers Are Begging For Masks. Is The President Listening? Health care professionals are still going to work each day without sufficient masks, gloves, gowns and other supplies, and are begging for proper personal protective equipment (P.P.E.). In a country that spends more on health care than anywhere else on the planet, masks are being rationed or reused, and some hospital workers are even using novelty rain ponchos to protect themselves. Health care workers around the country are falling ill and dying — The Brooklyn Hospital Center estimated a third of its doctors and nurses are home sick with the virus. Meanwhile, President Trump has openly accused health care workers of being wasteful and hoarding masks. (Sanya Dosani, 4/6)
Boston Globe: Why I Don't Feel Safe Wearing A Face Mask I thought I could use one of my old bandanas as a mask. But then my voice of self-protection reminded me that I, a Black man, cannot walk into a store with a bandana covering the greater part of my face if I also expect to walk out of that store. The situation isn't safe and could lead to un-intended attention, and ultimately a life-or-death situation for me. For me, the fear of being mistaken for an armed robber or assailant is greater than the fear of contracting COVID-19. (Aaron Thomas, 4/5)
The Washington Post: How Long Will We Doctors Last? There are tents outside our hospitals. Every time I see them, I stop, startled. Their drab and dirty flaps seem so out of place against the grand facades of world-class hospitals. Desperate times, desperate measures. The last time I worked in a tent was West Africa in 2014, during the Ebola outbreak. In those same tents, I saw too much pain, loneliness and death. People dying alone. I never thought I'd have to see or experience that ever again. I never wanted to. Once was painful enough. (Craig Spencer, 4/3)
Bloomberg: Coronavirus: 884 Hidden Deaths Are Revealed, And More To Come In one day last week, France's official death toll from Covid-19 rose by a staggering 1,355. The cause was not just the severity and speed of a coronavirus disease that has infected more than 1 million people and killed 50,000 around the world, but also the brutality of fresh data. The new tally included 884 deaths in nursing homes that had gone uncounted since the start of the crisis. While that should stoke concerns over the quality of the statistics the general public and policy makers are poring over every day — and on the likely under-counting of deaths — it should also alert us to an unfolding tragedy happening on the pandemic's front lines. It's not just hospitals that need help, but all institutions that care for the frail and infirm. (Lionel Laurent, 4/6)
CNN: How The Very Rich Are Different In The Covid-19 Fight I have spent two decades reporting on people at the nexus of money, power and culture. I've written books about corruption among the

country's wealthiest 1%, Wall Street greed and the ruthlessness of New York real estate titans. So these past few weeks I have been on the phone to many people who are not stuck, like me, in a New York City apartment, where we are on constant alert for the ominous sound of sirens puncturing the silence with increasing frequency. (Vickey Ward, 4/6)

The New York Times: Will The Virus Trigger A Second Arab Spring? On a recent visit to Libya, I met a family living in an improvised shelter in a displaced persons camp east of Tripoli. One of the tens of thousands Libyan families uprooted by war, the family of seven was living in a room barely 20 paces long and half as wide. A clothesline, a pile of mattresses, a hot plate and the stench of body odor filled the room. Outside, they faced a shortage of potable water and abusive taunts from locals. The spread of the novel coronavirus will have a devastating effect on the Middle East's communities of refugees and migrants. The pandemic may also bring into focus the legitimacy and governance deficit of increasingly troubled Middle Eastern regimes. (Frederic Wehrey, 4/6)

Recent Morning Briefings

- Today, April 6
- Friday, April 3
- Thursday, April 2
- Wednesday, April 1
- Tuesday, March 31
- Monday, March 30

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/06 12:14:05
Delivered Date:	2020/04/06 12:14:57
Message Flags:	Unread

From:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject:	Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries
Date:	2020/03/26 13:26:00
Priority:	Normal
Type:	Note

Diabetes &Metabolic Syndrome: Clinical Research &Reviews

Available online 26 March 2020

In Press, Journal Pre-proof

What are Journal Pre-proof articles?

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries

Author links open overlay panelAwadhesh KumarSingh[a]

AkritiSingh[b]AltamashShaikh[c]RituSingh[a]AnoopMisra[def]

https://protect2.fireeye.com/url?k=f82c0e82-a47827a9-f82c3fbd-0cc47a6d17cc-4f38351565a4ad80&u=https://doi.org/10.1016/j.dsx.2020.03.011Get rights and content

Highlights

•Some drugs have been tried for Coronavirus Disease-2019 (COVID-19).

•Chloroquine and Hydroxychloroquine has shown some promise in treatment of COVID-19 and should be fast tracked for further research.

•We also present available guidelines and propose use of these drugs in COVID-19.

Abstract

Background and aims

No drugs are currently approved for Coronavirus Disease-2019 (COVID-19), although some have been tried. In view of recent studies and discussion on chloroquine and hydroxychloroquine (HCQ), we aimed to review existing literature and relevant websites regarding these drugs and COVID-19, adverse effects related to drugs, and related guidelines.

Aims and methods

We systematically searched the PubMed database up till March 21, 2020 and retrieved all the articles published on chloroquine and HCQ and COVID-19.

Results

Two small human studies have been conducted with both these drugs in COVID-19, and have shown significant improvement in some parameters in patients with COVID-19.

Conclusion

Considering minimal risk upon use, a long experience of use in other diseases, cost-effectiveness and easy availability across India, we propose that both these drugs are worthy of fast track clinical trial for treatment, and may be carefully considered for clinical use as experimental drugs. Since HCQ has been approved for treatment of diabetes in India, it should be further researched in diabetes and COVID-19, a subgroup where significant mortality has been shown.

Keywords

COVID-19
Chloroquine
Hydroxychloroquine
Diabetes

1. Introduction

Novel coronavirus (2019-nCoV), officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of the (Corona Virus Disease 2019) COVID-19, emerged in Wuhan, Hubei province, China. On 11th March 2020, The World Health Organization (WHO) declared this disease as pandemic [1]. Chinese Centre for Disease Control and Prevention showed an increased mortality in people with diabetes (2.3% *vs.* 7.3%; overall *vs.* in patients with diabetes respectively) from a report of 72,314 cases of COVID-19 [2]. People with diabetes and COVID-19 may need special attention and clinical care [3]. In the absence of any known efficient therapy and because of the situation of a "public-health emergency", many drugs have been tried recently in the treatment for COVID-19 that includes a low-cost antimalarial drug chloroquine and its derivative hydroxychloroquine (HCQ), along with several other antiviral drugs. Because HCQ has been approved in the treatment of type 2 diabetes in India since 2014 as a third- or fourth-line drug, it would be interesting to research its impact in patients with diabetes, infected with COVID-19.

Reports gathered so far have suggested that a number of drugs could be potential candidates for the treatment of COVID-19, although the clinical effectiveness of these drugs have not yet been fully evaluated. The list of these drugs has been summarized in Table 1 [[4], [5], [6]].

Table 1. Drugs in pipeline for COVID-19[4], [5], [6]

Drugs	Types	Mechanisms of action	Past evidences
Chloroquine	4-aminoquinoline	Not clearly known, changes the pH of endosomes and believed to prevent viral entry, transport and post-entry events	Inhibits infection of cells by SARS-CoV-2 *in vitro*, approved for malaria treatment and prophylaxis

Drugs	Types	Mechanisms of action	Past evidences
Hydroxychloroquine	4-aminoquinoline	Not clearly known, changes the pH of endosomes and believed to prevents viral entry, transport and post-entry events	Inhibits infection of cells by SARS-CoV-2 *in vitro*, approved for malaria prophylaxis and autoimmune disease (e.g. rheumatic diseases). Approved for treatment of T2DM in India
Remdesivir	Adenosine nucleotide analogues	Inhibits viral application	Effective against SARS and MERS
Ribavirin	Nucleoside analogue	Inhibits viral RNA synthesis and mRNA capping	No evidence in SARS (potential harm) and MERS
Ribavirin plus Interferon		Inhibits viral replication	Mixed result against MERS
Camostat Mesilate	Protease inhibitors	Blocks viral maturation and entry to cells	Effectively blocked SARS-CoV-2 in lung cells *in vitro*
Lopinavir/Ritonavir	Protease inhibitors	Blocks viral cellular entry	Effective against SARS-CoV-1 both *in vitro* and human studies, approved for HIV-1 treatment
Darunavir/Cobicistat	Protease inhibitors	Blocks viral cellular entry	Established anti-HIV medication. No activity against coronaviruses or other respiratory viruses. No *in vitro* or clinical data.
Favipiravir	RNA polymerase inhibitors	Inhibits viral RNA-dependent polymerase	Broad-spectrum anti-viral against influenza, arenavirus, bunyavirus and filovirus
Umifenovir	Fusion inhibitor	Inhibits fusion between viral and cellular membrane	Antiviral against other Corona viruses
Interferon-ß1	Cytokines	Stimulate innate antiviral immunity.	MERS-CoV appears to be more sensitive than SARS-CoV *in vitro* studies. Anti-MERS-CoV action noted in animal studies.
Interferon beta plus Lopinavir/Ritonavir		Interferon beta inhibits viral replication	Ongoing study for SARS-Cov-2 and MIRACLE trial for MERS
Aerosolized interferon α	Cytokines	Stimulate innate antiviral immunity.	Case report suggested benefit in MERS
Oseltamivir	Neuraminidase inhibitor	Inhibits viral replication	No effect in SARS *in vitro* studies. No evidence in SARS and MERS
Baloxivir marboxil	Viral endonuclease inhibitor	Inhibits influenza virus multiplication	Approved for uncomplicated influenza only. Oral route.

Drugs	Types	Mechanisms of action	Past evidences
Tocilizumab, Sarilumab Eculizumab	Monoclonal antibody	IL-6 inhibitor, blocks cytokine storm.	No data on SARS or MERS. Tocilizumab reduced fever and oxygen requirement in COVID-19, approved for rheumatoid arthritis.
SARS-Cov-2 specific protease drug candidate	Protease inhibitors	Blocks viral infectivity	No data available
SARS-Cov-2 specific antibodies	Antibody	Binds to virus and block infection, binds to infected cells and change the immune system	Inhibits SARS-CoV-2 entry into cells *in vitro*

SARS- severe acute respiratory syndrome, MERS- Middle-East respiratory syndrome, HIV- Human Immunodeficiency syndrome, T2DM – type 2 diabetes, COVID-19- Corona virus disease 19.

In this review article, we have systematically searched the medical data base until March 20, 2020 and collated all the available evidences that have emerged so far on the efficacy of chloroquine and hydroxychloroquine, in the treatment of patients with COVID-19, with or without diabetes and present a perspective on both these compounds. Additionally, we have also pooled the currently on-going trials with both these compounds against the COVID-19.

2. Methods

We systematically searched the PubMed database up till March 21, 2020 using key words chloroquine AND COVID-19, and hydroxychloroquine AND COVID-19 and retrieved a total of 13 articles. The two articles that were written in Chinese were excluded. In addition, we also accessed and retrieved the full text of the cross references of importance from these 11 articles written in English. Moreover, we also accessed the currently ongoing trials with both these compounds from ClinicalTrials.gov.

3. Results

3.1. Studies of chloroquine and hydroxychloroquine conducted *in vitro*

Experimental studies have suggested that chloroquine is a proven anti-malarial drug that has the capability of inhibiting the replication of several intracellular micro-organisms including coronaviruses *in vitro*. It is also believed that chloroquine may have a varied mechanism of action which may differ depending upon the pathogen studied. It has been increasingly learnt that the anti-viral and anti-inflammatory activities of chloroquine may have a role in the treatment of patients with novel COVID-19. Chloroquine increases endosomal pH and interferes with the glycosylation of cellular receptor of SARS-CoV and thereby it has the potential to block viral infection [7]. In addition, chloroquine also inhibits the quinone reductase-2, which is involved in sialic acid biosynthesis (an acidic monosaccharides of cell transmembrane proteins required for ligand recognition) that makes this agent a broad antiviral agent. It is important to note that both human coronavirus HCoV-O43 and orthomyxoviruses uses sialic acid moieties as a receptor. Moreover, chloroquine changes the pH of lysosomes and likely inhibits cathepsins, that leads to the formation of the autophagosome which cleaves SARS-CoV-2 spike protein. Furthermore, chloroquine through the inhibition of MAP-kinase interferes with SARS-CoV-2 molecular crosstalk, besides altering the virion assembly, budding and interfering with the proteolytic processing of the M protein [7,8]. Previous experimental studies have also demonstrated that chloroquine has potent anti-SARS-CoV-1 effects *in vitro*, primarily attributable to a deficit in the glycosylation receptors at the virus cell surface, so that it cannot bind to the angiotensin-converting enzyme 2 (ACE2) expressed in lung, heart, kidney and intestine. Since SARS-CoV-2 utilizes the similar surface receptor ACE2, it is

believed that chloroquine can also interfere with ACE2 receptor glycosylation thus prevents SARS-CoV-2 attachment to the target cells [[6], [7], [8], [9]]. Chinese researchers who studied the effect of chloroquine *in vitro* (using Vero E6 cell line infected by SARS-CoV-2) found chloroquine to be highly effective in reducing viral replication that can be easily achievable with standard dosing due to its favorable penetration in tissues including the lung [6,10].

Since the structure and mechanism of action of chloroquine and hydroxychloroquine (HCQ) are exactly same except an additional hydroxy moiety in one terminal in HCQ, both act as a weak base that can change the pH of acidic intracellular organelles including endosomes/lysosomes, essential for the membrane fusion. It is believed that both the agents could be effective tools against SARS-CoV-1 and SARS-CoV-2 [10,11]. However, an important question that still remains is whether HCQ has a similar effect on SARS-CoV-2 infection. Some data show HCQ effectively inhibited both the entry, transport and the post-entry stages of SARS-CoV-2, similar to the chloroquine and one study found HCQ to be a more potent agent than chloroquine in inhibiting SARS-CoV-2 *in vitro* [12,13]. In addition, HCQ acts effectively on other intracellular bacterial infections such as Coxiella burnetii (Q fever) and Tropheryma whipplei (Whipple's disease) [14,15]. Addition of hydroxyl molecule makes HCQ less permeable to blood-retinal barrier and allows faster clearance from retinal pigment cell, thereby suggesting a lesser risk of retinal toxicity with HCQ, as compared to chloroquine [16]. Furthermore, the narrow therapeutic and safety index margin with chloroquine makes HCQ a safer option than chloroquine.

An additional issue to be considered in severely sick patients is cytokine storm associated with disease severity of SARS-CoV-2 [17].The significant decrease in the production of pro-inflammatory markers and cytokines with HCQ has made this agent a successful disease modifying anti-inflammatory agent in the treatment of various autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome. Long-term clinical safety profile of HCQ is better than that of chloroquine, that allows higher daily dose of HCQ with less drug-drug interactions.

3.2. Studies conducted with chloroquine and hydroxychloroquine in human COVID-19

The anti-viral and anti-inflammatory actions of chloroquine have led to numerous trials urgently in the face of global health emergency. A Chinese study involving more than 100 patients of COVID-19 found chloroquine superior to the control group in reducing symptom duration, exacerbation of pneumonia including radiological improvement and promoting virus-negative seroconversion without any severe side effects [18]. This represents the first human trial ever conducted with chloroquine against COVID-19. Although the detailed results of this trial are not yet published and only available in a letter form, interestingly, this early result led China to include chloroquine in the prevention and treatment of COVID-19 pneumonia. Moreover, The National Health Commission of the People's Republic of China recommended inclusion of chloroquine in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19. In this study, chloroquine was given in dose of 500 mg of chloroquine twice daily in mild to severe COVID-19 pneumonia (see Table 1).

The second human study which is currently available was conducted with HCQ. In an open-label, non-randomized trial (n = 36) conducted in Marseille, France, Gautret et al. found that HCQ alone and combination of HCQ plus azithromycin was highly and significantly effective in clearing viral nasopharyngeal carriage (measured by polymerase chain reaction [PCR]) in only three-to six days in COVID-19 subjects, compared to control. The virological clearance day-6 post-inclusion (primary outcome) with HCQ *vs.* control was 70.0% versus 12.5%, respectively ($p = 0.001$). In addition, the virological clearance at day-6 post-inclusion in HCQ plus azithromycin, HCQ and control arm was 100%, 57.1% and 12.5% respectively ($p < 0.001$). This data suggests a synergistic effect of azithromycin with HCQ. Indeed, azithromycin has shown an antiviral effect against Zika and Ebola viruses in *in vitro* studies; however, it is not yet known whether it has any action against COVID-19 as well [19]. These results of

converting a potential carrier to a seronegative patient are of importance with regards to preventing community transmission of COVID-19. Since the data from Wuhan, China showed that some patients were carrier as long as up to 37 days (usually around 20 days), results of this study are very encouraging in the context of converting a patient to a seronegative subject within 6 days. Interestingly, this study also showed that the effect of HCQ was significantly higher ($p < 0.05$) in symptomatic patients as compared to asymptomatic patients with COVID-19. The authors have acknowledged limitations of the study; a small sample size, dropout of six patients and limited follow-up, apart from the non-randomized and open-label nature of the trial. A close look in to this study also suggests that the Cycle threshold (Ct) value for nasopharyngeal swab PCR to call it as a sample negative, was lower (Ct value > 35 was deemed as negative for virus) compared to conventional Ct threshold of >40. Ct is defined as the number of cycles to be run for the PCR test to turn positive. In other words, lower the number of Ct denotes more virus is present and lesser number of cycles are required to hit the threshold. Moreover, nasopharyngeal swab PCR is a less sensitive tool, compared to PCR of Broncho-alveolar lavage and sputum in COVID-19. Furthermore, exclusion of five patients (26%) receiving HCQ from the overall analysis, dilutes the final results.

Nevertheless, based on limited available evidences to date, and given the prevailing pandemic of COVID-19, some of the institutions and or organizations have already recognized the utility of chloroquine and HCQ [20]. The expert consensus from the Department of Science and Technology and Health Commission of Guangdong province published on 20th February (based on *in vitro* evidence and still unpublished clinical experience) chloroquine phosphate tablet at a dose of 500 mg twice per day for 10 days for patients diagnosed as mild, moderate and severe cases of SARS-CoV-2 pneumonia in the absence of contraindication to the drug [21]. A Central Clinical Task Force from Korea who have treated 27 cases of COVID-19 recommend using lopinavir 400mg/Ritonavir 100 mg BID or Chloroquine 500 mg orally per day or Hydroxychloroquine 400 mg orally per day for 7–10 days, in moderate to severe case of COVID-19 [22]. Similarly, The Dutch Center of Disease control in a public document on its website, also suggested the use of chloroquine in those having severe COVID-19 infection admitted in the intensive care unit [23]. Table 2 summarizes the recommendation and dosing from all the various groups [[21], [22], [23], [24], [25], [26], [27], [28]].

Table 2. Available Guidelines (as of March 21, 2020) in the treatment of COVID-19 for Chloroquine and Hydroxychloroquine[19] [21], [22], [23], [24], [25], [26], [27], [28].

Study/Guidelines/Country	**Dose (adults)**
Expert consensus from Department of Science and Technology and Health Commission of Guangdong province, China[21]	Chloroquine phosphate 500 mg BID for 10 days.
Central Clinical Task Force, Korea[22]	Moderate to severe COVID-19: Lopinavir 400mg/Ritonavir 100 mg BID or Chloroquine 500 mg orally per day or Hydroxychloroquine 400 mg orally per day for 7–10 days.
Centre for Disease Control and Prevention, Atlanta, MICC Version 1 (March 12, 2020)[23]	URTI plus positive PCR: • Chloroquine phosphate 500 mg BID for 5 days. • Oseltamivir 150 mg BID for 5 days. COVID-19 Pneumonia:

Study/Guidelines/Country	Dose (adults)
	• Chloroquine phosphate 500 mg BID for 5 days plus Darunavir 800 mg/Cobicistat 150 mg OD for 2 weeks. • Atazanavir 400 mg OD for 2 weeks plus Oseltamivir 150 mg BID for 5 days.
The Dutch Center of Disease Control[24]	600 mg of Chloroquine base followed by 300 mg after 12 h on day 1, then 300 mg × 2/day per person on days 2–5.
Italian Society of Infectious and Tropical Diseases (Lombardy Section)[25]	Mild to moderate COVID-19: Lopinavir/ritonavir plus Chloroquine 500 mg × 2/day or Hydroxychloroquine 200 mg per day for 10 days. Severe or critical COVID-19: Remdesivir plus Chloroquine 500 mg × 2/day or Hydroxychloroquine 200 mg per day for 10–20 days.
Mount Sinai Health System, Canada[26]	Moderate to severe COVID-19: Hydroxychloroquine 400 mg BID x 2 doses then 12 h later start 400 mg OD for 5–10 days.
Surviving Sepsis Campaign, The Society of Critical Care Medicine and the European Society of Intensive Care Medicine.[27]	Insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19 at this point of time.
Clinical guidance for patients with suspected or confirmed COVID-19 in Belgium[28]	Mild/Moderate/Severe COVID-19: Hydroxychloroquine 400 mg at diagnosis, 400 mg 12 h later, followed by 200 mg BID for 5 days, Or, Chloroquine 600 mg at diagnosis and 300 mg 12 h later followed by 300 mg BID for 5 days (Consider lopinavir 400 mg/ritonavir 100 mg BID for 14 days as a second choice only if HCQ and chloroquine is contraindicated, provided it can be administered within 10 days after onset of symptoms) Critical COVID-19: Remdesivir 200 mg loading dose i.v within 30 min followed by 100 mg OD for 2–10 days (Hydroxychloroquine is second option if Remdesivir is unavailable)
Clinical guidance for patients with suspected or confirmed COVID-19 in Netherland[28]	Mild/moderate/severe COVID-19: Chloroquine 600 mg on day 1, then 300 mg BID for 5 days (lopinavir/ritonavir as second option) Critical COVID-19: Remdesivir for 10 days plus chloroquine for 5 day
Gautret et al., Marseille, France[13]	Hydroxychloroquine 200 mg TID for 10 days.

OD-once daily, BID-twice daily, TID-thrice daily, URTI- upper respiratory tract infection, PCR-polymerase chain reaction, i.v - intravenous.

4. Discussion

The antiviral activity of chloroquine and HCQ have been identified in the *in vitro* studies and the growth of many different viruses have been inhibited in the cell culture line by both the agents, including the SARS coronavirus. Mice studies have also demonstrated activity of these agents against human coronavirus OC43, enterovirus EV-A71, Zika virus and influenza A H5N1. However, no benefit of chloroquine was seen in the prevention of influenza and dengue infection in a randomized, double-blind, placebo-controlled, clinical trial [29,30]. Similarly, chloroquine was active in *ex vivo* studies but not in the *in vivo* studies against ebolavirus, nipah and influenza viruses [[31], [32], [33]]. Data of chloroquine against chikungunya virus is even more intriguing. While chloroquine had satisfactory antiviral activity against chikungunya *in vitro*, animal studies showed increase in virus replication, aggravation of fever and incomplete viral clearance [34]. Human trials of chloroquine showed no improvement in chikungunya acute illness and rather an increase in chronic arthralgia was observed during post-illness period, compared to the controls [35]. The role of chloroquine against Human Immunodeficiency Virus was inconclusive [36]. The only viral disease where chloroquine was modestly effective so far before COVID-19 era was chronic hepatitis C suggesting an increased virological response to pegylated interferon plus ribavirin [37]. Therefore, the results of chloroquine and HCQ so far done against COVID-19, more promising than previous trial in other viral diseases. Moreover, these drugs are of low cost, reasonably safe (see below), and widely available in countries where malaria is endemic.

4.1. Cautions and contraindication with chloroquine and hydroxychloroquine

Expectedly, some precautions will be needed while using both these drugs that include frequent monitoring of hematological parameters (RBC, WBC and platelet counts), measurement of serum electrolytes, blood glucose (because of hypoglycemic potential of HCQ) and hepatic as well as renal functions. Since both these drugs have the potential to prolong QTc, routine electrocardiography is essential prior to starting these drugs. Co-administration of other drugs known to prolong the QTc interval (such as anti-arrhythmic, anti-depressants, anti-psychotics, anti-histaminic, teneligliptin, ondansetron and moxifloxacin etc.) must be avoided [38,39]. Moreover, addition of azithromycin to HCQ as done in French trial by Gautret et al. may increase the risk of QTc prolongation. Perform ECG daily if QTc is 450–500 msec. Additionally, hypoglycemia must be looked for in patients with diabetes especially with concurrent use of chloroquine/HCQ and lopinavir/ritonavir. Chloroquine and HCQ should not be used concurrently with lopinavir/ritonavir and remdisivir for anticipated QTc prolongation. Finally, pharmacovigilance on visual and mental disturbance is also closely required.

Although there are sporadic case reports of chloroquine-induced cardiomyopathy and reversible heart failure in the literature, many studies and large meta-analysis conducted in patients with rheumatoid arthritis pointed to a reduced cardiovascular risk with both these compounds [40]. Nevertheless, since both the drug has potential to prolog QTc, a baseline ECG should be done in patients with established cardiovascular disease.

All clinicians using these drugs must know contraindication to both these compounds; hypersensitivity to these agents, retinopathy, porphyria, epilepsy, pre-existing maculopathy, G6PD deficiency, recent myocardial infarction and QTc >500 msec Chloroquine is not contraindicated in pregnancy.

5. Conclusion

Although evidence of chloroquine and HCQ is limited (based on the experimental data and only two small human trials), considering the potentially favorable benefit-risk balance of chloroquine and HCQ in absence of any other valid treatment option, we believe that such treatment could be useful in the current context of pandemic COVID-19 outbreak. We have summarized current consideration and proposed line of management in Table 3. The low cost of chloroquine and HCQ could also be an effective strategy to counter COVID-19 (especially in patients with diabetes and other co-morbidities in

whom mortality is high) in resource constrained and COVID-19 overburdened heath care systems in middle- and low-income counties including India.

Table 3. Based on the available evidence so far (including *in vitro, ex vivo* and *in vivo* studies – both experimental and two human studies) and considering the benefit-risk ratio as well as the low cost of chloroquine and hydroxychloroquine in Indian context, we propose the following regime, until more evidence is available -

Timing of intervention	Proposed
Chemoprophylaxis	• No conclusive evidence so far; however, chloroquine or HCQ could be researched as a prophylactic agent in endemic areas. Recent guidelines from Indian Council of Medical Research recommend it as prophylactic agent (see reference 42 for indication and dose) • Note: HCQ can be used as an adjunct to control glycemia in adult patients with type 2 diabetes (approved for treatment in India). However, role of such adjunctive treatment for testing its potential role as prophylaxis of COVID-19 in diabetes has not been researched but could be attempted (in view of above) considering a higher mortality in patients with diabetes, as compared to non-diabetic subjects with COVID-19.
Confirmed COVID-19	A. Chloroquine phosphate: @$ 1. COVID-19 URTI: 500 mg BID for 5 days. 2. COVID-19 LRTI: 500 mg BID for 10 days. B. Hydroxychloroquine: @$ Loading dose: 400 mg BID day 1, then Maintenance dose: 200 mg BID for 5–10 days. C. Monitor and watch for side effects*

@ watch for hypoglycemia in diabetes especially with concurrent use of lopinavir/ritonavir, $ should not be used concurrently with lopinavir/ritonavir and remdisivir due to increased QTc prolongation, * complete blood count, renal, hepatic profile and ECG – watch for QTc prolongation, URTI- upper respiratory tract infection, LRTI- lower respiratory tract infection, HCQ-hydroxychloroquine, BID – twice daily.

Table 4. Ongoing trials with chloroquine and hydroxychloroquine as of March 21, 2020.

Study title	Types of intervention	Intervention vs. comparator	n	Country	ClinicalTrial.Org identifier
Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID19: A Randomized Control Trial (THDMS-COVID19)	Treatment	Antiviral drugs plus Chloroquine PBO	80	Thailand	NCT04303299
Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV)	Prophylaxis	Chloroquine PBO	10,000	UK	NCT04303507

Study title	Types of intervention	Intervention vs. comparator	n	Country	ClinicalTrial.Org identifier
Treatment of Mild Cases and Chemoprophylaxis of Contacts as Prevention of the COVID-19 Epidemic (HCQ4COV19)	Treatment and prophylaxis in two separate groups	Darunavir/Cobicistat plus Chloroquine PBO	3040	Germany	NCT04304053
The Clinical Study of Carrimycin on Treatment Patients With COVID-19	Treatment	Carrimycin Lopinavir/ritonavir Arbidol Chloroquine PBO	520	China	NCT04286503
Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients with Mild Coronavirus Disease (COVID-19)	Treatment	Lopinavir/ritonavir HCQ	150	Korea	NCT04307693
Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)	Treatment	HCQ PBO	30	China	NCT04261517
Post-exposure Prophylaxis for SARS-Coronavirus-2	Post exposure prophylaxis	HCQ PBO	1500	United States	NCT04308668

HCQ-hydroxychloroquine, PBO- placebo, N - number.

Future directions:

1. Intervention trials planned for COVID-19: Several trials are currently underway with both chloroquine and HCQ in patients with COVID-19 at different doses. A search of The ClinicalTrial.org database dated March 21, 2020 showed 4 trials with chloroquine and 3 trials with HCQ which is currently under progress and have been summarized in Table 4. A list of 23 trials are already enlisted with both compounds at Chinese Clinical Trial Registry (https://protect2.fireeye.com/url?k=b6f7744a-eaa35d61-b6f74575-0cc47a6d17cc-5b5f26e6f179330f&u=http://www.chictr.org.cn/) [41]. We believe that it would be wise to conduct a quick interim analysis from these trials as soon as possible to find out the results that can be applied to the masses across the globe to curb the menace of COVID-19 pandemic.
2. Research for resistance to drugs in already mutating virus strains: Another area which needs to be explored further is resistance to chloroquine and HCQ that may be present with different strains of the virus.
3. Role of these drugs in COVID-19 chemoprophylaxis: Another knowledge gap that still remains is about role of these drugs in chemoprophylaxis. We still do not know whether these compounds can be useful to prevent the transmission of the virus, especially for healthcare workers. This needs to be tested in further studies.
4. Use of HCQ in patients with diabetes in India where it is already approved for treatment: It would be interesting to research COVID-19 infection in patients with diabetes who are already

on HCQ for treatment of diabetes. Further, the effect of HCQ on glycemia, cardiovascular function and viral load, in patients with diabetes needs to be researched.

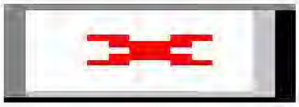
Declaration of competing interest

We hereby declare that we have no conflict of interest related to this article.

References

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/26 13:25:29
Delivered Date:	2020/03/26 13:26:00
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: The PALM Trial honored with the Society for Clinical Trials' prestigious David Sackett Trial of the Year Award for 2020
Date: 2020/04/21 13:30:36
Priority: Normal
Type: Note



Society for Clinical Trials

The PALM Trial honored with the Society for Clinical Trials' prestigious David Sackett Trial of the Year Award for 2020

21-Apr-2020 1:15 PM EDT, bySociety for Clinical Trials

Newswise — Arlington Heights, Ill., April 21, 2020 -- The Society for Clinical Trials (SCT) is pleased to announce that the prestigious David Sackett Trial of the Year Award for 2020 has been awarded to the Pamoja Tulinde Maisha (PALM ["Together Save Lives"] in the Kiswahili language) trial, an international group of investigators for their work in identifying safe effective therapies for Ebola – a highly deadly hemorrhagic fever virus.

"Amid the current global burden of COVID-19, the PALM trial not only highlights the critical importance of conducting rigorous clinical trials to establish effective therapies but also the necessary interdisciplinary and collaborative resolve to successfully execute clinical trials under urgent circumstances," said Dr. Dean Fergusson, Ottawa Hospital Research Institute, President of SCT.

During the second largest Ebola outbreak declared on August 1st, 2018 in the Democratic Republic of Congo, 2,196 of 3,296 cases (67 percent) died as reported on November 17th, 2019. No known therapeutic countermeasures were licensed at the beginning of this outbreak. Clinical trials evaluating interventions for Ebola are difficult to conduct due to the unpredictable and episodic nature of the disease and the lack of research infrastructure in outbreak locations.

The PALM trial evaluated four investigational therapies for Ebola during the outbreak in the Democratic Republic of the Congo. Patients of any age who had a positive result for Ebola virus were enrolled. All patients received standard care and were randomly assigned in a 1:1:1:1 ratio to one of four experimental drugs: intravenous administration of the triple monoclonal antibody ZMapp (the control group), the antiviral agent remdesivir, the single monoclonal antibody MAb114, or the triple monoclonal antibody REGN-EB3. On August 9th, 2019, an independent Data and Safety Monitoring Board recommended discontinuing ZMapp and Remdesivir because 28-day mortality rates in MAb114 and REGN-EB3 were substantially lower. The effective therapies (MAb114 and REGN-EB3) were immediately adopted in the field.

"With results that were published within one year of study start, the PALM trial demonstrated that scientifically and ethically sound clinical research can be conducted during disease outbreaks and can

help inform the outbreak response," said Dr. Scott Evans, George Washington University, Chair of the SCT Trial of the Year Committee.

The PALM trial was jointly led by the National Institute for Biomedical Research (INRB/DRC) and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIAID/NIH) as part of an international research consortium coordinated by the World Health Organization (WHO). The consortium included additional support from the Alliance for International Medical Assistance (ALIMA), Doctors without Borders (Médecins Sans Frontières, MSF) and the International Medical Corps (IMC). Pharmaceutical partners included Gilead Sciences Inc, Mapp Biopharmaceutical Inc, Regeneron Pharmaceuticals and Ridgeback Biotherapeutics. The trial was published in the New England Journal of Medicine (DOI: 10.1056/NEJMoa1910993).

The SCT will be holding a special webinar on International Clinical Trials Day, May 20th, 2020 to recognize the PALM trial and gain insights into the trial conception and execution. Key PALM trialists will include Professor Jean-Jacques Muyembe and Dr. Placide Mbala from the Institut National pour la Recherche Biomedicale in the Democratic Republic of the Congo; Dr. Lori Dodd from the National Institute of Allergy and Infectious Diseases (NIAID); and Dr. Olivier Tshiani from Leidos Biomedical Research, Inc. (LBR). Discussion will also include how findings and knowledge from PALM can support COVID response efforts. Of note, one of the therapies in the PALM trial, remdesivir, is being studied extensively for treatment of coronavirus infection. Details of the SCT David Sackett Trial of the Year webinar can be found at https://protect2.fireeye.com/url?k=737068e5-2f256135-737059da-0cc47a6a52de-030863b4a733bc67&u=http://www.sctweb.org/.

Each year since 2008, the SCT has awarded the David Sackett Trial of the Year Award to a randomized, controlled trial published (either electronically or in print) in the previous calendar year that best fulfills the following standards:

- • Improves the lot of humankind;
- • Provides the basis for a substantial, beneficial change in healthcare;
- • Reflects expertise in subject matter, excellence in methodology, and concern for study participants;
- • Overcomes obstacles in implementation; and
- • Based on the presentation of its design, execution, and results is a model of clarity and intellectual soundness.

Nominations are submitted by Society members, investigators, and interested scholars from around the world. The 2019-2020 Trial of the Year selection committee included: Marc Buyse, Bob Dworkin, Scott Evans (Chair), Toshimitsu Hamasaki, Frank Rockhold, and Yves Rosenberg. Dr. David L. Sackett was a dedicated long-time SCT member and a pioneer in evidence-based medicine and champion of clinical trials.

###

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/21 13:29:59
Delivered Date:	2020/04/21 13:30:36

Message Flags: Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Lancet Digital Health: A real-time dashboard of clinical trials for COVID-19
Date: 2020/04/25 09:28:42
Priority: Normal
Type: Note

The Lancet Digital Health

Available online 24 April 2020
In Press, Corrected Proof
What are Corrected Proof articles?

The Lancet Digital Health

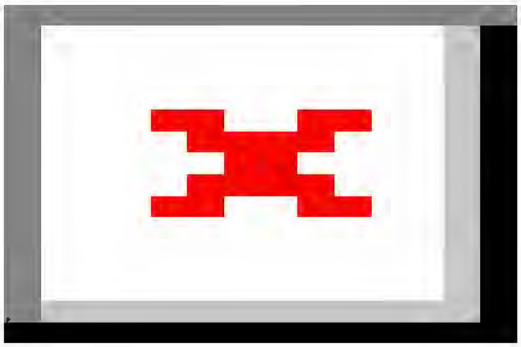
Correspondence
A real-time dashboard of clinical trials for COVID-19

Author links open overlay panel Kristian Thorlund[a] Louis Dron[a] Jay Park[b] Grace Hsu[a] Jamie I Forrest[b] Edward J Mills[a]

https://doi.org/10.1016/S2589-7500(20)30086-8 Get rights and content

In response to the global coronavirus disease 2019 (COVID-19) emergency, clinical trial research assessing the efficacy and safety of clinical candidate interventions to treat COVID-19 are emerging at an unprecedented rate. As of April 21, 2020, well over 500 clinical trials have been registered at the various international and national clinical trial registry sites. Findings from randomised clinical trials that have been published as of April 21, 2020, have investigated the efficacy of lopinavir–ritonavir compared with standard of care,[1] hydroxychloroquine compared with best supportive care,[2] favipiravir compared with arbidol,[3] and lopinavir–ritonavir compared with arbidol.[4] Other non-randomised trials have investigated hydroxychloroquine versus hydroxychloroquine combined with azithromycin.[5] Over 300 trials are enrolling participants and cover further investigations of the above drugs and promising therapies such as remdesivir, IL-6 inhibitors (tocilizumab and sarilumab), convalescent plasma therapy, stem-cell transfusion, vaccine candidates, several other well known direct acting antiv irals, and traditional Chinese medicines. Most of these trials will offer comparative efficacy data versus standard of care according to local COVID-19 treatment guidelines, but a handful of randomised controlled trials will also provide head-to-head evidence between high profile interventions. The figure shows the network of

completed, ongoing, and planned COVID-19 interventional clinical trials of these interventions or intervention groups that are being explored in at least two trials.



1. • Download : Download full-size image

Figure. Evidence network of COVID-19 clinical trials of top 15 interventions
Circles (node) represent interventions or intervention groups (categories). Lines between two circles indicate comparisons in clinical trials. The numbers on the lines are the number of clinical trials making the specific comparison. Circular arrows and numbers indicate the number of non-comparative clinical trials in which that intervention is included. A few trials examining combination therapies are excluded from the figure due to space limitations. COVID-19=coronavirus disease 2019. LPV/r (lopinivir–ritonavir). *Includes trials on hydroxychloroquine and chloroquine.

Given the accelerated rate at which trial information and findings are emerging, an urgent need exists to track clinical trials, avoid unnecessary duplication of efforts, and understand what trials are being done and where. In response, we have developed a COVID-19 clinical trials registry to collate all trials. Data are pulled from the International Clinical Trials Registry Platform, including those from the Chinese Clinical Trial Registry, ClinicalTrials.gov, Clinical Research Information Service - Republic of Korea, EU Clinical Trials Register, ISRCTN, Iranian Registry of Clinical Trials, Japan Primary Registries Network, and German Clinical Trials Register. Both automated and manual searches are done to ensure minimisation of duplicated entries and for appropriateness to the research questions. Identified studies are then manually reviewed by two separate reviewers before being entered into the registry. Concurrently, we have developed artificial intelligence (AI)-based methods for data searches to identify potential clinical studies not captured in trial registries. These methods provide estimates of the likelihood of importance of a study being included in our database, such that the study can then be reviewed manually for inclusion. Use of AI-based methods saves 50–80% of the time required to manually review all entries without loss of accuracy. Finally, we will use content aggregator services, such as LitCovid, to ensure our data acquisition strategy is complete. With this three-step process, the probability of missing important publications is greatly diminished and so the resulting data are representative of global COVID-19 research efforts.

Trials for COVID-19 are then mapped according to geographical, trial, patient, and intervention characteristics, when these data are available. These data are stored securely in a backend database and outputs are visualised on a front-end feature.
As trial findings are communicated, these data must be centralised and meta-analysed in real-time. Syntheses of these trials are urgently needed to assist clinicians, researchers, and policy makers to make evidence-informed decisions to minimise the morbidity and mortality due to COVID-19.
We declare no competing interests.

References

1

B Cao, Y Wang, D Wen, *et al.***A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19**
N Engl J Med (2020)
published online March 18.
DOI:10.1056/NEJMoa2001282
Google Scholar

2

J Chen, L Liu, P Liu, *et al.***A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)**
J Zhejiang Univ (Med Sci) (2020)
published online March 6.
DOI:10.3785/j.issn.1008-9292.2020.03.03
Google Scholar

3

C Chen, J Huang, P Yin, *et al.***Favipiravir versus arbidol for COVID-19: a randomized clinical trial**
medRxiv (2020)
published onine April 8.
DOI: 10.1101/2020.03.17.20037432
(preprint)
Google Scholar

4

X Yao, F Ye, M Zhang, *et al.***In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**
Clin Infect Dis (2020)
published online March 9.
DOI: 10.1093/cid/ciaa237
Google Scholar

5

P Gautret, JC Lagier, P Parola, *et al.***Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial**
Int J Antimicrob Agents (2020)
published online March 20.
DOI:10.1016/j.ijantimicag.2020.105949
Google Scholar

Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/25 09:28:07
Delivered Date:	2020/04/25 09:28:42
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: NYT: Harsh Steps Are Needed to Stop the Coronavirus, Experts Say https://nyti.ms/39drb1X
Date: 2020/03/22 19:45:27
Priority: Normal
Type: Note

Harsh Steps Are Needed to Stop the Coronavirus, Experts Say

Scientists who have fought pandemics describe difficult measures needed to defend the United States against a fast-moving pathogen.

A beach stroller in the Coney Island neighborhood of Brooklyn on Saturday.Credit...Victor J. Blue for The New York Times

Donald G. McNeil Jr.

By Donald G. McNeil Jr.

- March 22, 2020, 6:00 p.m. ET

Terrifying though the coronavirus may be, it can be turned back. China, South Korea, Singapore and Taiwan have demonstrated that, with furious efforts, the contagion can be brought to heel.

Whether they can keep it suppressed remains to be seen. But for the United States to repeat their successes will take extraordinary levels of coordination and money from the country's leaders, and extraordinary levels of trust and cooperation from citizens. It will also require international partnerships in an interconnected world.

There is a chance to stop the coronavirus. This contagion has a weakness.

Although there are incidents of rampant spread, as happened on the cruise ship Diamond Princess, the coronavirus more often infects clusters of family members, friends and work colleagues, said Dr. David L. Heymann, who chairs an expert panel advising the World Health Organization on emergencies.

No one is certain why the virus travels in this way, but experts see an opening nonetheless. "You can contain clusters," Dr. Heymann said. "You need to identify and stop discrete outbreaks, and then do rigorous contact tracing."

But doing so takes intelligent, rapidly adaptive work by health officials, and near-total cooperation from the populace. Containment becomes realistic only when Americans realize that working together is the only way to protect themselves and their loved ones.

In interviews with a dozen of the world's leading experts on fighting epidemics, there was wide agreement on the steps that must be taken immediately.

Those experts included international public health officials who have fought AIDS, malaria, tuberculosis, flu and Ebola; scientists and epidemiologists; and former health officials who led major American global health programs in both Republican and Democratic administrations.

Americans must be persuaded to stay home, they said, and a system put in place to isolate the infected and care for them outside the home. Travel restrictions should be extended, they said; productions of masks and ventilators must be accelerated, and testing problems must be resolved.

But tactics like forced isolation, school closings and pervasive GPS tracking of patients brought more divided reactions.

It was not at all clear that a nation so fundamentally committed to individual liberty and distrustful of government could learn to adapt to many of these measures, especially those that smack of state compulsion.

"The American way is to look for better outcomes through a voluntary system," said Dr. Luciana Borio, who was director of medical and biodefense preparedness for the National Security Council before it was disbanded in 2018.

"I think you can appeal to people to do the right thing."

In the week since the interviews began, remarkable changes have come over American life. State governments are telling residents they must stay home. Nonessential businesses are being shuttered. The streets are quieter than they have been in generations, and even friends keep a wary distance. What seemed unthinkable just a week ago is rapidly becoming the new normal.

What follows are the recommendations offered by the experts interviewed by The Times.

Scientists must be heard

The White House holds frequent media briefings to describe the administration's progress against the pandemic, often led by President Trump or Vice President Mike Pence, flanked by a rotating cast of officials.

Many experts, some of whom are international civil servants, declined to speak on the record for fear of offending the president. But they were united in the opinion that politicians must step aside and let scientists both lead the effort to contain the virus and explain to Americans what must be done.

Just as generals take the lead in giving daily briefings in wartime — as Gen. Norman Schwarzkopf did during the Persian Gulf war — medical experts should be at the microphone now to explain complex ideas like epidemic curves, social distancing and off-label use of drugs.

The microphone should not even be at the White House, scientists said, so that briefings of historic importance do not dissolve into angry, politically charged exchanges with the press corps, as happened again on Friday.

Instead, leaders must describe the looming crisis and the possible solutions in ways that will win the trust of Americans.

Above all, the experts said, briefings should focus on saving lives and making sure that average wage earners survive the coming hard times — not on the stock market, the tourism industry or the president's health. There is no time left to point fingers and assign blame.

"At this point in the emergency, there's little merit in spending time on what we should have done or who's at fault," said Adm. Tim Ziemer, who was the coordinator of the President's Malaria Initiative from 2006 until early 2017 and led the pandemic response unit on the National Security Council before its disbanding.

"We need to focus on the enemy, and that's the virus."

Stop transmission between cities

The next priority, experts said, is extreme social distancing.

If it were possible to wave a magic wand and make all Americans freeze in place for 14 days while sitting six feet apart, epidemiologists say, the whole epidemic would sputter to a halt.
The virus would die out on every contaminated surface and, because almost everyone shows symptoms within two weeks, it would be evident who was infected. If we had enough tests for every American, even the completely asymptomatic cases could be found and isolated.
The crisis would be over.
Obviously, there is no magic wand, and no 300 million tests. But the goal of lockdowns and social distancing is to approximate such a total freeze.
To attempt that, experts said, travel and human interaction must be reduced to a minimum.
Italy moved incrementally: Officials slowly and reluctantly closed restaurants, churches and museums, and banned weddings and funerals. Nonetheless, the country's death count continues to rise.
The United States is slowly following suit. International flights are all but banned, but not domestic ones. California has ordered all residents to stay at home; New York was to shutter all nonessential businesses on Sunday evening.
But other states have fewer restrictions, and in Florida, for days spring break revelers ignored government requests to clear the beaches.
On Friday, Dr. Anthony S. Fauci, chief medical adviser to the White House Coronavirus Task Force, said he advocated restrictive measures all across the country.
In contrast to the halting steps taken here, China shut down Wuhan — the epicenter of the nation's outbreak — and restricted movement in much of the country on Jan. 23, when the country had a mere 500 cases and 17 deaths.
Its rapid action had an important effect: With the virus mostly isolated in one province, the rest of China was able to save Wuhan.
Even as many cities fought their own smaller outbreaks, they sent 40,000 medical workers into Wuhan, roughly doubling its medical force.
In a vast, largely closed society, it can be difficult to know what is happening on the ground, and there is no guarantee that the virus won't roar back as the Chinese economy restarts.
But the lesson is that relatively unaffected regions of the United States will be needed to help rescue overwhelmed cities like New York and Seattle. Keeping these areas at least somewhat free of the coronavirus means enacting strict measures, and quickly.

Stop transmission within cities

Within cities, there are dangerous hot spots: One restaurant, one gym, one hospital, even one taxi may be more contaminated than many identical others nearby because someone had a coughing fit inside.
Each day's delay in stopping human contact, experts said, creates more hot spots, none of which can be identified until about a week later, when the people infected there start falling ill.
To stop the explosion, municipal activity must be curtailed. Still, some Americans must stay on the job: doctors, nurses, ambulance drivers; police officers and firefighters; the technicians who maintain the electrical grid and gas and phone lines.
The delivery of food and medicine must continue, so that people pinned in their homes suffer nothing worse than boredom. Those essential workers may eventually need permits, and a process for issuing them, if the police are needed to enforce stay-at-home orders, as they have been in China and Italy.
People in lockdown adapt. In Wuhan, apartment complexes submit group orders for food, medicine, diapers and other essentials. Shipments are assembled at grocery warehouses or government pantries and dropped off. In Italy, trapped neighbors serenade one another.
It's an intimidating picture. But the weaker the freeze, the more people die in overburdened hospitals — and the longer it ultimately takes for the economy to restart.

South Korea avoided locking down any city, but only by moving early and with extraordinary speed. In January, the country had four companies making tests, and as of March 9 had tested 210,000 citizens — the equivalent of testing 2.3 million Americans.
As of the same date, fewer than 9,000 Americans had been tested.
Everyone who is infected in South Korea goes into isolation in government shelters, and phones and credit card data are used to trace their prior movements and find their contacts. Where they walked before they fell ill is broadcast to the cellphones of everyone who was nearby.
Anyone even potentially exposed is quarantined at home; a GPS app tells the police if that person goes outside. The fine for doing so is $8,000.
British researchers are trying to develop a similar tracking app, albeit one more palatable to citizens in Western democracies.

Fix the testing mess

Testing must be done in a coordinated and safe way, experts said. The seriously ill must go first, and the testers must be protected.
In China, those seeking a test must describe their symptoms on a telemedicine website. If a nurse decides a test is warranted, they are directed to one of dozens of "fever clinics" set up far from all other patients.
Personnel in head-to-toe gear check their fevers and question them. Then, ideally, patients are given a rapid flu test and a white blood cell count is taken to rule out influenza and bacterial pneumonia.
Then their lungs are visualized in a CT scanner to look for "ground-glass opacities" that indicate pneumonia and rule out cancer and tuberculosis. Only then are they given a diagnostic test for the coronavirus — and they are told to wait at the testing center.
The results take a minimum of four hours; in the past, if results took overnight, patients were moved to a hotel to wait — sometimes for two to three days, if doctors believed retesting was warranted. It can take several days after an exposure for a test to turn positive.
In the United States, people seeking tests are calling their doctors, who may not have them, or sometimes waiting in traffic jams leading to store parking lots. On Friday, New York City limited testing only to those patients requiring hospitalization, saying the system was being overwhelmed.

Isolate the infected

As soon as possible, experts said, the United States must develop an alternative to the practice of *isolating* infected people at home, as it endangers families. In China, 75 to 80 percent of all transmission occurred in family clusters.
That pattern has already repeated itself here. Seven members of a large family in New Jersey were infected; four have already died. After a lawyer in New Rochelle, N.Y., fell ill, his wife, son and daughter all tested positive.
Instead of a policy that advises the infected to remain at home, as the Centers for Disease and Prevention now does, experts said cities should establish facilities where the mildly and moderately ill can recuperate under the care and observation of nurses.
Wuhan created many such centers, called "temporary hospitals," each a cross between a dormitory and a first-aid clinic. They had cots and oxygen tanks, but not the advanced machines used in intensive care units.
American cities now have many spaces that could serve as isolation wards. Already New York is considering turning the Jacob K. Javits Convention Center into a temporary hospital, along with the Westchester Convention Center and two university campuses.
Gov. Ron DeSantis of Florida said on Saturday that state officials were also considering opening isolation wards.

In China, said Dr. Bruce Aylward, leader of the World Health Organization's observer team there, people originally resisted leaving home or seeing their children go into isolation centers with no visiting rights — just as Americans no doubt would.
In China, they came to accept it.
"They realized they were keeping their families safe," he said. "Also, isolation is really lonely. It's psychologically difficult. Here, they were all together with other people in the same boat. They supported each other."

Find the fevers

Because China, Taiwan and Vietnam were hit by SARS in 2003, and South Korea has grappled with MERS, fever checks during disease outbreaks became routine.
In most cities in affected Asian countries, it is commonplace before entering any bus, train or subway station, office building, theater or even a restaurant to get a temperature check. Washing your hands in chlorinated water is often also required.
"They give you a sticker afterward," said Dr. Heymann, who recently spent a week teaching in Singapore. "I built up quite a collection."
In China, having a fever means a mandatory trip to a fever clinic to check for coronavirus. In the Wuhan area, different cities took different approaches.
Cellphone videos from China show police officers knocking on doors and taking temperatures. In some, people who resist are dragged away by force. The city of Ningbo offered bounties of $1,400 to anyone who turned in a coronavirus sufferer.
The city of Qianjiang, by contrast, offered the same amount of money to any resident who came in voluntarily and tested positive.
Some measures made Western experts queasy. It is difficult to imagine Americans permitting a family member with a fever to be dragged to an isolation ward where visitors are not permitted.
"A lot of people's rights were violated," Dr. Borio said.
Voluntary approaches, like explaining to patients that they will be keeping family and friends safe, are more likely to work in the West, she added.

Trace the contacts

Finding and testing all the contacts of every positive case is essential, experts said. At the peak of its epidemic, Wuhan had 18,000 people tracking down individuals who had come in contact with the infected.
At the moment, the health departments of some American counties lack the manpower to trace even syphilis or tuberculosis, let alone scores of casual contacts of someone infected with the coronavirus.
Dr. Borio suggested that young Americans could use their social networks to "do their own contact tracing." Social media also is used in Asia, but in different ways.
China's strategy is quite intrusive: To use the subway in some cities, citizens must download an app that rates how great a health risk they are. South Korean apps tell users exactly where infected people have traveled.
When he lectured at a Singapore university, Dr. Heymann said, dozens of students were in the room. But just before he began class, they were photographed to record where everyone sat.
"That way, if someone turns up infected later, you can find out who sat near them," Dr. Heymann said. "That's really clever."
Contacts generally must remain home for 14 days and report their temperatures twice a day.

Make masks ubiquitous

American experts have divided opinions about masks, but those who have worked in Asia see their value.

There is very little data showing that flat surgical masks protect healthy individuals from disease. Nonetheless, Asian countries generally make it mandatory that people wear them. In China, the police even used drones to chase individuals down streets, ordering them to go home and mask up.

The Asian approach is less about data than it is about crowd psychology, experts explained.

All experts agree that the sick must wear masks to keep in their coughs. But if a mask indicates that the wearer is sick, many people will be reluctant to wear one. If everyone is required to wear masks, the sick automatically have one on and there is no stigma attached.

Also, experts emphasized, Americans should be taught to take seriously admonitions to stop shaking hands and hugging. The "W.H.O. elbow bump" may look funny, but it's a legitimate technique for preventing infection.

"In Asia, where they went through SARS, people understand the danger," Dr. Heymann said. "It's instilled in the population that you've *got* to do the right thing."

Preserve vital services

Federal intervention is necessary for some vital aspects of life during a pandemic.

Only the federal government can enforce interstate commerce laws to ensure that food, water, electricity, gas, phone lines and other basic needs keep flowing across state lines to cities and suburbs.

Mr. Trump has said he could compel companies to prioritize making ventilators, masks and other needed goods. Some have volunteered; the Hanes underwear company, for example, will use its cotton to make masks for hospital workers.

He also has the military; the Navy is committing two hospital ships to the fight. And Mr. Trump can call up the National Guard. As of Saturday evening, more than 6,500 National Guard members already are assisting in the coronavirus response in 38 states, Puerto Rico and the District of Columbia.

High-level decisions like these must be made quickly, experts said.

"Many Western political leaders are behaving as though they are on a tightrope," said Dr. David Nabarro, a W.H.O. special envoy on Covid-19 and a veteran of fights against SARS, Ebola and cholera. "But there is no choice. We must do all in our power to fight this," he added. "I sense that most people — and certainly those in business — get it. They would prefer to take the bitter medicine at once and contain outbreaks as they start rather than gamble with uncertainty."

Produce ventilators and oxygen

The roughly 175,000 ventilators in all American hospitals and the national stockpile are expected to be far fewer than are needed to handle a surge of patients desperate for breath.

The machines pump air and oxygen into the lungs, but they normally cost $25,000 or more each, and neither individual hospitals nor the federal emergency stockpile has ever had enough on hand to handle the number of pneumonia patients that this pandemic is expected to produce.

New York, for example, has found about 6,000 ventilators for purchase around the world, Governor Cuomo said. He estimated the state would need about 30,000.

The manufacturers, including a dozen in the United States, say there is no easy way to ramp up production quickly. But it is possible other manufacturers, including aerospace and automobile companies, could be enlisted to do so.

Ventilators are basically air pumps with motors controlled by circuits that make them act like lungs: the pump pushes air into the patient, then stops so the weight of the chest can push the air back out.

Automobiles and airplanes contain many small pumps, like those for oil, water and air-conditioning fluid, that might be modified to act as basic, stripped-down ventilators. On Sunday, Mr. Trump tweeted that Ford and General Motors had been "given the go-ahead" to produce ventilators.

Providers, meanwhile, are scrambling for alternatives.

Canadian nurses are disseminating a 2006 paper describing how one ventilator can be modified to treat four patients simultaneously. Inventors have proposed combining C-PAP machines, which many apnea sufferers own, and oxygen tanks to improvise a ventilator.
The United States must also work to increase its supply of piped and tanked oxygen, Dr. Aylward said. One of the lessons of China, he noted, was that many Covid-19 patients who would normally have been intubated and on ventilators managed to survive with oxygen alone.

Retrofit hospitals

Hospitals in the United States have taken some measures to handle surges of patients, such as stopping elective surgery and setting up isolation rooms.
To protect bedridden long-term patients, nursing homes and hospitals also should immediately stop admitting visitors and do constant health checks on their staffs, said Dr. James LeDuc, director of the Galveston National Laboratory at the University of Texas Medical Branch.
The national stockpile does contain some prepackaged military field hospitals, but they are not expected to be nearly enough for a big surge.
In Wuhan, the Chinese government famously built two new hospitals in two weeks. All other hospitals were divided: 48 were designated to handle 10,000 serious or critical coronavirus patients, while others were restricted to handling emergencies like heart attacks and births.
Wherever that was impractical, hospitals were divided into "clean" and "dirty" zones, and the medical teams did not cross over. Walls to isolate whole wards were built, and — as in Ebola wards — doctors went in one end of the room wearing protective gear and left by the other end, where they de-gowned under the eyes of a nurse to prevent infection.

Decide when to close schools

As of Saturday, schools in 45 states were closed entirely, but that is a decision that divided experts.
"Closing all schools may not make sense unless there is documented widespread community transmission, which we're not seeing in most of the country," said Dr. Thomas R. Frieden, a former C.D.C. director under President Barack Obama.
It is unclear how much children spread coronavirus. They very seldom get sick enough to be hospitalized, which is not true of flu. Current testing cannot tell whether most do not even become infected.
In China, Dr. Aylward said, he asked all of the doctors he spoke to whether they had seen any family clusters in which a child was the first to be infected. No one had, he said, which astonished him.
That leaves a quandary. Closing schools is a normal part of social distancing; after all, schools are the workplaces for many adults, too. And when the disease is clearly spreading within an individual school, it must close.
But closing whole school districts can seriously disrupt a city's ability to fight an outbreak. With their children stuck at home, nurses, doctors, police officers and other emergency medical workers cannot come to work.
Also, many children in low-income families depend on the meals they eat at schools.
Cities that close all schools are creating special "hub schools" for the children of essential workers. In Ohio, the governor has told school bus drivers to deliver hot meals to children who normally got them at school.

Recruit volunteers

China's effort succeeded, experts said, in part because of hundreds of thousands of volunteers. The government declared a "people's war" and rolled out a "Fight On, Wuhan! Fight On, China!" campaign. It made inspirational films that combined airline ads with 1940s-style wartime propaganda. The ads were somewhat corny, but they rallied the public.

Many people idled by the lockdowns stepped up to act as fever checkers, contact tracers, hospital construction workers, food deliverers, even babysitters for the children of first responders, or as crematory workers.

With training, volunteers were able to do some ground-level but crucial medical tasks, such as basic nursing, lab technician work or making sure that hospital rooms were correctly decontaminated.

Americans often step forward to help neighbors affected by hurricanes and floods; many will no doubt do so in this outbreak, but they will need training in how not to fall ill and add to the problem.

"In my experience, success is dependent on how much the public is informed and participates," Admiral Ziemer said. "This truly is an 'all hands on deck' situation."

Prioritize the treatments

Clinicians in China, Italy and France have thrown virtually everything they had in hospital pharmacies into the fight, and at least two possibilities have emerged that might save patients: the anti-malaria drugs chloroquine and hydroxychloroquine, and the antiviral remdesivir, which has no licensed use.

There is not proof yet that any of these are effective against the virus. China registered more than 200 clinical trials, including several involving those treatments, but investigators ran out of patients in critical condition to enroll. Italy and France have trials underway, and hospitals in New York are writing trial protocols now.

One worry for trial leaders is that chloroquine has been given so much publicity that patients may refuse to be "randomized" and accept a 50 percent chance of being given a placebo.

If any drug works on critical cases, it might be possible to use small doses as a prophylactic to prevent infection.

An alternative is to harvest protective antibodies from the blood of people who have survived the illness, said Dr. Peter J. Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine in Houston.

The purified blood serum — called immunoglobulin — could possibly be used in small amounts to protect emergency medical workers, too.

"Unfortunately, the first wave won't benefit from this," Dr. Hotez said. "We need to wait until we have enough survivors."

Find a vaccine

The ultimate hope is to have a vaccine that will protect everyone, and many companies and governments have already rushed the design of candidate vaccines. But as Dr. Fauci has explained multiple times, testing those candidate vaccines for safety and effectiveness takes time.

The process will take at least a year, even if nothing goes wrong. The roadblock, vaccine experts explained, is not bureaucratic. It is that the human immune system takes weeks to produce antibodies, and some dangerous side effects can take weeks to appear.

After extensive animal testing, vaccines are normally given to about 50 healthy human volunteers to see if they cause any unexpected side effects and to measure what dose produces enough antibodies to be considered protective.

If that goes well, the trial enrolls hundreds or thousands of volunteers in an area where the virus is circulating. Half get the vaccine, the rest do not — and the investigators wait. If the vaccinated half do not get the disease, the green light for production is finally given.

In the past, some experimental vaccines have produced serious side effects, like Guillain-Barre syndrome, which can paralyze and kill. A greater danger, experts said, is that some experimental vaccines, paradoxically, cause "immune enhancement," meaning they make it more likely, not less, that recipients will get a disease. That would be a disaster.

One candidate coronavirus vaccine Dr. Hotez invented 10 years ago in the wake of SARS, he said, had to be abandoned when it appeared to make mice more likely to die from pneumonia when they were experimentally infected with the virus.

In theory, the testing process could be sped up with "challenge trials," in which healthy volunteers get the vaccine and then are deliberately infected. But that is ethically fraught when there is no cure for Covid-19. Even some healthy young people have died from this virus.

Reach out to other nations

Wealthy nations need to remember that, as much as they are struggling with the virus, poorer countries will have a far harder time and need help.

Also, the Asian nations that have contained the virus could offer expertise — and desperately needed equipment. Jack Ma, the billionaire founder of Alibaba, recently offered large shipments of masks and testing kits to the United States.

Wealthy nations ignored the daily warnings from Tedros Adhanom Ghebreyesus, the W.H.O.'s director general, that far more aggressive efforts at isolation and contact tracing were urgently needed to stop the virus.

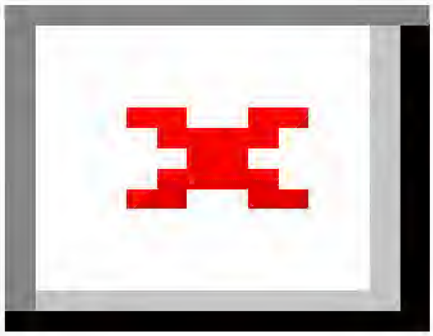
"Middle income and poorer nations are following the advice of international organizations while the most advanced nations find it so hard to implement it," Dr. Nabarro said. "That must change."

In declaring the coronavirus a pandemic, Dr. Tedros called for countries to learn from one another's successes, act with unity and help protect one another against a threat to people of every nationality. "Let's all look out for each other," he said.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/22 19:45:05
Delivered Date:	2020/03/22 19:45:27

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: LA Times: Here's what scientists still wish they knew about the coronavirus
Date: 2020/04/22 12:36:53
Priority: Normal
Type: Note

Here's what scientists still wish they knew about the coronavirus



Virus Outbreak

Unknowns

A man in Detroit wears a protective mask while waiting for a bus. Scientists would like to know more about which public health strategies are most effective at preventing the coronavirus from spreading. (Paul Sancya / Associated Press)

By Amina KhanStaff Writer

April 21, 2020

9 PM

With some states getting ready to lift their stay-at-home orders and relax their social distancing measures, it may seem that health officials have the coronavirus outbreak under control.

But researchers say there's still much they don't know about the virus — and the answers to their questions could help determine when it will be safe for life to return to normal.

The mysteries scientists are most eager to solve have shifted somewhat since this coronavirus began sickening people in Wuhan, China, in late 2019. Instead of learning more about its origins and predicting how widely it might spread, the priority now for many researchers is to find ways to treat those who are sick and protect those who aren't.

The Times spoke with several scientists to find out which issues are at the top of their minds as they work to understand the coronavirus and COVID-19, the disease it causes.

Which treatments actually work?

Doctors have tried a variety of drugs, including medicines developed to treat malaria, autoimmune diseases and Ebola. Despite high hopes for some of them, so far none has been proven to be a silver bullet.

The National Institutes of Health released its first set of treatment guidelines for COVID-19 on Tuesday, warning healthcare providers to exercise caution with their patients. The Food and Drug Administration has not yet approved any medicines to treat the new disease, and the jury is still out on potential treatments such as the Ebola drug remdesivir, which is still being tested in clinical trials.

For now, the agency isn't giving advice on the malaria drug chloroquine or several drugs of high interest, many of which are undergoing clinical trials.

However, the agency does recommend that clinicians avoid using hydroxychloroquine in combination with the antibiotic azythromycin, in part because of its potential to cause erratic heart rhythms. It also frowns on the combination of the HIV drugs lopinavir and ritonavir, which is sold under the brand name Kaletra.

The NIH also discouraged the use of other classes of drugs, including interferons, Janus kinase inhibitors, ACE inhibitors and angiotensin receptor blockers (although COVID-19 patients can have the latter two if they were already taking them for other conditions such as cardiovascular disease). Systemic corticosteroids should be avoided for most hospitalized patients who are not critically ill, according to the new guidelines, which will be updated as more data become available.

"Definitive clinical trial data are needed to identify optimal treatments for this disease," an expert panel convened by the NIH wrote.

One of the quickest ways to speed treatments to patients is to test drugs that have already been through safety testing in the context of another disease. Among others, researchers are trying anticoagulation medicines because they may mitigate the blood clotting experienced by some critically ill COVID-19 patients.

Drugs aren't the only treatment options on the table, said Dr. Kathryn Stephenson, who runs the clinical trial unit at Beth Israel Deaconess Medical Center's Center for Virology and Vaccine Research. There's a deceptively straightforward technique being tried called proning, in which clinicians turn patients onto their stomachs. This appears to help drain the lungs and improve patients' oxygen levels. (The NIH panel recommends this practice for certain COVID-19 patients on mechanical ventilators who have refractory hypoxemia.)

Sorting through the mass of information being produced on these treatments, and determining which results are reliable, will be a big challenge moving forward, researchers said.

"People are trying lots of different things," Stephenson said. "We're all struggling right now with what of these treatments, if any of them, actually work."

Which antibodies confer immunity, and how many do you need?

Tests that can reliably identify people who have been infected with the coronavirus are needed to determine how many people may have developed immunity, which in turn will help guide decisions on when and how the economy can be reopened and people can resume their normal, daily lives.

Serology tests look for antibodies — specialized biomolecules made by the body in response to infection by a particular pathogen — in samples of blood serum.

The problem is that not all antibodies are neutralizing antibodies that attach to the surface of a viral particle and prevent it from attacking the body's cells, said Dr. George Rutherford, an epidemiologist at UC San Francisco. On top of that, scientists aren't completely sure which antibodies are connected to a protective immune response for this particular virus.

That's a key metric for creating vaccines, he pointed out.

"Vaccines need to produce neutralizing antibody, and the neutralizing antibodies have to protect against reinfection," Rutherford said. "So I think that goes right to the top of my list of scientific questions."

Stephenson agreed.

"Many of these blood tests are proposed as a way to detect who is immune and ready to go back to work," she said. "But we don't know how to interpret those levels yet."

It's also unclear what concentration of antibodies is needed to actually confer immunity, Stephenson said. It's possible that a low level might not protect as well as a high level. Either way, scientists need to know how much a vaccine will need to trigger the body to produce in order to be effective.

Determining what antibody level defends against the virus is also important to researchers investigating a treatment known as convalescent plasma. The hypothesis is that antibodies in the blood fluids of COVID-19 survivors can be transfused to patients to help them fight an active infection. (Preliminary study results are promising.)

But if different survivors have different levels of antibodies in their blood, the plasma from one former COVID-19 patient may not be as effective as plasma from another, Stephenson said.

Who is immune, and for how long?

We don't just need to know which antibodies confer immunity, said Yonatan Grad, an infectious disease epidemiologist at Harvard University. Scientists also need to figure out which COVID-19 survivors have high levels of immunity and how long that protection lasts.

For example, do people who have mild symptoms or no symptoms develop an immune response that's as strong and as durable as people who weathered more severe infections? If not, what's the range of immune response? Does age influence a survivor's immune protection? What other factors may be at play?

Answering these questions will help illuminate the extent of immune protection different communities have — and what a potential reopening of the economy might look like, researchers said.

Which mitigation strategies are actually working?

Public health officials and policymakers have instituted all kinds of policies to slow the spread of COVID-19 and help "flatten the curve." They've closed schools, shuttered *nonessential* businesses, ordered residents to remain indoors and advised them to wear masks and observe social distancing rules if they absolutely must venture out.

Governors around the country are developing plans to lift some of these restrictions. The problem is that we don't yet know which of them are actually working and whether any of them can be safely relaxed, Grad said.

"Which social-distancing efforts have actually been effective in flattening the curve?" Grad said. "Does it require the most stringent of these mitigation efforts — that everyone try to stay at home as much as possible — or does having kids go to school matter?"

Keep in mind that each community experiences the outbreak in a different way, Grad said. There are many reasons for this, including different starting times and different contact patterns among members of those communities.

"This pandemic is made of many very local epidemics," he said.

Yvonne Maldonado, an infectious disease epidemiologist at Stanford University, agreed.

"If you take away 'shelter at home,' what do you leave in its place?" she said.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/22 12:36:23
Delivered Date:	2020/04/22 12:36:53
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Bloomberg: Chinese biotech firm censured for false claim on Gilead's coronavirus drug
Date: 2020/03/02 12:13:31
Priority: Normal
Type: Note

Chinese biotech firm censured for false claim on Gilead's coronavirus drug

- • BrightGene Bio-Medical Technology has not been licensed by Gilead to make its experimental drug known as remdesivir

Published: 7:01pm, 2 Mar, 2020
Updated: 7:51pm, 2 Mar, 2020

Members of the World Health Organisationâ€™s coronavirus expert investigation group conduct field research at a hospital in Wuhan, capital of Hubei province and epicentre of the outbreak. Photo: TPG

Members of the World Health Organisation's coronavirus expert investigation group conduct field research at a hospital in Wuhan, capital of Hubei province and epicentre of the outbreak. Photo: TPG

A Chinese biotech company which claimed to be able to manufacture an experimental drug from Gilead Sciences, with the potential to treat the novel coronavirus, was censured for disclosing inaccurate information.

The Shanghai Stock Exchange said in a statement on Sunday that BrightGene Bio-Medical Technology has not gained approval from China's drug regulator to make the drug known as remdesivir, which is seen as the leading candidate in the race to find a treatment for the coronavirus that has now sickened more than 88,000 and killed over 3,000.

BrightGene also has not been licensed by the patent owner – Gilead – to make the drug, nor has it obtained "the relevant qualifications" for mass production of the therapy, according to the stock exchange. Shares fell by the daily limit of 20 per cent intraday on Monday.

Gilead's experimental drug, which has not been licensed or approved for use anywhere in the world, is being tested in clinical trials at hospitals in the central Chinese city of Wuhan, the epicentre of the coronavirus outbreak, as well as in other Asian nations.

BrightGene's announcement on February 12 that it had managed to manufacture remdesivir in mass quantities garnered global headlines and sent its stock up nearly 60 per cent last month to touch a record high. The stock exchange's reprimand comes as concerns grow that researchers and drug makers in China and elsewhere are seizing on the global panic around the growing epidemic to get attention for less-than-credible scientific work.

BrightGene, for example, had only been able to make remdesivir in a small quantity for clinical research and not commercial production and its elision of this difference led to the spread of "unclear, inaccurate information", said the stock exchange.

BrightGene's board secretary Wang Zhengye, who gave interviews to local media outlets saying the company's drug is not for just for laboratory use but for mass production, was also reprimanded by the exchange.

With the novel coronavirus now being reported in more than 65 countries, exuberance among investors and medical companies around the development of treatments and vaccines is running the risk of becoming irrational and diverting resources from the most crucial scientific work.

Risk of coronavirus spreading globally now 'very high', World Health Organisation says

Nearly 300 clinical trials have been registered in China so far to study the efficacy of various coronavirus treatments from Gilead's remdesivir and AbbVie's anti-HIV therapy Kaletra, to traditional Chinese medicine and even soy milk.

The design and execution of some of these trials have raised concerns among scientists, according to an article published last week in the *Chinese Journal of Epidemiology*.

The surge of trials has also led to a scramble for patients as test subjects, thus potentially delaying the progress of serious research that could lead to the discovery of effective therapies.

World Health Organisation assistant director-general Bruce Aylward called for researchers to prioritise the most promising studies last week and said that Chinese researchers are facing difficulty recruiting enough patients into trials for remdesivir, which he said is the only drug that may be effective.

"We are doing lots of other studies with things that are less promising," he said.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/02 12:13:13
Delivered Date:	2020/03/02 12:13:31
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Immunity: SARS-CoV-2 Vaccines: Status Report https://bit.ly/3dYYARr
Date: 2020/04/06 15:03:59
Priority: Normal
Type: Note

SARS-CoV-2 Vaccines: Status Report

Author links open overlay panelFatimaAmanat[12]FlorianKrammer[2]
https://protect2.fireeye.com/url?k=f180816e-add588be-f180b051-0cc47a6a52de-fd5db4a7a910c00e&u=https://doi.org/10.1016/j.immuni.2020.03.007Get rights and content
open access
SARS-CoV-2, the causal agent of COVID-19, first emerged in late 2019 in China. It has since infected more than 870,000 individuals and caused more than 43,000 deaths globally. Here, we discuss therapeutic and prophylactic interventions for SARS-CoV-2 with a focus on vaccine development and its challenges. Vaccines are being rapidly developed but will likely come too late to affect the first wave of a potential pandemic. Nevertheless, critical lessons can be learned for the development of vaccines against rapidly emerging viruses. Importantly, SARS-CoV-2 vaccines will be essential to reducing morbidity and mortality if the virus establishes itself in the population.

Main Text

On December 31, 2019, several cases of pneumonia of unknown etiology were reported in Wuhan, China. The outbreak had started in early December or November (Huang et al., 2020), and the number of cases rose quickly; more than 80,000 infections were reported in China as of March 15, 2020, including more than 3,000 deaths. At the time of this review (April 6, 2020), the disease, termed COVID-19 (coronavirus disease 2019), had become pandemic and spread to more than 203 countries and territories, including community transmission in countries like the United States, Germany, France, Spain, Japan, Singapore, South Korea, Iran, and Italy and a large-scale outbreak with more than 600 cases on the cruise ship *Diamond Princess*. As of April 1, more than 870,000 cases and 43,000 deaths had been reported globally, with rapid growth of numbers in many countries. The causative agent of the outbreak was swiftly identified as betacoronavirus with a genomic sequence closely related to that of the severe acute respiratory syndrome (SARS) coronavirus from 2003, earning the new virus the name SARS-CoV-2 (Gorbalenya et al., 2020, Wu et al., 2020, Zhou et al., 2020, Zhu et al., 2020). SARS-CoV-2 likely originated in bats but might have been amplified in an intermediate host. Initial work showed that it can use angiotensin-converting enzyme 2 (ACE2) from bats, civet cats, swine, cats, ferrets, non-human primates (NHPs), and humans as a receptor (Letko et al., 2020, Wan et al., 2020, Zhou et al., 2020). Transmission of the infection to a pet dog in Hong Kong suggests that canine ACE2 can also be recognized by SARS-CoV-2. Pangolins, protected animals that are traded illegally in Asia and elsewhere, have been proposed as a potential amplifying host by some studies (Lam et al., 2020, Zhang et al., 2020). The initial reports from China and elsewhere note that although most COVID-19 cases present mild to moderate pathology, approximately 20% percent of cases are severe (Chen et al., 2020, Guan et al., 2020, Huang et al., 2020, Novel Coronavirus Pneumonia Emergency Response Epidemiology Team and AuthorAnonymous, 2020, Wang et al., 2020). The case fatality rate (CFR) seems to be age dependent, with a higher percentage in the elderly, especially men, and an overall interim CFR of approximately 1%–3%. The number of individuals with undetected, mild cases could be much higher than the official case

number, which would lead to a lower infection fatality rate (IRF). South Korea, a country that put a massive effort into testing and has already tested tens of thousands of samples, reports much lower CFRs than countries without extensive testing like Spain, Iran, or the United States. The CFR is disproportionally high in Italy (currently 7.3%), likely because of a large number of mild cases missed combined with a relatively older population and a healthcare system that is overwhelmed with cases.

The reproductive number (R_0) of the infection, that is, the number of cases directly generated by one case in a population in which all individuals are susceptible to infection, is estimated to be 2–3 (Li et al., 2020). Given the severity of the disease, which in most age groups is above that of seasonal influenza or pandemic H1N1 (2009) influenza, vaccines and therapeutics to tackle this novel virus are urgently needed.

Coronaviruses, in Brief

SARS-CoV-2 is part of the *Coronaviridae* family, whose members are named after their crown-like appearance under the electron microscope caused by the surface glycoproteins that decorate the virus. The family includes two subfamilies: *Letovirinae* and *Orthocoronavirinae*. *Orthocoronavirinae* includes the genera *Alphacoronvirus*, *Betacoronovirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Alphacoronaviruses and betacoronaviruses typically infect only mammals, whereas gammacoronoviruses and deltacoronaviruses typically infect avian species and sometimes mammals (Cui et al., 2019). Coronaviruses are common human pathogens; two types of alphacoronaviruses (229E and NL63) and two types of betacoronaviruses (OC43 and HKU1) circulate in humans and cause common cold. More pathogenic coronaviruses for humans include SARS-CoV-1, the Middle Eastern respiratory syndrome coronavirus (MERS-CoV), and now SARS-CoV-2, which are all betacoronaviruses.

Coronaviruses have a large (30+ kb) single-stranded positive-sense RNA genome encoding for several open reading frames. One frame encodes the spike protein (S protein), a class I fusion protein that mediates attachment of the virus to cell surface receptors followed by uptake into endosomes (for most coronaviruses). Proteolytic cleavage of the S protein and fusion of viral and endosomal membranes trigger release of viral RNA into the cytosol (reviewed in Fehr and Perlman, 2015). The RNA contains a 5′ cap structure and a 3′ poly(A) tail that allows expression of the replicase, which is encoded by approximately two-thirds of the genome. The other third codes for the structural and accessory proteins. The replicase is expressed as two polyproteins: pp1a and pp1ab; these include up to 16 nonstructural proteins (nsps). The nsps are generated by processing of pp1a and pp1ab by 2–3 viral proteases encoded within the replicase. Many nsps then assemble into the replicase-transcriptase complex that—in the host cell cytosol—produces anti-sense genome, new viral genome, and subgenomic RNA that serves as mRNA. Structural proteins S, matrix (M) protein, and envelope (E) are then generated and inserted into the endoplasmatic reticulum and follow the secretory pathway to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). A minority of coronaviruses also encode a hemagglutinin esterase (HE). In many coronaviruses, the S protein is cleaved into two subunits, S1 and S2, often by furin-like proteases. The RNA genome associates with nucleoprotein and then buds into the ERGIC, forming virus particles. After assembly, virions are transported to the cell surface in vesicles and are exocytosed. Several accessory proteins, which seem to be important for pathogenesis, are also expressed but not all are functionally characterized.

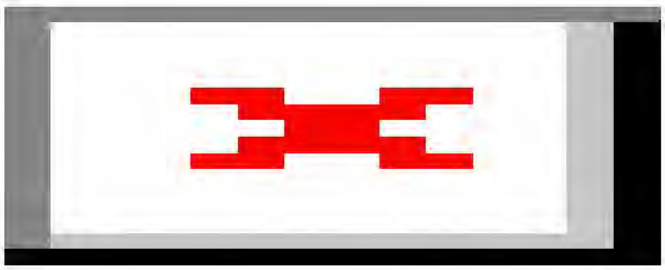
Therapeutics for SARS-CoV-2 Infections

Clinical trials with the nucleotide analog remdesivir (ClinicalTrials.gov: NCT04257656, NCT04252664, NCT04280705, etc.) and protease inhibitors (ClinicalTrials.gov: NCT04255017, NCT04276688, etc.), as well as other treatment options, are ongoing in China and the United States, and trial results are expected within weeks. Remdesivir works against coronaviruses closely related to SARS-CoV-2 in animal models, as well as against the related MERS-CoV, including in NHPs (Agostini et al., 2018, Brown et al., 2019, de Wit et al., 2020, Sheahan et al., 2017, Sheahan et al., 2020). Remdesivir was also tested for

treatment of ebolavirus infections in humans (and found to be less successful than other treatments by Mulangu et al., 2019); therefore, safety data exist for this therapeutic agent, which should accelerate the process of clinical testing against SARS-CoV-2. Remdesivir's mechanism of action as a nucleotide analog is not clear, but it likely terminates RNA synthesis, leads to incorporation mutagenesis, or both (Agostini et al., 2018). In addition, a combination of the two licensed HIV inhibitors, lopinavir and ritonavir, is also being tested in clinical trials (e.g., ClinicalTrials.gov: NCT04264858, etc.). Lopinavir is a bona fide protease inhibitor, whereas ritonavir was initially designed as protease inhibitor but was found to boost the half-life of lopinavir by inhibiting cytochrome P450 (Hull and Montaner, 2011). The combination was compassionately used as treatment for SARS-CoV-1 in 2003–2004 and showed some promise (Chu et al., 2004). Effectiveness of the combination was limited in mice but appreciable in NHP models of MERS-CoV (Chan et al., 2015, Sheahan et al., 2020). The mechanism of action of lopinavir is not clear, but it likely inhibits one or more coronavirus proteases. Other treatment options with ongoing or planned clinical trials include dosing recombinant human ACE2 to neutralize the virus and prevent lung damage (ClinicalTrials.gov: NCT04287686) and using the antiviral arbidol, a fusion inhibitor (Kadam and Wilson, 2017, Teissier et al., 2011). Another interesting option is the use of convalescent serum as treatment; clinical trials to test this are ongoing in China (ClinicalTrials.gov: NCT04264858, placebo control, not recruiting yet), and compassionate use of this strategy has recently started in the US (e.g. at Mount Sinai Medical Center, NY). Similarly, polyclonal human immunoglobulin G (IgG) derived from transgenic cows could be used, because this strategy has been successful for MERS-CoV in animal models (Luke et al., 2016) and has been tested for safety in clinical trials (ClinicalTrials.gov: NCT02788188). Many of these trials will have results within months, and if remdesivir (produced by Gilead) and/or lopinavir plus ritonavir (produced by AbbVie as Kaletra and Aluvia, respectively) show effectiveness, they could potentially be used widely within a short time frame. Compassionate use of these drugs has already been reported for SARS-CoV-2 infections (Holshue et al., 2020, Lim et al., 2020).

What Do We Know about Betacoronavirus Vaccine Design?

During the 2009 H1N1 influenza virus pandemic, vaccine producers switched their production pipelines quickly from producing trivalent seasonal influenza virus vaccines to monovalent pandemic vaccines. This was basically just a change of strains and established and approved processes, established release criteria, and existing correlates of protection could be used (Krammer and Palese, 2015). Still, it took six months until the vaccine was ready to be distributed and used, and it came too late to affect the second pandemic wave, which took place in the United States in fall 2009. This time, we are facing a new challenge in the form of a virus that has just emerged in humans, and the response will be more complex because there are no existing vaccines or production processes for coronavirus vaccines. Vaccine technology has significantly evolved in the last decade, including the development of several RNA and DNA vaccine candidates, licensed vectored vaccines (e.g., Ervebo, a vesicular stomatitis virus [VSV]-vectored ebolavirus vaccine, licensed in the European Union), recombinant protein vaccines (e.g., Flublok, an influenza virus vaccine made in insect cells, licensed in the United States), and cell-culture-based vaccines (e.g., Flucelvax, an influenza virus vaccine made in mammalian cells). SARS-CoV-2 was identified in record time, and its genomic sequence was swiftly made widely available by Chinese researchers (Wu et al., 2020, Zhou et al., 2020, Zhu et al., 2020). In addition, we know from studies on SARS-CoV-1 and the related MERS-CoV vaccines that the S protein on the surface of the virus is an ideal target for a vaccine. In SARS-CoV-1 and SARS-CoV-2, this protein interacts with the receptor ACE2, and antibodies targeting the spike can interfere with this binding, thereby neutralizing the virus (Figure 1). The structure of the S protein of SARS-CoV-2 was solved in record time at high resolution, contributing to our understanding of this vaccine target (Lan et al., 2020a, Wrapp et al., 2020). Therefore, we have a target antigen that can be incorporated into advanced vaccine platforms.



1. • Download : Download high-res image (524KB)
2. • Download : Download full-size image

Figure 1. Overview of Potential SARS-CoV-2 Vaccine Platforms

The structure of a coronavirus particle is depicted on the left, with the different viral proteins indicated. The S protein is the major target for vaccine development. The spike structure shown is based on the trimeric SARS-CoV-1 spike (PDB: 5XL3). One trimer is shown in dark blue, and the receptor binding domain, a main target of neutralizing antibodies, is highlighted in purple. The other two trimers are shown in light blue. SARS-CoV-2 vaccine candidates based on different vaccine platforms have been developed, and for some of them, pre-clinical experiments have been initiated. For one mRNA-based candidate, a clinical trial recently started to enroll volunteers shortly (ClinicalTrials.gov: NCT04283461). However, many additional steps are needed before these vaccines can be used in the population, and this process might take months, if not years. [1]For some candidates, cGMP processes have already been established. [2]Clinical trial design might be altered to move vaccines through clinical testing quicker.

Several vaccines for SARS-CoV-1 were developed and tested in animal models, including recombinant S-protein-based vaccines, attenuated and whole inactivated vaccines, and vectored vaccines (Roper and Rehm, 2009). Most of these vaccines protect animals from challenge with SARS-CoV-1, although many do not induce sterilizing immunity. In some cases, vaccination with the live virus results in complications, including lung damage and infiltration of eosinophils in a mouse model (e.g., Bolles et al., 2011, Tseng et al., 2012) and liver damage in ferrets (e.g., Weingartl et al., 2004). In another study, vaccination with inactivated SARS-CoV-1 led to enhancement of disease in one NHP, whereas it protected 3 animals from challenge (Wang et al., 2016). The same study identified certain epitopes on the S protein as protective, whereas immunity to others seemed to be enhancing disease. However, in almost all cases, vaccination is associated with greater survival, reduced virus titers, and/or less morbidity compared with that in unvaccinated animals. Similar findings have been reported for MERS-CoV vaccines (Agrawal et al., 2016, Houser et al., 2017). Therefore, whereas vaccines for related coronaviruses are efficacious in animal models, we need to ensure that the vaccines, which are developed for SARS-CoV-2, are sufficiently safe.

Another consideration for effective coronavirus vaccine development might be waning of the antibody response. Infection with human coronaviruses does not always induce long-lived antibody responses, and re-infection of an individual with the same virus is possible after an extended period of time (but only in a fraction of individuals and resulting in mild or no symtpoms), as shown in human challenge studies (Callow et al., 1990). Antibody titers in individuals that survived SARS-CoV-1 or MERS-CoV infections often waned after 2–3 years (Liu et al., 2006, Wu et al., 2007) or were weak initially (Choe

et al., 2017). Despite that, re-infections are unlikely in the short term. Of note, re-infections after days of recovery have been reported recently but appear to be the consequences of false negative test results (Lan et al., 2020b). However, they could happen when humoral immunity wanes over months and years. An effective SARS-CoV-2 vaccine will need to overcome these issues to protect in a scenario in which the virus becomes endemic and causes recurrent seasonal epidemics.

SARS-CoV-2 infection causes the most severe pathology in individuals above 50 years of age. The reason for this is not clear, but many viral infections have milder manifestations in naive younger individuals than in naive older individuals. Because older individuals are more affected, it will be important to develop vaccines that protect this segment of the population. Unfortunately, older individuals typically respond less well to vaccination because of immune senescence (Sambhara and McElhaney, 2009). For influenza, which is problematic for older adults, specific formulations for this segment of the population include more antigen or an adjuvant (DiazGranados et al., 2013, Tsai, 2013). Protection in older individuals appears to require higher neutralization titers against influenza virus than in younger individuals (Benoit et al., 2015), and this issue might need to be addressed for SARS-CoV-2. If vaccination in older individuals is not effective, they could still benefit indirectly if vaccination is able to stop transmission of the virus in younger individuals.

Only a small number of SARS-CoV-1 vaccines made it to phase I clinical trials before funding dried up because of eradication of the virus from the human population through non-pharmaceutical interventions when case numbers were still small. Results from these trials, performed with an inactivated virus vaccine and a spike-based DNA vaccine, are encouraging because the vaccines were safe and induced neutralizing antibody titers (Lin et al., 2007, Martin et al., 2008). Some neutralizing monoclonal antibodies isolated against SARS-CoV-1, like CR3022 (ter Meulen et al., 2006, Tian et al., 2020), can cross-react to the receptor binding domain of SARS-CoV-2. This suggests that SARS-CoV-1 vaccines might cross-protect against SARS-CoV-2. However, because these vaccines have not been developed further than phase I, they are currently not available for use. Vaccines against MERS-CoV, also targeting the MERS-CoV S protein, are in pre-clinical and clinical development, including vaccines based on modified vaccinia Ankara vectors, adenovirus vectors, and DNA-based vaccines, and several of them are supported by the Coalition for Epidemic Preparedness Innovation (CEPI) (Yong et al., 2019). However, it is unlikely that MERS-CoV vaccines induce strong cross-neutralizing antibodies to SARS-CoV-2 because of the phylogenetic distance between the two viruses. Nevertheless, we can still learn a lot from these vaccines about how to move forward with SARS-CoV-2 vaccine design (Pallesen et al., 2017).

The Current Pipeline for SARS-CoV-2 Vaccines

The development of vaccines for human use can take years, especially when novel technologies are used that have not been extensively tested for safety or scaled up for mass production. Because no coronavirus vaccines are on the market and no large-scale manufacturing capacity for these vaccines exists as yet (Table 1), we will need to build these processes and capacities. Doing this for the first time can be tedious and time consuming (Figure 1). CEPI has awarded funds to several highly innovative players in the field, and many of them will likely succeed in eventually making a SARS-CoV-2 vaccine. However, none of these companies and institutions have an established pipeline to bring such a vaccine to late-stage clinical trials that allow licensure by regulatory agencies, and they do not currently have the capacity to produce the number of doses needed. An mRNA-based vaccine, which expresses target antigen *in vivo* in the vaccinee after injection of mRNA encapsulated in lipid nanoparticles, co-developed by Moderna and the Vaccine Research Center at the National Institutes of Health, is currently the furthest along, and a phase I clinical trial recently started (ClinicalTrials.gov: NCT04283461). Curevac is working on a similar vaccine but is still in the pre-clinical phase. Additional approaches in the pre-clinical stage include recombinant-protein-based vaccines (focused on the S protein, e.g., ExpreS2ion, iBio, Novavax, Baylor College of Medicine, University of Queensland, and Sichuan Clover Biopharmaceuticals), viral-vector-based vaccines (focused on the S protein, e.g., Vaxart, Geovax, University of Oxford, and

Cansino Biologics), DNA vaccines (focused on the S protein, e.g., Inovio and Applied DNA Sciences), live attenuated vaccines (Codagenix with the Serum Institute of India, etc.), and inactivated virus vaccines (Figure 1; Table 1). All of these platforms have advantages and disadvantages (Table 1), and it is not possible to predict which strategy will be faster or more successful. Johnson &Johnson (J&J) (Johnson &Johnson, 2020) and Sanofi (2020) recently joined efforts to develop SARS-CoV-2 vaccines. However, J&J is using an experimental adenovirus vector platform that has not yet resulted in a licensed vaccine. Sanofi's vaccine, to be made using a process similar to the process used for their approved Flublok recombinant influenza virus vaccine (Zhou et al., 2006), is also months, if not years, from being ready for use in the human population.

Table 1. Overview of Vaccine Production Platforms and Technologies for SARS-CoV-2

Platform	Target	Existing, Licensed Human Vaccines Using the Same Platform	Advantages	Disadvantages
RNA vaccines	S protein	No	No infectious virus needs to be handled, vaccines are typically immunogenic, rapid production possible.	Safety issues with reactogenicity have been reported.
DNA vaccines	S protein	No	No infectious virus needs to be handled, easy scale up, low production costs, high heat stability, tested in humans for SARS-CoV-1, rapid production possible.	Vaccine needs specific delivery devices to reach good immunogenicity.
Recombinant protein vaccines	S protein	Yes for baculovirus (influenza, HPV) and yeast expression (HBV, HPV)	No infectious virus needs to be handled, adjuvants can be used to increase immunogenicity.	Global production capacity might be limited. Antigen and/or epitope integrity needs to be confirmed. Yields need to be high enough.
Viral vector-based vaccines	S protein	Yes for VSV (Ervebo), but not for other viral vectored vaccines	No infectious virus needs to be handled, excellent preclinical and clinical data for many emerging viruses, including MERS-CoV.	Vector immunity might negatively affect vaccine effectiveness (depending on the vector chosen).
Live attenuated vaccines	Whole virion	Yes	Straightforward process used for several licensed human vaccines, existing infrastructure can be used.	Creating infectious clones for attenuated coronavirus vaccine seeds takes time because of large genome size. Safety testing will need to be extensive.

Platform	Target	Existing, Licensed Human Vaccines Using the Same Platform	Advantages	Disadvantages
Inactivated vaccines	Whole virion	Yes	Straightforward process used for several licensed human vaccines, existing infrastructure can be used, has been tested in humans for SARS-CoV-1, adjuvants can be used to increase immunogenicity.	Large amounts of infectious virus need to be handled (could be mitigated by using an attenuated seed virus). Antigen and/or epitope integrity needs to be confirmed.

Understanding the Time Frames

Why does this take so long? As mentioned earlier, there are currently no approved human coronavirus vaccines. In addition, many technologies used (production platforms, vectors, etc.) are new and need to be tested thoroughly for safety. The target for the vaccine, the S protein, has been identified, and vaccine candidates are being generated. This is usually followed by two important steps that are typically needed before bringing a vaccine into clinical trials. First, the vaccine is tested in appropriate animal models to see whether it is protective. However, animal models for SARS-CoV-2 might be difficult to develop. The virus does not grow in wild-type mice and only induced mild disease in transgenic animals expressing human ACE2 (Bao et al., 2020). Other potential animal models include ferrets and NHPs, for which pathogenicity studies are ongoing. Even in the absence of an animal model that replicates human disease, it is possible to evaluate the vaccine because serum from vaccinated animals can be tested in *in vitro* neutralization assays. Post-challenge safety data should also be collected in these cases to assess for complications such as the ones seen SARS-CoV-1 and MERS-CoV vaccines. Second, vaccines need to be tested for toxicity in animals, e.g., in rabbits. Usually, viral challenge is not part of this process, because only the safety of the vaccine will be evaluated. This testing, which has to be performed in a manner compliant with GLP (Good Laboratory Practice), typically takes 3–6 months to complete. For some vaccine platforms, parts of the safety testing might be skipped if there is already sufficient data available for similar vaccines made in the same production process.

Vaccines for human use are produced in processes that comply with current Good Manufacturing Practice (cGMP) to ensure constant quality and safety of vaccines. This requires dedicated facilities, trained personnel, proper documentation, and raw material that was produced to be of cGMP quality. These processes have to be designed or amended to fit SARS-CoV-2 vaccines. For many vaccine candidates in the preclinical phase, such processes do not yet exist and have to be developed from scratch.

Once sufficient pre-clinical data are available and initial batches of the vaccine have been produced that are of cGMP quality, clinical trials might be initiated. Typically, clinical development of vaccines starts with small phase I trials to evaluate the safety of vaccine candidates in humans. These are followed by phase II trials (formulation and doses are established to initially prove efficacy) and finally by phase III trials, in which the efficacy and safety of a vaccine need to be demonstrated in a larger cohort. However, in an extraordinary situation like the current one, this scheme might be compressed and an accelerated regulatory approval pathway might be developed. If efficacy is shown, a vaccine might be licensed by regulatory agencies.

Another important point is that production capacity to produce sufficient amounts of cGMP-quality vaccine needs to be available. For vaccines based on existing vaccine platforms, e.g., inactivated or live attenuated vaccines, this can be relatively easily achieved, because existing infrastructure can be used (Table 1). For vaccines based on novel technologies, e.g., mRNA, this capacity needs to be built, and this typically takes time. Although it would be beneficial if even a limited number of doses were available to protect health care workers and the most vulnerable segments of the population, the goal should be to make vaccines available to the global population. This will be challenging. Even for influenza virus vaccines, for which many production facilities exist in high-income countries, as well as low- and middle-income countries, the demand in the case of a pandemic would by far exceed the production capacity. Finally, it takes time to distribute vaccines and administer them. To vaccinate a large proportion of the population would likely take weeks. Given that the population is currently naive to SARS-CoV-2, it is highly likely that more than one dose of the vaccine will be needed. Prime-boost vaccination regimens are typically used in such cases, and the two vaccinations are usually spaced 3–4 weeks apart. It is likely that protective immunity will be achieved only 1–2 weeks after the second vaccination. This therefore adds another 1–2 months to the timeline. Even if shortcuts for several of the steps mentioned earlier can be found, it is unlikely that a vaccine would be available earlier than 6 months after the initiation of clinical trials. Realistically, SARS-CoV-2 vaccines will not be available for another 12–18 months.

What are potential solutions for these long time frames in the future? One possibility is to build production capacity, to be globally distributed if possible, that can be activated in the event of new emerging viruses. From today's perspective, only a few types of viruses are likely to cause respiratory disease that leads to rapid global spread. Surveillance in the animal reservoir paired with virus characterization studies can identify members of virus families that have the potential to cause pandemics. Vaccine candidates using these isolates could then be produced, tested in animals to determine the mechanisms of protection, and tested in humans to establish the safety of the vaccines. It is unlikely that the same viruses that are chosen as vaccine candidates will later cause outbreaks. However, if the vaccine candidate is sufficiently closely related, sequences for the vaccines could be quickly switched and the vaccines for the newly emerging viruses could be swiftly produced and moved to late-stage clinical trials right away (while large-scale production is ramped up globally). In addition, stockpiled vaccines based on the initial candidates could be deployed, even if slightly mismatched to the strain causing the outbreak (a strategy that is currently used for H5 and H7 avian influenza virus vaccines). This would allow a response within a few weeks and could potentially stop a virus locally before it becomes pandemic. An alternative but challenging solution would be the development of broadly protective vaccines that cover whole virus families or genera. This effort is ongoing for influenza viruses (Erbelding et al., 2018) and could potentially be applied to coronaviruses, or at least betacoronaviruses. Both of these options are costly and require global political will and vision.

Concluding Remarks

Considering the deep dive stock markets have taken in recent weeks and given the expected effect of a pandemic on the economy, funding for vaccine production infrastructure that would allow a swift response to emerging viruses looks like a great investment. However, without a pandemic looming, such investments have rarely been made in the past, except for H5 and H7 subtype influenza viruses. Now would be the right time to consider investing in vaccines against emerging viruses that can lead to loss of human lives and burden the global economy. An investment of a few billion dollars would allow us to have sufficient surveillance, appropriate vaccine candidates, and infrastructure ready that could churn out vaccines for use in the global population quickly and effectively, potentially stopping an emerging virus in its tracks. In addition, we need well-developed emergency plans that allow us to develop, test, produce, and distribute vaccines within weeks, not months or years. This would need tight coordination among pharmaceutical companies, governments, regulatory agencies, and the World Health

Organization (WHO), as well as novel and out-of-the-box approaches to cGMP production, release processes, regulatory science, and clinical trial design.

For SARS-CoV-2, vaccines might come too late to affect the first wave of this pandemic. However, they might be useful if additional waves occur later or in a post-pandemic scenario in which SARS-CoV-2 continues to circulate as a seasonal virus. In addition, lessons learned from handling this outbreak will allow us to be better prepared in the future. The viruses will keep coming.

Acknowledgments

We thank Francesco Berlanda-Scorza for providing feedback on this manuscript. Work on influenza virus vaccines and immunity in the Krammer laboratory is supported by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Influenza Vaccine Innovation Centers (CIVIC) contract 75N93019C00051, NIAID Centers of Excellence for Influenza Research and Surveillance (CEIRS) contract HHSN272201400008C, and NIAID grants AI117287 and AI128821, as well as funding from the U.S. Department of Defense and the Bill and Melinda Gates Foundation. Work on SARS-CoV-2 reagents is supported by CEIRS and institutional seed funding; reagents are being deposited into BEI Resources to support SARS-CoV-2 research and countermeasure development.

References

Agostini et al., 2018

M.L. Agostini, E.L. Andres, A.C. Sims, R.L. Graham, T.P. Sheahan, X. Lu, E.C. Smith, J.B. Case, J.Y. Feng, R. Jordan, *et al.***Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease**
MBio, 9 (2018)
e00221-18
Google Scholar

Agrawal et al., 2016

A.S. Agrawal, X. Tao, A. Algaissi, T. Garron, K. Narayanan, B.H. Peng, R.B. Couch, C.T. Tseng**Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus**
Hum. Vaccin. Immunother., 12 (2016), pp. 2351-2356
CrossRefView Record in ScopusGoogle Scholar

Bao et al., 2020

L. Bao, W. Deng, B. Huang, H. Gao, L. Ren, Q. Wei, P. Yu, Y. Xu, J. Liu, F. Qi, *et al.***The Pathogenicity of 2019 Novel Coronavirus in hACE2 Transgenic Mice**
bioRxiv (2020), 10.1101/2020.02.07.939389
Google Scholar

Benoit et al., 2015

A. Benoit, J. Beran, J.M. Devaster, M. Esen, O. Launay, G. Leroux-Roels, J.E. McElhaney, L. Oostvogels, G.A. van Essen, M. Gaglani, *et al.***Hemagglutination Inhibition Antibody Titers as a Correlate of Protection Against Seasonal A/H3N2 Influenza Disease**
Open Forum Infect. Dis., 2 (2015), p. ofv067
Google Scholar

Bolles et al., 2011

M. Bolles, D. Deming, K. Long, S. Agnihothram, A. Whitmore, M. Ferris, W. Funkhouser, L. Gralinski, A. Totura, M. Heise, R.S. Baric**A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge**
J. Virol., 85 (2011), pp. 12201-12215

View Record in ScopusGoogle Scholar

Brown et al., 2019

A.J. Brown, J.J. Won, R.L. Graham, K.H. Dinnon 3rd, A.C. Sims, J.Y. Feng, T. Cihlar, M.R. Denison, R.S. Baric, T.P. Sheahan**Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase**
Antiviral Res., 169 (2019), p. 104541
Article
Download PDFGoogle Scholar

Callow et al., 1990

K.A. Callow, H.F. Parry, M. Sergeant, D.A. Tyrrell**The time course of the immune response to experimental coronavirus infection of man**
Epidemiol. Infect., 105 (1990), pp. 435-446
View Record in ScopusGoogle Scholar

Chan et al., 2015

J.F. Chan, Y. Yao, M.L. Yeung, W. Deng, L. Bao, L. Jia, F. Li, C. Xiao, H. Gao, P. Yu, *et al.***Treatment With Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset**
J. Infect. Dis., 212 (2015), pp. 1904-1913
CrossRefView Record in ScopusGoogle Scholar

Chen et al., 2020

N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, *et al.***Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study**
Lancet, 395 (2020), pp. 507-513
Article
Download PDFView Record in ScopusGoogle Scholar

Choe et al., 2017

P.G. Choe, R.A.P.M. Perera, W.B. Park, K.H. Song, J.H. Bang, E.S. Kim, H.B. Kim, L.W.R. Ko, S.W. Park, N.J. Kim, *et al.***MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015**
Emerg. Infect. Dis., 23 (2017), pp. 1079-1084
CrossRefView Record in ScopusGoogle Scholar

Chu et al., 2004

C.M. Chu, V.C. Cheng, I.F. Hung, M.M. Wong, K.H. Chan, K.S. Chan, R.Y. Kao, L.L. Poon, C.L. Wong, Y. Guan, *et al.*, HKU/UCH SARS Study Group**Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings**
Thorax, 59 (2004), pp. 252-256
View Record in ScopusGoogle Scholar

Cui et al., 2019

J. Cui, F. Li, Z.L. Shi**Origin and evolution of pathogenic coronaviruses**
Nat. Rev. Microbiol., 17 (2019), pp. 181-192
CrossRefView Record in ScopusGoogle Scholar

de Wit et al., 2020

E. de Wit, F. Feldmann, J. Cronin, R. Jordan, A. Okumura, T. Thomas, D. Scott, T. Cihlar, H. Feldmann**Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection**
Proc. Natl. Acad. Sci. USA (2020), 10.1073/pnas.1922083117
Google Scholar

DiazGranados et al., 2013
C.A. DiazGranados, A.J. Dunning, E. Jordanov, V. Landolfi, M. Denis, H.K. Talbot**High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009–2010 season**
Vaccine, 31 (2013), pp. 861-866
Article
Download PDFView Record in ScopusGoogle Scholar
Erbelding et al., 2018
E.J. Erbelding, D.J. Post, E.J. Stemmy, P.C. Roberts, A.D. Augustine, S. Ferguson, C.I. Paules, B.S. Graham, A.S. Fauci**A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases**
J. Infect. Dis., 218 (2018), pp. 347-354
CrossRefView Record in ScopusGoogle Scholar
Fehr and Perlman, 2015
A.R. Fehr, S. Perlman**Coronaviruses: an overview of their replication and pathogenesis**
Methods Mol. Biol., 1282 (2015), pp. 1-23
CrossRefView Record in ScopusGoogle Scholar
Gorbalenya et al., 2020
A.E. Gorbalenya, S.C. Baker, R.S. Baric, R.J. de Groot, C. Drosten, A.A. Gulyaeva, B.L. Haagmans, C. Lauber, A.M. Leontovich, B.W. Neuman, *et al.***The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2**
Nat. Microbiol. (2020), 10.1038/s41564-020-0695-z
Google Scholar
Guan et al., 2020
W.-J. Guan, Z.-Y. Ni, Y. Hu, W.-H. Liang, C.-Q. Ou, J.-X. He, L. Liu, H. Shan, C.-L. Lei, D.S.C. Hui, *et al.***Clinical characteristics of 2019 novel coronavirus infection in China**
N. Engl. J. Med. (2020), 10.1056/NEJMoa2002032
Google Scholar
Holshue et al., 2020
M.L. Holshue, C. DeBolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce, C. Spitters, K. Ericson, S. Wilkerson, A. Tural, *et al.*, Washington State 2019-nCoV Case Investigation Team**First Case of 2019 Novel Coronavirus in the United States**
N. Engl. J. Med., 382 (2020), pp. 929-936
CrossRefView Record in ScopusGoogle Scholar
Houser et al., 2017
K.V. Houser, A.J. Broadbent, L. Gretebeck, L. Vogel, E.W. Lamirande, T. Sutton, K.W. Bock, M. Minai, M. Orandle, I.N. Moore, K. Subbarao**Enhanced inflammation in New Zealand white rabbits when MERS-CoV reinfection occurs in the absence of neutralizing antibody**
PLoS Pathog., 13 (2017), p. e1006565
CrossRefGoogle Scholar
Huang et al., 2020
C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, *et al.***Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China**
Lancet, 395 (2020), pp. 497-506
Article
Download PDFView Record in ScopusGoogle Scholar
Hull and Montaner, 2011
M.W. Hull, J.S. Montaner**Ritonavir-boosted protease inhibitors in HIV therapy**

Ann. Med., 43 (2011), pp. 375-388
CrossRefView Record in ScopusGoogle Scholar

Johnson and Johnson, 2020
Johnson and Johnson**What You Need to Know About the Latest on the Coronavirus—and a Potential Preventive Vaccine**
(2020)
https://protect2.fireeye.com/url?k=1da0e693-41f5ef43-1da0d7ac-0cc47a6a52de-4a8bb78466d06788&u=https://www.jnj.com/latest-news/what-you-need-to-know-about-coronavirus-and-a-potential-johnson-johnson-vaccine
Google Scholar

Kadam and Wilson, 2017
R.U. Kadam, I.A. Wilson**Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol**
Proc. Natl. Acad. Sci. USA, 114 (2017), pp. 206-214
CrossRefView Record in ScopusGoogle Scholar

Krammer and Palese, 2015
F. Krammer, P. Palese**Advances in the development of influenza virus vaccines**
Nat. Rev. Drug Discov., 14 (2015), pp. 167-182
CrossRefView Record in ScopusGoogle Scholar

Lam et al., 2020
T.T.-Y. Lam, M.H.-H. Shum, H.-C. Zhu, Y.-G. Tong, X.-B. Ni, Y.-S. Liao, W. Wei, W.Y.-M. Cheung, W.-J. Li, L.-F. Li, *et al.***Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China**
bioRxiv (2020), 10.1101/2020.02.13.945485
Google Scholar

Lan et al., 2020a
J. Lan, J. Ge, J. Yu, S. Shan, H. Zhou, S. Fan, Q. Zhang, X. Shi, Q. Wang, L. Zhang, X. Wang**Crystal structure of the 2019-nCoV spike receptor-binding domain bound with the ACE2 receptor**
bioRxiv (2020), 10.1101/2020.02.19.956235
Google Scholar

Lan et al., 2020b
L. Lan, D. Xu, G. Ye, C. Xia, S. Wang, Y. Li, H. Xu**Positive RT-PCR Test Results in Patients Recovered From COVID-19**
JAMA. (2020), 10.1001/jama.2020.2783
Google Scholar

Letko et al., 2020
M. Letko, A. Marzi, V. Munster**Functional assessment of cell entry and receptor usage for Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage betacoronaviruses**
Nat. Microbiol. (2020), 10.1038/s41564-020-0688-y
Google Scholar

Li et al., 2020
Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K.S.M. Leung, E.H.Y. Lau, J.Y. Wong, *et al.***Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia**
N. Engl. J. Med. (2020), 10.1056/NEJMoa2001316
Google Scholar

Lim et al., 2020

J. Lim, S. Jeon, H.Y. Shin, M.J. Kim, Y.M. Seong, W.J. Lee, K.W. Choe, Y.M. Kang, B. Lee, S.J. Park**Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR**
J. Korean Med. Sci., 35 (2020), p. e79
Google Scholar

Lin et al., 2007
J.T. Lin, J.S. Zhang, N. Su, J.G. Xu, N. Wang, J.T. Chen, X. Chen, Y.X. Liu, H. Gao, Y.P. Jia, *et al.***Safety and immunogenicity from a phase I trial of inactivated severe acute respiratory syndrome coronavirus vaccine**
Antivir. Ther. (Lond.), 12 (2007), pp. 1107-1113
View Record in ScopusGoogle Scholar

Liu et al., 2006
W. Liu, A. Fontanet, P.H. Zhang, L. Zhan, Z.T. Xin, L. Baril, F. Tang, H. Lv, W.C. Cao**Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome**
J. Infect. Dis., 193 (2006), pp. 792-795
CrossRefView Record in ScopusGoogle Scholar

Luke et al., 2016
T. Luke, H. Wu, J. Zhao, R. Channappanavar, C.M. Coleman, J.A. Jiao, H. Matsushita, Y. Liu, E.N. Postnikova, B.L. Ork, *et al.***Human polyclonal immunoglobulin G from transchromosomic bovines inhibits MERS-CoV *in vivo***
Sci. Transl. Med., 8 (2016), p. 326ra21
CrossRefGoogle Scholar

Martin et al., 2008
J.E. Martin, M.K. Louder, L.A. Holman, I.J. Gordon, M.E. Enama, B.D. Larkin, C.A. Andrews, L. Vogel, R.A. Koup, M. Roederer, *et al.*, VRC 301 Study Team**A SARS DNA vaccine induces neutralizing antibody and cellular immune responses in healthy adults in a Phase I clinical trial**
Vaccine, 26 (2008), pp. 6338-6343
Article
Download PDFView Record in ScopusGoogle Scholar

Mulangu et al., 2019
S. Mulangu, L.E. Dodd, R.T. Davey Jr., O. Tshiani Mbaya, M. Proschan, D. Mukadi, M. Lusakibanza Manzo, D. Nzolo, A. Tshomba Oloma, A. Ibanda, *et al.*, PALM Writing Group, PALM Consortium Study Team**A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics**
N. Engl. J. Med., 381 (2019), pp. 2293-2303
CrossRefView Record in ScopusGoogle Scholar

Pallesen et al., 2017
J. Pallesen, N. Wang, K.S. Corbett, D. Wrapp, R.N. Kirchdoerfer, H.L. Turner, C.A. Cottrell, M.M. Becker, L. Wang, W. Shi, *et al.***Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen**
Proc. Natl. Acad. Sci. USA, 114 (2017), pp. E7348-E7357
CrossRefView Record in ScopusGoogle Scholar

Roper and Rehm, 2009
R.L. Roper, K.E. Rehm**SARS vaccines: where are we?**
Expert Rev. Vaccines, 8 (2009), pp. 887-898
CrossRefView Record in ScopusGoogle Scholar

Sambhara and McElhaney, 2009

S. Sambhara, J.E. McElhaney**Immunosenescence and influenza vaccine efficacy**
Curr. Top. Microbiol. Immunol., 333 (2009), pp. 413-429
CrossRefView Record in ScopusGoogle Scholar

Sanofi., 2020
Sanofi.**Sanofi joins forces with U.S. Department of Health and Human Services to advance a novel coronavirus vaccine**
(2020)
https://protect2.fireeye.com/url?k=c285e089-9ed0e959-c285d1b6-0cc47a6a52de-d8a23fae9237a22e&u=http://www.news.sanofi.us/2020-02-18-Sanofi-joins-forces-with-U-S-Department-of-Health-and-Human-Services-to-advance-a-novel-coronavirus-vaccine
Google Scholar

Sheahan et al., 2017
T.P. Sheahan, A.C. Sims, R.L. Graham, V.D. Menachery, L.E. Gralinski, J.B. Case, S.R. Leist, K. Pyrc, J.Y. Feng, I. Trantcheva, *et al.***Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses**
Sci. Transl. Med., 9 (2017)
eaal3653
Google Scholar

Sheahan et al., 2020
T.P. Sheahan, A.C. Sims, S.R. Leist, A. Schäfer, J. Won, A.J. Brown, S.A. Montgomery, A. Hogg, D. Babusis, M.O. Clarke, *et al.***Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV**
Nat. Commun., 11 (2020), p. 222
Google Scholar

Novel Coronavirus Pneumonia Emergency Response Epidemiology Team and AuthorAnonymous, 2020
Novel Coronavirus Pneumonia Emergency Response Epidemiology Team**The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) in China**
Zhonghua Liu Xing Bing Xue Za Zhi, 41 (2020), pp. 145-151
Google Scholar

Teissier et al., 2011
E. Teissier, G. Zandomeneghi, A. Loquet, D. Lavillette, J.P. Lavergne, R. Montserret, F.L. Cosset, A. Böckmann, B.H. Meier, F. Penin, E.I. Pécheur**Mechanism of inhibition of enveloped virus membrane fusion by the antiviral drug arbidol**
PLoS ONE, 6 (2011), p. e15874
CrossRefGoogle Scholar

ter Meulen et al., 2006
J. ter Meulen, E.N. van den Brink, L.L. Poon, W.E. Marissen, C.S. Leung, F. Cox, C.Y. Cheung, A.Q. Bakker, J.A. Bogaards, E. van Deventer, *et al.***Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants**
PLoS Med., 3 (2006), p. e237
CrossRefGoogle Scholar

Tian et al., 2020
X. Tian, C. Li, A. Huang, S. Xia, S. Lu, Z. Shi, L. Lu, S. Jiang, Z. Yang, Y. Wu, T. Ying**Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody**
Emerg. Microbes Infect., 9 (2020), pp. 382-385
CrossRefView Record in ScopusGoogle Scholar

Tsai, 2013

T.F. Tsai**Fluad®-MF59®-Adjuvanted Influenza Vaccine in Older Adults**
Infect. Chemother., 45 (2013), pp. 159-174
CrossRefView Record in ScopusGoogle Scholar

Tseng et al., 2012
C.T. Tseng, E. Sbrana, N. Iwata-Yoshikawa, P.C. Newman, T. Garron, R.L. Atmar, C.J. Peters, R.B. Couch**Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus**
PLoS ONE, 7 (2012), p. e35421
CrossRefGoogle Scholar

Wan et al., 2020
Y. Wan, J. Shang, R. Graham, R.S. Baric, F. Li**Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS**
J. Virol. (2020), 10.1128/JVI.00127-20
Google Scholar

Wang et al., 2020
D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, *et al.***Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan**
JAMA (2020), 10.1001/jama.2020.1585
Google Scholar

Wang et al., 2016
Q. Wang, L. Zhang, K. Kuwahara, L. Li, Z. Liu, T. Li, H. Zhu, J. Liu, Y. Xu, J. Xie, *et al.***Immunodominant SARS Coronavirus Epitopes in Humans Elicited both Enhancing and Neutralizing Effects on Infection in Non-human Primates**
ACS Infect. Dis., 2 (2016), pp. 361-376
CrossRefView Record in ScopusGoogle Scholar

Weingartl et al., 2004
H. Weingartl, M. Czub, S. Czub, J. Neufeld, P. Marszal, J. Gren, G. Smith, S. Jones, R. Proulx, Y. Deschambault, *et al.***Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets**
J. Virol., 78 (2004), pp. 12672-12676
View Record in ScopusGoogle Scholar

Wrapp et al., 2020
D. Wrapp, N. Wang, K.S. Corbett, J.A. Goldsmith, C.L. Hsieh, O. Abiona, B.S. Graham, J.S. McLellan**Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation**
Science, 367 (2020), pp. 1260-1263
CrossRefView Record in ScopusGoogle Scholar

Wu et al., 2020
F. Wu, S. Zhao, B. Yu, Y.M. Chen, W. Wang, Z.G. Song, Y. Hu, Z.W. Tao, J.H. Tian, Y.Y. Pei, *et al.***A new coronavirus associated with human respiratory disease in China**
Nature, 579 (2020), pp. 265-269
CrossRefView Record in ScopusGoogle Scholar

Wu et al., 2007
L.P. Wu, N.C. Wang, Y.H. Chang, X.Y. Tian, D.Y. Na, L.Y. Zhang, L. Zheng, T. Lan, L.F. Wang, G.D. Liang**Duration of antibody responses after severe acute respiratory syndrome**
Emerg. Infect. Dis., 13 (2007), pp. 1562-1564
CrossRefView Record in ScopusGoogle Scholar

Yong et al., 2019
C.Y. Yong, H.K. Ong, S.K. Yeap, K.L. Ho, W.S. Tan**Recent Advances in the Vaccine Development Against Middle East Respiratory Syndrome-Coronavirus**
Front. Microbiol., 10 (2019), p. 1781
View Record in ScopusGoogle Scholar
Zhang et al., 2020
T. Zhang, Q. Wu, Z. Zhang**Pangolin homology associated with 2019-nCoV**
bioRxiv (2020), 10.1101/2020.02.19.950253
Google Scholar
Zhou et al., 2020
P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C.L. Huang, *et al.***A pneumonia outbreak associated with a new coronavirus of probable bat origin**
Nature, 579 (2020), pp. 270-273
CrossRefView Record in ScopusGoogle Scholar
Zhou et al., 2006
Z. Zhou, P. Post, R. Chubet, K. Holtz, C. McPherson, M. Petric, M. Cox**A recombinant baculovirus-expressed S glycoprotein vaccine elicits high titers of SARS-associated coronavirus (SARS-CoV) neutralizing antibodies in mice**
Vaccine, 24 (2006), pp. 3624-3631
Article
Download PDFView Record in ScopusGoogle Scholar
Zhu et al., 2020
N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, *et al.*, China Novel Coronavirus Investigating and Research Team**A Novel Coronavirus from Patients with Pneumonia in China, 2019**
N. Engl. J. Med., 382 (2020), pp. 727-733
CrossRefView Record in ScopusGoogle Scholar
View Abstract

No articles found.

Citing articles (0)

Social Media

- Tweets: 2

View details

Elsevier logo

- About ScienceDirect
- Remote access
- Shopping cart
- Advertise

- Contact and support
- Terms and conditions
- Privacy policy

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/06 15:03:33
Delivered Date:	2020/04/06 15:03:59
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Subject: A new antiviral drug heading into clinical trials offers hope for COVID-19 treatment /Scientists are hopeful that a new drug -- called EIDD-2801 -- could change the way doctors treat COVID-19 https://bit.ly/2RgrN0r

Date: 2020/04/07 10:32:58

Priority: Normal

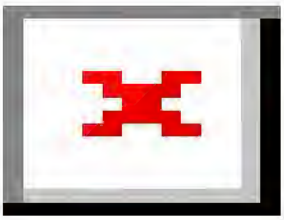
Type: Note

6-Apr-2020

A new antiviral drug heading into clinical trials offers hope for COVID-19 treatment

Scientists are hopeful that a new drug -- called EIDD-2801 -- could change the way doctors treat COVID-19

University of North Carolina at Chapel Hill



IMAGE

IMAGE: Dr. Timothy Sheahan in 2017 works in a lab at the UNC-Chapel Hill Gillings School of Global Public Health. view more

Credit: Photo Courtesy of Mary Lide Parker

Scientists are hopeful that a new drug -- called EIDD-2801 -- could change the way doctors treat COVID-19. The drug shows promise in reducing lung damage, has finished testing in mice and will soon move to human clinical trials.

As of April 3, the novel coronavirus SARS-CoV-2 had infected more than 1 million people with COVID-19 and caused more than 58,000 deaths in a worldwide pandemic. Currently, no antiviral drugs have been approved to treat SARS-CoV-2 or any of the other coronaviruses that cause human disease.

Researchers at the UNC-Chapel Hill Gillings School of Global Public Health are playing a key role in the development and testing of EIDD-2801. Virologists in the lab of William R. Kenan Jr. Distinguished Professor of epidemiology Ralph Baric, are working with colleagues in the lab of Mark Denison, Edward Claiborne Stahlman Professor of pediatrics at Vanderbilt University Medical Center (VUMC), and with George Painter, chief executive officer of the nonprofit DRIVE (Drug Innovation Ventures at Emory) and director of the Emory Institute for Drug Development (EIDD), where EIDD-2801 was discovered.

The results of the team's most recent study were published online April 6 by the journal *Science Translational Medicine*. The paper includes data from cultured human lung cells infected with SARS-CoV-2, as well as mice infected with the related coronaviruses SARS-CoV and MERS-CoV.

The study found that, when used as a prophylactic, EIDD-2801 can prevent severe lung injury in infected mice. EIDD-2801 is an orally available form of the antiviral compound EIDD-1931; it can be taken as a pill and can be properly absorbed to travel to the lungs.

When given as a treatment 12 or 24 hours after infection has begun, EIDD-2801 can reduce the degree of lung damage and weight loss in mice. This window of opportunity is expected to be longer in humans, because the period between coronavirus disease onset and death is generally extended in humans compared to mice.

"This new drug not only has high potential for treating COVID-19 patients, but also appears effective for the treatment of other serious coronavirus infections," said senior author Baric.

Compared with other potential COVID-19 treatments that must be administered intravenously, EIDD-2801 can be delivered by mouth as a pill. In addition to ease of treatment, this offers a potential advantage for treating less-ill patients or for prophylaxis -- for example, in a nursing home where many people have been exposed but are not yet sick.

"We are amazed at the ability of EIDD-1931 and -2801 to inhibit all tested coronaviruses and the potential for oral treatment of COVID-19. This work shows the importance of ongoing National Institutes of Health (NIH) support for collaborative research to develop antivirals for all pandemic viruses, not just coronaviruses" said Andrea Pruijssers, the lead antiviral scientist in the Denison Lab at VUMC.

Denison was senior author of a December 2019 study that first reported that EIDD-1931 blocked the replication of a broad spectrum of coronaviruses.

These interinstitutional collaborators, supported by an NIH grant through the University of Alabama at Birmingham, also performed the preclinical development of remdesivir, another antiviral drug currently in clinical trials of patients with COVID-19. In the new *Science Translational Medicine* paper, Maria Agostini, a postdoctoral fellow in the Denison lab, demonstrated that viruses that show resistance to remdesivir experience higher inhibition from EIDD-1931.

"Viruses that carry remdesivir resistance mutations are actually more susceptible to EIDD-1931 and vice versa, suggesting that the two drugs could be combined for greater efficacy and to prevent the emergence of resistance," said Painter.

Clinical studies of EIDD-2801 in humans are expected to begin later this spring. If they are successful, the drug could not only be used to limit the spread of SARS-CoV-2, but also could control future outbreaks of other emerging coronaviruses.

"With three novel human coronaviruses emerging in the past 20 years, it is likely that we will continue to see more," said first author Timothy Sheahan, a Gillings assistant professor of epidemiology and a collaborator in the Baric Lab. "EIDD-2801 holds promise to not only treat COVID-19 patients today, but to treat new coronaviruses that may emerge in the future."

###

Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Sent Date: 2020/04/07 10:32:33

Delivered Date: 2020/04/07 10:32:58

Message Flags: Unread

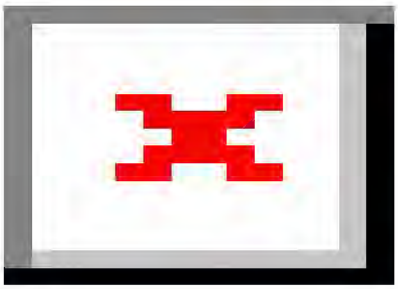
From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: RNZ audio: Professor Peter Doherty: No Covid-19 magic bullets yet https://bit.ly/2VI4X4R
Date: 2020/04/26 12:21:51
Priority: Normal
Type: Note

science health
26 Apr 2020

Professor Peter Doherty: No Covid-19 magic bullets yet

From Sunday Morning, 8:10 am on 26 April 2020
Listen

We're still hearing about patient trials of the Ebola drug Remdesivir and the malaria drug Hydroxychloroquine for treatment of Covid-19 patients, but Nobel Prize-winning professor Peter Doherty, from the Department of Microbiology and Immunology at the University of Melbourne, says neither option is shaping as a potential remedy to the pandemic. There are more than 70 potential vaccines being developed at the moment, but he doesn't think a successful option will be in place anytime soon.



Peter Doherty

Peter Doherty Photo: Casamento Photography

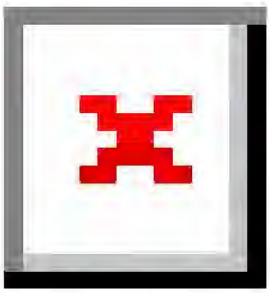
Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Sent Date:	2020/04/26 12:21:40
Delivered Date:	2020/04/26 12:21:51
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: FDA EUA Allows States to Receive Unapproved COVID-19 Treatments
Date: 2020/03/30 12:27:25
Priority: Normal
Type: Note

FDA EUA Allows States to Receive Unapproved COVID-19 Treatments

Posted 30 March 2020 | By Zachary Brennan



FDA EUA Allows States to Receive Unapproved COVID-19 Treatments Opening the door to the wider use of unapproved but potential COVID-19 treatments, the US Food and Drug Administration (FDA) late Sunday issued an emergency use authorization (EUA) to allow the US Biomedical Advanced Research and Development Authority (BARDA) to distribute donated hydroxychloroquine sulfate and chloroquine phosphate products to doctors, who can decide whether to prescribe them to hospitalized teen and adult patients with COVID-19 when a clinical trial is not available or feasible.

This is FDA's first EUA for a therapeutic product.

The donations to be distributed, the Department of Health and Human Services (HHS) said Sunday, include 30 million doses of hydroxychloroquine sulfate from Novartis' Sandoz and one million doses of chloroquine phosphate from Bayer Pharmaceuticals. Hydroxychloroquine sulfate and chloroquine phosphate were previously approved by FDA to treat other conditions, including malaria and lupus.

"The suggested dose under this EUA for hydroxychloroquine sulfate to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible, is 800 milligrams of hydroxychloroquine sulfate on the first day of treatment and then 400 milligrams daily for four to seven days of total treatment based on clinical evaluation. The suggested dose and duration may be updated as data from clinical trials becomes available," FDA said.

"The suggested dose under this EUA for chloroquine phosphate to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible, is 1 gram of chloroquine phosphate on day one, followed by 500 milligrams daily for four to seven days of total treatment based on clinical evaluation," FDA added.

But some are skeptical that these treatments will provide benefits.

Luciana Borio, VP of In-Q-Tel and former FDA chief scientist, criticized the decision on Sunday, saying the EUA was issued "despite the total lack of scientific evidence that chloroquine/hydroxychloroquine are beneficial in the treatment of COVID-19. EUA is supposed to be issued when the evidence indicates that benefits outweigh the risks."

Clifford Lane, a 40-year veteran of the US National Institute for Allergy and Infectious Diseases, also told Politico last week: "I've looked at the available human data, I don't see anything in that literature that appears to show any benefit."

A recent, non-randomized observational study that did not have a control group tested the use of hydroxychloroquine and azithromycin in 80 people in Marseille, France. The researchers noted "a clinical improvement in all but one 86 year-old patient who died, and one 74 year old patient still in intensive care unit," but some are questioning parts of the study and wondering if more, individual patient information will be released.

And HHS even concedes that although anecdotal reports suggest that these drugs may offer some benefit in the treatment of hospitalized COVID-19 patients, clinical trials are still necessary to provide scientific evidence that they are effective.

President Donald Trump, who has said the use of hydroxychloroquine and azithromycin "have a real chance to be one of the biggest game changers in the history of medicine," said Sunday that they are being administered to 1,100 patients in New York as part of trials.

Other Treatments

Meanwhile, the use of another unapproved but potential COVID-19 treatment, Gilead's antiviral remdesivir, is expanding as hospitals or physicians can apply for emergency use of remdesivir for multiple severely ill patients at a time, Gilead CEO Daniel O'Day said in an open letter over the weekend.

"While it will take some time to build a network of active sites, this approach will ultimately accelerate emergency access for more people. Initial sites in the United States are up and running as of yesterday, and it is expected that sites in additional countries will be activated soon," he wrote, noting remdesivir has been used in more than 1,000 patients so far.

Last week, Gilead came under scrutiny after obtaining an orphan drug designation for remdesivir but the company ultimately asked FDA to rescind the designation. O'Day also said the previous compassionate use program for remdesivir will continue for children and pregnant women.

Meanwhile, Regeneron Pharmaceuticals and Sanofi said Monday that the first patient outside of the US has been treated as part of a Phase 2/3 trial evaluating Kevzara (sarilumab) in patients hospitalized with severe COVID-19. The trial has been initiated in Italy, Spain, Germany, France, Canada, Russia and the US.

"Data from a single-arm study in China suggest that the interleukin-6 pathway may play an important role in the overactive inflammatory response in the lungs of patients with COVID-19," said George

Yancopoulos, chief scientific officer of Regeneron.

Letter of Authorization to BARDA

HHS

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/30 12:26:59
Delivered Date:	2020/03/30 12:27:25
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Bloomberg: Inoculating the World May Mean Reviving Old Curbs on Patents (3)
Date: 2020/04/02 11:15:30
Priority: Normal
Type: Note

Inoculating the World May Mean Reviving Old Curbs on Patents (3)

April 2, 2020, 10:22 AM

- • Israel, Germany dust off patent suspension rules amid pandemic
- • U.K.'s Crown Use rules available to overturn patents if needed

German Chancellor Angela Merkel described the coronavirus as the greatest challenge facing her country since the end of World War II. Germany's parliament took that message to heart as part of a package to fight the virus, extending powers to suspend patent rights, a tool last used in the country in 1949.

Governments around the world are reviving rarely used legislation or pledging new measures to ensure that they have the drugs they need to battle the pandemic. Israel last month invoked an emergency patent-suspension clause in its 1967 code for the first time, allowing it to import a generic version of AbbVie Inc.'s Kaletra, which has shown signs of combating coronavirus.

In the U.K., so-called Crown Use rules allow the government to suspend protections it would normally grant a patent holder. Those have been used just a handful of times since 1945, but that could change. "If there is a drug supply shortage, governments aren't going to be squeamish about ordering companies to do what they think is necessary," said James Tumbridge, a lawyer with Venner Shipley in London. In wartime Britain, companies were provided a measure of fair compensation for their rights. "I can see there being pushback and legal challenges elsewhere from pharma manufacturers if they're ordered to produce products at uneconomical prices," said Tumbridge.

Postwar Germany

Germany's law stipulates that patent holders must be indemnified, part of long-standing legislation allowing the government to use a patent for the "public good." It was last invoked in 1949 when the newly established Federal Republic of Germany needed to supply military equipment to the Allied Powers.

The association representing Germany's biggest research-focused drugmakers argues patent protection limits are unnecessary as market forces are already a positive dynamic.

"The numerous projects looking for vaccines and medication in the corona crisis show that two things are working well: competition among pharma companies and the output of their research pipelines," said VFA President Han Steutel.

Patents give their owners the right to block competitors from making copycat drugs. A company that goes ahead and makes a copy also could be ordered to compensate the firm with the branded product an amount that could exceed what the copycat earned.

Existing Products

Germany has yet to invoke its refurbished tool but may do so if shortages emerge, says Julia Schoenbohm, a patent lawyer at Linklaters in Frankfurt.

"The rule will come out primarily in case of shortages for existing products that already have patent protection," Schoenbohm said. "If a company cannot produce sufficient amounts, others should be able to help and not be blocked by patents."

Drugmakers are feeling the pressure. Chicago-based AbbVie on March 20 said it wouldn't enforce its patents on Kaletra, a day after Israel authorized imports of the generic version. Gilead Sciences Inc. has faced backlash over the years for its pricing of infectious disease treatments.

'Pandemic Profiteering'

The California drugmaker asked the U.S. Food &Drug Administration to drop extended monopoly rights on remdesivir, a potential Covid-19 treatment. Eliminating that special status means Gilead waives an extra seven years of exclusivity for the medication. Still, the company has come under criticism from health relief group Medecins Sans Frontieres.

"Gilead has no business profiteering from this pandemic and must commit to not enforce or claim its patents and other exclusive rights," MSF said in a March 27 statement. "Otherwise, Gilead is setting itself up to charge whatever it wants for remdesivir."

Gilead CEO Daniel O'Day said the following day that the company will work to "ensure affordability and access" of the drug. Test results on whether the drug can treat the virus are expected later this month.

SoftBank's Fortress Targets Virus Test Maker in U.S. Patent Suit

The risk of negative publicity hasn't prevented some investors from suing over alleged virus patent violations. Fortress Investment Group LLC last month sued Biomerieux SA, the developer of new coronavirus tests, saying the French company used some of its patented technology.

The U.S. is the wild card. Washington lawmakers have never invoked compulsory licensing or broken drug patent laws, but states could pressure the federal government to take action.

"I'd be very surprised if the U.S. government would ever go against the principles of the free market," said Tahir Amin, co-executive director of the Initiative for Medicines, Access &Knowledge. "Getting a lower price is one thing, but overriding intellectual property rights is a different thing."

President Donald Trump, however, hasn't been afraid to use a bully pulpit to get to companies to fall into line with his policies, especially in an election year. He castigated General Motors Co. for being too slow in shifting to making badly-needed medical ventilators, even though it was the automaker's idea.

The government holds all the cards in negotiations with manufacturers because federal statutes give them a right to the best price and the potential windfall for a company with a vital product is huge, said Joe Allen, executive director and founder of Bayh-Dole 40, which educates the public about government-funded research.

"I can't even imagine how much vaccine you're going to have to produce, because you're going to really want to inoculate the whole world," said Allen. "I don't think price is going to be a problem, but if it was, the government has the right under its emergency powers to take anything that they want to meet a crisis."

(Adds patent scope of patent protection in ninth paragraph.)

Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Sent Date:	2020/04/02 11:12:13
Delivered Date:	2020/04/02 11:15:30
Message Flags:	Unread

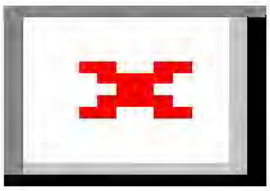
From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Guardian: 'The more vaccine projects we have, the better our chances'
Date: 2020/03/29 10:22:42
Priority: Normal
Type: Note

'The more vaccine projects we have, the better our chances'

Leading scientist Adam Finn warns of stumbles along the way to Covid-19 immunisation

Robin McKie

Sat 28 Mar 2020 16.06 EDT



Laboratory efforts to develop a coronavirus vaccine.

There are at least 60 Covid-19 vaccine projects under way or in planning. Photograph: Douglas Magno/AFP via Getty Images

The chances of an individual Covid-19 vaccine project producing a successful outcome are low, one of Britain's leading immunisation experts has warned. "Science does not have a track record where most of our vaccine projects work," Professor Adam Finn, of Bristol University said last week. "We have a track record where most of them don't work."

Finn's warning came as doctors and epidemiologists stressed how difficult it would be to contain the disease until people can be immunised against it.

The crucial point is that if individual projects have low prospects of success, many different approaches will have to be taken to find one that does provide protection against Covid-19.

"It is like the Grand National," said Finn. "A lot of horses start off but only a few make it to the finishing line. And that is why we are going to need a lot of different vaccine projects to start off with – because only one or two are likely to make it to become fully fledged vaccines. This is not a one-horse race.

"At present, I would estimate there are at least 60 Covid-19 vaccine projects that have started up or are in planning. But the more there are, the better things will be."

Most Covid-19 vaccine projects that have been announced so far have been for a type known as RNA/DNA vaccines. These involve taking genetic material from a virus and injecting into animals or human volunteers. This approach is quicker than other methods which typically involve creating pieces of a virus and using them to stimulate a person's immune system against it.

However, RNA/DNA vaccines – which are a recent development – have yet to be developed for use in human beings. "They are quicker to start up but we have much less experience with them compared with standard approaches."

All these projects have promise, Finn stressed, but most of those being launched to tackled Covid-19 were unlikely to work in the end. "The trouble is that we do not have a technology that allows us to be confident from the outset that a vaccine will be effective."

In addition, vaccines that do stimulate strong immune responses can also have adverse side-effects or may even make a disease worse. An example is provided by Dengue fever, which is spread by mosquitoes in Asia and South America. "A vaccine was developed to protect children against one type of Dengue," said Finn. "Then it was found that it actually made them more susceptible to a second type of the disease."

For these reasons, vaccines have to be put through lengthy trials to ensure any dangerous side-effects are revealed. "We will have been cautious and not rush forward," Finn added.

On the other hand, it was possible that one of the projects would produce a vaccine that just sailed along, he said. It might turn out to be easy to manufacture, have no side-effects, produce a good immune response, while in trials it prevented volunteers from getting sick compared with those in a control group. For good measure,a factory would be ready to manufacture it.

"In those circumstances, you would have a vaccine in less than a year," said Finn. "But it is almost certainly not going to happen like that. There will be stumbles along the way."

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/29 10:22:32
Delivered Date:	2020/03/29 10:22:42
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Subject: Mother Jones: Dr. Anthony Fauci Is the "Perfect Man for This Moment." /AIDS activists like Peter Staley know why. https://bit.ly/3aVCFsA

Date: 2020/04/07 11:12:13

Priority: Normal

Type: Note

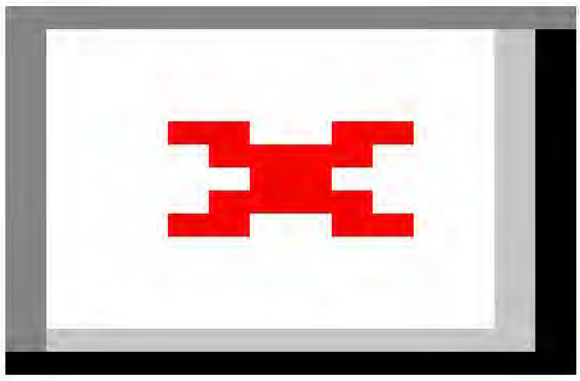
21 hours ago

Dr. Anthony Fauci Is the "Perfect Man for This Moment." If Trump Sidelines Him, We're Screwed.

AIDS activists like Peter Staley know why.

James West

James West
Deputy Editor, DigitalBio | Follow



Dr. Anthony Fauci and Dr. Deborah Birx at a White House briefing by the coronavirus task forceManuel Balce Ceneta/AP

For indispensable reporting on the coronavirus crisis and more, subscribe to *Mother Jones'* newsletters.

Once I began recovering from COVID-19, I wanted to understand what it means to be part of a growing cohort of survivors: What was happening in my body? And how should I think about my membership in this strange new class of people? I wanted to hear from scientists, survivors, and others who have been on the front lines of outbreaks before, to learn how I and others like me might help kickstart life after the plague.

That reporting led me to one of my own heroes, Peter Staley, a veteran HIV/AIDS activist and a central figure in ACT UP, a group that used the tools of direct action and civil disobedience to put AIDS on the map and crack open access to medical treatment—work that was featured in the 2012 documentary *How to Survive a Plague*.

Staley has also collaborated with Dr. Anthony Fauci and Dr. Deborah Birx, the top scientists on Trump's coronavirus task force. In this interview, republished below, Staley reflects on how to keep Fauci and Birx in the room and in Trump's ear during consequential tussles over public policy, as internal disagreements inevitably break into public view. (Over the weekend, *Axios* reported a heated exchange between Fauci and Trump's anti-China trade adviser, Peter Navarro, over the use and efficacy of the malaria drug hydroxychloroquine.)

Losing just one of the top scientists to a Trump tantrum or a Twitter roasting is too perilous, Staley warned. "We shouldn't be relying on just two experts to fight this thing," he said. "We're in a very dangerous position."

This interview has been edited for length and clarity. You can also listen to it on the latest episode of the *Mother Jones Podcast*. Don't miss Staley's recollections of wine-soaked dinners with Fauci.

Tell me about your current work, and how you're doing.

I've been doing AIDS activism around PrEP, the drug that blocks HIV infections, including working with leading public health officials on that issue. People like Anthony Fauci and Deborah Birx.

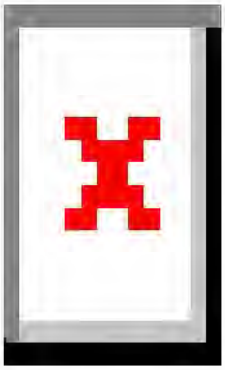
A bunch of us have leaped into COVID activism. Many of us have gotten used to this, when new pandemics hit, being very drawn to it because, frankly, we get triggered. We see politicians acting poorly almost from the get-go. It reminds us of what we all went through.

The world considers us, rightly, one of the most connected patient advocacy groups. We're in this unique position of knowing all the players that fight epidemics, whether it be political leaders, or epidemiologists, or public health officials, or researchers, or front-line docs. So we're well-positioned to run interference when issues arise.

What does "run interference" mean?

When New York City's mayor was not listening to his public health experts as quickly as he should have early in this crisis, we looked for all sorts of tactics and methods for putting a fire under his ass. We were trying to *drum up, stir up, and throw!* Eventually, he got to a place where he is now very quickly deferring to the public health experts.

But we had a real crisis there for two weeks. He was sitting down with 30 people, and the public health experts were outnumbered. He was going with the more comforting advice. That's a classic dangerous mistake that politicians make during the beginning of an epidemic. You just want to pull your hair out. Every day you lose, the fallout is exponential down the road.



Peter Staley in 2013.

I listened to a podcast this week from some Republican politicos who were all musing about how we'll have to wait until this all plays out to judge Trump's response to this pandemic. But that is just so crazy. It's so false because 90 percent of what Trump needed to do needed to happen in February, and it didn't. So we know *now*. We don't have to wait until the end. We know now that he messed up big time. All your work during an epidemic has to be loaded in the front end. That first month is the reason we might have 100,000 to 200,000 deaths in the US. Yes, everything after may prevent a million deaths, but the 100,000 to 200,000 deaths were preventable. Very preventable, and Trump didn't do it. He didn't do it. The deaths are all on his head, as far as I'm concerned. The blood is all on his hands. The people dying now are Trump deaths, hashtag #TrumpDeaths.

"The blood is all on his hands. The people dying now are Trump Deaths."

For those of us lucky enough to have seen *How to Survive a Plague*,the brilliant David France documentary about your work, ACT UP, and the early medical activism around HIV, we've seen you tussle with health authorities. What kind of historical echoes are you feeling right now? How is Trump receiving medical advice from the establishment?

I'm not sure we heard much at the beginning. He had gutted the [National] Security Council's pandemic working group, whose sole job was to bring a new pandemic to a president's attention as soon as it was starting. It was probably a combination of the distrusting of science and expert advice, but also the fact that he was actively trying to unravel everything Obama created.

I don't know exactly when Fauci was called in to actually see the president, but from what I'm piecing together, it was pretty late in the process. Everything was too little too late.

Listen to James West's conversation with veteran AIDS activist Peter Staley on this episode of the Mother Jones Podcast:

Peter, you've had a lot to do with Dr. Anthony Fauci. You've been quoted elsewhere as friends, and you speak of him with great respect. The respect you have for him has solidified over the years?

Yeah, I consider Fauci one of the great heroes in the fight against HIV/AIDS and continue to work with him on that fight. We meet and talk fairly regularly. As part of that ongoing fight, a bunch of us had another "Fauci Dinner," as we call them, four years ago now. Right after he turned 75. And we asked

him, "Tony, do we have to start finding a replacement? You're 75!" It was a major worry of ours because his wealth of experience fighting HIV/AIDS, we still needed it.
He cleared that up pretty strongly and convincingly. He said, "No, I think I've got a good 10 years left in me," which would make him 85. He mentioned how he was still running every day and that his resting heart rate was better than it was when he was running when he was 50 years old. He felt great. And that he really wanted to, like us, finish the job we had started.
That was the primary motivation for wanting to die at his desk: the hope that he could be there when we actually got vaccines that worked against HIV. We've been working with him ever since to finish that work, finish that job. He was central to the creation of PEPFAR, which has saved millions of lives around the world. There are now 24 million people taking HIV therapies around the world.
To clarify, that's the foreign policy instrument under George W. Bush that was a global health initiative?
Right. Started by what, at that point, was the worst president of our lifetimes. Fauci helped convince that president to do what ends up being Bush Junior's greatest legacy, and that is saving millions of lives of people with HIV around the world. Tony was really the architect of designing that program and figuring out how to thread that needle and get into the State of the Union speech. It's had bipartisan support ever since. I think we're seeing much the same from him lately with COVID, and even more recently with HIV. Trump announced a domestic AIDS plan for fighting HIV/AIDS in a State of the Union address, and that shocked his base and shocked everyone. Tony's fingerprints were all over that.
He's working his Fauci magic in the Trump administration now. I noticed you said he's the only guy in Washington who Trump can't fire. Is that true?
Yeah, I think his job is incredibly secure. That's actually never been my worry. First off, he's a civil servant, so Trump can't fire him directly. He would have to tell HHS Secretary Azar to do it. I'm pretty convinced that it would be a Saturday night massacre [*laughs*]. But he could, overnight, just like [Robert] Redfield, the CDC director, he could be sidelined. He could still be filling a seat at the task force meeting, but Pence wouldn't call on him. He would no longer be taken from the task force meetings into the Oval Office for one-on-one time with Trump. That's when he would lose all influence against COVID-19.
Because the man is charming, right? I imagine that in person, he has that "X-factor" that can bring people on board, one-on-one?
Exactly. That's why he's kind of the perfect man for this moment. He has this rare combination of being one of the leading experts in the world on fighting epidemics combined with personal skills that allow him to interact with political leaders with very little scientific expertise in a way that very quickly engenders trust. He never talks down to people. You meet him and you very quickly realize that he's the smartest guy in the room, but he doesn't treat you that way at all. He doesn't talk down to you at all. He reaches a hand out and pulls you up the learning curve with him, very quickly and easily. And all of a sudden you start feeling smarter because you're getting it.
He's doing all of this with a New Yorker, Brooklyn "let's have a beer together" accent, or in our case, a couple hundred bottles of wine over the last three decades!
He never bullshitted us, but we knew we were being wined and dined. We knew he was charming. We knew there wasn't a homophobic bone in his body.
I've been noticing the Twitter echo chamber reacting to some of the more obvious messaging to Trump by Dr. Deborah Birx, where it seems, to those of us watching without the decoder ring you have, to be a bit like blowing smoke up his ass. How useful is it for us to be criticizing her in this moment?
I think some of it has been useful and some of it hasn't when it comes to Dr. Birx. I met her a few times. When I taught at Harvard in 2016, I invited her to be one of the guest speakers. I came into this COVID stuff with huge respect for her based on what others were saying. I've watched those friends who adore her become quite shocked and worried over the last couple weeks at many of her statements.

I think we've been trying to put them into two categories. While the progressive Twitterverse has slammed her harder for the comments that seemed to ingratiate herself to Trump, that's actually the category of statements that most of the AIDS activists who work with her are willing to let slide. We're willing to write those off as tactical, as a way for her to stay at the table and to keep her voice as one that he listens to, knowing that that is Mission No. 1 right now for all of us. If you want to save lives during COVID, Mission No. 1 is keeping Tony Fauci and Deborah Birx's voice trusted in Trump's ear. So whatever they need to do to do that, they get a pass in my book.

But she had been coupling that with a mischaracterization of actual facts and data. She has mischaracterized the modeling that came out of the UK. She has been dismissive of frontline health care workers' alarming warnings about ventilators. And she mischaracterized the state of the epidemic in vast areas of the country. So when she starts playing fast and loose with the facts, that just raises huge red flags for all of us. And quite a few of her friends let her know it. I think she got the message. Fingers crossed that she kind of got swept up in Trump's propaganda machine for 10 days and now has a clearer head and won't misspeak again.

But it's not something that isn't fixable. Frankly, at this point, we're in a very dangerous position. It's like Trump and his foreign policy. At the beginning of his administration, he was surrounded by adults in the room. And then he slowly started firing all the adults and hiring sycophants on foreign policy, whether it was his generals or his foreign policy establishment. And now there are no experts in the room on foreign policy. It's just sycophants.

"If we lose Birx, then we're in a very dangerous place."

Now we have an epidemic. He brings in some expertise, but not many, and now a few have been sidelined. We're really down to two. We're down to Birx and Fauci, and that's not a good place to be in. We shouldn't be relying on just two experts to fight this thing. And if we lose Birx, then we're in a very dangerous place. So, I would rather help her stay in the room and hope that she gets better at it. And definitely, I hope she stops bullshitting the American people.

I want to turn to this predicament of my own. As you know, I've recovered from COVID-19, and have been trying to enroll in various plasma trials. [Read about that here.] The trials are regulated by the FDA under typical blood bank rules: Men who have had sex with men in the last 12 months can't donate. What do you think about that, both as a matter of AIDS activism and specifically for this particular moment, when it seems critical to have healthy 38-year-old gay men like me, who have recovered from COVID-19, to be helping out?

I have quite a few gay friends who are recovering from COVID right now. So the group is quickly expanding. The fact that you are being blocked from helping in an incredibly positive way to save lives is just utter craziness. For me, as a long-term AIDS activist, it makes me want to scream because folks may not realize this, but a lot of what AIDS activists helped build is now being used to fight COVID.

Two examples. The largest clinical trial system at NIAID, which is the National Institutes of Allergy Infectious Disease, the division at NIH that Tony Fauci runs, is being used for COVID trials. This clinical trial system that AIDS activists helped create with patient advocates as part of the system, and it's been running smoothly for decades now, that's stepping into the breach to quickly launch COVID trials.

Second example. Gilead just announced that Remdesivir, one of the possible treatments for COVID, has been granted expanded access by the FDA to let tens of thousands of people use it outside of the clinical trials.

There have been various versions of expanded-access language added to FDA regulations. Almost all of it got written between 1987 and 1992, ACT UP's first five years. All right?

So all of these regulations that are allowing wider access to COVID therapies right now were because of AIDS activists. And the whole reason the FDA is able to act so quickly now is because of what we helped build. And to tell us now, this community that created much of the system that our government uses to fight epidemics, to say "no, thank you" to this community when we want to individually help to save

lives, something's really wrong with that. It triggers all the feelings we felt during the early years of the AIDS crisis when the country was just saying, "We don't care." Just leaving us to die. This policy is going to cost lives.

[Since speaking with Staley, the FDA, in a major announcement, said it will reduce donation restrictions for gay and bisexual men from a 12-month abstinence window to three months. "Progress!" Staley texted me. "But they still need to include a no-window exception for these plasma studies, using HIV viral load tests to assure safety."]

How do you think we come together to beat this thing back, and what's your diagnosis for our optimism right now? Are you optimistic?

Well, I'm able to tap a little of optimism that I wasn't able to tap during the first few years of AIDS activism. Our activism was about turning the entire country around to actually pay attention. And then it was about finding treatments that we really didn't even know if they were out there. So a lot of us didn't know whether we would live long enough to see the fruits of our activism.

Today, we actually had the knowledge even before COVID started of how to nip it in the bud. And what the world is going through is a failure of political leadership to use that knowledge and use those tools. But those tools are still there. And if political leaders start letting the scientists run things, which we're being to see, then things will turn around.

So it's a mix. It's a mix of knowing we can beat this and being very triggered by the fact that politicians let this get as bad as it did.

And very triggered and horrified that I know people who have died. Terrence McNally was a man who I've adored from afar, whose plays I've seen all through the AIDS years, who himself had managed to avoid the virus and get through those plague years only to be felled by COVID and the stupidity of another Republican president.

Hope is just...it's there. People need it. People need to know that we can get through this. I am hopeful we will. But there's a lot of justifiable anger and sadness, and the sadness is just starting. We're going to lose a lot of people. We're all going to know someone. We're not going to be able to have the funerals. At least we had funerals during the plague years. We often talk about the funerals of how they emotionally scarred us because we were going to so many, but it's also what allowed us to get through those years, the fact that we could all gather and hug.

One of the great lessons I took from *How to Survive a Plague*, and as a gay man growing up in the shadow of the AIDS crisis, is how useful outrage was to you as an activist, the channeling of that rage, the anger and frustration, the throwing of ashes at the White House, and staging die-ins, and being angry as a tactic of pushing hard change through. That's one of the lessons I've taken from my gay heroes who were able to reset the stage. Maybe optimism was the wrong question for you. Maybe it should be about rage, and how to direct it?

Yeah. No outrage, anger. It is completely legitimate. I am filled to the brim with it right now, and that's totally legitimate. And the trick for all of us is using that in a helpful way. Sometimes it's almost impossible to do. You got to kind of explode.

"If you find yourself spending more than five minutes out of your day trying to try and to destroy Deborah Birx, maybe you're mis-targeting your anger."

But the difference between a useful activist and just a frothing activist is one who channels their rage. All of us have to figure out how to channel it. If you find yourself spending more than five minutes out of your day trying to try and to destroy Deborah Birx, maybe you're mistargeting your anger. Because there's a guy called Donald Trump who you should be laserlike focused on.

And even within your own world, there's a level of misinformation, and conspiracy theories, and Trump supporters, and right-wing media, and anti-science people on the left and the right who are making things worse. We all need to target our anger to those enemies and fight against that. We need to

defend science at all costs. We need to listen to science, scientists, and the experts, and defend them at all costs. This is all about the targeting, and anger can screw that up.
That's my message to everybody. That anger is legitimate. That rage is totally legitimate. But it's useless unless you target it well and use it for good. That will make you a great activist.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/07 11:11:17
Delivered Date:	2020/04/07 11:12:13
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Bloomberg: Drugs Authorized for Covid-19? Why There's Skepticism: QuickTake
Date: 2020/03/31 18:50:47
Priority: Normal
Type: Note

Drugs Authorized for Covid-19? Why There's Skepticism: QuickTake

March 30, 2020, 2:50 PM

Because the coronavirus responsible for the Covid-19 pandemic is new to humans, doctors lack vaccines to prevent it and proven medicines to treat it. Researchers and companies are scrambling to fill the void. In normal times, the process of approving new drugs is slow and painstaking. It can be accelerated in times of crisis such as these, but at the risk of doing more harm than good.

1. Are any Covid-19 treatments approved?

The U.S. Food and Drug Administration in late March controversially issued an Emergency Use Authorization providing for two malaria drugs, chloroquine and hydroxychloroquine, to be distributed and prescribed by doctors to Covid-19 patients. The move came after President Donald Trump repeatedly touted the drugs. Such authorizations are permitted during a crisis when a product's "known and potential benefits" outweigh its "known and potential risks."

2. Why the controversy?

The FDA's decision and Trump's championing of the drugs have been criticized by scientists as premature. In a small study in France, hydroxychloroquine showed promising results, but the trial's methodology has been challenged, and in another small trial in China, the drug was no more effective than conventional care. And it carries significant side effects. Some people have been sickened, with reported deaths in the U.S. and France, after taking various versions to try to ward off or treat Covid-19. Plus panic-buying of hydroxychloroquine has created shortages of the drug for patients with malaria and the autoimmune disease lupus, for whom it is a proven therapy.

3. How do scientists prove a treatment is effective?

Even if a treatment shows promise in laboratory, animal or early human experiments, rigorous testing is needed to prove that it's both safe and effective. That requires carefully structured and monitored tests known as clinical trials. Typically, these studies are designed to show that patients who get the drug do better than those who don't, and that the results aren't a product of chance. The trials try to subtract all the other influences and factors that might disguise the true effectiveness of the drug. For one thing, patients often recover from viral illness on their own, or improve because of supportive care such as rest and hydration. And some really sick patients might not respond to treatment no matter how effective it is. Treatments that don't have approval from regulators such as the U.S. Food and Drug Administration should be viewed with extreme caution. The FDA and the U.S. Federal Trade Commission have warned multiple companies to stop selling unproven treatments for coronavirus.

4. How long does it take to prove efficacy?

It depends. Drugs that are already approved against one infection and shown to be safe can be tested for effectiveness against another in a matter of months. Experimental drugs may take longer to test, as they have to go through initial studies to evaluate whether they are safe. Other factors that can slow the process include the supply of drug candidates and the availability of patients to test them in. The trials also have to be approved by ethics watchdogs and drug regulators. According to a 2017 review, the median time for regulators to approve a new drug in 2015 was 333 days in the U.S., 422 days in Europe, and 639 days in China. China has since expedited its process. When drugs are deemed to fill an immediate need, regulators can speed them through the approval process using a number of paths.

5. What's being tested against Covid-19?

More than 100 clinical trials have been launched in China to study everything from anti-flu drugs and antibody-containing plasma from recovered patients, to traditional Chinese herbal medicine. A smaller number have been announced in countries including the U.S., South Korea and Thailand. World Health Organization researchers have identified as the most promising agent remdesivir, an experimental antiviral made by Gilead Sciences Inc. originally as a treatment for Ebola. In animal studies, it produced encouraging results against related coronaviruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Remdesivir trial results are expected from China in late April. Larger trialsof chloroquine and hydroxychloroquine are starting. In a study in China published March 18, AbbVie Inc.'s Kaletra, an HIV treatment combining two drugs, failed to improve the condition of coronavirus patients. Another small, preliminary trial of the flu medication favipiravir, or Avigan, made by Fujifilm Holdings Corp. produced more promising results.

6. What about vaccines?

Moving at record speed, researchers began preliminary human testing of an experimental Covid-19 vaccine in mid-March in the Seattle area. It was developed by the U.S. National Institute of Allergy and Infectious Diseases in collaboration with the biotechnology company Moderna Inc. Additional trials are expected as some of the world's biggest companies are working on vaccine projects. GlaxoSmithKline has teamed upwith China-based Clover Biopharmaceuticals, while Sanofi and Johnson &Johnson are in separate collaborations with the U.S. government's Biomedical Advanced Research and Development Authority. Widespread testing of experimental vaccines is important to reduce the possibility that they cause harm after being rolled out, as has been the case a number of times in the past.

7. How soon might there be a vaccine?

Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases, said that it would take about a year and a half to complete trials of experimental coronavirus vaccines, scale up production and make a licensed product widely available. There's no guarantee trials will yield a successful vaccine, however. Moderna's experimental product is a so-called messenger RNA vaccine, an unconventional approach that has yet to produce a vaccine licensed for human use. SARS killed nearly 800 people in a 2002-2003 outbreak, and there still isn't an approved vaccine. In a project that could deliver a vaccine sooner, researchers in four countries will test a shot that's already licensed to prevent tuberculosis to see if it will protect health workers against the coronavirus.

The Reference Shelf

- • Related QuickTakes on what you need to know about Covid-19, how the virus spreads, whether to wear a mask, whether the virus is seasonal, and how the pandemic is being fought.
- • The U.S. National Institutes of Health compares the drug approval process in the U.S. to that in China.

- • A commentary published by George Mason University's Mercatus Center examines China's reforms of its drug approval process.

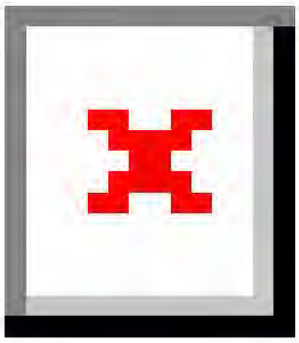
Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/31 18:50:28
Delivered Date:	2020/03/31 18:50:47
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: STAT: New data on Gilead's remdesivir, released by accident, show no benefit for coronavirus patients. Company still sees reason for hope https://bit.ly/2x7x6Zy
Date: 2020/04/23 14:08:31
Priority: Normal
Type: Note

New data on Gilead's remdesivir, released by accident, show no benefit for coronavirus patients. Company still sees reason for hope

By Ed Silverman @Pharmalot, Adam Feuerstein @adamfeuerstein, *and* Matthew Herper @matthewherper
April 23, 2020



Bottles of Remdesivir Bottles of remdesivir in a hospital for Covid-19 patients in Wuhan, China. *FeatureChina via AP*

The antiviral medicine remdesivir from Gilead Sciences failed to speed the improvement of patients with Covid-19 or prevent them from dying, according to results from a long-awaited clinical trial conducted in China. Gilead, however, said the data suggest a "potential benefit."

A summary of the study results was inadvertently posted to the website of the World Health Organization and seen by STAT on Thursday, but then removed.....

more

Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/23 14:08:09
Delivered Date:	2020/04/23 14:08:31
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Bloomberg: WHO Adopts Test Method That Helped Stifle Ebola for Coronavirus
Date: 2020/03/19 12:12:56
Priority: Normal
Type: Note

WHO Adopts Test Method That Helped Stifle Ebola for Coronavirus

By
Thomas Mulier
and
John Lauerman
March 19, 2020, 9:31 AM EDT

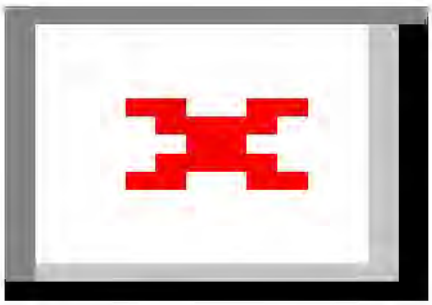
- • Four therapies will be pitted against each other, led by WHO
- • Same approach found treatment that's helping smother Ebola

The World Health Organization is taking the drug-testing approach that helped stifle Ebola's latest resurgence and using it against the new coronavirus.

At least 10 countries including France, Spain and Switzerland agreed to join a trial called Solidarity that the global agency is coordinating, simultaneously testing four therapies by pitting them against each other.

The strategy is designed to speed up a process that can take years as doctors scour laboratories for promising treatments against the new virus.

"It's an unprecedented opportunity to come together as one against a common enemy," WHO Director-General Tedros Adhanom Ghebreyesus said in a briefing Wednesday.



relates to WHO

Adopts Test Method That Helped Stifle Ebola for Coronavirus

In the absence of drugs and vaccines, health officials are urging -- or in some cases compelling -- people to stay at home to avoid infecting others.

Finding treatments against a new disease can a painstaking process. Ebola drugs were particularly difficult to identify because the disease often struck quickly, going back undercover before clinicians had the opportunity to finish testing potential treatments.

Think Big

New treatments are often evaluated in trials that pit them one-on-one against another drug or a placebo, which can slow the march toward finding the most effective intervention. For Ebola, the problem was finally addressed by the appearance of new antivirals and the use of a so-called master protocol that tests numerous therapies en masse.

"Multiple small trials with different methodologies may not give us the clear, strong evidence we need about which treatments help to save lives," Tedros said.

In the Solidarity trials, researchers will test four therapies, some of which are already used in people, to treat Covid-19: Gilead Sciences Inc.'s experimental remdesivir, AbbVie Inc.'s Kaletra (used to treat HIV infection), Kaletra with an anti-inflammatory treatment called interferon-beta, and the malaria drug chloroquine.

China has included chloroquine in treatment recommendations for Covid-19. Ongoing studies showed that Kaletra, a combination of the drugs lopinavir and ritonavir, gave little benefit, according to early results published Wednesday in the New England Journal of Medicine. Additional medicines may be added and some of the original treatments may be cut out as the trial progresses.

All these therapies will be compared against each other as well as the standard of care, which may include measures such as patient support and the use of ventilators -- machines that help severely ill patients breathe.

In the Ebola trials, researchers compared the impact of several drugs including remdesivir. When a Regeneron Pharmaceuticals Inc. drug showed clear superiority against the deadly infection, the study was stopped early so the medicine could be given to more patients.

Argentina, Bahrain, Canada, Iran, Norway, South Africa and Thailand have also agreed to participate in the coronavirus trials, Tedros said.

It's been a month since the last case of Ebola in Congo, the WHO director-general said Wednesday. If that continues, that outbreak will be declared over in less than a month.
— With assistance by Tim Loh, and Jason Gale

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/19 12:11:34
Delivered Date:	2020/03/19 12:12:56
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: KFF Daily Global Health Policy Report, Friday, April 10, 2020
Date: 2020/04/10 11:18:02
Priority: Normal
Type: Note

KFF Daily Global Health Policy Report

Friday, April 10, 2020

In The News

COVID-19 Threatens Global Peace, Security, U.N. SG Guterres Tells Security Council; Foreign Policy Examines U.N. Role During Pandemic

Bloomberg: U.N. Chief Urges Divided Security Council to Act on Coronavirus

"United Nations Secretary-General António Guterres urged members of the Security Council to come together to fight the global coronavirus outbreak, marking the first time the divided 15-nation body discussed the pandemic. 'The engagement of the Security Council will be critical to mitigate the peace and security implications of the Covid-19 pandemic,' Guterres told council members in a closed-door video conference on Thursday..." (Wainer, 4/9).

Foreign Policy: Can the United Nations Survive the Coronavirus?

"...Since the World Health Organization declared a pandemic on March 11, a host of international dignitaries, including U.N. Secretary-General António Guterres and leaders from China and Estonia to Tunisia, France, and Russia, have vied with one another to fill the geopolitical vacuum, putting forward a succession of plans to address the health crisis. But each effort has met stiff resistance or indifference, raising questions about the ability of the U.N. to function effectively with a declining American superpower unwilling, and seemingly unable, to guide the world through the health calamity, and the capacity of a rising China to forge a concerted international response to a pandemic that started on its soil..." (Lynch, 4/8).

Additional coverage of Guterres's comments at the Security Council briefing is available from AP and U.N. News.

Link to individual story

IMF, Reports Warn Novel Coronavirus Pandemic Impacts Will Widen Inequalities, Heavily Impact Global Economies

Financial Times: Effects of pandemic will widen inequality, report finds (Staton, 4/10).

Reuters: IMF chief says pandemic will unleash worst recession since Great Depression (Shalal/Lawder, 4/9).

U.N. News: Coronavirus-driven debt crisis threatens poor countries already at risk, says U.N. report (4/9).

Link to individual story

Gavi To Disburse Up To $200M To Help Lower-Income Countries Address COVID-19; Vaccine Alliance Chooses To Halt Mass Vaccination Campaigns In Many Countries

Reuters: GAVI to disburse $29 million to help COVID fight in 13 countries

"The GAVI vaccine alliance will disburse $29 million to help health systems in 13 lower-income countries fight COVID-19, it said on Thursday, part of a $200 million program approved by its board last month..." (Nebehay, 4/9).

Science: Pandemic brings mass vaccinations to a halt
" 'A devil's choice.' That's how Seth Berkley, head of GAVI, the Vaccine Alliance, describes the dilemma facing global health organizations in the past few weeks. They could either continue to support mass vaccination campaigns in poor countries but risk that they would inadvertently help spread COVID-19 — or recommend their suspension, inevitably triggering an upsurge of many other infectious diseases. In the end, they chose the latter, and mass vaccination campaigns against a host of diseases are now grinding to a halt in many countries..." (Roberts, 4/10).
Link to individual story

As COVID-19 Cases Stabilize In Some European Countries, Asia Braces For 2nd Wave; U.N. Human Rights Chief Warns Pandemic Worsening Inequality, Repression

CIDRAP News: Nations eye COVID-19 lockdown extensions as global cases rise
"With COVID-19 activity showing some early signs of stabilizing in parts of Europe, some governments are considering extending their lockdown orders, as cases are still surging or picking up in other parts of the continent. Meanwhile, cases are accelerating in part of Asia, including Indonesia, Singapore, and Japan, and economic leaders are grappling with the pandemic's economic impact and how to fund the response..." (Schnirring, 4/9).
The Guardian: Global coronavirus cases pass 1.5 million amid fears of second wave of outbreaks
"Confirmed global coronavirus infections have passed the 1.5 million mark, as a new study of containment measures in China suggests that countries preparing to ease their lockdowns will have to continuously monitor potential new cases to prevent a second deadly outbreak. ... In the U.S., figures showed that a staggering one in 10 workers — 16.8 million — had lost their jobs in the past three weeks. There are fears that the total could hit 20 million by the end of the month. While countries such as Spain and Italy reported that their rates of infection were beginning to plateau, others reported record one-day rises, including Russia, where the president, Vladimir Putin, warned that the coming weeks would be decisive in the fight against the virus..." (Beaumont, 4/9).
VOA: U.N. Official Says Coronavirus is Worsening Repression and Inequality
"U.N. High Commissioner for Human Rights Michele Bachelet warned the coronavirus pandemic is likely to widen existing inequalities around the world if left unchecked, with the poor, the disabled, the homeless, minorities, women, and elderly among others most at risk. At a virtual meeting, the human rights chief also had stern criticism for governments that she said are using health emergency measures to justify repression and expand their powers..." (Schlein, 4/10).
AP: Africa must not be 'neglected' in virus fight, officials say (Anna, 4/9).
Devex: These countries have only a handful of ventilators (Smith, 4/9).
Financial Times: France to reallocate Africa aid money for fight against coronavirus (Aboud/Pilling, 4/9).
New York Times: Coronavirus Finds Fuel in a World of Migrants (Beech, 4/10).
U.N. News: Living apart, 'we must stand together' to battle coronavirus pandemic — U.N. rights chief (4/9).
Washington Post: Among the most vulnerable to coronavirus: The tens of millions who carry HIV and tuberculosis (Bearak/Slater, 4/9).
Washington Post: E.U. strikes deal to help hardest-hit countries, as strain of coronavirus threatens to fracture the bloc (Harlan et al., 4/9).
Link to individual story

WHO To Launch COVID-19 Funding Appeal Amid Trump Administration's Heightened Scrutiny Of U.N. Agency

The Guardian: The WHO v. coronavirus: why it can't handle the pandemic
"...[I]t is possible to imagine a world in which every nation respects the WHO's authority, follows its advice and lets it coordinate the flow of information, resources and medical equipment across national boundaries to areas of greatest need. That is not the world we live in. ... [T]he WHO is desperately struggling to get its 194 member states to actually follow its guidance. ... There is a simple reason for this. For all the responsibility vested in the WHO, it has little power..." (Buranyi, 4/10).
POLITICO: Trump team ramps up scrutiny of funds to WHO
"U.S. agencies and departments that channel money to the World Health Organization have been asked not to send more such funds this fiscal year without first obtaining higher-level approval, two people familiar with the issue said. The decision comes after President Donald Trump threatened to cut off funding to the U.N. global health body over allegations that the WHO's leaders are too friendly to China and made missteps in the early days of the coronavirus crisis..." (Toosi/Diamond, 4/9).
Reuters: WHO's new funding appeal for coronavirus fight to top $1 billion: diplomats
"The World Health Organization (WHO) is preparing to launch an appeal soon for more than $1 billion to fund operations against the COVID-19 pandemic through year-end, diplomats told Reuters on Thursday. It comes against the backdrop of a salvo lobbed by U.S. President Donald Trump against the WHO over its handling of the COVID-19 pandemic and suggestions from his administration it might re-evaluate U.S. funding..." (Nebehay, 4/9).
Additional coverage of the WHO's COVID-19 response, as well as controversy over its leadership and relationship with China, is available from The Hill, POLITICO, Quartz, Reuters (2), and U.N. News.
Link to individual story

Trump Administration Officials Discuss COVID-19 Pandemic, Hear Calls To Loosen Iran Sanctions

CNN Business: White House reverses position after blocking health officials from appearing on CNN
"Vice President Mike Pence's office reversed course on Thursday afternoon, after declining for days to allow the nation's top health officials to appear on CNN and discuss the coronavirus pandemic, in what was an attempt to pressure the network into carrying the White House's lengthy daily briefings in full..." (Darcy, 4/10).
CNN: Barr calls coronavirus restrictions 'draconian' while health experts say they're helping lower death projections
"Attorney General William Barr on Wednesday called current restrictions to mitigate the spread of coronavirus 'draconian,' as the White House coronavirus task force's health experts have lauded such measures as helpful to lowering the rate of spread..." (Shortell/Stracqualursi, 4/9).
Roll Call: Calls grow for Trump to relax humanitarian sanctions on Iran
"The Trump administration is coming under increasing pressure to modify its sanctions on Iran to allow medicine and medical equipment to be imported into the Islamic Republic, which is struggling to manage a coronavirus health disaster..." (Oswald, 4/9).
Link to individual story

War-Torn Yemen Records 1st Coronavirus Case; COVID-19 Becomes Leading Cause Of Death Per Day In U.S.; U.K. PM Leaves ICU, Still Under Treatment

AFRICA

The Guardian: Foreigners targeted in Central African Republic as coronavirus fears grow (Losh, 4/10).
New Humanitarian: Zimbabwe's triple threat: Coronavirus, food shortages, and an economy in meltdown (Mukeredzi, 4/9).

Reuters: In Uganda, mothers in labor die amidst coronavirus lockdown (Biryabarema/Akwiri, 4/9).
Reuters: Some African countries heading for coronavirus peak in weeks: WHO (Carsten et al., 4/9).

ASIA

Foreign Policy: Taiwan Is Exporting Its Coronavirus Successes to the World (Aspinwall, 4/9).
The Guardian: 'Delivers the stats like no other': New Zealand's Covid-19 crush on health chief (Roy, 4/9).
NBC News: Taiwan's coronavirus success bolsters case for joining WHO, experts say (Sui, 4/9).

EUROPE

The Hill: Italy reports 4,204 new cases of coronavirus (Axelrod, 4/9).
New York Times: Iceland's 'Test Everyone' Goal Has Skeptics, but It May Be Working (Ortiz, 4/9).
NPR: U.K. Prime Minister Boris Johnson Leaves ICU Amid Treatment For COVID-19 (Dwyer, 4/9).
Reuters: Spain's coronavirus death toll curve flattening at last (Keeley/Landauro, 4/10).
The Telegraph: No end to lockdown in sight as U.K. coronavirus deaths rise by 938 in a day (Fawehinmi et al., 4/9).

LATIN AMERICA

New York Times: Indigenous Groups Isolated by Coronavirus Face Another Threat: Hunger (Turkewitz et al., 4/9).
Reuters: Brazil minister resists calls for wider use of hydroxychloroquine (Paraguassu et al., 4/9).
Reuters: Chile plans 'release certificates' for recovered coronavirus patients (Laing, 4/9).

MIDDLE EAST

Al Jazeera: Coronavirus widespread among Saudi royal family: Report (4/9).
Reuters: War-ravaged Yemen confirms first coronavirus case, braces for more (Ghobari et al., 4/10).

NORTH AMERICA

AP: PM: Canada's first wave of cases won't end until the summer (Gillies, 4/9).
AP: Mexico City seeks to help home-bound, homeless in pandemic (4/10).
Newsweek: Coronavirus Becomes Number One Cause of Death Per Day in U.S., Surpassing Heart Disease and Cancer (Impelli, 4/9).
Link to individual story

Media Outlets Report On Efforts To Develop Novel Coronavirus Treatments, Vaccines

The Atlantic: The Best Hopes for a Coronavirus Drug (Zhang, 4/8).
Financial Times: Covid-19 drugs could be made for $1 per day, say academics (Mancini, 4/9).
The Lancet: Regulators split on antimalarials for COVID-19 (Jaffe, 4/11).
Nature: If a coronavirus vaccine arrives, can the world make enough? (Khamsi, 4/9).
New York Times: At the Center of a Storm: the Search for a Proven Coronavirus Treatment (Kolata, 4/9).
Quartz: A 'bridge to a vaccine': The race to roll out antibody-based Covid-19 drugs (McDonnell, 4/8).
Reuters: Key China coronavirus hospital says HIV drug beneficial to patients (Goh et al., 4/9).
Science: Can prophylactic drugs keep fragile health systems running? (Kupferschmidt, 4/10).
Science: Is France's president fueling the hype over an unproven coronavirus treatment? (Sciama, 4/9).
VOA: China Recruits Volunteers for Phase 2 Coronavirus Vaccine Trial (Xie, 4/9).
Wall Street Journal: The Bats Behind the Pandemic (Ridley, 4/9).
Link to individual story

Scientists Working To Understand Immunity To Novel Coronavirus, Whether Patients' Infections Can 'Reactivate'

Scientific American: What Immunity to COVID-19 Really Means

"...At this early stage of understanding the new coronavirus, it is unclear where COVID-19 falls on the immunity spectrum. Although most people with SARS-CoV-2 seem to produce antibodies, 'we simply don't know yet what it takes to be effectively protected from this infection,' says Dawn Bowdish, a professor of pathology and molecular medicine and Canada Research Chair in Aging and Immunity at McMaster University in Ontario. Researchers are scrambling to answer two questions: How long do SARS-CoV-2 antibodies stick around? And do they protect against reinfection?..." (McKenna, 4/10).

Bloomberg: Coronavirus May 'Reactivate' in Cured Patients, Korean CDC Says (Park, 4/9).

Financial Times: Mystery surrounds 'cured' patients who tested positive (White/Jung-a, 4/10).

Link to individual story

Locust Swarms Continue To Impact East Africa, Threatening Food Security; Response Complicated By COVID-19

Al Jazeera: Uganda faces food shortage as coronavirus disrupts locust fight

"Farmers in Uganda are bracing for a fresh onslaught of desert locusts after two swarms entered the country from neighboring Kenya last week, threatening to destroy crops and intensify hunger amid the struggle to contain the coronavirus pandemic. Countries across East Africa are battling the worst locust outbreak in decades, with the U.N.'s Food and Agriculture Organization (FAO) warning on Wednesday that the situation remained 'extremely alarming' as hopper bands and an increasing number of new swarms form in parts of the region. ... The fight against the ravaging pests has been complicated by flight bans imposed to slow the spread of COVID-19, the highly infectious respiratory disease caused by the new coronavirus. The restrictions have significantly delayed deliveries of pesticides in countries across the region..." (Okiror, 4/9).

Additional coverage of locust swarms in Africa and implications for food security is available from AP, Bloomberg, and U.N. News.

Link to individual story

Bill Gates Comments On U.S. COVID-19 Response, Other Aspects Of Pandemic

NPR: Bill Gates, Who Has Warned About Pandemics For Years, On The U.S. Response So Far

"Five years ago, Microsoft co-founder Bill Gates gave a TED Talk about global pandemics, warning that the world was not ready to take one on. Now, in the midst of such an outbreak, he has been thinking about how to make up for lost time. Gates has invested in coronavirus research as well as global health more broadly. ... In a conversation with NPR's Ari Shapiro, Gates gives the U.S. response high marks for social distancing efforts but low marks for testing..." (Glen, 4/9).

Additional coverage of comments made by Bill Gates in relation to COVID-19 is available from CNBC, Financial Times, and The Hill.

Link to individual story

Devex Explores Potential Candidates For USAID Administrator Role In Wake Of Green's Resignation

Devex: Who will succeed Mark Green at USAID?

"In the wake of Mark Green's resignation as administrator of the U.S. Agency for International Development, speculation about a potential successor has begun to build among Washington insiders. Multiple sources with knowledge of the process believe that Jim Richardson, currently the director of the State Department's Office of U.S. Foreign Assistance Resources, could have the inside track on the nomination at this point. ... After Green steps down on Friday, John Barsa, currently the assistant administrator for Latin America and the Caribbean, will take over as acting administrator. Barsa was a surprise pick for that job, with many assuming that Deputy

Administrator Bonnie Glick would take the helm until the White House nominated and confirmed a permanent administrator. Richardson's is not the only name to surface as a potential replacement for Green..." (Igoe, 4/10).
Link to individual story

More News In Global Health

BBC: Yemen: World Food Programme to cut aid by half in Houthi-controlled areas (4/10).
Devex: NGOs lay off, furlough staff as financial crisis bites (Worley, 4/9).
Devex: Watch: Former OFDA chief gives Trump administration a 'D' on its COVID-19 response (Kumar, 4/10).
The Guardian: Tanzania to ease education ban on pregnant girls — but not in classrooms (McCool, 4/10).
Quartz: How the military secured a coronavirus drug that has yet to win FDA approval (MacLellan, 4/9).
STAT: It's difficult to grasp the projected deaths from Covid-19. Here's how they compare to other causes of death (Begley/Empinado, 4/9).
STAT: Social distancing is controlling Covid-19; now scientists need to figure out which measures are most effective (Begley, 4/9).
Link to individual story

Editorials and Opinions

Editorial, Opinion Pieces Discuss Various Aspects Of COVID-19 Pandemic, Response

Bloomberg: We're Too Quick to Call a Coronavirus Peak
Mark Gongloff, editor with Bloomberg Opinion (4/8).
Bloomberg: China's Participation in the WHO Comes at a Price
Eli Lake, Bloomberg Opinion columnist (4/9).
CNN: Virology in the time of coronavirus: What a difference a month makes — and the most important questions we still need to answer
Tom Frieden, president and CEO of Resolve to Save Lives and senior fellow for global health at the Council on Foreign Relations, and Cyrus Shahpar, director of preventing epidemics at Resolve to Save Lives (4/9).
The Conversation: How Africa has developed its scientific research capabilities
Moses John Bockarie, honorary chief specialist scientist at the South African Medical Research Council (4/8).
The Conversation: Coronavirus an 'existential threat' to Africa and her crowded slums
David Sanderson, professor and inaugural Judith Neilson chair in architecture at UNSW (4/9).
Devex: Opinion: 3 things frontline health workers need to battle COVID-19
Polly Dunford, president and CEO of IntraHealth International (4/10).
The Guardian: Coronavirus is the greatest global science policy failure in a generation
Richard Horton, doctor and editor-in-chief of The Lancet (4/9).
The Hill: Financial recovery and prevention of disasters must be inclusive
Vinod Thomas, visiting professor at the Asian Institute of Management (4/9).
The Lancet: Palliative care and the COVID-19 pandemic
Editorial Board (4/11).
The Lancet: The gendered dimensions of COVID-19
Editorial Board (4/11).
The Lancet: Centering sexual and reproductive health and justice in the global COVID-19 response
Kelli Stidham Hall, founding director and principal investigator at the Center for Reproductive Health Research in the SouthEast (RISE) at Emory, and colleagues (4/11).

Project Syndicate: The Invisible Killers
Edoardo Campanella, fellow at the Center for the Governance of Change at IE University in Madrid (4/10).
Science Magazine: G20 leaders must answer to COVID-19
Caroline Atkinson, senior adviser at the Rock Creek Group (4/10).
The Telegraph: To protect our own populations and economies from Covid-19, the world must work together
Anne-Marie Trevelyan, secretary of state for international development and MP for Berwick-upon-Tweed, and colleagues (4/9).
TIME: What We Must Do to Prevent a Global COVID-19 Depression
Klaus Schwab, founder and executive chair of the World Economic Forum, and Guido Vanham, professor of virology at the University of Antwerp (4/9).
Washington Post: The pandemic strengthens the case for universal basic income
Ishaan Tharoor, writer at the Washington Post (4/10).
Washington Post: The pandemic means the Trump administration must stop mistreating USAID
Josh Rogin, columnist for the Global Opinions section of the Washington Post and political analyst for CNN (4/9).
Washington Times: To stop COVID-19 pandemic, America needs a sanitizing line of defense
Gary D. Alexander, Pennsylvania's Human Services Secretary from 2011-2013 and Rhode Island's Secretary of Health and Human Services from 2006-2011 (4/9).
Washington Times: Words matter in fight against coronavirus
Deborah Simmons, opinion writer and senior correspondent at the Washington Times (4/9).
Wired: We Need a Covid-19 Vaccine — Let's Get It Right the First Time
Maryn McKenna, senior fellow at the Schuster Institute for Investigative Journalism at Brandeis University (4/8).
Link to individual story

From the Global Health Policy Community

Multilateral Groups, Private Sector, NGOs, Discuss Various Aspects Of COVID-19 Pandemic, Response

Brookings: Africa needs debt relief to fight COVID-19
Ngozi Okonjo-Iweala, nonresident distinguished fellow for global economy and development at the Africa Growth Initiative at Brookings, and colleagues (4/9).
Clinton Health Access Initiative: How can we support health workers? Invest in them.
Katie Ruffing, Community Health Systems associate; Attila Yaman, Health Workforce Strategy and Investment senior associate; and Tej Nuthulaganti, senior director of the Global Health Workforce Program, all with the Clinton Health Access Initiative (4/6).
Friends of the Global Fight Against AIDS, Tuberculosis and Malaria: Global Fund creates mechanism to respond to COVID-19 and protect gains in global AIDS, Tuberculosis and Malaria responses (4/9).
Global Fund to Fight AIDS, Tuberculosis and Malaria: Global Fund Partners Unite to Fight (4/9).
Merck: Merck Announces $3M Commitment to Address Critical Maternal Health Needs During COVID-19 Pandemic (4/9).
ONE: G20: Cancel debt to support vulnerable countries during COVID 19 (4/9).
Treatment Action Group: Treatment Action Group Information Note on BCG and SARS-CoV-2/COVID-19 (4/9).
UNAIDS: UNAIDS condemns misuse and abuse of emergency powers to target marginalized and vulnerable populations (4/9).
UNICEF: Don't let children be the hidden victims of COVID-19 pandemic
Henrietta Fore, executive director of UNICEF (4/9).

United Nations: World Faces 'Gravest Test' since Founding of United Nations, Secretary-General Tells Security Council, Calling for Unity to Address COVID-19 Pandemic (4/9).
WHO Africa: Drawing on Ebola readiness to tackle COVID-19 (4/9).
World Bank: COVID-19 (Coronavirus) Drives Sub-Saharan Africa Toward First Recession in 25 Years (4/8).
Link to individual story

From the U.S. Government

NIH Begins Clinical Trial To Evaluate Malaria Drug As Potential Therapy For COVID-19

NIH: NIH clinical trial of hydroxychloroquine, a potential therapy for COVID-19, begins
"A clinical trial to evaluate the safety and effectiveness of hydroxychloroquine for the treatment of adults hospitalized with coronavirus disease 2019 (COVID-19) has begun, with the first participants now enrolled in Tennessee. The Outcomes Related to COVID-19 treated with hydroxychloroquine among In-patients with symptomatic Disease study, or ORCHID Study, is being conducted by the Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network of the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health. ... Hydroxychloroquine is used to treat malaria and rheumatoid conditions such as arthritis. In various studies, the drug has demonstrated antiviral activity, an ability to modify the activity of the immune system, and has an established safety profile at appropriate doses, leading to the hypothesis that it may also be useful in the treatment of COVID-19. The drug is not without risks as even short term use can cause cardiac arrythmias, seizures, dermatological reactions, and hypoglycemia..." (4/9).
Link to individual story

From the Kaiser Family Foundation

KFF Analyzes CARES Act; Other Resources Examine Global, Domestic Issues Related To COVID-19 Pandemic

KFF: The Coronavirus Aid, Relief, and Economic Security Act: Summary of Key Health Provisions On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security (CARES) Act was signed into law, marking the third and largest major U.S. legislative initiative to address COVID-19 to date. (The first was the Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020, signed into law on March 6, followed by the Families First Coronavirus Response Act, signed into law on March 18.) The CARES Act contains a number of health-related provisions focused on the outbreak in the United States, including paid sick leave, insurance coverage of coronavirus testing, nutrition assistance, and other programs and efforts. It also includes support for the global response. This issue brief includes summaries of key health-related provisions of the act (Moss et al., 4/9).
KFF: COVID-19 Coronavirus Tracker — Updated as of April 10, 2020 (4/10).
Additional KFF COVID-19 resources, including those focused on the response and impact within the U.S., are available here. KFF's new blog series "Coronavirus Policy Watch" is available here.
Link to individual story

Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Sent Date:	2020/04/10 11:17:30
Delivered Date:	2020/04/10 11:18:02
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Subject: BioCentury trackers: COVID-19 clinical vaccines and therapies / Clinical, Preclinica https://bit.ly/34hdj5L https://bit.ly/39OQBTK

Date: 2020/04/06 11:07:41

Priority: Normal

Type: Note

COVID-19 clinical vaccines and therapies

BioCentury is tracking vaccines and therapeutics being studied for COVID-19. The list contains compounds that are approved in any territory, or that have entered clinical trials for COVID-19 or any other indication. Companies and investigators with compounds to add should email the details to covid19portal@biocentury. Scroll to the bottom to download the list.

Given the urgent need for information about the COVID-19 crisis, BioCentury is providing information and analysis for free, at https://protect2.fireeye.com/url?k=22c281f0-7e9788e3-22c2b0cf-0cc47adb5650-d2e045b4b4ea9966&u=https://www.biocentury.com/coronavirus.

Chart

Compound	Sponsor	Modality	Type	Phase (COVID-19)	Phase (other indications)	Original indication
Chloroquine phosphate	Multiple	Small molecule	Therapy	EUA	Approved globally	Malaria
Azithromycin	Multiple	Small molecule	Therapy	Phase IV	Approved globally	Bacterial infections
Dexamethasone	Dr. Negrin University Hospital	Small molecule	Therapy	Phase IV	Approved globally	Inflammatory conditions
Kaletra lopinavir / ritonavir (Aluvia)	AbbVie	Small molecule	Therapy	Phase IV	Approved globally	HIV

Original indication						
Methylprednisolone	Beijing Chao Yang Hospital	Small molecule	Therapy	Phase IV	Approved globally	Inflammatory conditions
Actemra tocilizumab (RoActemra)	Roche	Antibody	Therapy	Phase III	Approved globally	Rheumatoid arthritis
BCG Vaccine	Multiple	Vaccine	Vaccine	Phase III	Approved globally	Tuberculosis
Colchicine	Multiple	Small molecule	Therapy	Phase III	Approved globally	Gout
Hydroxychloroquine	Multiple	Small molecule	Therapy	Phase III	Approved globally	Malaria
Naproxen	Assistance Publique - Hôpitaux de Paris	Small molecule	Therapy	Phase III	Approved globally	Pain
Olumiant baricitinib	Multiple	Small molecule	Therapy	Phase III	Approved globally	Rheumatoid arthritis
Oseltamivir	Multiple	Small molecule	Therapy	Phase III	Approved globally	Influenza
Prezcobix darunavir / cobicistat (Rezolsta)	Johnson &Johnson	Small molecule	Therapy	Phase III	Approved globally	HIV
Sildenafil	Tongji Hospital	Small molecule	Therapy	Phase III	Approved globally	Erectile dysfunction
Avastin bevacizumab	Multiple	Antibody	Therapy	Phase II/III	Approved globally	Cancer
Alvesco ciclesonide	Korea University Guro Hospital	Small molecule	Therapy	Phase II	Approved globally	Asthma
Cozaar losartan	Multiple	Small molecule	Therapy	Phase II	Approved globally	Hypertension
Gilenya fingolimod	Novartis	Small molecule	Therapy	Phase II	Approved globally	Multiple sclerosis
Thalidomide	First Affiliated Hospital of Wenzhou Medical University	Small molecule	Therapy	Phase II	Approved globally	Multiple myeloma, others
Jakavi ruxolitinib	Incyte; Novartis	Small molecule	Therapy	Phase I/II; Phase III planned	Approved globally	Myelofibrosis; Polycythemia vera; Graft-versus-host disease (GvHD)
Soliris eculizumab	Alexion	Antibody	Therapy	Expanded access	Approved globally	Paroxysmal nocturnal

Original indication

						hemoglobinuria (PNH)
Alpha-1 antitrypsin	Grifols	Protein	Therapy	Preclin	Approved globally	Alpha-1 antitrypsin deficiency
Dactinomycin	Cleveland Clinic	Peptide	Therapy	Preclin	Approved globally	Cancer
Intravenous immunoglobulin	Grifols	Protein	Therapy	Preclin	Approved globally	Immunodeficiencies
Mercaptopurine	Cleveland Clinic	Small molecule	Therapy	Preclin	Approved globally	Cancer, autoimmune disorders
Sirolimus	Cleveland Clinic	Macrocycle	Therapy	Preclin	Approved globally	Prevent transplant rejection, other
Toremifene	Cleveland Clinic	Small molecule	Therapy	Preclin	Approved globally	Cancer
Sylvant siltuximab	EUSA Pharma	Antibody	Therapy	Expanded access	Approved in U.S., EU, others	Idiopathic multicentric Castleman disease
Kevzara sarilumab	Regeneron / Sanofi	Antibody	Therapy	Phase II/III	Approved in U.S., EU, Japan	Rheumatoid arthritis
Kineret anakinra	Swedish Orphan Biovitrum	Protein	Therapy	Phase II/III	Approved in U.S., EU	Rheumatoid arthritis; neonatal-onset multisystem inflammatory disease
Giapreza angiotensin II	La Jolla Pharmaceutical	Peptide	Therapy	Expanded access	Approved in U.S., EU	Hypotension
Genosyl DS inhaled nitric oxide system	Vero Biotech	Drug-device combo	Therapy	Expanded access	Approved in U.S.	Hypoxic respiratory failure in neonates
Gamifant emapalumab	Swedish Orphan Biovitrum	Antibody	Therapy	Phase II/III	Approved in U.S.	Hemophagocytic lymphohistiocytosis
Leukine sargramostim	Partner Therapeutics	Protein	Therapy	Phase IV	Approved in U.S.	Adjunct to stem cell transplant in hematological cancers
Aviptadil	NeuroRx / Relief	Peptide	Therapy	Phase II	Approved in EU	Erectile dysfunction
Avigan favipiravir	Fujifilm	Small molecule	Therapy	Phase III	Approved in Japan	Influenza
Ifenprodil (NP-120)	Algernon	Small molecule	Therapy	Phase II	Approved in Japan,	Neurological disorders

Original indication

					South Korea	
Thymosin alpha 1	Shanghai Jiao Tong University School of Medicine	Peptide	Therapy	Phase III	Approved in China	HBV, HCV
Riavax tertomotide HCl (GV1001)	Gemvax &Kael Bio	Peptide	Therapy	Preclin	Approved in South Korea	Cancer
Carrimycin	Shenyang Tonglian	Macrocycle	Therapy	Phase IV	Approved in China	Bacterial infections
Ganovo danoprevir + ritonavir	Ascletis Pharma	Small molecule	Therapy	Phase IV	Approved in China	HCV
Arbidol umifenovir	Ruijin Hospital	Small molecule	Therapy	Phase IV	Approved in China and Russia	Influenza
SACT-COV19 (3 undisclosed repurposed drugs)	Aptorum / Covar	Small molecule	Therapy	Preclin	Approved in undisclosed territories	Undisclosed
FlueDase (DAS181)	Ansun Biopharma	Fusion protein	Therapy	Phase III	Phase III	Viral respiratory infections
Tradipitant	Vanda	Small molecule	Therapy	Phase III	Phase III	Inflammatory conditions
Mesenchymal stem cells (MSCs)	Multiple	Cell therapy	Therapy	Phase I/II	Phase III	Multiple
Human amniotic fluid	University of Utah	Biologic	Therapy	Phase I	Phase III	Multiple
PLX cells	Pluristem	Cell therapy	Therapy	Expanded access	Phase III	Critical limb ischemia
Ampion	Ampio Pharmaceutical	Peptide	Therapy	Preclin; Expanded access planned	Phase III	Knee osteoarthritis
AT-001	Applied Therapeutics	Small molecule	Therapy	Emergency IND	Phase III	Diabetic cardiomyopathy
Apabetalone	Resverlogix	Small molecule	Therapy	Preclin	Phase III	Cardiovascular disease
Reproxalap	Aldeyra	Small molecule	Therapy	Preclin	Phase III	Ocular inflammation
Remdesivir	Gilead Sciences	Small molecule	Therapy	Phase III	Phase II/III	Ebola

Original indication						
Leronlimab (PRO 140)	CytoDyn	Antibody	Therapy	Expanded access; Phase II planned	Phase II/III	HIV; breast cancer
CYNK-001	Celularity / Sorrento	Cell therapy	Therapy	Phase I/II	Phase II	Hematological cancers
Natural Killer (NK) Cells	Multiple	Cell therapy	Therapy	Phase I/II	Phase II	Cancer
SNG001 (inhaled interferon-beta-1a)	Synairgen	Protein	Therapy	Phase II	Phase II	COPD, Asthma
ASC09 and ASC09/ritonavir	Ascletis Pharma	Small molecule	Therapy	Phase III	Phase II	HIV
CD24Fc	OncoImmune, Inc.	Protein	Therapy	Phase III	Phase II	Graft-versus-host disease (GVHD)
APN01 (rhACE2)	Apeiron	Protein	Therapy	In clinic	Phase II	Acute respiratory distress syndrome; others
IFX-1	InflaRx	Antibody	Therapy	In clinic	Phase II	Inflammatory conditions
C21	Vicore Pharma	Small molecule	Therapy	Phase II planned	Phase II	Idiopathic pulmonary fibrosis; Pulmonary fibrosis in systemic sclerosis
OT-101	Mateon	Antisense	Therapy	Preclin; IND planned	Phase II	Cancer
PP-001	Panoptes Pharma	Small molecule	Therapy	Clinical trial planned	Phase II	Uveitis
Aerosurf	Windtree	Peptide	Therapy	Preclin	Phase II	Respiratory distress syndrome in premature infants
Low-dose oral interferon-α	Xiamen Weiyang	Protein	Therapy	Preclin	Phase II	Multiple infectious and pulmonary diseases
Panaphix	KomiPharm	Small molecule	Therapy	Preclin	Phase II	Pain
Vicromax	BioSig	Small molecule	Therapy	Preclin	Phase II	HCV
MSCs-derived exosomes	Cellular Biomedicine Group	Cell therapy	Therapy	Phase I	Phase I/II	Cerebrovascular disorders

Original indication						
EDP1815	Evelo	Bacteria	Therapy	Preclin	Phase Ib	Psoriasis, atopic dermatitis
Dental pulp mesenchymal stem cells	CAR-T (Shanghai) Biotechnology	Cell therapy	Therapy	Phase I	Phase I	Knee osteoarthritis
BDB-001	Beijing Defengrei	Antibody	Therapy	Phase II	Phase I	Inflammatory conditions
PUL-042 Inhalation Solution	Pulmotect, Inc.	Peptide + DNA oligonucleotide	Therapy	Phase II	Phase I	Prevents pulmonary infection
hzVSF-v13	ImmuneMed	Antibody	Therapy	Expanded access; Phase II planned	Phase I	HCV; influenza
ADX-629	Aldeyra	Small molecule	Therapy	Preclin	Phase I	Autoimmune disorders
mRNA-1273	Moderna / National Institutes of Health (NIH)	RNA vaccine	Vaccine	Phase I	N/A	COVID-19
NestCell	Cellavita	Cell therapy	Therapy	Phase I	N/A	COVID-19
Pathogen-specific aAPC	Shenzhen Genoimmune Medical Institute	Cellular vaccine	Vaccine	Phase I	N/A	COVID-19
Recombinant novel coronavirus vaccine (Adenovirus Type 5 Vector)	CanSino Biologics	Viral vector	Vaccine	Phase I	N/A	COVID-19
LV-SMENP-DC + antigen-specific CTLs	Shenzhen Genoimmune Medical Institute	Cellular vaccine	Vaccine	Phase I/II	N/A	COVID-19
Convalescent Plasma	Multiple	Biologic	Therapy	Phase II	N/A	COVID-19
Undisclosed anti-PD-1 antibody	Southeast University, China	Antibody	Therapy	Phase II	Undisclosed	Cancer
Kainos small molecule antivirals	Kainos Medicine	Small molecule	Therapy	Preclin	Undisclosed	Undisclosed viral infections
Data from BioCentury Inc.						

Download data

The most advanced phase is shown; many products are being tested in multiple trials of different phases. For generics being studied in a single trial, the sponsor of that trial is listed. For generics in several trials sponsored

by multiple universities, hospitals or government agencies are conducting trials, the sponsor is listed as "multiple." Branded products with manufacturer-sponsored trials or manufacturer involvement in academic-sponsored trials are listed under the manufacturer name.

Updated April 3, 2020

COVID-19 vaccines and therapies: preclinical

BioCentury is tracking vaccines and therapeutics for COVID-19. The list below contains compounds that have not advanced beyond preclinical development for any indication. Companies and investigators with compounds to add should email the details to covid19portal@biocentury. Scroll to the bottom to download the list.

Given the urgent need for information about the COVID-19 crisis, BioCentury is providing information and analysis for free, at https://protect2.fireeye.com/url?k=a17b5c65-fd2e5576-a17b6d5a-0cc47adb5650-7b82f36f4eafa582&u=https://www.biocentury.com/coronavirus.

Updated on April 3, 2020

Chart

Compound	Sponsor	Modality	Type	Phase (COVID-19)	Farthest Phase (other indications)	Original indication
Anti-SARS-CoV-2 hyperimmune globulin	Grifols	Antibody	Therapy	Preclin	Preclin	COVID-19
CV-15 (iCP-NI)	Cellivery Therapeutics	Peptide	Therapy	Preclin	Preclin	Sepsis
EIDD-2801	Emory University; Ridgeback Biotherapeutics	Small molecule	Therapy	Preclin	Preclin	Influenza; Chikungunya; SARS; MERS; Venezuelan Equine

Original indication						
						Encephalitis Virus
ISR50	ISR	Small molecule	Therapy	Preclin	Preclin	HBV
NCP112	NovaCell Technology	Peptide	Therapy	Preclin	Preclin	Multiple autoimmune/ inflammatory
Neumifil	Pneumagen	Protein	Therapy	Preclin	Preclin	Influenza; RSV
PRTX007	Primmune Therapeutics	Small molecule	Therapy	Preclin	Preclin	Cancer
Unnamed	Baylor College of Medicine; University of Texas Medical Branch; New York Blood Center; Fudan University	Protein-based	Vaccine	Preclin	Preclin	SARS
WP1122	Moleculin Biotech	Small molecule	Therapy	Preclin	Preclin	Brain cancer
Kainos small molecule antivirals	Kainos Medicine	Small molecule	Therapy	Preclin	Undisclosed	Undisclosed
Ad26 SARS-CoV-2	Johnson &Johnson; Beth Israel Deaconess Medical Center; BARDA	Viral vector	Vaccine	Preclin	N/A	COVID-19
AdCOVID	Altimmune; University of Alabama	Viral vector	Vaccine	Preclin	N/A	COVID-19
BNT162	BioNTech; Pfizer; Fosun Pharma	RNA vaccine	Vaccine	Preclin	N/A	COVID-19
COVID-19 S-Trimer Vaccine	Sichuan Clover Biopharmaceuticals; Dynavax	Protein-based	Vaccine	Preclin	N/A	COVID-19
COVID-HIG	Emergent BioSolutions; BARDA	Antibody	Therapy	Preclin	N/A	COVID-19
COVID-EIG	Emergent BioSolutions	Antibody	Therapy	Preclin	N/A	COVID-19
DPX-COVID-19	IMV	Protein-based	Vaccine	Preclin	N/A	COVID-19
IBIO-200	iBio; Texas A&M University	Protein-based	Vaccine	Preclin	N/A	COVID-19
INO-4800	Inovio Pharmaceuticals; Beijing Advaccine Biotechnology; Ology Bioservices	DNA vaccine	Vaccine	Preclin	N/A	COVID-19
ISR50	ISR	Small molecule	Therapy	Preclin	Preclin	HBV

Original indication						
NI007	Neurimmune; Ethris	Antibody; RNA	Therapy	Preclin	N/A	COVID-19
rCIG	GigaGen	Antibody	Therapy	Preclin	N/A	COVID-19
SAB-185	SAB Biotherapeutics; BARDA	Antibody	Therapy	Preclin	N/A	COVID-19
STI-4398	Sorrento Therapeutics	Fusion protein	Therapy	Preclin	N/A	COVID-19
STI-6991	Sorrento Therapeutics	Cellular vaccine	Vaccine	Preclin	N/A	COVID-19
TAK-888	Takeda Pharmaceutical	Antibody	Therapy	Preclin	N/A	COVID-19
TNX-1800	Tonix Pharmaceuticals; Southern Research Institute	Engineered live attenuated virus	Vaccine	Preclin	N/A	COVID-19
Unnamed	AbCellera Biologics; Eli Lilly	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Amgen; Adaptive Biotechnologies	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	AstraZeneca	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Beroni Group; Tianjin University	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Brii Bio; Tsinghua University; Third People's Hospital of Shenzhen	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Celltrion	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Distributed Bio	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Eutilex	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Flanders Institute for Biotechnology (VIB); Ghent University	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Harbour BioMed; Mount Sinai	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	ImmunoPrecise Antibodies; EVQLV	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Israel Institute for Biological Research (IIBR); Dyadic International	Antibody	Therapy	Preclin	N/A	COVID-19

Original indication						
Unnamed	Israel Institute for Biological Research (IIBR); Dyadic International	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Junshi Biosciences; Chinese Academy of Sciences	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Kamada	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Medicago; Laval University	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	National Institutes of Health	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Regeneron Pharmaceuticals	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Twist Bioscience; Vanderbilt University Medical Center	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Vanderbilt University Medical Center; Ology Bioservices	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Vir Biotechnology; Biogen	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Vir Biotechnology; WuXi Biologics	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Vir Biotechnology; Xencor	Antibody	Therapy	Preclin	N/A	COVID-19
Unnamed	Vir Biotechnology; Generation Bio	Antibody; Gene therapy	Therapy	Preclin	N/A	COVID-19
Unnamed	AlloVir; Baylor College of Medicine	Cell therapy	Therapy	Preclin	N/A	COVID-19
Unnamed	Cidara Therapeutics	Fusion protein	Therapy	Preclin	N/A	COVID-19
Unnamed	NanoViricides	Nanoparticle	Therapy	Preclin	N/A	COVID-19
Unnamed	CEL-SCI Corporation; University of Georgia	Peptide	Therapy	Preclin	N/A	COVID-19
Unnamed	Sirnaomics	siRNA	Therapy	Preclin	N/A	COVID-19
Unnamed	Vir Biotechnology; Alnylam Pharmaceuticals	siRNA	Therapy	Preclin	N/A	COVID-19
Unnamed	Enanta Pharmaceuticals	Small molecule	Therapy	Preclin	N/A	COVID-19
Unnamed	Insilico Medicine	Small molecule	Therapy	Preclin	N/A	COVID-19

Original indication						
Unnamed	RA Capital	Small molecule	Therapy	Preclin	N/A	COVID-19
Unnamed	Heat Biologics; University of Miami	Cellular vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	Anges; Osaka University; Takara Bio	DNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	Applied DNA Sciences; Takis Biotech	DNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	Cobra Biologics; Karolinska Institutet	DNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	Entos Pharmaceuticals	DNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	Zydus Cadila	DNA vaccine; Live attenuated vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	Institut Pasteur; University of Pittsburgh; Themis Medicare; CEPI	Engineered live attenuated virus	Vaccine	Preclin	N/A	COVID-19
Unnamed	University of Hong Kong; CEPI	Engineered live attenuated virus	Vaccine	Preclin	N/A	COVID-19
Unnamed	Shenzhen Kangtai Biological Products	Inactivated vaccine; Protein-based; Nucleic acid-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Codagenix; Serum Institute of India	Live attenuated vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	AJ Vaccines	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Akers Biosciences; Premas Biotech	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	British American Tobacco	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	ExpreS2ion Biotech Holding; AdaptVac; University of Tübingen; Leiden University Medical Center; University of	Protein-based	Vaccine	Preclin	N/A	COVID-19

Original indication						
	Copenhagen; Wageningen University					
Unnamed	G+FLAS Life Sciences	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Generex Biotechnology; EpiVax	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	iBio; Beijing CC-Pharming	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Israel Institute for Biological Research (IIBR); Dyadic International	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Medicago; Laval University	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Novavax; Emergent BioSolutions	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Sanofi; BARDA	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Scripps Research	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Sichuan University State Key Laboratory of Biotherapy; Zhejiang Teruisi Pharmaceutical; Chengdu National GLP Center; Sichuan Provincial People's Hospital; Chengdu Institute of Biological Products (Sinopharm)	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	University of Queensland; Dynavax; CEPI	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	University of Saskatchewan	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Vaxil Bio	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Voltron Therapeutics; Hoth Therapeutics	Protein-based	Vaccine	Preclin	N/A	COVID-19
Unnamed	Arcturus Therapeutics; Duke-NUS Medical School	RNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	CureVac	RNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	eTheRNA immunotherapies; EpiVax	RNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	Imperial College London	RNA vaccine	Vaccine	Preclin	N/A	COVID-19

Original indication						
Unnamed	RNACure Biopharma; Fudan University; Shanghai JiaoTong University	RNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	Translate Bio; Sanofi	RNA vaccine	Vaccine	Preclin	N/A	COVID-19
Unnamed	GeoVax Labs; BravoVax	Viral vector	Vaccine	Preclin	N/A	COVID-19
Unnamed	Greffex	Viral vector	Vaccine	Preclin	N/A	COVID-19
Unnamed	MIGAL Galilee Research Institute	Viral vector	Vaccine	Preclin	N/A	COVID-19
Unnamed	ReiThera	Viral vector	Vaccine	Preclin	N/A	COVID-19
Unnamed	Sumagen	Viral vector	Vaccine	Preclin	N/A	COVID-19
Unnamed	Vaxart; Emergent BioSolutions	Viral vector	Vaccine	Preclin	N/A	COVID-19

Data from BioCentury Inc.

Download data

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/06 11:06:47
Delivered Date:	2020/04/06 11:07:41
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Subject: FDA --- Coronavirus (COVID-19) Update: FDA Continues to Accelerate Development of Novel Therapies for COVID-19

Date: 2020/03/31 17:10:14

Priority: Normal

Type: Note

FDA News Release

Coronavirus (COVID-19) Update: FDA Continues to Accelerate Development of Novel Therapies for COVID-19

For Immediate Release:

March 31, 2020

As part of the Trump Administration's all-hands-on-deck approach across public, academic and private sectors to combat the COVID-19 pandemic, the U.S. Food and Drug Administration stood up a new program to expedite the development of potentially safe and effective life-saving treatments. The program, known as the Coronavirus Treatment Acceleration Program (CTAP), is using every tool at the agency's disposal to bring new therapies to sick patients as quickly as possible, while at the same time supporting research to further evaluate whether these medical countermeasures are safe and effective for treating patients infected with this novel virus.

"The FDA is announcing a new, comprehensive public-private approach to bring coronavirus treatments to market as fast as possible," said HHS Secretary Alex Azar. "As part of this new program, the FDA is cutting red tape, redeploying staff and working day and night to review requests from companies, scientists and doctors who are working toward therapies. We are grateful to the men and women of the FDA who have been working in concert with industry and other parts of HHS to support potential coronavirus treatments for weeks now. Each day, President Trump's all-of-America approach is making progress and providing new hope in our fight against the coronavirus."

There are a large number of companies and researchers developing and evaluating COVID-19 related therapies. Given the urgent nature of the pandemic, under the FDA's accelerator program, staff from the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research are providing regulatory advice, guidance and technical assistance as quickly as possible. As part of this work, the FDA is triaging requests from developers and scientists seeking to develop new drug and biologic therapies, getting the relevant FDA staff in touch with them and providing rapid, interactive input to get studies underway quickly. For example, the FDA has reviewed study protocols within 24 hours in many cases and has reviewed single-patient expanded access requests generally within three hours. The FDA is also collaborating with federal partners, developers and researchers to create protocols that can be used across institutions and programs to streamline efforts.

"Quickly after the emergence of this virus, we began working directly with federal health partners, academia and industry to advance medical countermeasures against COVID-19. Our staff continues to work across all sectors to expedite the development of numerous, innovative potential prevention and treatment approaches. We are also looking at pragmatic and expedited ways to make these products available to patients, while still ensuring the FDA's standards are met," said FDA Commissioner Stephen

M. Hahn. "Accelerating the investigation of products that could potentially benefit people affected by the COVID-19 pandemic is one of the FDA's highest priorities. We want to help patients by expediting promising treatments and are committed to maximizing our regulatory flexibility and proactively bringing the best innovators together to ensure we are getting the right treatments to the right patients at the right time."

To support these goals, the FDA has, among other things, redeployed medical and regulatory staff to serve on review teams dedicated to COVID-19 therapies, streamlined processes and operations for developers and scientists to send inquiries and requests and provided resources to health care providers and researchers to help them submit emergency requests to use investigational products.

There are a variety of therapeutic areas being evaluated, including antiviral drugs like remdesivir that might treat the specific virus, as well as host targets, such as interleukin-6 (IL-6) receptor inhibitors that may be helpful in reducing lung inflammation and improving lung function in COVID-19 patients. There's also interest in examining whether therapies such as convalescent plasma and hyperimmune globulin, antibody-rich blood products that are taken from blood donated by people who have recovered from the virus, could shorten the length or lessen the severity of the illness. Work is also ongoing to evaluate whether existing therapies such as chloroquine and hydroxychloroquine (with or without other medications) help treat patients with COVID-19.

The FDA also recognizes the potential for many different real-world data sources to complement traditional clinical studies and speed the process of evaluating the impact of potential COVID-19 therapies. To that end, the agency is advancing relationships with partners in the public and private sectors to rapidly collect and analyze information in areas such as illness patterns and treatment outcomes.

The FDA's efforts to facilitate the development of COVID-19 therapies are focused on expediting the development of data on these medical countermeasures that can meet the agency's world-respected gold standard for full FDA approval, which relies on data from adequate and well-controlled trials to most efficiently determine if an experimental treatment can safely and effectively benefit patients.

The FDA will continue to enhance and expand its work across the federal government and innovators in academia and industry to accelerate COVID-19 treatments and other medical countermeasures. The agency will outline additional information in the near future to provide a greater understanding of the full breadth of work in this area, to the extent permitted by confidentiality laws.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

###

Inquiries

Media:

Michael Felberbaum

240-402-9548

Consumer:

888-INFO-FDA

Related Information

- Coronavirus Disease (COVID-19)

- Coronavirus Treatment Acceleration Program (CTAP)
- What are Medical Countermeasures?

Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/31 17:09:56
Delivered Date:	2020/03/31 17:10:14
Message Flags:	Unread

From:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject:	Two Generic Drugs Being Tested in U.S. in Race to Find Coronavirus Treatments hydroxychloroquine, losartan
Date:	2020/03/19 12:44:54
Priority:	Normal
Type:	Note

Two Generic Drugs Being Tested in U.S. in Race to Find Coronavirus Treatments

By Reuters

- • March 19, 2020Updated 7:44 a.m. ET

• • (Reuters) - U.S. researchers, following the lead of scientists in other countries, have launched studies to see whether widely-available, low-cost generic drugs can be used to help treat the illness caused by the new coronavirus.

There are currently no vaccines or treatments for the highly-contagious COVID-19 respiratory illness, so patients can only receive supportive care for now.

But a 1,500-person trial, led by the University of Minnesota, began this week to see whether malaria treatment hydroxychloroquine can prevent or reduce the severity of COVID-19. Two other trials are studying the blood pressure drug losartan as a possible treatment for the disease.

The malaria drug, also being tested in China, Australia and France, was touted earlier this week by Tesla Chief Executive Elon Musk, who recovered from malaria in 2000 after taking the medication.

Besides having a direct antiviral effect, hydroxychloroquine suppresses the production and release of proteins involved in the inflammatory complications of several viral diseases.

"We are trying to leverage the science to see if we can do something in addition to minimizing contacts," said Dr. Jakub Tolar, dean of the University of Minnesota Medical School and vice president for clinical affairs. "Results are likely in weeks, not months."

Most people infected with the new coronavirus develop only mild flu-like symptoms, but around 20 percent can have more severe disease that can lead to pneumonia requiring hospitalization.

The fast-spreading virus, which emerged in China in December and is now in more than 150 countries, has infected more than 214,000 and killed over 8,700 people worldwide, including at least 145 in the United States. Experts say it could take a year or more to have a preventive vaccine ready, so effective treatments are desperately needed.

A French team on Tuesday said initial results from a 24-patient trial of hydroxychloroquine showed that 25% of patients given the drug still carried the coronavirus after six days, compared with 90% of patients given a placebo.

Tolar said he bought 1,500 doses of hydroxychloroquine for a "laughable" amount of money. "We don't need a multibillion-dollar investment. It is part of the beauty of this approach," he said.

But he and others cautioned that people should not be using any prescription drugs without medical oversight.

"These treatments should be used only in hospitals by critical care specialists," said Dr. Russel Buhr, critical care pulmonologist at the University of California, Los Angeles.

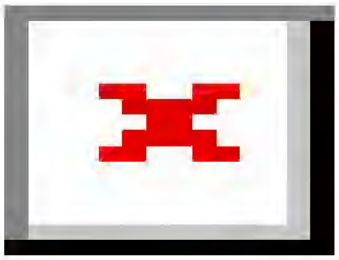
Also this week, the University of Minnesota launched two trials testing losartan - one to measure whether the hypertension drug reduces the risk of organ failure for COVID-19 patients who have been hospitalized, and another looking at whether the drug can limit the need for hospitalizations.
Losartan is an angiotensin receptor 1 (AT1R) blocker, which researchers say could play a role in blocking an enzyme used by the virus to bind to cells.
Pharmaceutical companies are also working to develop treatments for COVID-19, including Gilead Sciences Inc's experimental antiviral drug remdesivir, which is given to hospitalized patients via intravenous infusion over several days.
The New England Journal of Medicine earlier this month described how the drug was successfully used on the first patient infected by the novel coronavirus in the United States.
Results from a remdesivir trial in China could come early next month, while Gilead has begun two international trials of the drug that previously failed as a potential Ebola treatment. And the National Institutes of Health last month began testing it on patients in a U.S. trial.
"We are focusing on high risk patients," said Dr. Andre Kalil, infectious disease specialist at the University of Nebraska Medical Center and the U.S. trial's lead investigator. "Our hope is that remdesivir will show that patients will be improving faster."
Companies including Regeneron Pharmaceuticals Inc, Eli Lilly and Co and Takeda Pharmaceutical Co have begun to develop coronavirus treatment candidates, but human testing of their drugs has not yet started.
Anti-inflammatory drugs, like Regeneron's Kevzara and Roche Holding AG's Actemra, have been used to treat the lung inflammation caused by COVID-19.
But in a disappointment, Chinese investigators reported this week that Kaletra, a combination HIV drug sold by AbbVie, failed to improve outcomes for seriously ill COVID-19 patients.
(Reporting By Deena Beasley; Editing by Bill Berkrot)

Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date: 2020/03/19 12:44:33
Delivered Date: 2020/03/19 12:44:54
Message Flags: Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: WSJ: Hundreds Receive Plasma From Recovered Coronavirus Patients in National Study
Date: 2020/04/21 11:01:57
Priority: Normal
Type: Note

Hundreds Receive Plasma From Recovered Coronavirus Patients in National Study

Researchers seek evidence about plasma therapy outcomes and new knowledge for future outbreaks



Melissa Cruz, an emergency room technician in Renton, Wash., who had Covid-19, donated plasma on April 17.
Photo: lindsey wasson/Reuters
By
Amy Dockser Marcus
April 21, 2020 8:06 am ET

Six hundred severely ill Covid-19 patients have received blood plasma from recovered patients in a study researchers hope sheds light on whether the experimental therapy improves health outcomes and yields other useful data outside the scientific rigor of a traditional clinical trial.

The patients are participating in a national expanded-access program authorized in early April by the federal Food and Drug Administration. Expanded access, also known as compassionate use, is often sought by patients with life-threatening illnesses for which there are no approved therapies, or who can't participate in clinical trials.

The utility of data from compassionate-use studies is a source of debate within the medical and scientific community, where the gold standard for determining a new drug's safety and efficacy has long been the controlled clinical trial. In those traditional randomized trials, one group of patients gets the experimental drug and a control group gets either the standard therapy or a placebo.

Critics say it is impossible for compassionate-use studies to show whether a drug is working, because every patient in those studies gets the compound, with no control group for comparison. Opponents also worry that patients could become reluctant to enroll in traditional clinical trials for fear they won't get the experimental therapy.

Without a control group, though, researchers can't be certain what is making the difference. Age, gender, weight, underlying health conditions, socioeconomic status and doctors' own biases all can influence a patient's outcome. And in many diseases, including Covid-19, some patients are going to get better on their own. As a result, compassionate use has been viewed as a way to give patients emergency access to experimental therapies rather than a source of reliable data.

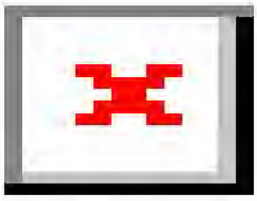
"Will expanded access give us the same data as a perfect randomized, controlled trial? No," said Michael Joyner of the Mayo Clinic in Rochester, Minn., and principal investigator of the expanded-access convalescent plasma project. "Will we gain insight under unusual circumstances? Yes."

As of Sunday, the University Hospital in Madison, Wis., part of UW Health, had transfused 11 Covid patients with convalescent plasma under the expanded-access protocol, said William Hartman, an anesthesiologist and one of the investigators on the study. Eight of the patients were in life-threatening situations and now are in various stages of recovery, he said. The other three received plasma before or just after admission to the intensive-care unit and have shown improvement: One was discharged from the hospital; one was taken off a ventilator within a day and symptoms have improved. The third hasn't worsened and hasn't required ICU admission, he said.

"There is no lab test that proves convalescent plasma caused these results," Dr. Hartman said. "Based on when we gave them the transfusion and the outcomes, we are encouraged."

Between 5,000 and 10,000 people may ultimately be eligible to enroll in the convalescent plasma program, the Mayo Clinic's Dr. Joyner said. Investigators will compare patients who get the plasma with similar patients who didn't receive it, such as very ill patients at a hospital where the therapy wasn't available. Researchers hope the knowledge they gather can inform future trials and aid doctors and researchers in another outbreak.

Another analysis of compassionate-use data, about the experimental drug remdesivir from Gilead Sciences Inc. published in the New England Journal of Medicine, came under criticism. Scientists pointed out that the Covid-19 patients received the drug in centers around the world where care may have differed, data on some patients was incomplete and there was no comparison group.



A phlebotomist processes a convalescent plasma donation at the Central Seattle Donor Center of Bloodworks Northwest on April 17.

Photo: lindsey wasson/Reuters

That study's first author, Jonathan Grein, of Cedars-Sinai Medical Center in Los Angeles, said given how little is known about the coronavirus and how to treat it, "I think at this point any information is potentially helpful." He said the study, funded by Gilead Sciences, noted the findings were limited and preliminary. "It is a starting point, an opportunity to aggregate our initial experiences," he said.

There also are traditional randomized controlled studies of remdesivir under way.

The FDA has shown flexibility in accepting expanded-access data during the drug-approval process, particularly for rare conditions. The FDA also has worked closely with companies trying to extract "real world evidence" about patients' experiences with new or experimental drugs from sources such as electronic health records.

Convalescent plasma has been tried as a potential intervention in previous public-health emergencies, including for Ebola and severe acute respiratory syndrome (SARS), according to H. Clifford Lane, clinical director at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. But because robust randomized clinical trials weren't conducted, "there is still no clear data to support that it has been of benefit."

Even with the added rigor, Dr. Lane said it would be difficult to tell whether plasma therapy or something else is responsible for any possible improvement in the Covid-19 patients. "Maybe the patients improved because as doctors got more practice treating Covid patients they did a better job, and not because the intervention had an effect," he said. In the end, "thousands of anecdotes are still just thousands of anecdotes."

Dr. Lane said the NIH is involved in efforts to launch randomized controlled clinical trials of manufactured intravenous immunoglobulin containing antibodies prepared from the serum of many recovered Covid patients.

Holly Fernandez Lynch, an assistant professor of medical ethics at the University of Pennsylvania, said she supports trying to glean as much information as possible from the use of experimental therapies. Nonetheless, since very little is yet known about the coronavirus itself, patient outcomes will be even more difficult to analyze compared with better-understood diseases.

"There is a sense of emergency and feeling we don't have time to get answers," she said. "If we keep acting like we can't study the interventions, then we will be in the same position next time and still not know how to effectively treat people."

Still, the compassionate-use data on plasma therapy may help shape future studies. Peter Marks, director of the FDA Center for Biologics Evaluation and Research, said, "They may get a readout on some questions sooner than we would have, had this been a conventional trial."

Other randomized controlled trials in the works include one to test convalescent plasma given prophylactically to those at risk of Covid-19 infection, says Shmuel Shoham of Johns Hopkins University School of Medicine, the principal investigator on that trial. With Covid-19, there is room for both broad access to experimental therapies and controlled trials, he said. "There are enough questions that are worth investigating, and sadly a lot of patients."

Write to Amy Dockser Marcus at amy.marcus@wsj.com

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/21 11:00:58
Delivered Date:	2020/04/21 11:01:57
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Wpost: Coronavirus live updates: Grand Princess cruise ship to dock in Oakland; Virginia announces second case
Date: 2020/03/08 13:59:56
Priority: Normal
Type: Note

Coronavirus live updates: Grand Princess cruise ship to dock in Oakland; Virginia announces second case

A woman wearing a protective face walks with her luggages inside Milan's main train station as Italian authorities prepare to lock down Lombardy to prevent the spread of the highly infectious coronavirus in Milan, Italy, March 7, 2020. (Alex Fraser) A woman wearing a protective face walks with her luggages inside Milan's main train station as Italian authorities prepare to lock down Lombardy to prevent the spread of the highly infectious coronavirus in Milan, Italy, March 7, 2020. (Alex Fraser)

By
Derek Hawkins,
Gerry Shih,
Paul Schemm,
Lateshia Beachum and
Kim Bellware
March 8, 2020 at 1:34 p.m. EDT
Refresh for updates

The virus continued to spread across the United States, with Vermont, Missouri and Washington, D.C. reporting their first cases late Saturday and Virginia announcing a second case on Sunday. The outbreak has now reached more than 30 states, with nationwide cases surpassing 400.

On the West coast, the coronavirus-stricken Grand Princess cruise ship is scheduled to dock in Oakland sometime Monday after idling for days off the coast of San Francisco while officials debated where to send the roughly 3,500 people aboard.

In China, where the outbreak has begun to subside, a hotel in the country's southeast that served as a quarantine facility for 71 people collapsed late Saturday, killing at least 10 people and trapping scores in the rubble.

Latin America recorded its first death in the outbreak when an Argentine man with underlying health conditions died Saturday in Buenos Aires. The man tested positive for covid-19 after returning from a European trip.

To contain coronavirus,Italy will limit movement across much of its northern region, including the cities of Milan and Venice. The measures, the most drastic outside of China, place significant restrictions on 16 million people in a broad area that is Italy's economic engine.

Here are the latest developments:

- **• Rep. Joaquin Castro (D-Texas) tweeted that Grand Princess passengers were expected to be quarantined at the Lackland Air Force Base in San Antonio. The base has been a quarantine site for evacuees from the coronavirus epicenter in Wuhan, China, and others exposed to the virus aboard the Diamond Princess cruise ship last month.**
- **• Iran on Sunday reported 49 deaths and more than 700 cases of the new coronavirus over the past 24 hours, while Saudi Arabia suspended travel to and from a key eastern province and ordered businesses and government offices there closed after confirming four new cases of the novel coronavirus on Sunday, bringing the total number of infections to 11.**
- **• Chinese authorities announced 44 new cases of coronavirus on Saturday — a smaller daily rise than countries like South Korea — as cases continue to taper off sharply in the country where the epidemic first broke out.**
- **• An attendee at the Conservative Political Action Conference — a major annual right-wing gathering held in Maryland in February and attended by President Trump and Vice President Pence — tested positive Saturday for the virus, the host organization said, as the U.S. death toll rose to 19.**

Sign up for our coronavirus newsletter | Mapping the spread of the coronavirus | What you need to know about the virus | Post Reports: Your questions about coronavirus, answered

1:34 p.m.

German tourist dies in Red Sea hospital, in Egypt's first virus-related death

CAIRO — A 60-year-old German tourist died in a Red Sea hospital after being infected with the coronavirus, Egypt's Health Ministry said in a statement. The tourist's death is the country's first related to the virus.

The tourist had been in Egypt for seven days, the Health Ministry said. He traveled Friday from Luxor in southern Egypt to Hurghada along the country's Red Sea coast where he experienced symptoms. He tested positive at a hospital and was placed in intensive care after refusing to be quarantined at another medical facility, the Health Ministry said. His condition deteriorated Sunday, authorities said.

His death came a day after Health Ministry officials announced 33 new cases of the virus on a Nile cruise ship that traveled from Aswan and docked in Luxor Friday. The 19 infected passengers on the ship included Americans and 14 Egyptians. Twelve crew members reportedly had tested positive for the virus, but Egypt's health minister said 11 of those cases later tested negative. It's not known whether the German tourist was a passenger on the ship.

The total number of coronavirus cases in Egypt stands at 49. They include a Chinese citizen who later recovered, a Canadian oil worker and an Egyptian who recently returned from Serbia.

By Sudarsan Raghavan

AD

1:03 p.m.

Grand Princess captain tells passengers specific arrival time remains uncertain

The Grand Princess continues floating off the San Francisco coast with plans to dock at the Port of Oakland on Monday, but the specific time of arrival remains unclear, the ship's captain told passengers Sunday morning.

He said one passenger needing hospital care would be taken off the ship Sunday but government authorities have not yet told cruise officials when the remaining passengers would be able to arrive at port.

"We know this will be a disappointment to you, and we share in that disappointment," he said in the message, which was broadcast over the ship's loudspeakers. "However, we are required to follow the government instructions."

A passenger shared a recording of the message with The Washington Post.

More than 3,500 people are aboard the Grand Princess, and of the 46 tested for the coronavirus so far, 21 have tested positive. When the ship docks, the cruise line says, guests who are California residents will undergo health screenings and go to federal facilities in the state, while Americans from other states will be taken to locations elsewhere in the country. The crew will be quarantined and treated aboard, the cruise line said Saturday.

The captain said the ship would rendezvous with a U.S. Coast Guard cutter to collect prescription medicines and other medications for people on board. One of the passengers requires "shoreside hospital care," he said, so that person will go to shore. The captain did not elaborate on the person's condition or say whether the person was among those who tested positive. Cruise officials are hopeful for more details about arrival plans, the captain said, while acknowledging the difficulty of the "unusual circumstances" facing the passengers and crew alike.

By Mark Berman

AD

12:40 p.m.

Pence addresses concern about mask supplies, says more than a million tests distributed

Vice President Pence said Sunday that Congress will seek to ensure that health-care workers have access to needed masks when treating patients diagnosed with the novel coronavirus, as hospitals across the nation struggle to keep an adequate supply on site.

In an interview with Fox News's Jeanine Pirro, Pence, who has been tasked with leading the administration's response to the virus, said the manufacturing conglomerate 3M has been producing 35 million masks a month since January. "They ramped up when they heard about coronavirus," he said. The FBI made a bulk order with 3M last month as part of its "pandemic preparedness."

Federal regulations require hospital workers to throw away masks after a single use. Washington state officials have scrambled to have enough masks for health-care workers who are at the forefront of combating the spread of the virus. The state had the highest number of confirmed coronavirus cases and deaths in the United Statesas of Saturday. Pence reiterated that for most Americans, the threat of contracting the virus is low unless there are underlying health conditions. He also backed up President Trump's Friday assertion that the distribution of coronavirus testing kits has been good.

"Every state lab in the country can actually conduct coronavirus testing today," Pence said, stressing that more than a million tests have been distributed. He also credited the president with getting two commercial laboratories to collaborate on creating test kits for the virus that he said will be market-ready by the end of the week. The test includes a cotton swab that goes in the nose and can be processed in about four to six hours, he said.

Stephen M. Hahn, commissioner of food and drugs for the U.S. Food and Drug Administration, said in a statement Saturday that the Centers for Disease Control and Prevention has shipped enough test kits to public health laboratories to evaluate about 75,000 people.

"All public health laboratories that originally received a CDC test have received replacement tests," he said, adding that more than 1.1 million tests have been sent to nonpublic health labs. "Laboratories in areas with the highest need for testing based on the outbreak have received additional tests, however, all state public health labs now have tests available to them," Hahn said.

More than 1,500 patients have been evaluated using the CDC tests, he said.

By Lateshia Beachum

AD

12:03 p.m.

HUD Secretary Ben Carson refuses to discuss plan for 3,500 passengers on Grand Princess cruise ship

Federal officials gave no clear answer Sunday about what its role or response would be when 3,500 passengers stranded for two weeks aboard the Grand Princess cruise liner finally disembark in Oakland, Calif., on Monday. At least21 passengers on the ship have tested positive for the novel coronavirus.

In an appearance Sunday morning on ABC News's "This Week," Housing and Urban Development Secretary Ben Carson refused to discuss details of the federal response plan. Carson would share only that Vice President Pence and CEOs of major cruise lines met Saturday and would come up with a plan "within 72 hours of that meeting."

Cruise ship with thousands awaits test results as coronavirus continues spreading around the country

When pressed to give details on a plan with imminent implementation, Carson demurred, saying such an announcement should come from "one solitary person," presumably Pence, whom President Trump put in charge of leading the U.S. response to the outbreak.

"The plan will be in place by that time, but I don't want to preview the plan right now," Carson said, explaining the plan "hadn't been fully formulated."

The Trump administration has faced criticism for its handling of the epidemic,including its slow response in the early days of the outbreak and its delay in helping state and local officials on the front lines of the crisis prepare.

California officials on Sunday were more forthcoming about plans at the state and local level: Passengers needing urgent care will be treated at hospitals after they disembark; uninfected or asymptomatic passengers from California — roughly one-third of the passengers on the Grand Princess — will be held and tested in federally run isolation facilities in the state; and passengers from out of state will be taken to federal facilities outside California, the Los Angeles Times reported.

By Kim Bellware

AD

11:32 a.m.

CPAC chair says he has spoken to patient, talked to own doctor and taken precautions

American Conservative Union Chairman Matt Schlapp said Sunday in a Fox News interview that he had "incidental contact" with an attendee at the Conservative Political Action Conference who has since tested positive for the new coronavirus.

The brief interaction occurred nearly two weeks ago at the American Conservative Union-hosted conference in Maryland, which many White House officials attended. Schlapp, 52, said on "Fox &Friends Weekend" that he had a phone conversation on Saturday night with the patient, who is being treated in

New Jersey and "seems to be on the mend." The conservative grass-roots leader said he has been talking to his own doctor and taking precautions.
"I feel healthy as a horse. My kids do, as well," he said. "So there is no indications from anybody I've talked to that there are any more problems."
President Trump and Vice President Pence also attended the conference, but White House spokeswoman Stephanie Grisham told The Washington Post that neither of them had met or were in contact with the ill person. Schlapp echoed the White House's statement, adding that during the event he saw the president "scrub down his hand and clean his hands."
Maryland Gov. Larry Hogan (R) advised conference attendees to check their temperature twice a day and to notify their medical provider and health officials if they reach a temperature of 100.4 or more. Anyone with a fever, a cough or trouble breathing should remain in their home until health-care provider or the local health department instructs otherwise, Hogan said.
Schlapp said he would release more information "as we learn it."
"I want to reiterate," he said, "nobody who was at the conference should panic about what happened."
Sign up for our Coronavirus Updates newsletter to track the outbreak. All stories linked within the newsletter are free to access.
By Lateshia Beachum
AD
11:12 a.m.

No new Maryland cases as Gov. Hogan says state is doubling testing capacity

No new test results came back positive overnight, Maryland officials announced Sunday. The state stopped updating the public on the number of pending results because testing is no longer centralized in a state lab. Private laboratories also are conducting tests. Maryland announced three positive cases on Friday.
Maryland officials said they are working with Conservative Political Action Conference organizers to trace the interactions of a New Jersey patient with coronavirus who attended CPAC's event at National Harbor in Prince George's County in late February.
Gov. Larry Hogan (R) said in an appearance Sunday on NBC News's "Meet the Press" the state's testing capacity is about to double and, "at this point in time, we have the necessary resources."
But he also cautioned the coronavirus crisis "is escalating so rapidly. Information is changing on a daily basis, but also on an hourly basis."
Hogan, who at times criticized President Trump's style and decisions on other matters, did not answer whether he thought Trump might undermine the effectiveness of the federal response.
"Has the president been perfect in his communication? I can say he hasn't communicated the way I would and the way I might like him to, but I think the rest of the team has been doing a pretty good job," the governor said.
The expansion of testing beyond state laboratories also has widened the criteria for who can be tested for the virus. State guidance issued to physicians late Friday said, "Testing at commercial or hospital laboratories does not require health department review or approval, and is based on the clinical judgment of the health care provider."
By Erin Cox
AD
10:53 a.m.

Virginia officials announce second presumptive case of coronavirus

Virginia has its second presumptive case of coronavirus, health officials announced Sunday, bringing the total number of cases in the Washington area to seven.

Officials described the second presumptive positive patient as a Fairfax resident in their 80s who recently traveled on a Nile River cruise similar to other patients who have tested positive for covid-19. The patient was hospitalized on Thursday after developing symptoms a week earlier.

This announcement comes less than a day after the state announced its first presumptive positive patient — a U.S. Marine assigned to Fort Belvoir in Fairfax County. The patient returned recently from "official business" overseas, tweeted Jonathan Rath Hoffman, assistant to the secretary of defense for public affairs.

The Virginia Health Department said the state government is working with officials at the hospital and described the risk to the general public as low.

In addition to the two cases in Virginia, D.C. has reported two patients and Maryland has three.

Read more here.

By Kim Bellware and Rebecca Tan

AD

10:27 a.m.

Saudi Arabia isolates key province in coronavirus outbreak

ISTANBUL — Saudi Arabia suspended travel to and from a key eastern province and ordered businesses and government offices there closed after confirming four new cases of the novel coronavirus on Sunday, bringing the total number of infections to 11.

Authorities temporarily restricted traffic in and out of Qatif province, state media reported, quoting an official at the Interior Ministry. The official told the Saudi Press Agency that the measures were being taken to "prevent the spread of the virus" after all 11 cases were detected in Qatif. The region has a majority-Shiite population, and some of the first cases appeared in residents who recently had traveled to Iran, the epicenter of a wider outbreak across the Middle East. Qatif also has been the site of political and sectarian unrest against Saudi Arabia's Sunni rulers.

Authorities said Sunday Qatif residents would be allowed to return home but all businesses and government departments in the province should be closed, with the exception of "basic facilities to provide security … [and] supply necessary services." A resident of Qatif said roads out of the province already had been blocked. Authorities in a text message sent to teachers announced classes would be suspended for two weeks, according to a resident.

By Erin Cunningham

AD

9:52 a.m.

Trump defends 'fine tuned' coronavirus plan as virus continues to spread

President Trump on Sunday continued to defend his administration's efforts to contain the coronavirus outbreak in the nation, even as infections emerge in more states.

The White House has a "fine-tuned plan" against the spread of the novel coronavirus, Trump tweeted Sunday morning.

"We moved very early to close borders to certain areas, which was a Godsend," he wrote, praising Vice President Pence — the administration's point person on the response to the outbreak — for his efforts against the virus. "The Fake News Media is doing everything possible to make us look bad. Sad!"

The president's tweet came shortly after Virginia officials announced a second presumptive case Sunday morning, just a day after reporting its first case. Washington also announced its first two confirmed cases Saturday night. Trump was criticized Friday for remarks in which he appeared to discredit medical professionals standing next to him and rebuffed accusations that the administration has been slow in distributing coronavirus testing kits.

As The Post reported, the administration's effort "has been undermined by mixed messages, contradictions and falsehoods — many of them emanating from the president himself, including this week when he repeatedly spread false information about just how soon a coronavirus vaccine would be available."

Sign up for our Coronavirus Updates newsletter to track the outbreak. All stories linked within the newsletter are free to access.

By Lateshia Beachum

9:00 a.m.

Hong Kong announces third coronavirus fatality amid fears of outbreak resurgence

BEIJING — Hong Kong's Hospital Authority said Sunday evening that a 76-year-old woman died, marking the third coronavirus fatality in the semiautonomous city, as a government adviser warned the epidemic may flare up again at the end of the year.

The total number of confirmed cases in Hong Kong rose to 113 on Sunday as authorities confirmed four more infections, including a man who contracted the virus while traveling in Mumbai, officials said. Fifty-eight people have so far recovered and been discharged, the Hospital Authority added.

Hong Kong, adjacent to mainland China and one of the hardest-hit centers during the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak, has enacted some of the most stringent response measures in the world, including widespread school closures.

But a leading microbiologist who advises city officials warned cases might return in the winter as the virus spreads around the world from China and back. University of Hong Kong professor Yuen Kowk-yung said in a television interview Sunday, "we think the epidemic will not come to an end" by late 2020. "There will be what we called reverse import cases," Yuen said, according to the South China Morning Post. "In the beginning other countries feared us, now we fear them."

To prevent the contagion from being brought back to the Asian travel hub, Hong Kong has enacted mandatory 14-day quarantines for travelers arriving from Iran and some parts of South Korea and Italy. Mainland China is enforcing similar quarantine measures as its number of cases brought in from abroad soar, reaching 63 as of Saturday.

By Gerry Shih

8:51 a.m.

WHO praises Italian lockdown of the north to stop virus spread

ROME — The World Health Organization is praising Italy for its "genuine sacrifices" after the country announced it would greatly restrict movement across its northern regions to contain its coronavirus outbreak.

"The government &the people of Italy are taking bold, courageous steps aimed at slowing the spread of the #coronavirus &protecting their country &world," WHO Director General Tedros Adhanom Ghebreyesus said in a tweet on Sunday.

Italy overnight announced it would lock down three broad sections of the north, encompassing 85 percent of the country's total coronavirus cases. As of Sunday afternoon, there was still plenty of confusion about how the measures would be carried out or enforced.

Planes and trains were still running — with flights departing for international destinations from Milan and Venice — and it was unclear whether there was tighter screening for people getting on board. One government official in Rome, whose office was involved in the new decree, said dealing with the outgoing trains and planes was a "problem."

Prime Minister Giuseppe Conte, in his middle-of-the-night news conference, said people were allowed to leave the restricted zones only for emergencies, health issues or urgent work matters. "Not everything will stop," Conte said. "But from now on, we need to adopt the viewpoint that there are rules that need to be respected."

In a morning press briefing, the governor of the northern Veneto region, Luca Zaia, said he was unsure whether the decree had yet come officially into force. Zaia said his region was opposed to the new measures, and he had written to Conte requesting them to be repealed. "We all know laws are not precise to an inch," Zaia said. "But a decree this important should have gotten rid of some doubts that we want to clarify and deal with."

By Chico Harlan and William Booth

8:08 a.m.

WHO warning against Chinese traditional medicine absent from its Chinese and English language websites

BEIJING — Does the World Health Organization warn against relying on traditional herbal medicines as a remedy against the coronavirus?

Depends on which version of its website you're reading.

Chinese Internet users noticed Sunday that WHO appeared to warn people against smoking, wearing multiple masks, taking self-medication or taking traditional herbal medicine — in all languages but English and Chinese.

There is no mention of or any kind of warning against using traditional medicine in the Chinese and English versions of the website for users accessing the site from within China.

The discrepancy raised suspicions among some Chinese that WHO made the omission to appease the Chinese government under President Xi Jinping, who has strongly backed traditional Chinese medicine as part of a broader, nationalistic campaign to promote Chinese culture. WHO has not yet responded to a request for comment.

In China, as elsewhere, the coronavirus has revived long-standing debates about the efficacy of such medicine when it comes to contagious diseases, with many Chinese doctors pointing out that there is no scientific evidence to back the use of herbal remedies to treat covid-19, the disease caused by the coronavirus.

State media outlets and some state institutions — including the Wuhan Institute of Virology — have promoted the remedies, particularly a pill known as shuanghuanglian that has been widely used in China for decades to cure respiratory ailments and fight off infections. Reports promoting the drug, which is made from the bud of the *Lonicera japonica* honeysuckle flower and other plant sources, spurred a run on nationwide supplies and huge price spikes in early February.

More than 60,000 covid-19 patients have been treated with Chinese medicine, the Communist Party's official newspaper, the People's Daily, reported this week.

Clinical evidence of its efficacy, however, remains murky.

A 2014 literature review by researchers at the School of Chinese Medicine at the Chinese University of Hong Kong who examined hundreds of studies published in China found that shuanghuanglian may help

lessen symptoms like fever, cough and sore throat, but they warned that there was not enough evidence to reach a conclusion.

In the past month, WHO has repeatedly faced questions about its independence from contributor nations, particularly China, after itstop officials repeatedly praised China's handling of the outbreak and criticized other countries for cutting off transportation links with China at the start of the crisis.

WHO officials have strongly denied suggestions that their decisions and statements have been politically influenced.

China on Saturday announced an additional $20 million donation to WHO, which it said would help fight the coronavirus worldwide, particularly in developing countries.

By Gerry Shih

7:40 a.m.

Iran reports 49 new deaths, suspends flights to Europe

ISTANBUL — Iran on Sunday reported 49 deaths and more than 700 cases of the new coronavirus over the past 24 hours, as authorities urged citizens to stay home and avoid travel between cities.

The new cases bring the official death toll in Iran to 194, with a total of 6,566 infections, according to the Health Ministry.

The outbreak is one of the largest outside China, where it is believed the virus originated.

A number of Iranian officials have contracted the virus — which causes the respiratory disease known as covid-19 — and several have died from infection.

Also Sunday, Iran's flagship carrier IranAir suspended flights to Europe because of "restrictions" placed on the airline, state media reported, citing Iran's Civil Aviation Organization.

Sign up for our Coronavirus Updates newsletter to track the outbreak. All stories linked within the newsletter are free to access.

By Erin Cunningham

7:19 a.m.

Czech Prime Minister says Italy should bar its citizens from traveling in Europe

LONDON — The prime minister of the Czech Republic Sunday said Italy should bar all its citizens from traveling to other countries in Europe to contain the coronavirus.

"Italy should ban all its citizens from traveling to Europe, because we are not able to order such a thing within Schengen," Czech Prime Minister Andrej Babis told Czech Television Sunday.

"Schengen" is shorthand for the 26 countries in Europe where 420 million citizens of the member-states can travel freely across each other's borders without passport control. Most Schengen countries are members of the European Union, but the free travel area also includes non-EU members Iceland, Norway and Switzerland.

Italian Prime Minister Giuseppe Conte early Sunday announced his country was locking down a vast swath of its north, including all of the populous Lombardy region, with restrictions on movement applying to roughly 16 million people.

The Washington Post reported the Italian measures would mark the most significant coronavirus restrictions taken anywhere outside of China. It essentially would paralyze the most prosperous parts of Italy — from Venice to the economic capital of Milan — in an attempt to contain the virus.

By William Booth

7:09 a.m.

Italian governor tests positive for coronavirus — the second in two days

ROME — The governor of Italy's northern Piedmont region, Alberto Cirio, has tested positive for coronavirus, the ANSA news agency reported Sunday morning.

Cirio, 47, a member of the center-right Forza Italia party, is the second regional Italian leader in two days to contract the virus.

ANSA said Cirio's condition is "okay" and he will continue to stay on the job, "inevitably at a distance."

Cirio's Piedmont region has roughly 200 cases, and several parts of the region were put under lockdown early Sunday morning amid a government decree restricting travel across parts of the north.

Until this weekend, there had been relatively few high-profile cases in Italy, even as the virus spread rapidly across the country and infected nearly 6,000 people. But on Saturday, the leader of the country's center-left party, Nicola Zingaretti, said that he had contracted the disease and was in isolation at home. Zingaretti is also governor of the Lazio region, which includes Rome.

By Chico Harlan

6:30 a.m.

British finance minister says NHS will get 'whatever it needs' in battle against the virus

LONDON — Britain's Finance Minister Rishi Sunak Sunday said the government stands ready to give the National Health Service "whatever it needs" to fund its battle against the coronavirus contagion.

In his first broadcast interview, the newly appointed chancellor told Sky News the government not only would boost funding for the NHS but was prepared to help out struggling businesses as well.

"I'm working hard with the team to make sure that we have the interventions required to help anyone through a difficult period," Sunak said.

"First and foremost, supporting public services but also helping vulnerable people and also businesses to get through anything that might be coming our way," he said. "We stand ready to give the NHS whatever it needs."

Sunak, who controls the state budget, said he was preparing soon to issue a plan for helping businesses facing "cash flow" problems because of coronavirus.

Britain has 209 confirmed cases and two deaths caused by the novel virus. Epidemiologists say Britain likely will see 1,500 cases by the end of the week.

By William Booth

5:57 a.m.

Argentina confirms first coronavirus death in Latin America

A coronavirus patient in Argentina died Saturday, the country's health officials said, marking Latin America's first fatality in the outbreak.

The patient was a 64-year-old man with underlying health conditions, including diabetes, high blood pressure, chronic bronchitis and kidney failure, the Argentine Health Ministry said in a statement.

He had recently traveled to Europe and fell ill with a fever, cough and sore throat in Buenos Aires, where he lived.

He was admitted to an intensive care unit on March 3 and placed on a ventilator, according to the ministry.

Officials said they were tracing the man's close contacts to see who else may have been exposed.

By Derek Hawkins

5:46 a.m.

Toll in collapse of Chinese quarantine center climbs to 10; workers said pillar buckled during renovations

BEIJING — At least 10 people staying in a hotel during quarantine have died in southeastern China after the building collapsed Saturday evening, trapping 71 people, Chinese state media reported.

As of 4 p.m. Sunday, 48 people, including the 10 who died, had been pulled from the rubble of the Xinjia Hotel in Quanzhou, a city in Fujian province. Search operations are ongoing for those remaining. Photos from the scene showed firefighters pulling people, including young children, from piles of rubble.

Many local Chinese governments have requisitioned hotels to house workers returning from other cities and provinces after the Lunar New Year holiday. After a 14-day quarantine, they are allowed to resume work.

The collapse appeared to have occurred during renovations at the seven-story building, the official Xinhua News Agency reported, citing Quanzhou housing and construction bureau official Zhang Yi. It's not clear why the hotel was being renovated while it was serving as a quarantine facility. The hotel had 66 rooms on top of a lobby that was being worked on, Zhang said.

Zhang said construction workers reported to the building owner that a pillar on the first floor was noticeably bent less than five minutes before the entire structure crumbled. The building owner, who police have identified as a Quanzhou man surnamed Yang, is in custody, Xinhua reported.

Although construction and safety standards have improved in recent years, China is still often plagued by building collapses and industrial accidents.

Sign up for our Coronavirus Updates newsletter to track the outbreak. All stories linked within the newsletter are free to access.

By Gerry Shih

5:30 a.m.

Bahrain's Formula One race will be off-limits to the public due to the outbreak

DUBAI — Bahrain announced Sunday it will be holding its Formula One event for "participants only" because of the continuing global spread of the coronavirus.

The event, which in 2004 became the first Formula One race to be held in the Middle East, is the premier international sporting event for this tiny island kingdom in the Persian Gulf.

"Given the continued spread of Covid-19 globally, convening a major sporting event, which is open to the public and allows thousands of international travelers and local fans to interact in close proximity would not be the right thing to do at the present time," said a statement by the Bahrain International Circuit that was published by the official news agency.

The March 22 event will be televised.

Bahrain has reported 85 cases of covid-19, the disease caused by the novel coronavirus, with most being traced back to neighboring Iran, which with more than 5,000 cases has one of the world's worst outbreaks.

The country's Health Ministry on Saturday asked all travelers from Italy, South Korea, Egypt and Lebanon to quarantine themselves for two weeks from the day of their arrival. Any Bahrain citizens or foreign residents who have recently visited these countries should contact the government to schedule a medical exam and avoid contact with others.

Saudi Arabia meanwhile closed its land borders to all but commercial traffic. Arrivals to the country can only come in through one of three airports.

In the United Arab Emirates, 15 new cases were reported over the weekend, taking the total to 45, including two students. Schools are closed for the next month, and the government of this international travel hub has cautioned against all international travel.

Cultural and sporting events across the region have also been canceled.

By Paul Schemm

5:23 a.m.

New virus cases continue to drop in China, the origin of the epidemic

BEIJING — Chinese authorities announced 44 new cases of coronavirus on Saturday — a smaller daily rise than South Korea and other countries are experiencing — as cases taper off in the country where the epidemic first broke out.

The new national total of confirmed cases reached 80,695, and the death toll in China rose by 27 to 3,097. Tens of thousands of patients have been discharged from hospitals.

New infections appeared to be transmitting through travelers flying back to China from hot spots including Italy, where there is a large Chinese immigrant community. As of Saturday, China tallied a total of 63 cases of patients who contracted the disease abroad.

Beijing, the capital, said Saturday it found two new cases — travelers who arrived from Italy and Spain.

The epicenter of the outbreak, Wuhan, in Hubei province, accounted for 41 of the new cases discovered Saturday, but the rate of increase was a fraction of the steep rise in early February, when the province added thousands of new cases every day.

Wuhan said Saturday it was closing the largest of three makeshift hospitals as large numbers of patients are discharged and the outbreak fades after six weeks of strict quarantine measures.

By Gerry Shih

4:37 a.m.

Grand Princess cruise ship will dock in Oakland; timing unclear

After being stuck in limbo for days off the coast of San Francisco, the coronavirus-stricken Grand Princess cruise ship is headed to Oakland to dock, the cruise line said early Sunday.

The ship's captain initially told passengers disembarkation could begin Sunday, but Princess Cruises said in an update shortly after that the ship wouldn't berth in Oakland until sometime Monday.

Releasing passengers from the ship is likely to be complicated since the thousands of people aboard represent a mix of American and international travelers.

Guests who require medical treatment and hospitalization will be allowed off first and sent to medical facilities in California, Princess Cruises said.

After that, guests who are California residents will undergo health screening and then go to a federally operated facility in the state for testing and isolation, according to the cruise line.

The federal government will transport non-Californians to facilities in other states, Princess Cruises said, while the crew will be quarantined and treated aboard the vessel.

Earlier in the night, Rep. Joaquin Castro (D-Tex.) tweeted the ship was headed to Oakland and passengers were expected to be quarantined at the Lackland Air Force Base in San Antonio. The base has been a quarantine site for evacuees from the coronavirus epicenter in Wuhan, China, and others exposed to the virus aboard the Diamond Princess cruise ship last month.

A representative from the San Antonio Mayor's Office didn't immediately respond to a request for comment.

At least 19 crew members and two passengers from the Grand Princess have tested positive for covid-19. The ship was held in waters off San Francisco while officials debated whether to let the ship's roughly 3,500 people ashore.

Passengers learned about the decision to dock in Oakland from the ship's captain Saturday night.

"An agreement has been reached to bring our ship into the port of Oakland," Captain John Smith said, according to the Associated Press. "After docking, we will then begin a disembarkation process specified by federal authorities that will take several days."

"We are working to obtain more details overnight," Smith said. "I'm sorry I can't provide you more details right now."

By Derek Hawkins, Faiz Siddiqui and Scott Wilson

4:01 a.m.

D.C. health officials probe possible coronavirus exposure at Georgetown church

Hours after announcing the District's first coronavirus case, the D.C. Department of Health said early Sunday it was investigating whether members of a Georgetown church were exposed to the deadly virus.

The health department told The Washington Post in a statement it had determined that "an individual's visitation to Christ Church Georgetown warrants precautionary measures."

The department said it was recommending that the historic Episcopal church suspend services out of an abundance of caution.

"We are currently conducting an intensive investigation to identify any exposures to covid-19 that may have occurred at the church," the department said. "DC Health will reach out to potentially impacted congregants and visitors as we continue to gather more information to ensure the health and safety of the public."

A representative from Christ Church Georgetown did not immediately respond to requests for comment early Sunday.

The move came after D.C. officials announced Saturday evening that a man in his 50s had been hospitalized with covid-19, the disease caused by the novel coronavirus.

D.C. Mayor Muriel E. Bowser (D) said the man was not believed to have traveled outside the United States or been in close contact with anyone else who was infected. He was admitted to a hospital Thursday, and his infection was confirmed by the city's health lab Saturday afternoon.

The case is a presumptive positive, meaning the results haven't yet been confirmed by the Centers for Disease Control and Prevention.

Another man developed symptoms of covid-19 after traveling in the district, then went to a hospital in Maryland for testing, according to Bowser. His test results haven't been released yet.

The health department is tracing the patients' close contacts to find out who else may have been exposed. Officials said there was no widespread community transmission in the District and that the risk to residents remained low.

Sign up for our Coronavirus Updates newsletter to track the outbreak. All stories linked within the newsletter are free to access.

By Derek Hawkins and Clarence Williams

1:57 a.m.

Chinese hotel used for quarantine collapses, killing six

BEIJING — A hotel that served as a quarantine facility for 71 people collapsed in southeast China late Saturday, killing at least six people and trapping scores in the rubble, Chinese media reported.

About 50 people had been pulled out of the Xinjia hotel in Quanzhou in Fujian province as of 8:20 a.m., according to state media. Reports showed the structure reduced to a pile of splintered building materials and firefighters carrying survivors, including small children, out of the rubble.

Among the 50 rescued, six were dead as of Sunday morning, according to Xinhua News Agency.

Chinese media reports did not give an official explanation for the collapse or indicate whether it was because of shoddy construction or an accident. An eyewitness told the Economic News he heard a massive sound around dinnertime Saturday that he initially believed to be an explosion.

The building was about five stories high.

Many local Chinese governments have set aside hotels as quarantine facilities where workers who return from other cities and provinces after the Lunar New Year holiday must spend two weeks before they may resume work.

Although construction and safety standards have improved in recent years, China is plagued by building collapses and industrial accidents. The owner of the building has been placed under "police control" pending an investigation into whether the management was at fault for the collapse, Xinhua reported Sunday.

By Gerry Shih

1:38 a.m.

Oakland council member says top officials learned of plans to dock in city on Saturday night

SAN FRANCISCO — Oakland council member Larry Reid, of the city's Seventh District, said he was informed Saturday night that the cruise ship would dock in the city at a site known as Ports America in West Oakland.

Reid confirmed an initial tweet from Rep. Joaquin Castro (D-Tex.), who said the ship was going to dock in the city, and an announcement from the cruise captain that the ship was headed to Oakland Sunday where passengers would disembark, a process that could take days.

The news surprised city officials — particularly for the council, which Reid said did not have a hand in the decision. Reid said the Oakland Fire Department was expected to play a role in taking passengers off the ship.

Reid was puzzled, however, at the decision to dock the ship in Oakland instead of its original site in San Francisco.

"I just don't understand why if it's safe enough for them to offload the passengers into Oakland, why isn't it safe enough for them to offload the passengers in San Francisco, where they have the facilities for the cruise line that's docked in San Francisco on a daily basis?" he asked.

Reid said the decision was made between federal and state officials, who involved the city's mayor, Libby Schaaf, in discussions. Schaaf did not immediately respond to a request for comment. Reid said the governor's office held a conference call earlier Saturday night with top city officials informing them of an "urgent update" of the situation involving the ship.

Asked whether it seemed the move was a signal of Oakland's seeming second-fiddle status in political power, Reid said: "That's something they would say, and a lot of Oakland residents would say."

He demanded an explanation, saying he had concerns about the safety of the city's more than 400,000 residents.

"There are people that live in West Oakland," he said. "They may not live right there on the water, but the Port of America site is maybe a mile or mile and a half away from the residential neighborhoods in West Oakland."

By Faiz Siddiqui

12:59 a.m.

Missouri reports first coronavirus case

The coronavirus continued to spread through the Midwest, with Missouri officials reporting the state's first case late Saturday.

Officials said the patient was a woman in her 20s from St. Louis County who had recently traveled to Italy, whose northern provinces have been hit hard by the outbreak.

She is in isolation at home with family members who have also been isolated, according to a statement from Gov. Mike Parson (R). Health officials are investigating her close contacts and monitoring her symptoms.

"I am confident in the work of the Department of Health and Senior Services and the St. Louis County Public Health Department and know that they will do what they can to protect the health and safety of Missouri communities," Parson said.

The case is a presumptive positive, meaning that the state's lab results have not yet been confirmed by the Centers for Disease Control and Prevention.

Missouri's health department said it had tested 26 people for covid-19, the disease caused by the novel coronavirus, including the case announced Saturday. Three additional tests are awaiting results, according to the department.

At least five other Midwestern states had reported covid-19 cases as of Saturday night: Nebraska, Minnesota, Illinois, Indiana and Wisconsin.

By Derek Hawkins

12:51 a.m.

Grand Princess's arrival ashore is mired in uncertainty

SAN FRANCISCO — Carnival Cruise Line officials had no clearer indication Saturday of where the Grand Princess ship being held off California's coast was headed.

They said they had been in touch with federal and state officials as well as the Port of San Francisco. Frustration, however, was mounting about uncertainties as to when the ship would dock and where, as well as what Carnival officials called a lack of an established testing regimen for passengers and crew members, 21 of whom have tested positive for the novel coronavirus. Nineteen of the patients are employees.

"Our guests who expected to disembark today still do not know what to expect next," Jan Swartz, group president of Princess Cruises and Carnival Australia, said on a conference call with reporters Saturday. Passengers were dismayed about sparse information and the fact that they learned about positive tests for the virus through a Friday afternoon news conference.

"We, too, were disappointed that we were not officially notified and could share that with the guests in advance of the announcement being made," Swartz said.

Grant Tarling, chief medical officer for Carnival Corp., said he believed the virus arrived on the ship and infected the crew by community transmission from California. The patient originally infected, who was on a Feb. 11- 21 cruise, was from Placer County, Calif., and was served by two waiters who later tested positive for coronavirus aboard the ship.

That patient reported to the ship's medical center with what Tarling called a "six- to seven-day history of symptoms of acute respiratory illness."

"We believe his illness was probably community-acquired somewhere in California before he joined the ship," Tarling said. "We believe both the waiters that served that [person's] table may have been infected."

Aboard the ship, more than 3,500 passengers and crew are confined to their staterooms. There are 2,422 passengers and 1,111 staff members representing 64 countries, company officials said — including 2,016 passengers from the United States and 938 from California.

Among those who tested positive were crew members from the Philippines and passengers from the United States, the company said. Few of the crew members are from the United States, according to the officials.

Tarling said the Centers for Disease Control and Prevention had not settled on a testing protocol for crew and other passengers aboard the ship. It was unknown, he said, whether everyone on the ship would be tested or whether individuals would face a mandatory 14-day quarantine upon disembarking.

"There's a number of scenarios they are apparently still working on," said Tarling, who said the company had been in touch with the CDC. "One of them is testing, who will be tested. We do not know that information."

Vice President Pence has said people onboard will be quarantined as needed. CDC spokeswoman Belsie González said in an email Saturday that the agency is "committed to protecting the health and safety of all Americans."

"The U.S. Government is taking measures to protect the Grand Princess passengers and crew, their loved ones, the traveling public, and communities within the United States," González wrote.

By Faiz Siddiqui and Hannah Knowles

12:36 a.m.

United Airlines to offer free flight changes, shares plan for when passenger shows symptoms

United Airlines has created a coronavirus plan that includes free flight changes to adapt to how the virus is influencing travel, chief executive Oscar Munoz said in an email to customers Saturday.

"We are in the business of serving people and in the midst of this coronavirus outbreak it's important that we give you as much flexibility as possible when planning your next trip," he said. "But it's also important that we give you as much information as possible about the procedures we follow to clean our aircraft and maintain a sanitary environment once we're in the air."

From Saturday until March 31, any flights booked with the airline to any destination and of any price can be changed free over the next year.

The company has been communicating with the Centers for Disease Control and Prevention, the World Health Organization and other federal and global health agencies to make sure they are carrying out comprehensive and appropriate service.

Medical experts and industrial hygienists are overseeing airplane cleaning that includes wiping down most frequently used surfaces with "high-grade disinfectant and multipurpose cleaner," Munoz said.

The airline also has a plan in place should the CDC advise that a passenger who traveled onboard is displaying symptoms of coronavirus. The plane will be taken out of service and put through a thorough decontamination process.

Munoz told customers that all United Airlines planes have high-quality air circulation systems similar to what's found in most hospitals. However, to curtail person-to-person contact, attendants will wear gloves and hand beverages directly to customers.

Sign up for our Coronavirus Updates newsletter to track the outbreak. All stories linked within the newsletter are free to access.

By Lateshia Beachum

12:30 a.m.

Vermont reports first coronavirus case

Vermont health officials on Saturday night reported the state's first coronavirus case.

The patient is an adult who tested presumptive positive, meaning the lab results were awaiting confirmation from the Centers for Disease Control and Prevention, according to the Vermont Department of Health.

With Vermont's announcement, every New England state except Maine has reported cases of covid-19, the disease caused by the virus. Maine is still awaiting CDC approval for in-state testing.

The Vermont patient has been hospitalized in an isolation room, according to the health department.

Officials said they were investigating the person's travel history and tracing the person's close contacts.

"Those individuals will be assessed for their exposure risk and provided with guidance for their health, and recommendations for self-isolation or other restrictions," the health department said in a statement.

The department did not disclose how long the person had been infected or where the person was located.

"Our first thoughts are with this patient and for their recovery," Health Commissioner Mark Levine said in a statement.
Levine added that the state was expecting more cases. "While we had hoped the virus would not come to Vermont, we have been preparing for this eventuality," he said.
By Derek Hawkins

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/08 13:59:34
Delivered Date:	2020/03/08 13:59:56
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: NIAID: Antiviral Remdesivir Prevents Disease Progression in Monkeys with COVID-19
Date: 2020/04/17 14:06:42
Priority: Normal
Type: Note

Antiviral Remdesivir Prevents Disease Progression in Monkeys with COVID-19

Study Supports Clinical Testing Under Way Across U.S.

April 17, 2020

This scanning electron microscope image shows SARS-CoV-2 (round gold objects) emerging from the surface of cells cultured in the lab.

This scanning electron microscope image shows SARS-CoV-2 (round gold objects) emerging from the surface of cells cultured in the lab. SARS-CoV-2, also known as 2019-nCoV, is the virus that causes COVID-19. The virus shown was isolated from a patient in the U.S.

Credit: NIAID-RML

Early treatment with the experimental antiviral drug remdesivir significantly reduced clinical disease and damage to the lungs of rhesus macaques infected with SARS-CoV-2, the coronavirus that causes COVID-19, according to National Institutes of Health scientists.

The study was designed to follow dosing and treatment procedures used for hospitalized COVID-19 patients being administered remdesivir in a large, multi-center, clinical trial led by NIH's National Institute of Allergy and Infectious Diseases (NIAID). The scientists posted the work on the preprint server bioRxiv. The findings are not yet peer-reviewed and should not be considered clinical advice, but are being shared to assist the public health response to COVID-19. A study detailing the development of the rhesus macaque model of mild- to-moderate human disease, conducted by the same team of NIAID scientists, was posted to bioRxiv on March 21.

The current study of remdesivir, a drug developed by Gilead Sciences Inc. and NIAID-supported investigators, involved two groups of six rhesus macaques. One group of monkeys received remdesivir and the other animals served as an untreated comparison group. Scientists infected both groups with SARS-CoV-2. Twelve hours later the treatment group received a dose of remdesivir intravenously, and then received a daily intravenous booster dose thereafter for the next six days. The scientists timed the initial treatment to occur shortly before the virus reached its highest level in the animals' lungs.

Twelve hours after the initial treatment, the scientists examined all animals and found the six treated animals in significantly better health than the untreated group, a trend that continued during the seven-day study. They report that one of the six treated animals showed mild breathing difficulty, whereas all six of the untreated animals showed rapid and difficult breathing. The amount of virus found in the lungs was significantly lower in the treatment group compared to the untreated group, and SARS-CoV-2 caused less damage to the lungs in treated animals than in untreated animals.

The investigators note that the data supports initiating remdesivir treatment in COVID-19 patients as early as possible to achieve maximum treatment effect. The authors, from NIAID's Rocky Mountain Laboratories in Hamilton, Montana, also note that while remdesivir helped prevent pneumonia, it did not reduce virus shedding by the animals. "This finding is of great significance for patient management, where a clinical improvement should not be interpreted as a lack of infectiousness," they write.

ARTICLE:

B Williamson *et al.* Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2.

WHO:

Emmie de Wit, Ph.D., and Marshall Bloom, M.D., from NIAID's Laboratory of Virology are available to comment on this study.

Contact

To schedule interviews, contact
Ken Pekoc
(301) 402-1663
NIAIDNews@niaid.nih.gov

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/17 14:06:07
Delivered Date:	2020/04/17 14:06:42
Message Flags:	Unread

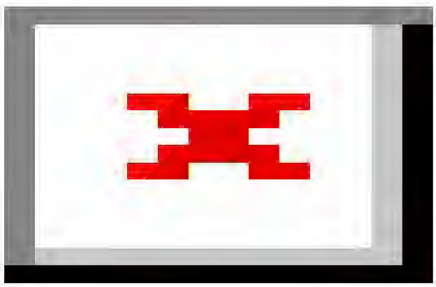
From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Atlantic: When the Solution to an Outbreak Was Right in Front of Us
Date: 2020/04/01 11:18:46
Priority: Normal
Type: Note

When the Solution to an Outbreak Was Right in Front of Us

During the yellow-fever epidemic of 1793 in Philadelphia, doctors dispensed advice that was sometimes quite harmful.

7:30 AM ET

Natalie Wexler



Bettman / Getty

As COVID-19, the disease caused by the coronavirus, has spread in recent weeks, so has bad information. Widely shared "tips" have included gargling with salt water or vinegar (thought to eliminate the virus); holding your breath for 10 seconds to see whether you can do it without coughing or experiencing distress (if you can, you supposedly don't have the virus); taking a few sips of water at least every 15 minutes (based on the theory that it will wash the virus into your stomach, where acid will kill it). None of these tips are backed by evidence. Still, despite early efforts by Facebook, Instagram, and Twitter to clamp down on false advice, the misinformation has continued to proliferate.

In the 18th century, it wasn't just folk remedies that led people astray. During the yellow-fever epidemic of 1793—localized to Philadelphia, then the nation's capital—doctors dispensed advice and "cures" that were sometimes quite harmful. From a 21st-century perspective, their desperate efforts would be laughable if the consequences hadn't been so tragic, especially when the remedy, to modern eyes, was quite apparent. People looking back at the pandemic of 2020, centuries from now, may shake their head at something equally "obvious" that doctors are missing today.

Yellow fever wasn't uncommon in the southeastern United States; Philadelphia's summer outbreak was unusual not only for its northerly location but also for its virulence. Over the course of four months, the epidemic would claim the lives of 5,000 residents, about 10 percent of the city's population.

At first, the city's doctors were divided on whether the disease that was rapidly killing off residents was anything unusual, with some dismissing the illness as run-of-the-mill "autumn fever." But Benjamin Rush, famous not only for being a physician but also for being a patriot during the Revolution, recognized the symptoms of yellowish skin and the vomiting of blood and black bile. He pronounced the sickness yellow fever, which hadn't erupted in the city for 30 years.

Even after agreeing on the problem, doctors disagreed on the cause. Some, like Rush, attributed the disease to local conditions—specifically to a load of coffee from Santo Domingo rotting on a city wharf, which was thought to be exuding noxious fumes. Others suspected the recent influx of refugees fleeing a slave rebellion in present-day Haiti, many of whom spoke of fevers back home. Either way, as some are wont to do now, they blamed the disease on another country.

Although germ theory wouldn't come along for another 70 years or so, people felt they could catch the disease by coming into contact with those who had it. More than 100 years later, scientists would discover that urban yellow fever is actually carried primarily by the mosquito *Aedes aegypti*, which has to bite an infected person and then transmit the disease by biting someone else. Philadelphians did notice an unusual number of mosquitoes in 1793, but failed to connect the insects to the disease.

Some medical recommendations issued in 1793 make sense now, while others seem absurd. Avoiding "all unnecessary intercourse" with infected persons and placing "a mark upon the door or window" of their house? Sure. Keeping the streets clean and avoiding "all fatigue of body or mind"? Okay. Strewing two inches of fresh earth in a room and changing the dirt twice daily, or taking frequent warm baths followed by ingesting five grains each of myrrh and black pepper? Not quite.

Doctors tried the traditional methods of coping with disease: alcoholic cordials, cool baths, bedclothes soaked in vinegar, and especially—to correct what was thought to be an imbalance in the body's "humors"—drawing blood and "purging" with emetics and laxatives. Nothing worked. One commentator at the time recalled that Benjamin Franklin had observed, years before, that the inhabitants of Barbados began to recover from the fever only after the doctors had run out of medicine.

David Oshinsky: The Epidemic That Preyed on Children

After a few weeks, Rush became convinced that the bleeding and purging simply hadn't been aggressive enough. He began administering large amounts of mercury as a purgative—doses criticized by some of his colleagues as "murderous" and fit only for a horse. If the other doctors had also known that mercury was toxic even at lower doses, no doubt the criticism would have been even more severe. Rush also advocated drawing four-fifths of a patient's blood. Because, like other doctors, Rush believed that the human body contained more than twice as much blood as it actually does, that amounted to far more blood than his already-weakened patients had in the first place. Many of his patients died, and some blamed Rush's "cure." But it wasn't clear that other approaches were working any better, and somehow, enough people managed to recover to give Rush and many others confidence in his methods.

Given the ineffectiveness—or downright harmfulness—of most 18th-century medicine, that people turned to folk remedies is understandable. In an attempt to purify the supposedly noxious air, residents lit bonfires and shot off guns—a clear danger in a hot and crowded city, and discouraged by doctors. But the governor of Pennsylvania himself took things a step further, ordering a small cannon to be hauled through the streets, stopping every few yards to fire.

While today people in hot spots like New York City try to defy mandates to "shelter in place," the "bad air" theory of disease led Philadelphia doctors to advise fleeing the area. Everyone who could afford to escape tried to do so, clogging roads and overburdening the modest inns that were often travelers' only options. Before the end of the fever, nearly 20,000 had left. The many abandoned houses led to a problem we don't see today, at least not yet: looting. On the other hand, the economic effects were

similar. One resident who stayed in the city reported in September that "business of every kind is stopped, and provisions double price."

People also started to fear Philadelphians. Major Christian Piercy, a Philadelphia potter, fell ill in a stagecoach in New Jersey. The other passengers forced him out, and a local landowner would allow him only an empty log cabin—where Piercy died alone, almost immediately. As far away as Massachusetts, Governor John Hancock issued a travel ban, directing each town to examine "all Persons, with the Baggage, and other Effects, by Land or Water, coming from Philadelphia, or any other infected Place." Postmasters used tongs to dip letters from Philadelphia into vinegar before opening them—the 18th-century equivalent of hand sanitizer. In the case of yellow fever, of course, these precautions were unnecessary. In places with no mosquitoes, there was no real danger of contagion.

Some myths are common to both the current pandemic and the epidemic of 1793—like the idea that African Americans are immune or less susceptible to the disease. Acting on that belief, Rush employed black people as nurses and gravediggers for yellow-fever victims. In the end, African American and white Philadelphians died in similar proportions. A less pernicious but equally persistent misconception is that garlic has protective powers. Rush reported that people in Philadelphia "chewed garlic constantly." During the current pandemic, one woman in China needed hospital treatment for a severe sore throat after consuming one and a half kilograms of raw garlic.

Eventually, what ended the yellow-fever epidemic was frost, which killed the mosquitoes. By November, the fever was disappearing, and those who had left or avoided Philadelphia—including President George Washington and Vice President John Adams—began cautiously to return.

One letter to the editor of a newspaper unwittingly hit upon what may have been the most valuable piece of advice. The author, identified as "A.B.," noted that the recent rains had produced a lot of mosquitoes, which was "distressing to the sick, and troublesome to those who are well." A.B. recommended pouring half a teaspoon of oil into the rainwater barrels where the insects bred, "which will quickly diffuse over the surface, and by excluding the air, will destroy the whole brood." Whether anyone in Philadelphia paid attention is not recorded.

Meanwhile, Jean Deveze, a French doctor with experience treating yellow fever in the West Indies, was running a hospital for victims. He was convinced, rightly, that the disease was not contagious, and he rejected Rush's techniques in favor of gentler remedies like "stimulants" and quinine—similar to modern treatments for yellow fever. But, partly because he was a foreigner and partly because victims were often beyond help by the time they arrived at the hospital, his efforts were largely overlooked. Today, in the midst of a global pandemic, perhaps some doctor or researcher who has discovered an effective weapon to fight COVID-19 is, like Deveze, toiling in obscurity.

We want to hear what you think about this article. Submit a letter to the editor or write to letters@theatlantic.com.

Natalie Wexler is a journalist based in Washington, D.C. She is the author of A More Obedient Wife: A Novel of the Early Supreme Court and The Knowledge Gap: The Hidden Cause of America's Broken Education System—And How to Fix It.

Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date: 2020/04/01 11:17:44
Delivered Date: 2020/04/01 11:18:46
Message Flags: Unread

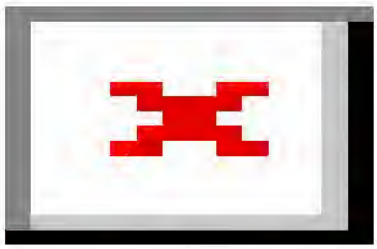
From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Axios: International coronavirus treatment trial uses AI to speed results
Date: 2020/04/10 09:33:14
Priority: Normal
Type: Note

4 hours ago - Health

International coronavirus treatment trial uses AI to speed results

Eileen Drage O'Reilly

Eileen Drage O'Reilly



Gloved hands holding packets of hydroxychloroquine tablets
Hydroxychloroquine is one of the drugs that will be included in the trial. Photo: John Philips/Getty Images

The first hospital network in the U.S. has joined an international clinical trial using artificial intelligence to help determine which treatments for patients with the novel coronavirus are most effective on an on-going basis.

Why it matters: In the midst of a pandemic, scientists face dueling needs: to find treatments quickly and to ensure they are safe and effective. By using this new type of adaptive platform, doctors hope to collect clinical data that will help more quickly determine what actually works.

"The solution is to find an optimal trade-off between doing something now, such as prescribing a drug off-label, or waiting until traditional clinical trials are complete."

— Derek Angus, senior trial investigator and professor at University of Pittsburgh School of Medicine, told a press briefing

State of play: No treatments have been approved for COVID-19 yet. Researchers have made headway in mapping how the virus attaches and infects human cells -- helping "guide drug developers, atom by atom, in devising safe and effective ways to treat COVID-19," National Institutes of Health director Francis Collins writes.

- • But new drugs take a long time to develop, partly because they must first be tested for safety before broadening to test for safety and efficacy.
- • While many companies are working on new treatments, others have focused on testing drugs for other conditions that have already met safety requirements.

What's new: The University of Pittsburgh Medical Center (UPMC) is the first American hospital system to join an international treatment trial called REMAP-COVID19, which is enrolling patients with COVID-19 in North America, Europe, Australia and New Zealand so far.

How it works: Starting Thursday, UPMC's system of 40 hospitals began offering the trial to patients who have moderate to severe complications from COVID-19, Angus said.

- • Patients in the trial will receive their current standard of care. About 12.5% will receive placebo at the launch and the rest will be randomly selected to multiple interventions with one or more antibiotics, antivirals, steroids, and medicines that regulate the immune system, including the drug hydroxychloroquine.
- • The platform, based on an existing one called REMAP-CAP, is integrated with UPMC's electronic health records and the data collected via a worldwide machine-learning system that continuously determines what combination of therapies is performing best.
- • As more data is collected, more patients will be steered toward the therapies doing well, Angus said.
- • The adaptive trial format, published Thursday in the journal *Annals of the American Thoracic Society*, can allow new treatments to be rolled into the trial.

"This idea came to us after the H1N1 [epidemic], when everyone scrambled to do traditional trials" but by the time those were established, the outbreak had moved on, Angus said. "We asked, how we can do this better."

The big picture: There are more than 400 listed clinical trials for treatments, therapies and vaccines related to COVID-19.

- • These include trials led by the NIH, which is also testing hydroxychloroquine and the antiviral drug remdesivir.
- • Others plan to evaluate HIV drug Kaletra, Mesoblast's stem cell treatment, experimental antibody treatments like SAB-301, monoclonal antibody treatments like REGN3048 and REGN3051, amongst others.

Go deeper: Podcast: Hydroxychloroquine questions

Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date: 2020/04/10 09:32:51

Delivered Date:	2020/04/10 09:33:14
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Subject: Wpost: Trump keeps touting an unproven coronavirus treatment. It's now being tested on thousands in New York.

Date: 2020/03/26 15:46:35

Priority: Normal

Type: Note

Trump keeps touting an unproven coronavirus treatment. It's now being tested on thousands in New York.

By **Christopher Rowland**, **Jon Swaine** and **Josh Dawsey**

March 26, 2020 at 3:29 p.m. EDT

New York is moving at unprecedented speed and scale in a human experiment to distribute tens of thousands of doses of anti-malarial drugs to seriously ill patients, spurred by political leaders including President Trump to try a treatment that is not proved to be effective against the coronavirus.

With no proven treatment for the coronavirus, and infections in New York topping 30,000, health experts say the Food and Drug Administration has moved with uncommon speed to authorize New York's sweeping plan to distribute the drugs through hospital networks.

Planning for such a complex initiative would ordinarily take up to nine months, those experts say. In New York, the U.S. epicenter of the covid-19 pandemic, that timeline has been compressed into three days.

While the effort has raised concerns among health experts about safety risks to patients and raising false hopes in the American public, Trump's direct intervention into complex medical issues, as well as New York Gov. Andrew M. Cuomo's embrace of the strategy has generated popular excitement about the drugs.

The attention by political leaders also has contributed to runs on supply and hoarding, which New York and other states have tried to block with executive orders restricting prescriptions.

New York will use three medications — hydroxychloroquine and chloroquine in combination with the antibiotic azithromycin — contributed by the Federal Emergency Management Agency and an unnamed drug company, said a New York state health

official, who spoke on the condition of anonymity todiscuss evolving plans candidly, in an interview Wednesday.

The first wave of patients will receive hydroxychloroquine and azithromycin, the New York official said.

Launching such a plan, the official said, "is something that normally would have been done in six to nine months and we're doing it in three or fonr days."

Patient ontcomes from the experiment will be gathered electronically and contribute to an "observational" trial being coordinated by the government, the official said. In an observational trial, which is considered less rigorous than a controlled trial comparing a treatment with a placebo, researchers see if a therapy is safe and effective by gathering and comparing the resnlts iu a large database.

In addition to mortality and overall recovery, the study will measure patients' overall viral load, duration on a ventilator and number of days in the hospital.

The FDA would not comment on any aspects of the massive New York experimental effort, citing its own confidentiality rules.

Ground-level hospital administrators are scrambling to set up the reporting programs so outcomes data from patients treated with the drugs can be reported back to the state and federal authorities.

"I have never seen anything like this. It is amazing how the country and everybody can pull together and come up with quick, innovative ways to try to attack it," said Onisis Stefas, chief pharmacy officer for Northwell Health, which has 22 hospitals in New York and has already been using the anti-malarial drugs to treat patients on a "compassionate-use" basis.

"Everybody's questioning it, and that's why these studies need to be done to confirm it," he said. "There aren't a lot of other options out there."
The initiative is freighted with equal parts hope and politics, which some health-care officials and states suggest are eclipsing science.

Nevada, via executive order, this week banned prescriptions of the drugs for the coronavirus until the results of rigorous clinical trials are known.

"We must deal with facts, not fiction," Nevada's chief state medical officer, Ishan Azzam, said. Nevada is among states trying to stop ruus and hoarding that have depleted supply for people who need the treatments forestablished uses, including lupus patients. New York's Cuomo in an executive order has also limited new prescriptions of the anti-malarial drugs to patients with previously approved FDA conditions and to coronavirus patients participating in state-sponsored experiments.

Despite some tantalizing early results, there is scant published evidence that the two anti-malarial drugs will have a benefit for coronavirus patients. More rigorous controlled clinical trials are being conducted in the United States, including in New York and Minnesota, and around the world to prove whether the drugs will work. Anthony S. Fauci, head of the National Institute for Allergy and Infectious Diseases, has repeatedly cautioned, from the same White House lectern as Trump, that indications of benefit so far are anecdotal.

But in the ahsence of viahle alternatives, there has been a glohal rush to try the drugs. Doctors and hospitals have virtually wiped out U.S. supplies by prescribing them "off label."

The low-cost generic pills have been on the market for decades for malaria, lupus and rheumatoid arthritis. Many experts have said they believe they are relatively safe, although hydroxychloroquine can cause dangerous heart problems and some specialists recommend electrocardiogram screening tests, especially when used in combination with azithromycin. The drugs also can cause permanent eye damage called retinopathy.

The FDA's qnick action on large-scale observational trials was spurred by Trump's sudden interest in the anti-malarial drugs. As Fauci and others urged caution, Rep. Mark Meadows (R-N.C.), Trump's incoming chief of staff, contacted a family doctor in Upstate New York who claims to have used them to successfully treat hundreds of suspected covid-19 cases.

Vladimir "Zev" Zelenko, a doctor in Monroe, N.Y., said in an interview that he was contacted by Meadows after posting an unsolicited video message to Trump on Facebook in which he told the president: "Please advise the country that they should be taking this medication."

The doctor also published an open letter on Google Docs to fellow medics outlining a treatment plan of recommended doses, which was picked up by conservative media.

Zelenko said that over one call and several text messages, Meadows was "very kind and receptive," and told him his treatment plan was being evaluated at high levels. A person close to Meadows, who like others spoke on the condition of anonymity to candidly discuss internal deliberations, confirmed the two had been in touch this week about the drugs, and said White House experts were evaluating the plan.

Another official said Trump saw Zelenko's treatment plan on television and flagged it in the White House.

Sean Hannity, the Fox News host and informal Trump adviser, read from Zelenko's open letter during a telephone conversation with Vice President Pence that aired on his prime-time show Monday evening. Rudolph W. Giuliani, the president's personal attorney, championed Zelenko's treatment plan on Twitter the following morning.

Since the start of the coronavirus outbreak, Zelenko, 46, has shared material on Facebook suggesting that the virus may have been deliberately developed by China as a population control device and that its threat was exaggerated by Democrats.

Zelenko acknowledged the drugs could have side effects. "They're not candy," he said. "However, this is an unprecedented health crisis, the world's under attack, this is battlefield medicine."

Supporters of using anti-malarial drugs against the coronavirus have cited several published studies using small patient groups in France, Japan and China. Some other, equally small analysis, has suggested there is no benefit.

But within a matter of days afterTrump expressed his support for the drugs last week, Cuomo announced Sunday that 70,000 doses of hydroxychloroquine and up to 750,000 doses of chloroquine are in the pipeline for New York's patients.

"There's a good basis to believe they could work," Cuomo said Sunday.

Although the scale and urgency of New York's efforts are new, trying uuproven drugs on patients who otherwise might die is common in American health care for cancer and many other ailments including rare diseases. The FDA has the power to grant such "compassionate-use" permission, both on an individual basis and under blanket protocols for larger populations, specialists said.

Drug manufacturer Gilead Sciences has said it is working with the FDA to develop a new, broader program of compassionate nse for its experimental antiviral drug remdesivir. If successful, the broader program will allow doctors to get the drug for severely ill coronavirus patients without having to seek individual permission from the company and FDA for each patient.

"On this scale, I think it is unprecedented. I have never seen anything like this," said Dianne Bourque, a lawyer specializing in FDA rules at the firm Mintz. "We are seeing an explosion of compassionate-use requests and I think that's a factor of many of our clients trying desperately to find anything that works for desperately ill people right now.
"People are throwing everything at this," she said.

The FDA is working quickly to accommodate such requests, Bourque added, including issuing compassionate-use approval over the past weekend.

The FDA is clearly reacting to pressure from Trump and the general public, who are clamoring for some sort of treatment, said Alison Bateman-House, a professor of population health at New York University and a specialist in compassionate-use programs. She said the FDA is doing the best it can to balance competing interests in a time of crisis.

"It is very dangerous to take your medical advice from someone who does not actually practice medicine," she said of Trump's boosterism statements about the anti-malarial drugs at the White House. Yet, she said, there is some reason to believe the treatments could have a beneficial effect, so large-scale compassionate-use trials could be appropriate.

"The FDA is caught between saying it wants good science, and good processes, and what evidence-based medicine requires," she said, "and this is what our bosses, the people and the president are telling us they want.

"Sometimes safeguarding the public health ... is not what the public wants at a given moment," Bateman-House said. "They want unfettered access."

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/26 15:46:14
Delivered Date:	2020/03/26 15:46:35
Message Flags:	Unread

From:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject:	Wpost Live updates: Trump weighs loosening of restrictions to jolt economy, against health officials' advice
Date:	2020/03/23 16:47:45
Priority:	Normal
Type:	Note

Live updates: Trump weighs loosening of restrictions to jolt economy, against health officials' advice

March 23, 2020 at 4:24 p.m. EDT

Refresh for updates

President Trump is weighing calls from some Republican lawmakers and White House advisers to scale back steps to contain the coronavirus despite the advice of federal health officials as a growing number of conservatives argue the impact on the economy has become too severe, according to several people with knowledge of the internal deliberations.

Loosening restrictions on social distancing would override the internal warnings of senior U.S. health officials, including Anthony S. Fauci, who have said the worst of the pandemic has yet to be felt in the United States.

But President Trump signaled growing weariness with "social distancing" and other aggressive steps advocated by health officials. "We cannot let the cure be worse than the problem itself," the president said in a tweet written in capital letters.

Here are some significant developments:

- • The nation's governors are getting far better marks for their handling of the coronavirus outbreak than President Trump, according to a new Monmouth University poll. Fifty percent of Americans say Trump has done a good job handling the crisis, while 72 percent say governors have done a good job — results that are consistent regardless of party affiliation or severity of outbreak in a particular state. Just 38 percent said the American public is handling it well.
- • Michigan, Ohio, Louisiana and Oregon became the latest states to announce stay-at-home orders. The governors of Maryland and Massachusetts ordered nonessential businesses to close, and Virginia's governor said schools would remain closed for the rest of the academic year.
- • Virus-ravaged Italy marked 608 coronavirus deaths Monday, bringing its total to 5,476 — more than any other country. The daily figure remains very high, but it has not continued to rise. Spain extended its lockdown for another 15 days as the national death toll surged more than 25 percent. Spain now has more than 33,000 confirmed cases, and the prime minister warned that "the worst is yet to come."
- • Doubts are growing about whether the Tokyo Olympics will go ahead as originally scheduled. Japanese leader Shinzo Abe told parliament that the Summer Games could be postponed after Canada's Olympic Committee said it would not send its athletes to Tokyo this summer. Australian officials also hinted that they may not send a delegation to Japan.

- • Senator and former presidential candidate Amy Klobuchar (D-Minn.) said Monday that her husband, John Bessler, has coronavirus. Sen. Rand Paul (R-Ky.) on Monday defended his decision not to self-quarantine in the week following his test for the coronavirus — a test his office announced Sunday came up positive. And convicted rapist and former Hollywood producer Harvey Weinstein believes he has the virus as well. He is being held in isolation at an Upstate New York facility.

4:24 p.m.

Pence says White House will reevaluate social-distancing guidance at end of March

During a visit to the Federal Emergency Management Agency, Vice President Pence on Monday echoed President Trump's suggestion that the federal government will take another look at its social-distancing recommendations for all Americans at the end of March.

"We thought it was important for every American to take action as tens of millions are to help us slow the spread," Pence told reporters at FEMA. "But at the end of this 15 days, we're going to get with our health experts, we're going to evaluate ways in which we might be able to adjust that guidance for the American people."

The 15-day period is set to expire March 30.

Late Sunday night, Trump suggested — in an all-caps tweet — he is considering restarting the economy and scaling back steps to contain the coronavirus pandemic, despite the advice of public health officials. "WE CANNOT LET THE CURE BE WORSE THAN THE PROBLEM ITSELF," Trump said in the tweet. "AT THE END OF THE 15 DAY PERIOD, WE WILL MAKE A DECISION AS TO WHICH WAY WE WANT TO GO!"

By Felicia Sonmez

AD

4:10 p.m.

Norwegian Jewel passengers are finally leaving the once-stranded cruise ship

Norwegian Jewel, which was turned away from ports in New Zealand, Fiji and Hawaii amid fears of the new coronavirus, was finally allowed to let its 2,000 passengers off the ship — in Hawaii.

After announcing last week no ships would be allowed to disembark passengers in the state, officials said Sunday they were developing a plan with Norwegian Cruise Line to do just that. The ship already had permission to refuel and restock in Honolulu.

Passengers were scheduled to board charter flights to Los Angeles, Sydney, London, Vancouver, British Columbia and Frankfurt, Germany, on Monday and into Tuesday. Everyone will stay on the ship until three hours before their flights, according to the cruise line, and all passengers will go through "enhanced medical screening" before they disembark.

No one on Norwegian Jewel has a confirmed or suspected case of the virus. About 1,000 crew members are staying on board.

By Hannah Sampson

AD

3:09 p.m.

Trump weighs restarting economy despite warnings from U.S. public health officials

President Trump is weighing calls from some Republican lawmakers and White House advisers to scale back steps to contain the coronavirus despite the advice of federal health officials as a growing number of conservatives argue the impact on the economy has become too severe, according to several people with knowledge of the internal deliberations.

Loosening restrictions on social distancing would override the internal warnings of senior U.S. health officials, including Anthony S. Fauci, who have said the worst of the pandemic has yet to be felt in the United States.

"WE CANNOT LET THE CURE BE WORSE THAN THE PROBLEM ITSELF," Trump said in a late-night tweet Sunday. "AT THE END OF THE 15 DAY PERIOD, WE WILL MAKE A DECISION AS TO WHICH WAY WE WANT TO GO!"

The 15-day period is set to end March 30.

Fauci, a member of the president's coronavirus task force, and other leading public health experts have told administration officials and Republican lawmakers that prematurely scaling back social distancing measures would hamper efforts to mitigate the virus and devastate U.S. hospitals, according to the people with knowledge of the conversations who, like others, spoke on the condition of anonymity to describe the private deliberations. More than 30,000 people in the United States have tested positive for the coronavirus, a number expected to dramatically increase in the coming days and potentially overwhelm America's health-care infrastructure.

But the push to reopen parts of the economy has gained traction among Republican lawmakers.

Read more here.

By Josh Dawsey, Yasmeen Abutaleb, Jeff Stein and John Wagner

AD

2:43 p.m.

WHO says no confirmation yet that loss of sense of smell or taste is early sign of the novel coronavirus

There are widespread reports that a loss of the sense of smell or taste could be linked to the early stages of a novel coronavirus infection, but experts at the World Health Organization say that, so far, they have not confirmed it as a symptom.

"We don't have the answer to that yet, although there's quite a bit of interest in this online," Maria Van Kerkhove, head of WHO's emerging diseases and zoonoses unit, said at a daily news briefing on Monday.

Some doctors have suggested that a loss or significant change to the senses of taste and smell could indicate that a person is infected with the coronavirus. On Friday, a group of British doctors advised that anyone who experiences these sensory losses should isolate themselves for seven days, even if they have no other symptoms.

WHO officials did not say that this was false but noted that they would need more evidence to confirm the thesis.

"This is something that we need to look into to really capture," Van Kerkhove said, adding that a number of countries were collecting data on the symptoms of early infections and that information would be looked at systematically.

Van Kerkhove said WHO was reaching out to these countries to find out whether they have identified a loss of smell or taste as an early symptom.

"We have a good handle on what the major ones are: Those are fevers. This is dry cough, and this is shortage of breath," said Van Kerkhove, adding that aches and pains and headaches also were found, while some — though "very few" overall — patients have gastrointestinal problems, runny noses or sneezing.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Adam Taylor
AD
2:38 p.m.

United Nations leader calls for global ceasefire

United Nations Secretary General António Guterres wants warring rivals to put down their firearms to help stop the spread of the novel coronavirus.

Guterres said Monday that areas devastated by conflict are creating more people vulnerable to the virus. Ongoing violence will likely lead to a devastating spread of the epidemic, he said.

"The most vulnerable — women and children, people with disabilities, the marginalized and the displaced — pay the highest price," Guterres said. "They are also at the highest risk of suffering devastating losses from covid-19."

By Lateshia Beachum
AD
2:29 p.m.

Pentagon expects to deploy Army field hospitals to New York, Seattle

)

Defense Secretary Mark T. Esper expects to deploy two U.S. Army field hospitals to New York City and Seattle this week to help combat the coronavirus pandemic but said it would be up to the Federal Emergency Management Agency to make the final call on which cities would receive them.

Speaking at a Pentagon news conference Monday, Esper said "prepare-to-deploy orders" had been issued to five expeditionary medial units, including the Army field hospitals, which he said he expected to provide 248 beds each.

"We are looking at deploying our field hospitals — which include the hospital, the equipment and medical professionals," Esper said. "My aim is to get them out this week."

The defense secretary said he expects the pop-up hospitals to provide excess capacity for hard-hit areas, as local authorities identify buildings that can be converted into temporary hospitals.

In New York City, for example, the Army Corps of Engineers and FEMA have begun working with local authorities to convert buildings into makeshift hospitals. An Army field hospital, Esper suggested, could provide extra capacity in the meantime.

Army field hospitals are essentially pop-up medical facilities that the military erects in tents, often near a battlefield to treat the wounded.

In addition, Esper said two U.S. military hospital ships were deploying. The first of the two, the USNS Mercy, is slated to leave San Diego and deploy to Los Angeles on Monday.

Esper said that he had spoken with as many as 10 governors, all of whom requested hospitals or hospital ships, but that the Pentagon won't be able to meet all the need as the pandemic unfolds.

By Paul Sonne
AD
2:08 p.m.

Governors get better marks for handling outbreak than Trump, poll finds

The nation's governors are getting far better marks for their handling of the coronavirus outbreak than President Trump, according to a new Monmouth University poll.
Fifty percent of Americans say Trump has done a good job handling the crisis, compared with 45 percent who say he has done a bad job.
But that assessment pales in comparison with how Americans view the response of their governors. Seventy-two percent of the public says their state's governor has done a good job, compared with 18 percent who say their governor is doing a bad job.
Positive reviews for governors are fairly consistent regardless of how widespread the outbreak is in the various states, according to Monmouth.
Trump's approval breaks sharply along partisan lines.
Eighty-nine percent of Republicans say he's doing a good job handling the outbreak, while 19 percent of Democrats agree. Among independents, 48 percent say Trump is doing a good job.
Public praise for the governors is much more consistent along party lines, with 76 percent of Democrats saying their governor is doing a good job and 73 percent of Republicans taking that view. Meanwhile, 67 percent of independents say their governor is doing a good job.
The poll also found that the American public doesn't give itself very high remarks for its response to the pandemic. Just 38 percent say the American public has done a good job dealing with the outbreak, while 45 percent say it has done a bad job.
Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.
By John Wagner
AD
2:03 p.m.

Italy announces 608 new deaths, slightly lower figure than in previous days

The Italian government announced Monday that the death toll from the novel coronavirus outbreak had increased by 608 to 5,476.
The number of cases had increased by 4,789 to bring the total to 63,927, according to Italy's Civil Protection agency.
The news was greeted with tentative optimism in Italy, as both figures showed a decline from the higher increases only a few days ago, suggesting that Italy's strict social-distancing measures may be slowing the outbreak.
The president of the national health service, Silvio Brusaferro, told reporters Monday that while it was not yet time to proclaim victory, Italy was finally seeing "the light at the end of the tunnel."
On Saturday, Civil Protection officials had announced 793 deaths from the coronavirus, and a day later they had announced 651. The rate of discovery of new cases also appeared to be slowing, down to an 8.1 percent increase on Monday from 13.5 percent on Saturday.
Italy remains the epicenter of the outbreak outside China, which still has the largest number of confirmed cases, though the death toll in Italy is higher. The infection rate among health workers also appears to be higher in Italy, according to officials.
On Monday, the Italian doctors association FNOMCEO said 24 doctors had died. A total of 4,824 health operators have been infected, according to Italy's Higher Health Institute (ISS).
In an earlier interview on Monday, Prime Minister Giuseppe Conte said Italy would need to redouble its efforts to beat the coronavirus. "The survival of the social and economic fabric of our country is at stake," Conte told La Stampa.

By Adam Taylor
AD
1:57 p.m.

More states order residents to stay indoors

As the novel coronavirus continues to cross state lines and claim lives in its wake, governors are issuing orders aimed at flattening the curve.

Michigan

On Monday, Michigan Gov. Gretchen Whitmer (D) ordered citizens to stay home and closed nonessential businesses for at least the next three weeks while the state tries to lower its growing total of positive coronavirus cases.

The order begins at 12:01 a.m. on Tuesday. Michigan has recorded 1,232 confirmed cases and 15 deaths as of Monday, Whitmer said in a news conference.

Michigan's rising caseload will likely cause a severe strain on the state's health-care system, Whitmer said. Pharmacies, grocery stores, gas stations and banks will remain open, as will delivery and carryout at restaurants. Other nonessential businesses could face fines and closure, she said.

A lack of direction and medical supplies from the federal government has exacerbated the situation in Michigan, Whitmer said. Michigan recently received its allotment from the National Strategic Stockpile, and it was barely enough to cover one shift at a local hospital, Whitmer said.

Schools will remain closed at least through April 13, and state leaders are exploring how people can cast their ballots at home in local elections in May, she said.

Massachusetts

Massachusetts Gov. Charlie Baker (R) issued a similar order that will take effect from noon on Tuesday until April 7 at noon. Baker said at a Monday news conference that he will also direct the state's Department of Public Health to issue a "stay at home advisory" that will outline self-isolation and social-distancing protocols.

The order came shortly after city and state representatives pressured him to sign a "stay at home order" in a public letter.

"I do not believe I can or should order U.S. citizens to be confined to their homes for days on end," he said, saying such an order did not make sense and was not realistic.

Baker's order will likely be enforced at the local level and carries a graduated set of penalties.

Maryland

Maryland Gov. Larry Hogan (R) also ordered all nonessential business shut down at 5 p.m. on Monday following a previous mandate of closing down casinos and racetracks earlier in the month.

Indiana

Indiana Gov. Eric Holcomb (R) delivered sweeping orders on Monday for Hoosiers to remain inside with exceptions for going out for essentials or for health-care needs.

Holcomb will also close the doors to all state government offices. Orders are effective from March 25 to April 7.

Hoosiers with soon-expiring licenses or registrations will receive an automatic extension from the governor that will prevent law enforcement from issuing citations for expired materials during the state's emergency.

By Lateshia Beachum
1:56 p.m.

Harvey Weinstein placed in isolation in prison as reports surface that he tested positive for coronavirus

Harvey Weinstein, who is serving a prison sentence in Upstate New York for sexual assault and rape, has tested positive for the novel coronavirus, according to the Associated Press.

The disgraced Hollywood producer, 68, arrived at a correctional facility near Buffalo last week after being housed at New York City's Rikers Island jail, where several inmates have tested positive for the virus.

Weinstein's test came back positive Sunday morning, Michael Powers, head of the New York State Correctional Officers and Police Benevolent Association, told Reuters. In an interview with The Washington Post on Monday, Powers said he was basing that information on the fact that Weinstein is in isolation, as are staff members who came into contact with him.

"I can't necessarily speak to anybody's health, but it's pretty well-known that as of yesterday he was confined and quarantined and isolated, and many of our members who were in that transport and dealt with Mr. Weinstein in any way, shape or form are in quarantine," Powers said.

Monday afternoon, Weinstein's publicist said in a statement that his team had been in touch with prison officials and are aware of his medical condition, but "at this time, we will neither confirm nor deny whether Mr. Weinstein has tested positive for the covid-19 virus. ... We will not discuss this matter any further."

The once-powerful producer was sentenced to 23 years in prison earlier this month for forcing oral sex on a former production assistant, Mimi Haleyi, and raping Jessica Mann, a onetime aspiring actress. After the verdict, Weinstein was taken to a hospital in New York for heart surgery. He has also experienced other medical issues, including diabetes and high blood pressure.

Powers said he was concerned about corrections officers at the New York facility who may have come in contact with Weinstein, as they lack the right protective equipment and several have already been quarantined.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Teo Armus and Emily Yahr

1:49 p.m.

Sen. Rand Paul defends decision not to self-quarantine after testing

Sen. Rand Paul (R-Ky.) on Monday defended his decision not to self-quarantine in the week following his test for the coronavirus — a test his office announced Sunday came up positive.

In a statement, Paul said at the time of the test, which he underwent in Washington, he felt it was "highly unlikely" he would be positive "since I have had no symptoms of the illness," and he was not aware of having had contact with anyone who had tested positive.

Paul said he decided to get tested because he and his wife had been traveling extensively, and he was considered at higher risk because he had part of his lung surgically removed seven months ago in the aftermath of injuries suffered in 2017 when he was attacked by his neighbor.

"For those who want to criticize me for lack of quarantine, realize that if the rules on testing had been followed to a tee, I would never have been tested and would still be walking around the halls of the Capitol," Paul said in his statement. "The current guidelines would not have called for me to get tested nor quarantined. It was my extra precaution, out of concern for my damaged lung, that led me to get tested."

Word of Paul's diagnosis Sunday prompted two of his fellow senators, Republicans Mike Lee and Mitt Romney, both of Utah, to announce they were self-quarantining because of their recent contact with him.

In his statement, Paul also cast doubt on one possibility of how he could have contracted the virus: his presence at a Speed Air Museum fundraiser in Louisville on March 7 attended by two people who later tested positive for the coronavirus.

"Unlike the other Kentucky government officials there, I had zero contact or proximity with either of the two individuals who later announced they were positive for COVID-19," Paul said, referring to the disease caused by the virus. "The event was a large affair of hundreds of people spread throughout the museum. ... I was not considered to be at risk since I never interacted with the two individuals even from a distance and was not recommended for testing by health officials."

By John Wagner

1:32 p.m.

New York governor says shutting off the economy was necessary, but unsustainable long-term

New York Gov. Andrew M. Cuomo (D), whose state is at the center of the coronavirus pandemic in the U.S., said Monday that he had "no second thoughts" about shutting down the economy by halting nonessential business.

But he said he was also aware that the shutdown is unsustainable, and that the state needs to begin planning how to restart the economy.

"I take total responsibility for shutting off the economy in terms of essential workers," Cuomo said during a news conference. "But we also have to start to plan the pivot back to economic functionality, right? You can't stop the economy forever."

His comments came as Trump signaled a sense of weariness with the economic toll of social distancing, tweeting Monday that "WE CANNOT LET THE CURE BE WORSE THAN THE PROBLEM ITSELF."

Asked about the president's comments, Cuomo responded that "you have to walk and chew gum in life" and no executive "has the luxury of being one-dimensional."

He said he stood by the measures taken, yet recognizes the economic ramifications.

"It is unsustainable to run this state or run this country with the economy closed down," he said. "We're spending hundreds of millions of dollars, you have people laid off — you have to get the economy up and running. So that has to be planned at the same time."

The governor said officials needed to begin to think about whether there was a point where some people — potentially those who are younger or have recovered from the virus — could return to the workforce. He said the idea was to balance "smart public health policy and smart economic policy."

He stressed, however, that the actions taken so far have not been overkill.

"I had a gentleman tell me, 'There's no way this state will ever reelect you because of what you did,' " Cuomo said. "Frankly, I don't even care about that. I did the right thing, and I'm proud of it."

By Brittany Shammas

1:13 p.m.

The new coronavirus is an evil genius. This is how it works in your body.

The deadly new coronavirus is little more than a packet of genetic material surrounded by a spiky protein shell one-thousandth the width of an eyelash, and it leads such a zombielike existence that it's barely considered a living organism.

But as soon as it gets into a human airway, the virus hijacks our cells to create millions more versions of itself.

There is a certain evil genius to how this coronavirus pathogen works: It finds easy purchase in humans without them knowing. Before its first host even develops symptoms, it is already spreading its replicas

everywhere, moving onto its next victim. It is powerfully deadly in some but mild enough in others to escape containment.

SARS-CoV-2 dwells in the upper respiratory tract, where it is easily sneezed or coughed onto its next victim. But in some patients, it can lodge itself deep within the lungs, where the disease can kill. That combination gives it the contagiousness of some colds, along with some of the lethality of its close molecular cousin SARS, which caused a 2002-2003 outbreak in Asia.

When viruses encounter a host, they use proteins on its surfaces to unlock and invade its unsuspecting cells. Then they take control of those cells' own molecular machinery to produce and assemble the materials needed for more viruses.

"It's switching between alive and not alive," said Gary Whittaker, a Cornell University professor of virology. He described a virus as being somewhere "between chemistry and biology."

Read more here.

By Sarah Kaplan, William Wan and Joel Achenbach

12:19 p.m.

Sen. Klobuchar says her husband has tested positive

Sen. Amy Klobuchar (D-Minn.) said Monday that her husband, John Bessler, a law professor at the University of Baltimore, has coronavirus.

After sharing the news on Twitter, Klobuchar elaborated on her husband's situation during a previously planned conference call advocating vote-by-mail options in the midst of the coronavirus outbreak.

"I just wanted to reiterate that one of the hardest things about this disease is he's in the hospital — he's been there a few days — and I can't even be by his side," Klobuchar said. "I think many families in America are now experiencing this and things that are much, much worse."

She said it took five days to get her husband's test back.

"I want to remind people that this is going to happen to everyone [having a loved one who contracts the virus], and it's why we need to take incredibly fast and immediate measures now" to bolster the health-care system and contain the spread, she said.

Klobuchar, who ended her presidential bid earlier this month, has been in Washington for anticipated votes on a stimulus bill that is being crafted in response to the coronavirus outbreak.

Klobuchar said in a statement that she and her husband have "been in different places for the last two weeks and I am outside the 14-day period for getting sick."

"My doctor has advised me to not get a test," she said. "As everyone is aware, there are test shortages for people who need them everywhere and I don't qualify to get one under any standard."

Sen. Rand Paul (R-Ky.) on Sunday becamethe first member of the Senate to announce he had tested positive for the coronavirus, prompting some of his colleagues to self-quarantine. Last week, Reps. Mario Diaz-Balart (R-Fla.) and Ben McAdams (D-Utah)announced they had tested positive.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By John Wagner and Elise Viebeck

12:17 p.m.

Merkel tests negative in initial screening; Germany's exponential virus growth curve may be flattening, top health official says

BERLIN — German Chancellor Angela Merkel has tested negative in her first screening for the novel coronavirus, a government spokesman said Monday.

The German leader has been in isolation since Sunday after being informed that a doctor she met with on Friday had tested positive for the coronavirus. Her office has said she is not experiencing any symptoms.

Spokesman Steffen Seibert told the news agency DPA that Merkel would continue to be tested for the virus.

"More tests will be done in the next few days," Seibert said.

Lothar Wieler, president of the German governmental agency responsible for disease control, also indicated Monday that measures undertaken in the past weeks may already be having an effect, after Merkel announced tougher restrictions on social contacts to curb the spread of the coronavirus.

"We see the trend that the exponential growth curve is somewhat flattening," Wieler said about new coronavirus cases in Germany.

"I am optimistic that these measures are already visible," he said of the country's efforts to implement social-distancing policies. In a news conference on Monday morning, he acknowledged that the signs of a flattening curve are still early, as the social-distancing rules have been in place only for a week in most states.

On Sunday, Merkel said human contact in public spaces should be limited to two people. The new rules, which she advised were not recommendations and would be enforced, apply only to those outside of the household, meaning members of a household living together could socialize in public.

All restaurants would be closed, with exceptions for takeout and delivery, Merkel said, as would hairdressers and other services that require close contact. Whenever possible, a distance of five feet should be maintained between people, the German leader said.

Germany has had nearly 26,000 confirmed cases of the novel coronavirus, the fifth-most of any nation, yet only slightly more than 100 deaths, far fewer than Italy, France, Spain and other European countries.

Adam Taylor contributed to this report.

By Luisa Beck and Rick Noack

12:12 p.m.

Social distancing necessary to save lives as public hospitals face potential overburdening, NYC mayor says

As President Trump appeared to show an interest in potentially scaling back "social distancing" measures, the mayor at the center of the U.S. outbreak argued Monday that the dramatic action was necessary to save lives.

Speaking during an appearance on CNN's "New Day," New York Mayor Bill de Blasio (D) questioned whether the country was willing to "turn away and ignore the challenges" facing those who are most vulnerable to the coronavirus. He said that if left unchecked, the virus will overburden the health-care system to the point where it cannot function.

"I understand people who say, 'Wow, this is an extraordinary sacrifice,' " de Blasio said. "It is, but if you don't slow this thing down, you'll sacrifice a lot more on the other end of the equation, and we've got to think about the human cost here."

With 10,764 confirmed cases and 99 fatalities as of Sunday, New York City has emerged as a hot spot for the virus. Its cases accounted for about third of those across the United States by Sunday, although officials noted that New York is testing more than any other state.

At that rate, de Blasio said, New York City's 11 public hospitals only have enough equipment and supplies to get through this week. He said the city was in desperate need of ventilators, and appealed to private citizens to provide them if possible.

"If we don't get ventilators this week, we're going to start losing lives we could have saved," de Blasio said. "I can't be blunter than that."
By Brittany Shammas
10:31 a.m.

Japan starts to plan for Olympics postponement; imposes 14-day self quarantine on U.S. travelers

TOKYO — Japan will ask visitors arriving from the United States to undergo 14 days of self-quarantine in the country, effective Thursday until the end of April, Prime Minister Shinzo Abe said Monday.
During that time, visitors will be asked to remain in places designated by the quarantine office and avoid public transportation, Abe said.
The move mirrors existing restrictions on visitors arriving from 38 countries, including the European Union, Britain, Egypt and Iran.
On Sunday, Japan's Foreign Ministry warned citizens to avoid nonessential travel to the United States, raising its travel advisory a notch to level 2.
Japanese authorities have also finally bowed to the inevitable and said Monday that they would start planning for a possible postponement of the Tokyo 2020 Summer Olympics because of the pandemic, with a decision expected within four weeks.
Yoshiro Mori, president of the Tokyo 2020 Organizing Committee, said the decision to consider a postponement, but not a cancellation, of the Games had been agreed to with International Olympic Committee President Thomas Bach on Sunday. Bach broke the news to athletes Sunday.
"What we are going to do before anything else is to start by simulating about whether we postpone one month, three months, five months, one year," Mori said. "We need to make a simulation about the various scenarios."
Japan had insisted until now that the Games must go ahead, although Abe said last week that the priority must be to hold the Olympics in a "complete manner."
Mori said the IOC and Japan would like to "closely examine" the various scenarios open to them over the next four weeks, adding that they would not start with the assumption that the Games would definitely have to be postponed but couldn't avoid discussing that possibility.
Read more here.
Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.
By Simon Denyer and Akiko Kashiwagi
10:06 a.m.

'We really, really need everyone to stay at home,' U.S. surgeon general says

U.S. Surgeon General Jerome M. Adams warned Monday of a worsening crisis in America as some people continue to disregard messages to stay home.
People choosing to visit beaches and national parks or spend time crowding around Washington's cherry blossoms is how the virus is going to keep spreading, Adams told NBC's "Today" show Monday.
Adams reminded the public that the numbers of coronavirus cases they see reported reflects what happened two weeks ago and stressed that mitigation measures, such as practicing social distancing and postponing elective surgeries, are designed to ignite a sense of urgency in Americans.

He noted, however, that they are only effective as early preventive tactics. Positive cases of coronavirus have ballooned to more than 35,000 in the United States, according to Johns Hopkins University &Medicine, although experts agree that the actual number of U.S. cases is much higher.

"Everyone needs to act as if they have the virus right now," Adams said, echoing words from the director of the National Institute of Allergy and Infectious Diseases, Anthony S. Fauci. "You could be spreading it to someone else, or you could be getting it from someone else. Stay at home."

Adams warned that all people are in danger of becoming infected and that the disease could potentially have a fatal result. He pointed to social media influencers such as Kylie Jenner as being able to spread the message about how important staying home is.

As most of the public is being asked to remain indoors, medical professionals who don't have the option to stay home are asking the president to enforce the Defense Production Act to boost supplies. The president has avoided invoking the law.

The government is already working with medical-supply makers such as 3M, Honeywell and Hanes to boost reserves of protective equipment for front-line workers, Adams said. Companies are producing at their maximum capacity to meet the demand, but the public has a role in decreasing the need for these items, he said.

"We're not going to ventilate out of this problem; we're not going to treat our way out of this problem," he said. "The way you stop the spread of an infectious disease like this is with mitigation measures and preventing people from getting it in the first place."

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Lateshia Beachum

10:00 a.m.

UAE, world-leading aviation hub, suspends all passenger flights and closes malls amid spike in cases

DUBAI — The United Arab Emirates, a global travel hub with a robust tourism sector, announced early Monday that in two days all incoming and outbound passenger flights would be suspended for the next two weeks to stem the spread of the novel coronavirus.

The announcement came with additional restrictions on daily life in the country. In two days, all shopping centers and malls will be shut down and restaurants will be allowed to serve meals only on a delivery or takeout basis. Residents are also being urged to wear face masks and remain home as much as possible.

Later on Monday, the Ministry of Health revealed that there were 45 new infections in the country — the biggest increase to date — bringing the total number of cases 198. There were two deaths over the weekend. According to the ministry, one person traveling from abroad did not observe home quarantine and went on to infect 17 others.

The decision to ban all flights follows contradictory messages on Sunday from the Emirates airline, the nation's flagship carrier. It first said it was phasing out all passenger flights and then clarified a few hours later that it was actually maintaining routes to several countries, including the United States and Britain. Emirates is one of the world's premier long-haul airlines, and its home base of Dubai is the world's busiest airport for international travel.

The new restrictions in the UAE bring it closer in line with its neighbors in the Persian Gulf region that have already closed restaurants and stores. Over the weekend, Saudi Arabia and Kuwait both went a step further and ordered nighttime curfews to stop people from going out and congregating. Saudi Arabia on Monday reported a jump of 115 new cases, bringing its total to 511.

The island kingdom of Bahrain, meanwhile, reported its second death from the coronavirus, a 51-year-old woman with "underlying medical issues," according to the Health Ministry. Bahrain has 334 cases. The victim returned from nearby Iran with the virus. Iran has the most cases in the region, with more than 21,000 reported infections.

By Paul Schemm

9:53 a.m.

Cuba dispatches medical brigade to hard-hit Italy

MIAMI — Cuba dispatched a 52-member medical brigade to help combat the still-exploding cases of the novel coronavirus in Italy, upholding a tradition of sending its physicians to help fight dangerous global outbreaks.

Members of the medical team, wearing masks and holding a Cuban flag as they disembarked, arrived on Sunday at Milan's Malpensa Airport, according to a video posted to Twitter by José Carlos Rodriguez Ruiz, Cuba's ambassador to Italy. The team's arrival follows the deployment of Cuban doctors to confront the pandemic in several nations in Latin America and the Caribbean — including Venezuela, Nicaragua, Guyana, Jamaica and Suriname.

Cuba's communist government, with the aid of the former Soviet Union, built its public health system during the Cold War, obtaining one of highest rates of doctors per capita in the developing world. Its medical system has been in decline since the fall of the Berlin Wall, but Cuba has still sent teams of medics to aid in international health crises, including the Ebola outbreaks in Africa.

Longer-term deals to station Cuban doctors abroad have brought financial windfalls for the Cuban government, although doctors receive little pay. In recent years, the Trump administration has sought to persuade Latin American countries to cancel contracts for Cuban doctors, resulting in the expulsion of hundreds of doctors from countries including Brazil, Bolivia and Ecuador.

The move to aid Italy marks a relatively rare Cuban medical mission to the developed world. Cuba's Health Ministry has confirmed 25 confirmed cases of covid-19 domestically, with 716 more suspected patients.

President Miguel Díaz-Canel announced late Friday that Cuba would close its borders to foreign nonresidents for 30 days, a decision likely to further slam a tourism industry already reeling from Trump administration efforts to sharply curtail American visitors to the island.

By Anthony Faiola

9:19 a.m.

Trump signals growing weariness with 'social distancing' and other steps advocated by health officials

President Trump is signaling interest in scaling back "social distancing" and other steps promoted by health officials to contain the novel coronavirus as a growing number of conservatives argue that impact on the U.S. economy has become too severe.

"WE CANNOT LET THE CURE BE WORSE THAN THE PROBLEM ITSELF," Trump said in a late night tweet Sunday written in capital letters. "AT THE END OF THE 15 DAY PERIOD, WE WILL MAKE A DECISION AS TO WHICH WAY WE WANT TO GO!"

The White House has promoted a 15-day period — started March 16 and set to expire later this month — to "slow the spread" of the deadly virus that includes following directions of state and local authorities that have resulted in shuttered schools, restaurants and other businesses.

Trump's tweet appeared to reflect impatience with the economic toll of such moves, and retweets by the president early Monday morning added to doubts about whether he is committed to staying the course.

Read more here.

By John Wagner
9:10 a.m.

The U.S. and Iran trade allegations of virus mismanagement as Iran urges nations to defy U.S. sanctions

BEIRUT — Secretary of State Mike Pompeo traded accusations of coronavirus mismanagement with Iran's leaders on Monday as Iran stepped up a campaign for relief from U.S. sanctions to help it deal with the crisis.

In a statement, Pompeo accused Iranian officials of lying about the true scale of its coronavirus crisis, of continuing flights to China as the covid-19 disease was spreading, of stealing money intended for medical supplies and hoarding medical equipment such as masks and gloves to sell on the black market. He was responding tocomments made by Supreme Leader Ali Khamenei on Sunday who rejected an offer of U.S. help on the grounds the United States may have created the coronavirus and therefore could not be trusted to help. Also, he added, the United States is failing to manage its own coronavirus problem.

The spat came as Iranian leaders called on world leaders to bypass U.S. sanctions on Iran to help it battle the coronavirus.

On his Twitter account, Iranian Foreign Minister Mohammad Javad Zarif said the United States is "impeding" the global effort to fight the pandemic.

"The ONLY remedy: DEFY U.S. mass punishment," he wrote.

Iran's Health Ministry said the number of infections had jumped by 1,411 to 23,049 in the past 24 hours. An additional 127 Iranians had died, it added, bringing the death toll to 1,812. Iran has the highest reported number of coronavirus cases in the Middle East and is the origin of many infections elsewhere in the region.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Liz Sly
8:39 a.m.

India and Jordan recommend limited use of anti-malaria drug promoted by Trump in fight against virus

NEW DELHI — India has recommended that medical workers and close contacts of people infected with the novel coronavirus be given "prophylactic" doses of an anti-malaria drug whose effectiveness in combating covid-19 remains unproven.

The recommendation is "only for prevention [and] only in these two circumstances," Balram Bhargava, the director general of the Indian Council of Medical Research, told reporters on Monday. The drug — hydroxychloroquine — would be available by prescription and should not instill a sense of "false security" in those taking it, the medical council said.

In Jordan, meanwhile, health authorities authorized the use of the drug as part of a strategy to treat serious cases of covid-19 but not as a preventive measure, reported Al Jazeera.

President Trump is a vocal proponent of making hydroxychloroquine widely available, against the advice of his own medical experts who say a large clinical trial must be conducted first.

In Nigeria, three people were hospitalized after overdosing on the drug, CNN reported. That prompted a senior health official to issue a statement saying there was no "hard evidence" of the drug's effectiveness in preventing or managing covid-19.

Nigeria currently has 22 confirmed cases.

By Joanna Slater

8:37 a.m.

Virus impact could burden societies for years, says OECD secretary general

The economic fallout of the global coronavirus pandemic could "burden our societies for years to come," Angel Gurría, secretary general of the Organization for Economic Cooperation and Development (OECD), wrote in an op-ed.

As the global economy appears headed for a prolonged downturn, Gurría said a recovery effort akin to President Franklin D. Roosevelt's New Deal or to the post-World War II Marshall Plan may be needed.

Gurría added the current impact of the pandemic — with millions of people under lockdown, supply chains disrupted and stocks highly volatile — already poses a bigger challenge than the 2008 financial crisis, according to the BBC.

"Even if you don't get a worldwide recession, you're going to get either no growth or negative growth in many of the economies of the world, including some of the larger ones, and therefore you're going to get not only low growth this year, but also it's going to take longer to pick up in the future," Gurría said, the BBC reported.

By Rick Noack
8:37 a.m.

Exhausted and bruised: Photos of Italian health workers fighting the pandemic go viral

With Italy emerging as the new epicenter of the global coronavirus outbreak, nurses and doctors working around the clock to save lives in the country are sharing photos of what it looks like to be fighting an out-of-control pandemic.

Their faces marked pink and purple from protective masks and their bodies tired from grueling hospital shifts, health workers are earning the respect of people worldwide with their hard-working, empathetic approach to the crisis — despite the dangerous and painful circumstances.

Many on social media have labeled the staff heroes, thanking them for their service at such an unprecedented time.

Italy has more than 46,000 active cases of the virus and 5,476 deaths. The country now has more fatalities than China, where the outbreak began late last year.

Earlier this month, Italian nurse Alessia Bonari took to her Instagram account to share a photo of herself after a shift at the hospital. The post generated more than 1 million likes, with thousands of people from around the world offering her their well-wishes and love.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Jennifer Hassan
8:28 a.m.

Fauci gets frank about Trump: 'I can't jump in front of the microphone and push him down'

Amid the ongoing coronavirus pandemic, Anthony S. Fauci, head of the National Institute of Allergy and Infectious Diseases, has been charged with a herculean task: trying to keep President Trump's public statements about the novel virus rooted in fact.

Now it appears that Fauci's frustration is showing.

When asked Sunday by Science magazine's Jon Cohen about having to stand in front of the nation as "the representative of truth and facts" when "things are being said that aren't true and aren't factual," the 79-year-old said there is only so much he can do.

"I can't jump in front of the microphone and push him down," Fauci said, referencing Trump. "Okay, he said it. Let's try and get it corrected for the next time."

The frank comment was just one part of a remarkable Q&A published Sunday in which Fauci shed light on his relationship with Trump, how the pair handles their differences and what happens before each coronavirus task force news conference.

On more than one occasion, Fauci has found himself in the uncomfortable position of having to publicly contradict the president — a risky action that could conceivably jeopardize the scientist's job.

Fauci acknowledged as much.

"To my knowledge, I haven't been fired," he told Cohen, laughing.

Read more here.

By Allyson Chiu

8:02 a.m.

Berlin struggles to keep its homeless population safe

BERLIN — The German capital of Berlin is planning to open a new shelter for its homeless residents by the end of this month, as Germany asks people to isolate themselves inside to slow infection rates. Homeless populations are particularly vulnerable to infections and the consequences of the coronavirus crisis.

"Many have preexisting conditions or suffer from addictions," said Kai-Gerrit Venske, a specialist on homelessness for the aid organization Caritas in Berlin. Shelters are often crowded, making social distancing nearly impossible.

"We are now trying to place beds farther apart," said Venske about ways his organization's shelters are trying to adapt to the coronavirus outbreak. "But there are no standards. Everyone is trying to reduce risks as much as possible."

Approximately 2,000 people are living on the streets in Berlin, according to a recent count by volunteers throughout the city, though some experts say the actual number is much higher. Berlin's total population is over 3.7 million people.

Tourists and locals who would in normal times donate money or food are staying away or indoors. Volunteers, many of whom are elderly and belong to at-risk groups, have isolated themselves.

The new shelter that is scheduled to open in Berlin will provide food, medical services and addiction counseling, according to Berlin city spokesman Stefan Strauß. Giving up drugs will not be a precondition for getting shelter, as that would keep people away, he said.

"We have to accept the problem," he said. "So we're offering a controlled use of drugs."

Psychological counseling will also be offered at the new shelter. "Many homeless people are no longer used to being in a facility during the day or in closed rooms," said Strauß. "We have to assume that it is also difficult for some to live in an accommodation at all."

By Luisa Beck

7:50 a.m.

India suspends domestic flights as cities go into lockdown mode

NEW DELHI — India's largest cities are shutting down everything but essential services and closed nearly all public transportation until the end of the month in a dramatic bid to check rising coronavirus infections.

The Civil Aviation Ministry also announced the suspension of all domestic flights from midnight Tuesday. Coupled with the cancellation of all passenger trains announced by the Railway Ministry on Sunday, this move brings the country to a virtual halt. Last week, all international flights were barred from landing in the country until March 29.

Although India has reported just seven deaths and 415 confirmed cases, much lower than Europe or the United States, its poor health infrastructure and high population density make it vulnerable to the threat posed by the virus.

In New Delhi, which includes the country's capital, authorities issued lockdown orders, asking residents to stay home, and sealed borders with two neighboring states. Mumbai, the financial capital, shut down its suburban train network that ferries 8 million people daily.

In Kolkata, in eastern India, the government shut down all commercial establishments and banned gatherings of more than seven people. Hyderabad, another major metropolis, ordered all private establishments that have been shut down to pay full salaries to employees and announced a one-time cash grant to the poor. Bangalore, a technology hub in south India, mandated all IT firms to institute work-from-home policies.

Services like groceries, pharmacies, banks and gas stations have been deemed essential and will remain open. Together the restrictions affect more than 65 million people, larger than the entire population of Italy.

On Sunday, a nationwide public curfew brought the country of 1.3 billion to a standstill. But the prime minister's call for people to come out to clap and bang utensils to thank health workers spawned confusion.

At 5 p.m., in several cities, people gathered in large groups in celebration, defeating the purpose of the curfew and leading some to criticize the government for its messaging tactics.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Niha Masih and Joanna Slater

7:17 a.m.

'Worst is yet to come': Death toll in Spain again surges more than 25 percent

The death toll from the coronavirus in Spain surged more than 25 percent within a day, according to authorities, rising from 1,720 on Sunday to 2,182 on Monday.

Confirmed cases in the virus-ravaged nation increased to 33,089 on Monday — one day after Spanish Prime Minister Pedro Sánchez said his government is planning to extend a nationwide lockdown an additional 15 days.

After Italy, Spain has been the hardest-hit country in Europe, with many cases centered in the capital, Madrid.

The Spanish government has taken drastic steps to curb new infections. More than one week ago, Spain became the second European country to impose a nationwide lockdown, ordering its more than 47 million people to mostly stay in their homes. Exceptions are made only for essential reasons, including work, medical appointments or to buy food.

Last Thursday, Spain also ordered all of its hotels to shut down within seven days.

"The worst is yet to come. We haven't reached the worst wave that will test the outer limits of our resources," Sánchez said in a televised address to the nation Sunday. "We have to gain time to get ahead of this risk."

The prime minister announced additional measures that allow the military to move patients, as well as further restricting travel from other countries, and the creation of a reserve stock of health supplies for future needs.

Pamela Rolfe contributed to this report.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Rick Noack
7:05 a.m.

'Hands, washing hands': Singers change up their lyrics for the coronavirus

In these strange times, no one can fault you for thinking that Neil Diamond wrote the first lines of "Sweet Caroline" about a pandemic.

"Where it began, I can't begin to knowing," the classic song opens. "But then I know it's growing strong."

The rest is not far off, either: "Was in the spring," he sings — presumably about a love affair.

Well, Diamond played on the 1969 hit in a video he posted to Twitter on Sunday, changing up the lyrics and turning everyone's favorite crowd-pleasing singalong into an anthem for social distancing.

"Hands, washing hands," he croons in the video, flanked by a lit fireplace and his dog Shamrock. "Don't touch me, I won't touch you."

He's not the only famous performer to do so. Last week, singer JoJo took to TikTok to perform a similarly amended version of her 2011 hit, "Leave (Get Out)," instead telling her fans to "stay in, right now — do it for humanity."

"Tell me why you're acting so confused, when the CDC laid it out for you," she asks, snapping her fingers and drumming on a kitchen table. "Come on, I know you're not dumb."

It hasn't been so successful for everyone. Last week, a cadre of celebrities assembled by Gal Gadot of "Wonder Woman" drew the collective scorn of the Internet after they urged viewers to stay strong while crooning out John Lennon's "Imagine" — presumably, from the comfort of their own very large homes.

But JoJo and Diamond both received warm receptions on social media, where fans praised them for lifting their spirits.

"I know we're going through a rough time right now," the 79-year-old songwriter said in his video. "But I love you, and I think maybe if we sing together, maybe we'll just feel a little bit better."

Let's just not get started on Madonna.

By Teo Armus
6:50 a.m.

Kiwis, stay home: Prime Minister Jacinda Ardern prepares New Zealand for month-long lockdown

New Zealand Prime Minister Jacinda Ardern announced Monday that the country would soon be moving to the highest alert level to save lives amid the growing coronavirus outbreak.

In a news conference, Ardern acknowledged that "these decisions will place the most significant restrictions on New Zealanders' movements in modern history."

New Zealand has more than 100 confirmed coronavirus cases, according to a tally updated by Johns Hopkins University, but no confirmed deaths. The government fears that the case number in the country of around 5 million could rise quickly, however.

"The worst-case scenario is simply intolerable. It would represent the greatest loss of New Zealanders' lives in our history, and I will not take that chance," Ardern said during the news conference in which she began preparing the entire population for a month of self-isolation.
She explained that the new measures would take New Zealand to Level 3 "immediately" and then to Level 4 by Wednesday. Ardern said that schools and businesses should prepare to close, and she urged neighbors to create group chats on messaging apps to stay closely connected during the crisis.
Arden said: "To be absolutely clear, we are now asking all New Zealanders who are outside essential services to stay at home and to stop all interaction with others outside of those in your household."
The move was widely praised on social media. "I really am filled with admiration for @jacindaardern - her time as NZ PM has carried many challenges but she is doing an extraordinary job leading in challenging times," read one tweet.
By Jennifer Hassan
6:30 a.m.

As coronavirus surges, a frantic Europe scrambles for hospital beds, ventilators, supplies

As coronavirus cases surge in the biggest infectious disease crisis to hit European hospitals in a century, officials and health care workers are scrambling to keep national health systems above water.
The mood in France has shifted from an initial nonchalance to heightened anxiety, as President Emmanuel Macron has imposed an increasingly strict lockdown period of 15 days, which officials have suggested may be extended. In Britain, which was particularly slow to act, government pronouncements are accompanied by a palpable sense of panic and ever more desperate appeals.
On Monday, Britain's Health Minister Matt Hancock told the BBC the country had access to over 12,000 ventilators — more than double the original figure a few days ago.
Countries are competing against one another for medical supplies on an international market that has been sucked dry. To address shortages, Spanish clothes manufacturers are turning their lines to making medical masks, and Parisian perfumers are producing hand sanitizer in an effort that harks back to wartime.
As the number of critically ill rises, analysts expect even the continent's best-prepared health systems to be stretched to their limits.
"There's been nothing on this scale in the postwar period," said Martin McKee, a professor of European public health at the London School of Hygiene and Tropical Medicine. "The problem is that health systems, we talk about them as adaptive, but they have the capacity to fall over. They can expand so much, but at some point, the whole thing collapses."
Some analysts say one advantage Europe has is centralized, socialized systems that may be easier to reorganize and adapt to changing needs. By comparison, some U.S. hospitals have said they might have to close if they do not receive financial relief.
Read more here.
Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.
By Loveday Morris, William Booth and Luisa Beck
6:17 a.m.

Pharma company halts emergency access to experimental antiviral drug

A major pharmaceutical company is halting access to an experimental drug used to treat the novel coronavirus in emergencies, it said Sunday.

Amid an "exponential increase" in requests for the drug, called remdesivir, Gilead Sciences said it wanted more of those receiving the antiviral to participate in a clinical trial.

President Trump and global health authorities alike had previously said the drug was the of the most promising of possible treatments for people who are severely ill with covid-19, the disease caused by the virus.

In recent weeks, the antiviral had been used to treat several hundred severely ill patients in the United States, Europe and Japan, the company said.

Yet the rapid spread of the virus around the world has increased demand and "flooded an emergency treatment access system that was ... never intended for use in response to a pandemic," the company said in a statement.

Gilead first needs to determine if remdesivir is safe and effective in treating covid-19, the disease caused by the virus. With no approved treatments or vaccines for the virus, most other patients have received only supportive care measures, like breathing assistance.

Remdesivir was one of nearly 70 drug candidates cited for its effectiveness in treating the coronavirus in a study published Sunday on the website bioRxiv. The researchers have submitted the paper to a journal for publication.

The scientists said repurposing the drugs on their list, some of which are already used to treat other diseases, may be faster than trying to invent a new antiviral from scratch.

Also on the list was chloroquine, a malaria medication that President Trump has called a "game-changer" in treating the virus. Anthony S. Fauci, the director of the National Institute of Allergy and Infectious Diseases, however, said there was only "anecdotal evidence" that chloroquine would be effective.

By Teo Armus
6:04 a.m.

The sun came out and Britons forgot all about social distancing and a spreading virus

LONDON — The sun came out over the weekend and thousands flocked to their local parks for bike rides, picnics, drinks and ice cream, despite the growing coronavirus outbreak and despite Prime Minister Boris Johnson's advice to socially distance.

Photos of congested car parks, children playing and groups strolling through London's famous Columbia Road flower market sparked frustration and concern on social media, causing Richmond Park — one of the city's eight royal parks — to trend in Britain.

Many condemned those seemingly refusing to adhere to the government advice. Labour lawmaker David Lammy tweeted: "Advice is not working. We need a lockdown in London."

"Meanwhile in London's Richmond Park," tweeted the Independent's Tom Richell alongside a video that showed groups of cyclists standing in proximity chatting and others enjoying snacks outside.

The official Twitter account for the Royal Parks said the situation was being constantly reviewed but reminded people that the advice "set out by the government is a priority and not a choice." It also announced the closure of cafes and takeaway services within the parks. A number of other parks have already closed.

"If people do not follow social distancing guidelines, we will have no choice but to close the parks," the charity said.

On Sunday, Boris Johnson faced tough questions over the current government advice, with many critics saying the measures are not strict enough. The prime minister said in a news conference that outdoor spaces were crucial for mental health and well being during such a period of uncertainty but added that the British government would be considering other measures if people were unable to social distance responsibly.

Photos and videos shared on social media of packed tube stations during the Monday morning commute added to the sense that a cultural shift toward social distancing had not set in.

By Jennifer Hassan

5:06 a.m.

European markets, U.S. stock futures slump

European stocks hovered near seven-year lows on Monday, underscoring investors' continued alarm about the economic toll of coronavirus shutdowns after U.S. lawmakers failed to agree on a rescue package.

With millions of households and businesses struggling with forced closures and a collapse in demand, investors have grown increasingly concerned that the pandemic will push the world into a deep recession.

The pan-European Stoxx 600 index and London's FTSE 100 both slumped 4.5 percent in early trading. U.S. futures were also down about 4 percent, pointing to another lower open on Wall Street.

Fears that policymakers will not be able to stave off further economic slowdowns deepened in the United States over the weekend as Washington remain deadlocked over a stimulus rescue package.

By Miriam Berger

4:39 a.m.

Hong Kong bans tourists, transiting passengers and closes bars to stave off fresh wave of outbreak

HONG KONG — Hong Kong's leader on Monday announced a ban on visitors entering or transiting through the city, and took the unprecedented step of banning the sale of alcohol in bars and restaurants after a jump in coronavirus infections in recent days.

Residents have "let their guard down a bit, in particular in respect to keeping social distance," Chief Executive Carrie Lam said. "This war is still ongoing, and this is a prolonged battle. We need cooperation from everyone."

The entry restrictions come into force at midnight on Wednesday. Hong Kong last week forced all foreign arrivals into mandatory quarantine, either at home or in isolation areas, and has now gone a step further.

The decision to ban the sale of liquor at bars and restaurants came after five coronavirus patients were found to be out drinking at bars in Lan Kwai Fong, a popular nightlife district. Lam said alcohol can fuel "intimate behavior," and that more vigilance was needed to ensure that this new wave of cases does not erode the city's early wins in fighting the virus.

Many of the new cases reported in recent days involved patients with a link to recent travel, fueling concerns about imported infections.

Singapore and Taiwan have also similarly restricted their territories to foreigners, as walls go up all over the world to curb the spread of the virus. Lam said she will review the policy after 14 days, and will try to mitigate the economic losses to bars and restaurants.

By Shibani Mahtani

4:10 a.m.

Moscow pledges to pay elderly residents $50 to stay home

MOSCOW — With Russia's coronavirus cases surging, residents of Moscow over the age of 65 will be required to stay home until April 14 — and the government is planning to pay them to stay indoors.

Moscow Mayor Sergei Sobyanin said on his personal blog that pensioners and individuals with chronic illnesses will receive an amount equivalent to roughly $50 "to compensate for additional costs that may arise in connection with the regime of self-isolation." Half will be paid up front and the other half will be paid after the quarantine is complete.

Sobyanin added that there will be a temporary stay on late fees for housing and communal services.

"I think that you may not like it and even internally protest. But please believe, it is dictated by sincere concern for you," Sobyanin wrote, addressing Moscow's "older generation."

Russia says it has recorded 438 confirmed coronavirus cases, 262 of them in Moscow. A week ago, there were fewer than 100 cases in Russia.

President Vladimir Putin is 67, but it's unlikely he'll comply with Sobyanin's self-isolation order. Putin's spokesman said last week that Putin hasn't been tested for the coronavirus, but that's because he's feeling great and everyone who has come in contact with him recently has been tested.

By Isabelle Khurshudyan

3:34 a.m.

California reports first case in state prison system

The first inmate within the California state prison system has tested positive for the new coronavirus, authorities said late Sunday, marking the outbreak's spread among an especially vulnerable population.

The unnamed inmate, a man at a state prison in Los Angeles County, is in stable condition and has been isolated since he first reported feeling sick on Thursday, according to a news release from the California Department of Corrections and Rehabilitation. He is being treated at the prison.

Public health officials worry that prisons are ripe for spreading the virus: Inmates share small cells, sleep just feet away from toilets, and are often come into contact with many others inside crowded facilities during the day.

While law enforcement officials nationwide have been taking measures to release inmates and lock up fewer new defendants, the pandemic already appears to be taking a toll on several lockups in the United States.

At least 21 inmates in New York City jails have tested positive for the coronavirus, some of them at Rikers Island. A watchdog agency that oversees those jails said the system was "facing a crisis," calling on law enforcement officials to release high-risk inmates as soon as possible.

Over the weekend, the federal prison system saw its first inmate test positive, at a prison in New York City.

Also overnight Monday, the U.S. Secret Service said that one of its employees had tested positive for the virus. The employee is currently in quarantine, agency spokeswoman Justine M. Whelan said, and had not been in contact with any employee or individual receiving Secret Service protection in nearly three weeks.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Teo Armus

2:33 a.m.

Australia to withdraw nonessential troops from Iraq and Afghanistan

Australia announced Monday it is withdrawing all nonessential personnel from Iraq and Afghanistan in response to the coronavirus pandemic.

"Nonessential personnel will be relocated to Australia's main logistics base in the Middle East and those who are close to concluding their operational duties will be able to return home," Australian Defense Minister Linda Reynolds said, according to the Sydney Morning Herald.

Reynolds described the draw-down as "temporary" and to "preserve the safety of our people and partners, and to limit the spread of covid-19 in operational areas."

It was not immediately clear how many military personnel would be withdrawn.

Australia has about 400 troops in Afghanistan and over 300 troops and diplomatic personnel in Iraq.

The U.S. ally previously pledged to withdraw its troops from Afghanistan if a tentative peace deal between the United States and the Taliban reached in March holds.

By Miriam Berger

1:58 a.m.

Analysis: How politicians are using the coronavirus to seize control

Governments everywhere are grappling with ways to stem the spread of the disease, while also bracing for critical shortfalls in medical supplies and hospital beds. Officials have implemented emergency protocols to clamp down on travel and push through relief measures.

In a time of crisis, such action is vital. But some leaders also appear to be exploiting the pandemic for their own political ends.

Numerous Arab monarchies and autocracies, including some under serious political pressure, have invoked public health imperatives to secure themselves a reprieve from mass protests. A widely criticized interim regime in Bolivia postponed planned elections in May as part of a slate of emergency measures, including a 14-day national quarantine. From Hong Kong to India to Russia, authorities cited the risk of spreading coronavirus as grounds to disperse anti-government demonstrations and bar large public gatherings.

And the United States isn't immune, either. President Trump's Department of Justice is reportedly seeking expanded emergency powers, including provisions for judges to have the power to detain people indefinitely. It's unlikely to be accepted by Congress.

Though public health concerns remain paramount, analysts are increasingly warning about the risk of the erosion of the rule of law.

Read more here.

By Ishaan Tharoor

1:43 a.m.

Asian markets slide as coronavirus fears continue to frighten investors

HONG KONG — Most Asian markets were firmly in the red Monday as economic disruption from the novel coronavirus continued to grip the region. But Japan's Nikkei posted modest gains as the central bank there pledged new stimulus measures through additional bond buying.

In India, trading was halted for the second time in two weeks as the country's main index slid 10 percent and the rupee slumped to a new low against the dollar. Fears have grown about a potentially devastating outbreak in South Asia, prompting Indian Prime Minister Narendra Modi and other officials to announce a lockdown of much of the country after confirmed cases jumped in recent days.

Elsewhere, investors had little reason to cheer, as political wrangling in Washington stalled progress on an economic relief package. Hong Kong's Hang Seng Index fell 4.4 percent and Australia's benchmark slumped 5.6 percent.

U.S. stock futures were still firmly in the red, with both Dow and S&P down almost 5 percent.

By David Crawshaw

1:03 a.m.

Trump suggests virus containment measures may be too extreme as Senate Democrats block relief measures

Senate Democrats blocked an enormous coronavirus stimulus bill from moving forward Sunday evening, as President Trump began echoing messages from other conservatives who say measures to fight the pandemic have gotten too extreme.

Lawmakers had hoped to pass a $1.8 trillion aid package by Monday to slow the precipitous economic downturn sparked by the pandemic. More than one in five Americans are effectively under quarantine and thousands are stranded abroad due to restrictions on international travel.

Yet even as the outbreak threatens a global recession, Democratic leaders complained the bill focuses too much on businesses at the expense of unemployed workers. After U.S. stock futures tanked, House Speaker Nancy Pelosi (D-Calif.) said Sunday that Democrats would be introducing their own bill to counter the outbreak's economic carnage.

As of late Sunday, more than 34,700 cases had been reported across the United States, marking a dramatic jump in cases in cases over the weekend. At least 400 people have died nationwide, and Sen. Rand Paul (R-Ky.) is self-quarantining after becoming the first senator to test positive.

Both Ohio and Louisiana both issued statewide stay-at-home orders over the weekend, joining California, New York and Illinois with similar rules. But Trump appeared to push back on such stringent measures on Twitter late Sunday.

"WE CANNOT LET THE CURE BE WORSE THAN THE PROBLEM ITSELF," he wrote on Twitter late on Sunday. "AT THE END OF THE 15 DAY PERIOD, WE WILL MAKE A DECISION AS TO WHICH WAY WE WANT TO GO!"

Also on Sunday, Trump suggested that health-care workers try to sanitize disposable masks. Although the federal government ordered 500 million new masks earlier this month to counter a shortage, the head of the Federal Emergency Management Agencycould not say Sunday when hospitals would receive them.

Manufacturers have taken the matter into their own hands, too. One company said its shipments of half a million N95 masks for medical workers will arrive in New York and Seattle starting Monday.

Sign up for our daily Coronavirus Updates newsletter to track the outbreak. All stories linked in the newsletter are free to access.

By Teo Armus

12:51 a.m.

Australia's chief medical officer urges people to report others who breach quarantine orders

In China and Israel, the government can use cellphones to track those violating quarantine. In Italy and France, police give out fines to people caught outside in violation of lockdown rules.

In Australia, authorities are taking a different approach: Urging people to tell on their friends.

Australia's Chief Medical Officer Brendan Murphy warned Monday that Australians returning from abroad were failing to self-quarantine for 14 days, as the country's latest regulations require.

"Every single Australian who lands on our shore, whether it's from a cruise ship or a plane, or any other means of transportation needs to rigorously quarantine for 14 days now," Murphy said, the Sydney Morning Herald reported. "So, if you know of anyone who has come back from overseas and is not quarantining, please come down very hard on them."
He added, "You are placing your fellow citizens at risk if you don't."
Murphy also urged Australians to maintain social distancing, and admonished those not limiting their interactions and staying home as much as possible.
"This world could last for some time," he said. "This is the world of social distancing. This is a new way of us interacting with each other all of the time."
Cases in Australia have increased in recent days, rising to over 1,300 as of Monday morning.
Australia already banned the entry of foreign nationals who are not permanent residents in a bid to slow the spread of coronavirus.
As of Monday, Prime Minister Scott Morrison ordered all pubs, clubs, places of worship, and cinemas to close, as well as for restaurants and cafes to switch to takeout orders only.
By Miriam Berger
12:51 a.m.

Patients with covid-19 share what it's like to get sick from the new coronavirus

Ritchie Torres, 32, a New York City councilman from the Bronx, first had nothing more than a "general sickly feeling." Then came a bad headache. He felt terrible. But for Torres, the worst effects of covid-19 so far have been mental: "It is psychologically unsettling to know I am carrying a virus that could harm my loved ones."
The Rev. Jadon Hartsuff, 42, an Episcopal priest in Washington, D.C., felt drained after a Sunday service on Feb. 23. He took a nap. No big deal — the service can be tiring. The next day at the gym, his muscles ached. He became fatigued, feverish, slightly dizzy. "I kept telling people I felt spongy," he recalls. "Like a kitchen sponge."
Mike Saag, 64, an infectious disease doctor in Alabama, developed a cough, like a smoker's hack. He was bone-tired, his mind foggy. About five days in, the misery intensified. "This is not something anybody wants to go through," he said Saturday. "I implore everyone to stay at home!"
These stories were offered in recent days by people in the U.S. who now know the new coronavirus and the disease it causes.
Read more here.
By Joel Achenbach, Ben Guarino and Ariana Eunjung Cha

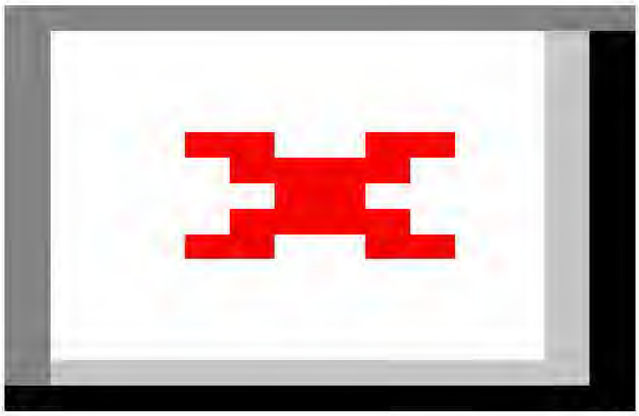
Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/23 16:47:20
Delivered Date:	2020/03/23 16:47:45
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: NIH Director's Blog: Pursuing Safe and Effective Anti-Viral Drugs for COVID-19
Date: 2020/04/17 10:12:21
Priority: Normal
Type: Note

NIH Director's Blog

Pursuing Safe and Effective Anti-Viral Drugs for COVID-19

Posted on April 17th, 2020 by Dr. Francis Collins



Senior hospital patient on a ventilator Stock photo/SoumenNath

Right now, the world is utterly focused on the coronavirus outbreak known as COVID-19. That's certainly true for those of us at NIH. Though I am working from home to adhere rigorously to physical distancing, I can't remember ever working harder, trying to do everything I can to assist in the development of safe and effective treatments and vaccines.

Over the past several weeks, a mind-boggling array of possible therapies have been considered. None have yet been proven to be effective in rigorously controlled trials, but for one of them, it's been a busy week. So let's focus on an experimental anti-viral drug, called remdesivir, that was originally developed for the deadly Ebola virus. Though remdesivir failed to help people with Ebola virus disease, encouraging

results from studies of coronavirus-infected animals have prompted the launch of human clinical trials to see if this drug might fight SARS-CoV-2, the novel coronavirus that causes COVID-19.

You may wonder how a drug could possibly work for Ebola and SARS-CoV-2, since they are very different viruses that produce dramatically different symptoms in humans. The commonality is that both viruses have genomes made of ribonucleic acid (RNA), which must be copied by an enzyme called RNA-dependent RNA polymerase for the virus to replicate.

Remdesivir has an affinity for attaching to this kind of polymerase because its structure is very similar to one of the RNA letters that make up the viral genome [1]. Due to this similarity, when an RNA virus attempts to replicate, its polymerase is tricked into incorporating remdesivir into its genome as a foreign nucleotide, or anomalous letter. That undecipherable, extra letter brings the replication process to a crashing halt—and, without the ability to replicate, viruses can't infect human cells.

Would this work on a SARS-CoV-2 infection in a living organism? An important step was just posted as a preprint yesterday—a small study showed infusion of remdesivir was effective in limiting the severity of lung disease in rhesus macaques [2]. That's encouraging news. But the only sure way to find out if remdesivir will actually help humans who are infected with SARS-CoV-2 is to conduct a randomized, controlled clinical trial.

In late February, NIH's National Institute of Allergy and Infectious Diseases (NIAID) did just that, when it launched a randomized, controlled clinical trial to test remdesivir in people with COVID-19. The study, led by investigators at the University of Nebraska Medical Center, Omaha, has already enrolled 805 patients at 67 testing sites. Most sites are in the United States, but there are also some in Singapore, Japan, South Korea, Mexico, Spain, the United Kingdom, Denmark, Greece, and Germany.

All trial participants must have laboratory-confirmed COVID-19 infections and evidence of lung involvement, such as abnormal chest X-rays, rattling sounds when breathing (rales) with a need for supplemental oxygen, or a need for mechanical ventilation. They are randomly assigned to receive either a round of treatment with remdesivir or a harmless placebo with no therapeutic effect. To avoid bias from creeping into patient care, the study is double-blind, meaning neither the medical staff nor the participants know who is receiving remdesivir.

There is also an early hint from another publication that remdesivir may benefit some people with COVID-19. Since the end of January 2020, Gilead has provided daily, intravenous infusions of the drug on a compassionate basis to more than 1,800 people hospitalized with advanced COVID-19 around the world. In a study of a subgroup of 53 compassionate-use patients with advanced complications of COVID-19, nearly two-thirds improved when given remdesivir for up to 10 days [3]. Most of the participants were men over age 60 with preexisting conditions that included hypertension, diabetes, high cholesterol, and asthma.

This may sound exciting, but these preliminary results, published in the *New England Journal of Medicine*, come with major caveats. There were no controls, participants were not randomized, and the study lacked other key features of the more rigorously designed NIH clinical trial. We can all look forward to the results from the NIH trial, which are are expected within a matter of weeks. Hopefully these will provide much-needed scientific evidence on remdesivir's safety and efficacy in people with COVID-19.

In the meantime, basic researchers continue to learn more about remdesivir and its interaction with the novel coronavirus that causes COVID-19. In a recent study in the journal Science, a research team, led by Quan Wang, Shanghai Tech University, China, mapped the 3D atomic structure of the novel coronavirus's polymerase while it was complexed with two other vital parts of the viral replication machinery [4]. This was accomplished using a high-resolution imaging approach called cryo-electron microscopy (cryo-EM), which involves flash-freezing molecules in liquid nitrogen and bombarding them with electrons to capture their images with a special camera.

With these atomic structures in hand, the researchers then modeled exactly how remdesivir binds to the polymerase of the novel coronavirus. The model will help inform future efforts to tweak the structure of the drug and optimize its ability to disrupt viral replication. Such detailed biochemical information will be vital in the weeks ahead, especially if data generated by the NIH clinical trial indicate that remdesivir is a worthwhile lead to pursue in our ongoing search for anti-viral drugs to combat the global COVID-19 pandemic.

References:

[1] Nucleoside analogues for the treatment of coronavirus infections. Pruijssers AJ, Denison MR. Curr Opin Virol. 2019 Apr;35:57-62.
[2] Respiratory disease and virus shedding in rhesus macaques inoculated with SARS-CoV-2 . Munster VJ, Feldmann F, Williamson BN, Scott D, Fischer ER, de Wit E et. al. BioRxiv. Preprint posted 21 March 2020.
[3] Compassionate use of remdesivir for patients with severe Covid-19. Grein J, Ohmagari N, Shin D, Brainard DM, Childs R, Flanigan T. et. al. N Engl J Med. 2020 Apr 10. [Epub ahead of publication]
[4] Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Gao Y, Yan L, Liu F, Wang Q, Lou Z, Rao A, et al. Science. 10 April 2020. [Epub ahead of publication]

Links:

Coronavirus (COVID-19) (NIH)
Accelerating COVID-19 Therapeutic Interventions and Vaccines (NIH)
NIH Clinical Trial of Remdesivir to Treat COVID-19 Begins (National Institute of Allergy and Infectious Diseases/NIH)
Developing Therapeutics and Vaccines for Coronaviruses (NIAID)
COVID-19, MERS &SARS (NIAID)

NIH Support: National Institute of Allergy and Infectious Diseases

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/17 10:11:42
Delivered Date:	2020/04/17 10:12:21
Message Flags:	Unread

From:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject:	One Health: Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses https://bit.ly/2JoJWFk
Date:	2020/03/28 15:32:40
Priority:	Normal
Type:	Note

One Health

Available online 27 March 2020, 100128

In Press, Journal Pre-proof

What are Journal Pre-proof articles?

One Health

Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses

Author links open overlay panelE. SusanAmirian[a]

Julie K.Levy[b]

https://doi.org/10.1016/j.onehlt.2020.100128Get rights and content

Abstract

Recent international epidemics of coronavirus-associated illnesses underscore the urgent medical and public health need for vaccine development and regulatory body approved therapies. In particular, the current coronavirus disease 2019 (COVID-19) pandemic has quickly intensified interest in developing treatment options to mitigate impact on human life. Remdesivir (GS-5734™) is a broad-spectrum antiviral drug that is now being tested as a potential treatment for COVID-19 in international, multi-site clinical trials. Currently available evidence about the antiviral effects of remdesivir against coronaviruses is primarily based on *in vitro* and *in vivo* studies (including some on a chemically related compound, GS-441524™), which have demonstrated largely favorable findings. As the pandemic progresses, information from human compassionate use cases will continue to accumulate before the clinical trials are concluded. It is imperative for public health practitioners and the One Health community to stay up to date on the most promising potential therapeutic options that are under investigation. Thus, the

purpose of this review is to synthesize the knowledge to date about remdesivir as a therapeutic option for coronaviruses, with a special focus on information relevant to the One Health community.

Keywords

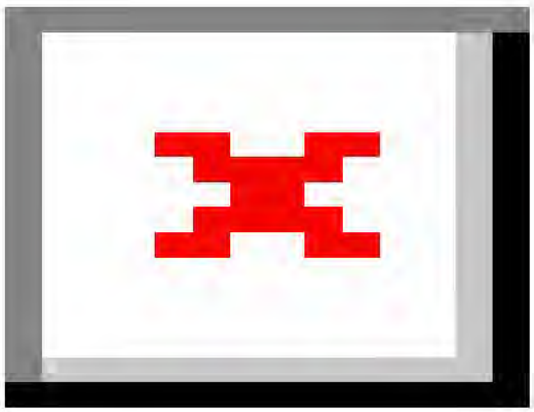
Remdesivir
GS-5734
Coronavirus
COVID-19
SARS-CoV-2
Compassionate use

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/28 15:32:26
Delivered Date:	2020/03/28 15:32:40
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: NYT: With Minimal Evidence, Trump Asks F.D.A. to Study Malaria Drugs for Coronavirus
Date: 2020/03/20 11:18:45
Priority: Normal
Type: Note

With Minimal Evidence, Trump Asks F.D.A. to Study Malaria Drugs for Coronavirus

The use of the existing drugs against the new virus is unproven, and some shortages have already been reported.



Production of the anti-malarial drug chloroquine last month at a factory in Nantong City in China. Production of the anti-malarial drug chloroquine last month at a factory in Nantong City in China. Credit...Feature China/Barcroft Media, via Getty Images

By Denise Grady and Katie Thomas

- • Published March 19, 2020Updated March 20, 2020, 11:04 a.m. ET

• • President Trump on Thursday exaggerated the potential of drugs available to treat the new coronavirus, including an experimental antiviral treatment and decades-old malaria remedies that hint of promise but so far show limited evidence of healing the sick.

No drug has been approved to treat the new coronavirus, and doctors around the world have been desperately administering an array of medicines in search of something to help patients, especially those who are severely ill.

The malaria drugs, chloroquine and hydroxychloroquine, are among the remedies that have been tried in several countries as the virus has spread around the world, killing at least 9,800.

Both drugs have gone into short supply in the United States this month, as word has spread of their potential benefit to coronavirus patients. Manufacturers of the generic products have said they are ramping up production. One company, Teva, said it would donate millions of pills of hydroxychloroquine to hospitals, and another company, Mylan, said it would restart production of the drug.

Doctors in China, South Korea and France have reported that the treatments seem to help. But those efforts have not involved the kind of large, carefully controlled studies that would provide the global medical community the proof that these drugs work on a significant scale.

In a White House briefing Thursday, Mr. Trump said the anti-malaria drugs had shown "tremendous promise."

"I think it's going to be very exciting," he said. "I think it could be a game changer, and maybe not."

The drugs' potential has been highlighted during broadcasts on one of Mr. Trump's favorite news channels, Fox News, where hosts like Laura Ingraham, Tucker Carlson and Jeanine Pirro have trumpeted the possibility of a real treatment.

"They've gone through the approval process," Mr. Trump said of the drugs. "It's been approved, and they did."

But the F.D.A. has not approved any drugs for use in the treatment of coronavirus, and the drugs were already available, to treat malaria as well as rheumatoid arthritis and lupus. To date, the F.D.A. has not added the coronavirus to the list of illnesses for which the drugs are specifically approved. Then again, doctors have been free to use both old malaria drugs for any purpose deemed appropriate.

At the briefing on Thursday, Dr. Stephen M. Hahn, who has been the commissioner of the Food and Drug Administration for only three months, tended to walk back some of the president's more inflated predictions that these drugs might vanquish the virus altogether.

He said Mr. Trump had asked the agency to look into chloroquine to fight the coronavirus, and that it was setting up a large clinical trial to evaluate the drug.

Some hospitals in the United States have already begun using the drugs for coronavirus patients, apparently reasoning that they may help and are unlikely to do harm. They are cheap and relatively safe. Laboratory studies have found that they prevent the coronavirus from invading cells, suggesting that the drugs could help prevent or limit the infection.

Not everyone can take the drugs: They are not safe for people who suffer from heart arrhythmia, or those with impaired kidneys or liver.

The University of Minnesota is conducting a study in which people who live with a coronavirus patient are being given hydroxychloroquine to find out if it can prevent the infection.

Dr. Hahn also said that the agency was allowing sick patients to use remdesivir, the not-yet-approved antiviral drug made by Gilead. Such so-called "compassionate use" programs allow patients to take unapproved, experimental drugs if they have no other options.

Remdesivir has already been given to patients on a compassionate-use basis, including the first coronavirus patient in the United States, who was treated in Washington State in late January.

Remdesivir is being studied in clinical trials, but the results are not available yet. It was studied to treat Ebola, but did not work well enough to be useful for that disease.

Dr. Hahn noted that the agency's job was to prove that drugs were safe and effective. "What's also important is not to provide false hope, but to provide hope," he said.

As word has spread about chloroquine's potential, demand in the United States has overwhelmed the country's only supplier of the drug, the New Jersey generic manufacturer Rising Pharmaceuticals. Chloroquine has been in short supply since March 9, according to the American Society of Health-System Pharmacists, which tracks drug shortages. Hydroxychloroquine, which is made by more companies, has been in shortage since Thursday.

Ira Baeringer, chief operating officer of Rising Pharmaceuticals, said his company had been tracking the use of the drug in China and elsewhere. They increased production about three weeks ago, he said, and are meeting all of their orders. But he acknowledged that pharmacies may currently have low stocks. "We are experiencing an extraordinary demand, as you can imagine, but we are shipping to all of the orders," Mr. Baeringer said. He noted that the product had not yet been extensively tested for coronavirus so it was unclear how well it works. "We're really trying to understand what the need is going to be."

On Thursday, the German manufacturer Bayer said it had donated three million tablets of chloroquine to the U.S. government for potential use as a treatment for coronavirus.

Bayer does not sell its chloroquine product in the United States, but has said it is seeking approval from the F.D.A. for it to be used on an emergency basis. Chloroquine, sold under the brand name Resochin by Bayer, was discovered by the company in 1934. Bayer said in a statement Thursday that it "appears to have broad spectrum antiviral properties and effects on the body's immune response."

The company said it had been in recent talks with the White House and several federal agencies to offer assistance.

Mr. Trump has previously made unfounded predictions that the coronavirus epidemic would soon disappear. On Thursday, he appeared to enlist the malaria drugs in that effort, even though Dr. Deborah Birx, the White House's coronavirus response coordinator, said the virus could return in the fall or winter of next year.

"If they work, your numbers are going to come down very rapidly," Mr. Trump said. "So, we'll see what happens, but there's a real chance that they might — they might work."

Sheila Kaplan contributed reporting.

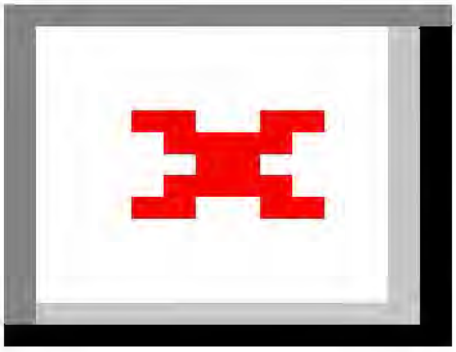
Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/20 11:18:32
Delivered Date:	2020/03/20 11:18:45
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: UNMC clinical trial still on despite suspended access to drug
Date: 2020/03/25 10:50:21
Priority: Normal
Type: Note

site-logo

UNMC clinical trial still on despite suspended access to drug

- Chris Dunker
- Mar 24, 2020 Updated 11 hrs ago
-



Study begins in US to test possible coronavirus treatment

Dr. Andre Kalil of the University of Nebraska Medical Center speaks in Omaha on Feb. 25. Kalil is overseeing a clinical trial of the anti-coronavirus drug remdesivir at the medical center.

Nati Harnik, Associated Press file photo

The company supplying an experimental drug for treating patients with COVID-19 said it is putting restrictions on "compassionate-use" requests to the antiviral drug.

The new limits won't affect the ongoing clinical trial of remdesivir at the University of Nebraska Medical Center.

Requests to Gilead Science by those infected with the coronavirus in the U.S. and Europe to try remdesivir saw "an exponential increase" after President Donald Trump touted the drug and two others as potential cures for the disease.
The antiviral therapy has proved effective against SARS and MERS — other respiratory diseases caused by varying strains of the virus — as well as against the Ebola virus.
"In recent weeks, there has been an exponential increase in compassionate-use requests for emergency access to remdesivir," the California-based company said Sunday in a news release.
"This has flooded an emergency treatment-access system that was set up for very limited access to investigational medicines and never intended for use in response to a pandemic," Gilead said.
The drug developer said it would grant exceptions to requests made by pregnant women or children under the age of 18, and was working on a new expanded release.
UNMC is one of six hospitals across the U.S. that has enrolled 80 patients in a clinical study of remdesivir sponsored by the National Institutes of Health.
At the announcement of the clinical trial in late February, Dr. Andre Kalil, an infectious disease expert at UNMC, said the trial would enroll as many as 400 patients from 50 sites around the world.
Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases and a member of the U.S. Coronavirus Task Force, said while the clinical trial was set up quicker than most, that its methods reflect "the gold standard for determining if an experimental treatment can benefit patients."
Also this week, the Food and Drug Administration announced remdesivir would be tagged with the agency's "orphan drug" designation, typically reserved for rare illnesses affecting fewer than a quarter-million people in the U.S.
The designation gives Gilead seven years of market exclusivity on the product, as well as tax incentives and other benefits.

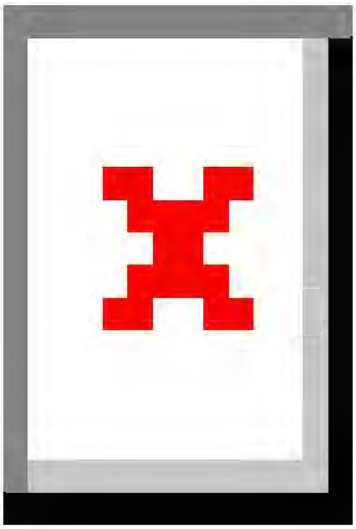
Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/25 10:49:37
Delivered Date:	2020/03/25 10:50:21
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Coronavirus treatment and risk to breastfeeding women
Date: 2020/03/05 09:41:27
Priority: Normal
Type: Note

4-Mar-2020

Coronavirus treatment and risk to breastfeeding women

Mary Ann Liebert, Inc./Genetic Engineering News



IMAGE

IMAGE: Providing unparalleled peer-reviewed research, protocols, and clinical applications to ensure optimal care for mother and infant. view more

Credit: Mary Ann Liebert, Inc., publishers

New Rochelle, NY, March 4, 2020--Little data is available about the ability of antiviral drugs used to treat COVID-19, coronavirus, to enter breastmilk, let alone the potential adverse effects on breastfeeding infants. A new perspective article reviewing what is known about the most commonly used drugs to treat coronavirus and influenza is published in *Breastfeeding Medicine*, the official journal of the Academy of Breastfeeding Medicine published by Mary Ann Liebert, Inc., publishers. Click here to read the protocol free on the *Breastfeeding Medicine* website.

Philip Anderson, PharmD, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, is the author of "Breastfeeding and Respiratory Antivirals: Coronavirus (COVID-19) and Influenza." The short answer to questions regarding drug therapy for COVID-19 is that currently there is no antiviral agent proven to be effective against this new infection. However, one investigational drug so far, remdesivir, appears promising to treat COVID-19, and it is in phase 3 clinical trials in patients. Dr. Anderson notes: "Nothing is known about the passage of remdesivir into breastmilk."

Arthur I. Eidelman, MD, Editor-in-Chief of *Breastfeeding Medicine*, states: "Given the reality that mothers infected with coronavirus have probably already colonized their nursing infant, continued breastfeeding has the potential of transmitting protective maternal antibodies to the infant via the breast milk. Thus, breastfeeding should be continued with the mother carefully practicing handwashing and wearing a mask while nursing, to minimize additional viral exposure to the infant."

###

About the Journal

Breastfeeding Medicine, the official journal of the Academy of *Breastfeeding Medicine*, is an authoritative, peer-reviewed, multidisciplinary journal published 10 times per year in print and online. The Journal publishes original scientific papers, reviews, and case studies on a broad spectrum of topics in lactation medicine. It presents evidence-based research advances and explores the immediate and long-term outcomes of breastfeeding, including the epidemiologic, physiologic, and psychological benefits of breastfeeding. Tables of content and a sample issue may be viewed on the *Breastfeeding Medicine* website.

About the Academy of Breastfeeding Medicine

The Academy of Breastfeeding Medicine (ABM) is a worldwide organization of medical doctors dedicated to the promotion, protection, and support of breastfeeding. Our mission is to unite members of the various medical specialties with this common purpose. For more than 20 years, ABM has been bringing doctors together to provide evidence-based solutions to the challenges facing breastfeeding across the globe. A vast body of research has demonstrated significant nutritional, physiological, and psychological benefits for both mothers and children that last well beyond infancy. But while breastfeeding is the foundation of a lifetime of health and well-being, clinical practice lags behind scientific evidence. By building on our legacy of research into this field and sharing it with the broader medical community, we can overcome barriers, influence health policies, and change behaviors.

About the Publisher

Mary Ann Liebert, Inc., publishers is a privately held, fully integrated media company known for establishing authoritative peer-reviewed journals in many promising areas of science and biomedical research, including Journal of Women's Health, Childhood Obesity, and Pediatric Allergy, Immunology, and Pulmonology. Its biotechnology trade magazine, GEN (Genetic Engineering &Biotechnology News) was the first in its field and is today the industry's most widely read publication worldwide. A complete list of the firm's 90 journals, books, and newsmagazines is available on the Mary Ann Liebert, Inc., publisher's website.

Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/05 09:40:40
Delivered Date:	2020/03/05 09:41:27
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: STAT: As the coronavirus spreads, a drug that once raised the world's hopes is given a second shot http://bit.ly/2U9ri9p
Date: 2020/03/16 08:44:58
Priority: Normal
Type: Note

As the coronavirus spreads, a drug that once raised the world's hopes is given a second shot

By ANDREW JOSEPH @DrewQJoseph
MARCH 16, 2020

A decade ago, a group of chemists cooked up a compound they simply called 3a and that, in lab experiments, fought off a number of different viruses. One was a type of coronavirus.

Now, the descendant of that molecule — Gilead Sciences' remdesivir — is being rushed to patients with infections from the novel coronavirus in hopes that it can reduce the intensity and duration of Covid-19 and ease the burden of the pandemic on health systems.

Remdesivir, in the spotlight as scientists and governments scramble to find a treatment for the disease, took a circuitous route to center stage. Born as a general antiviral candidate, researchers threw it at an array of viruses and saw where it stuck. It bounced along from Gilead's labs to academic centers, nudged by both federal taxpayer dollars and support from the company. It kept turning up whiffs of potential in cells and animals infected by other coronaviruses like SARS and MERS, but these bugs weren't causing sustained global crises. For years, Gilead was primarily focused on ushering remdesivir into trials and toward approval for a different kind of infection: Ebola.

But there's nothing like a pandemic to break the emergency glass on all possible options.

Remdesivir is now being tested in five Covid-19 clinical trials ….

more

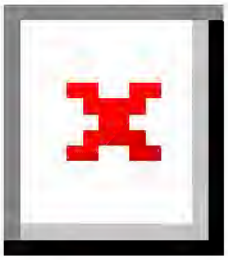
Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/16 08:44:39
Delivered Date:	2020/03/16 08:44:58
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: ACSH: Will Remdesivir Work in Humans? Monkey Data Suggest Yes
Date: 2020/04/03 07:56:28
Priority: Normal
Type: Note

Will Remdesivir Work in Humans? Monkey Data Suggest Yes

By Josh Bloom — March 31, 2020

Remdesivir, an antiviral drug that many are pinning their hopes on to help salve this pandemic nightmare, is now being tested in hundreds of trials. Results are expected within weeks. But the drug has already been tested in monkeys. And it worked.



Rhesus macaques Source: Wikipedia Commons

Within the coming weeks, we should be starting to get a picture of whether remdesivir will be a savior to the world, just another failed drug, or something in between.

There are already clues in a March 24th paper in PNAS called *"Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus mocaque model of MERS-CoV infection."*

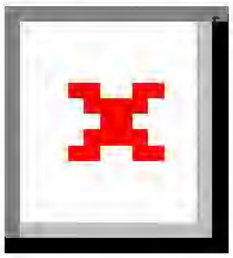
Something should stand out right away. The paper isn't studying the "right" virus; the title says MERS rather than SARS – the bug that is crippling us now. Perhaps worse still, remdesivir was discovered as a treatment for Ebola but failed. So isn't it vaguely disturbing that Gilead appears to be simply grasping at straws, hoping that it might work for *something*? No, it isn't.

1. Yes, it makes sense to study MERS

At the onset of the epidemic, remdesivir was already being studied in mouse and *in vitro* models of MERS, another coronavirus that was first identified in 2012.

But in order to have a chance of stopping SARS-CoV-2, the needlessly complex name given to what we just call "coronavirus", remdesivir needs to at the very least be able to stop the replication of the virus in a "test tube" as it did with MERS.

It does (Figure 1). Quite well.



(Figure 1) The EC_{50} values (lower means mare potent) of SARS (yellow arrow) and MERS (red arrow) are both approximotely 100 nM (nanomolar), which is equivalent to 0.1 micromolar. 100 nM inhibitors ore considered to be potent.

Remdesivir's effect on pre-treated and therapeutically treated animals

Animal models of human diseases vary widely in their ability to predict whether a drug will work in people. In general, bacterial and viral models are fairly predictive of efficacy in humans, and when the experiment is run in monkeys rather than rats, the relevance to human disease is greater still.

Procedure (Figure 2)

Eighteen rhesus macaques were divided into three groups, each containing 6 monkeys.

Group 1 - Three monkeys received only the vehicle solution (without drug) 24 hours prior to being infected and three more received the placebo 12 hours prior to infection.

Group 2 - Six monkeys received 5 mg of remdesivir per kilo of body weight 24 hours before being infected.

Group 3 - Six monkeys were treated with 5 mg of remdesivir per kilo of body weight 12 hours *after* being infected. Treatment was continued for six days and all 18 animals were euthanized.

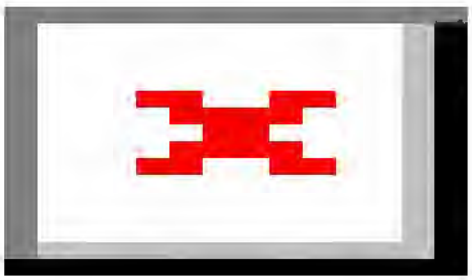
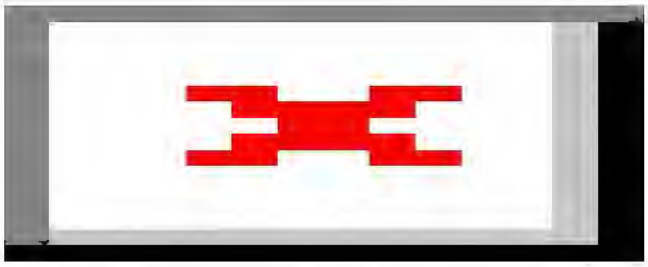


Figure 2. Experimental timeline. (Black circles, group 2) Prophylactic treatment began one day prior to inoculation. (Red circles, group 3) Therapeutic treatment was begun 12 hours post-Infection, 12 hours later, and then once per day. The black squares indicate clinical exams (every day).

Results (prophylactic treatment)
When the monkeys were treated with remdesivir 24 hours before they were inoculated (infected) the drug *completely protected them* from clinical signs of MERS disease. The pre-treated monkeys were also protected from MERS *lung lesions,* and the amount of viral replication in the lungs – the hallmark of the infection – was strongly inhibited.
Results (therapeutic treatment)
Although prophylactic use (black) of the drug resulted in almost complete protection of the animals, the data on therapeutic use (red) are less dramatic. It is clear that the drug works better prophylactically than therapeutically. Remdesivir reduced the viral load in respiratory tissues (left) and improved lung health as measured by x-ray. The control group is shown in gray (Figure 3).



The same trend was seen in other mucosal tissues (Figure 4).

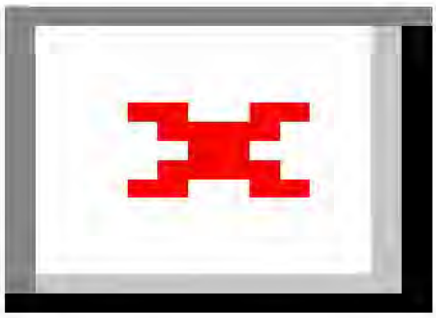
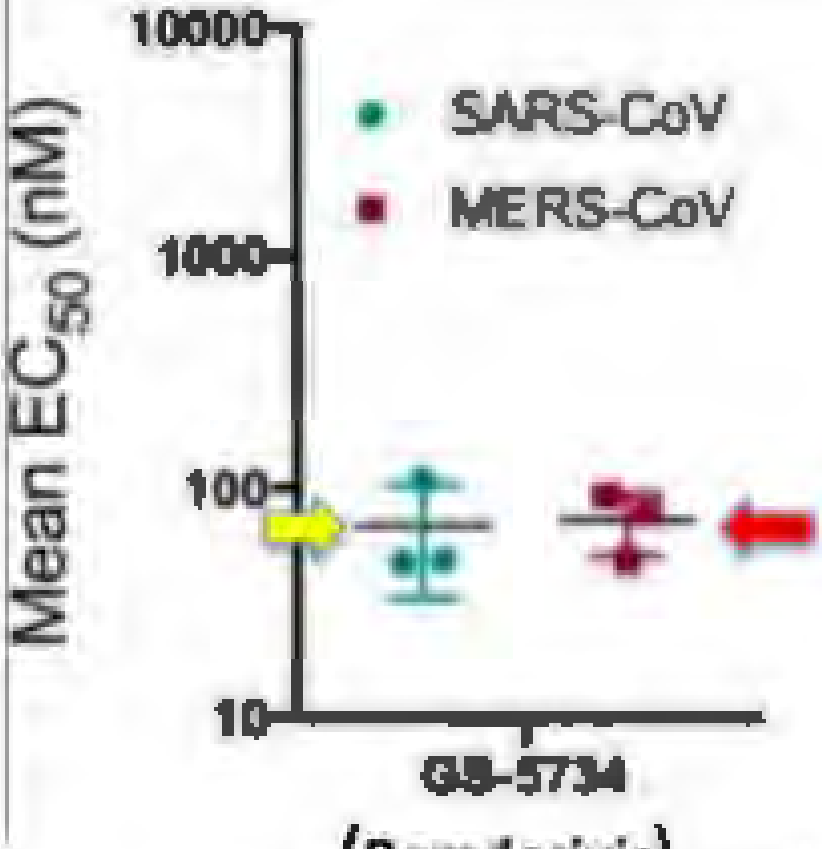


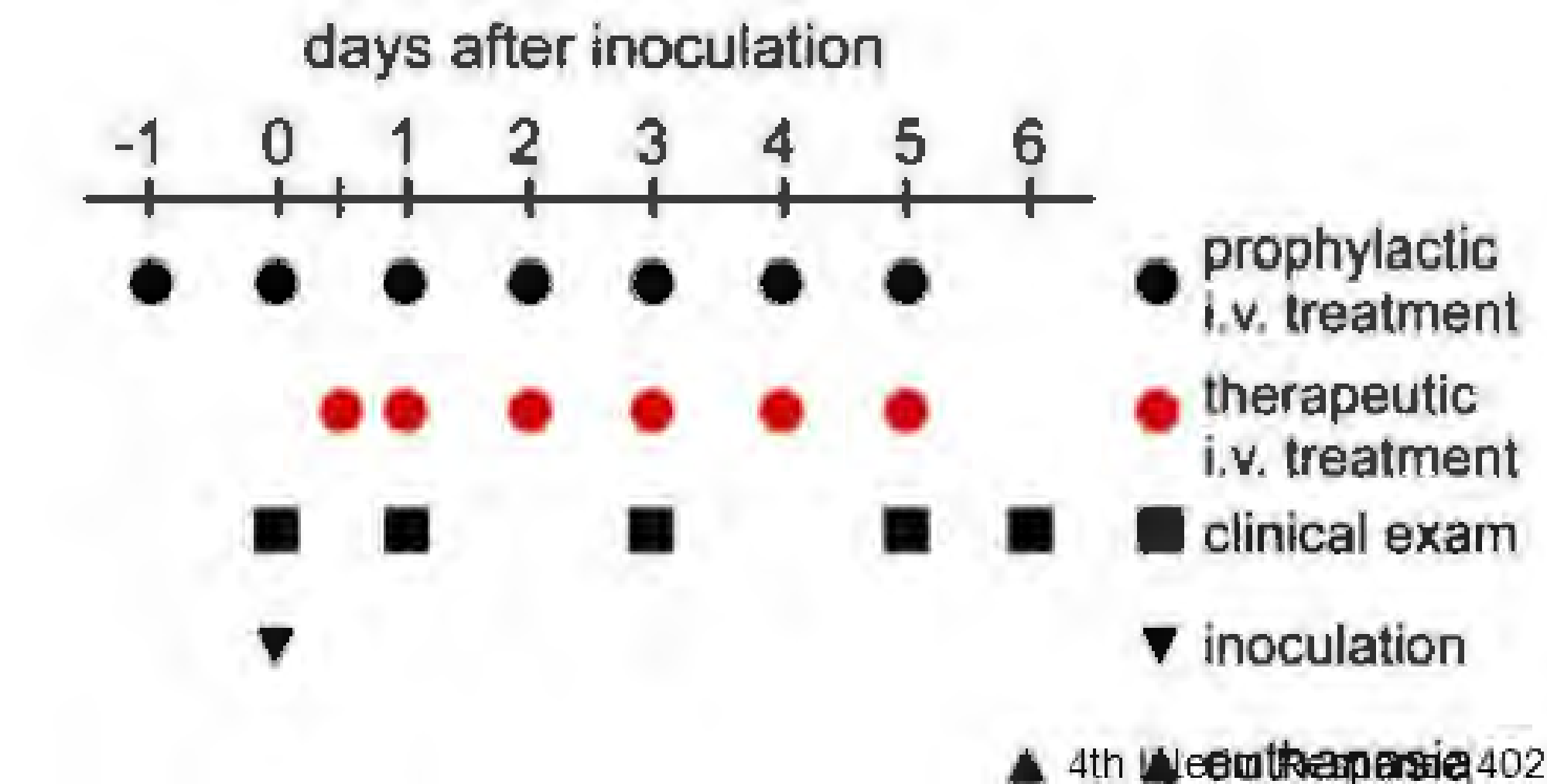
Figure 4. Viral load in different mucosal tissues.
Source for all figures: PNAS
Summary
Remdesivir passed the monkey tests with (more or less) flying colors. Even though the drug was tested against MERS, not SARS, it inhibits both viruses with similar potency. So MERS should be a good

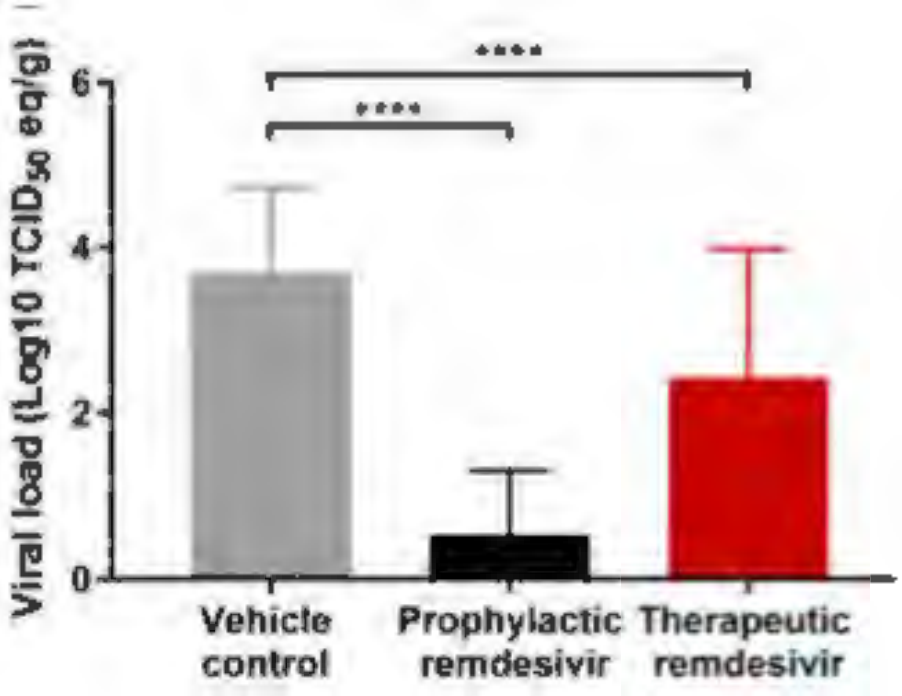
surrogate for the current coronavirus. What isn't clear is what the drug will do once a person is already infected. It won't clear all the virus from the lungs but it may slow down the replication so that the disease is less serious. Only human trials can determine this.
It is clear that, as the case with other antiviral drugs such as Tamiflu and Valtrex, the earlier remdesivir is given the better it works. This is consistent with the mechanism of the drug – inhibition of viral RNA synthesis, which is an early process in RNA viral replication.
If the inhibition of coronovirus in humans by remdesivir is consistent with that of MERS in rhesus macaques, we will have our first evidence-based tool against the virus. And not a moment too soon.
Disclaimer: I have a (pitifully) small amount of Gilead Stock in my IRA.

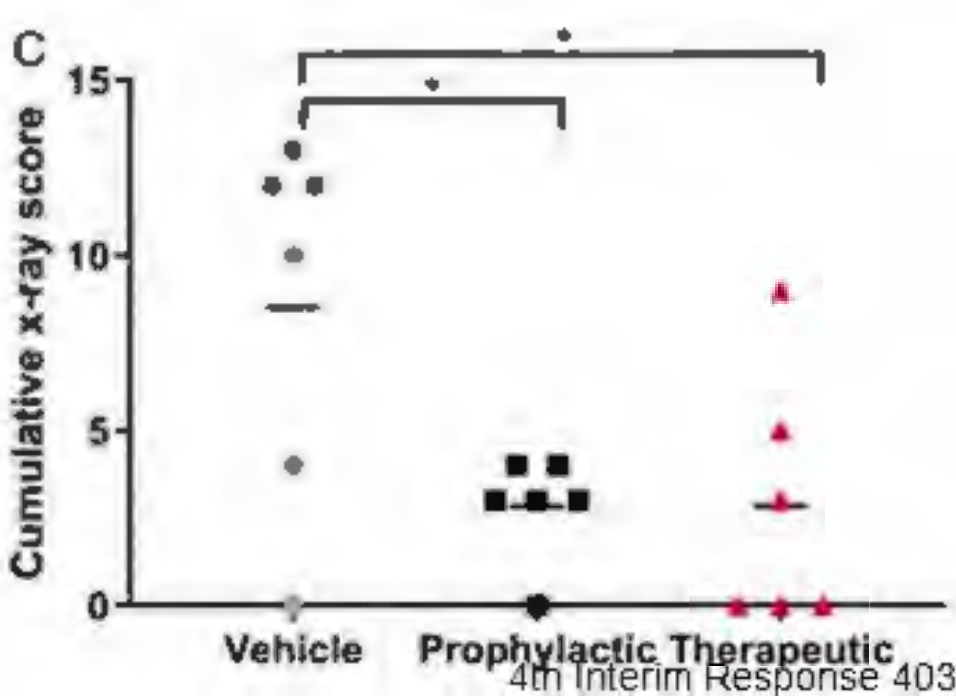
Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/03 07:56:11
Delivered Date:	2020/04/03 07:56:28
Message Flags:	Unread

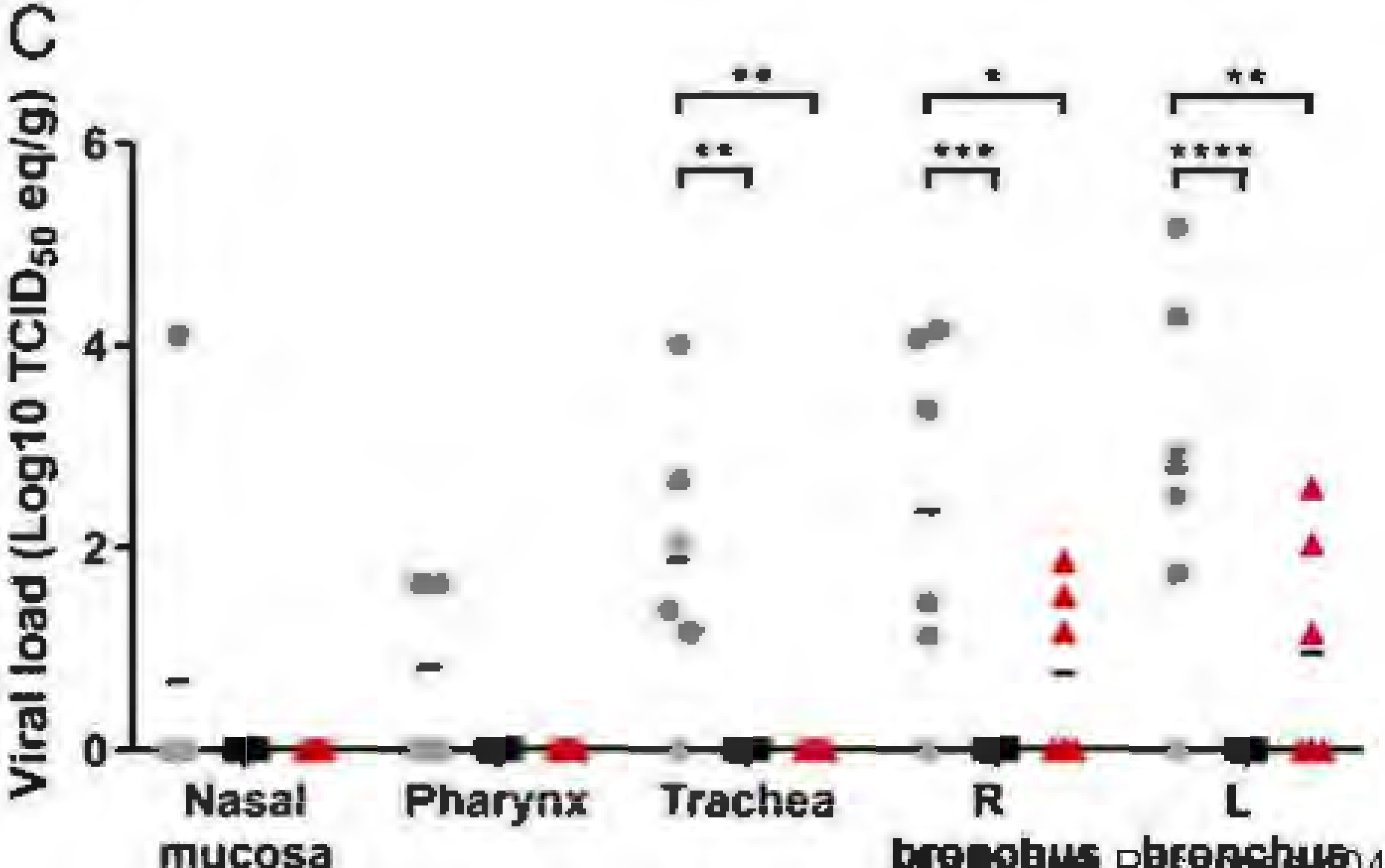

4th Interim Response 400


10000
1000
100
10
Mean EC_{50} (nM)
SARS-CoV
MERS-CoV
GS-5734
(Remdesivir)


days after inoculation
-1
0
1
2
3
4
5
6
prophylactic i.v. treatment
therapeutic i.v. treatment
clinical exam
inoculation
4th
euthanasie


Viral load (Log10 TCID50 eq/g)
6
4
2
0
****
****
Vehicle control
Prophylactic remdesivir
Therapeutic remdesivir


C
Cumulative x-ray score
15
10
5
0
*
*
Vehicle
Prophylactic
Therapeutic


C
Viral load (Log10 TCID50 eq/g)
6
4
2
0
**
*
**
**
***
****
Nasal mucosa
Pharynx
Trachea
R bronchus
L bronchus

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Lancet: Flooded by the torrent: the COVID-19 drug pipeline
Date: 2020/04/20 18:42:18
Priority: Normal
Type: Note

The Lancet
Volume 395, Issue 10232, 18–24 April 2020, Pages 1245-1246

Journal home page for The Lancet

World Report
Flooded by the torrent: the COVID-19 drug pipeline

Author links open overlay panelAsherMullard
https://doi.org/10.1016/S0140-6736(20)30894-1Get rights and content

The world is rushing to test potential COVID-19 treatments. But do we really need so many trials? Asher Mullard reports.

The coronavirus disease 2019 (COVID-19) drug pipeline is not growing at quite the same speed as the pandemic. But its rate of expansion is nevertheless cause for pause. In the months since COVID-19 has spread, researchers have launched more than 180 clinical trials of everything from repurposed antivirals and immunomodulators to unproven cell therapies and vitamin C. A further 150 trials are preparing to recruit patients.

For pandemic preparedness experts, this begs crucial questions. "Do we need 300 trials? Is that a good use of resources?" asks Daniel Bausch, director of the UK Public Health Rapid Support Team and infectious disease expert at the London School of Hygiene &Tropical Medicine. "I would probably say we don't."

There are good reasons to build up a full pipeline of COVID-19 drugs. Up to 90% of new entrants into clinical trials never make it to approval, and so investigators want to have as many shots on goal as possible. Scientific understanding of COVID-19 is also changing so quickly that it makes sense to keep options open. But other motives, including public relations and financial gain, might also be in play. "During a crisis, some people will go out of their way to sacrifice their lives, and others will hoard medicines and be complete jerks. On institutional levels, we have the same span of good actors and bad actors", says Bausch.

And in the absence of comprehensive trial coordination mechanisms, signs of disarray are emerging. "The scale of these trials is too small, and the variation in terms of how they are being run is too large", says John-Arne Røttingen, chief executive of the Research Council of Norway and proponent of a more collaborative approach. "These trials aren't really designed to answer the questions that need to be answered." Clinical trial literature, moreover, is riddled with drugs that looked promising in small trials only to prove ineffective in bigger, more rigorous studies.

Merdad Parsey, chief medical officer at Gilead, agrees. "We are seeing that the level of evidence on some of the therapeutics that are out there is not great. Given how broadly some of these agents are being used, this may impact our ability to actually detect signals with other molecules", he explains.

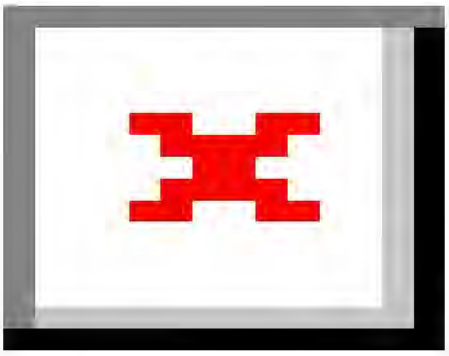
The research community faces a tricky dilemma, with little time for reflection. "On the one hand, we want to be coordinated. On the other hand, we don't want to spend too much time getting coordinated because the pace of this thing is so rapid", explains Parsey. "Everyone's doing their best", he adds.

"The most important things to get right are primary outcomes, inclusion and exclusion criteria, and standard of care", says Bin Cao, a pulmonary and critical care specialist at the China-Japan Friendship Hospital in Beijing. Cao helped to coordinate some of the first trials of COVID-19 drugs in China. Getting the standard of care right for these trials was particularly important, he adds, when systems were overwhelmed and so little was known about the disease.

WHO has now taken steps to provide greater coordination through its Solidarity trial, a study of four therapeutic approaches for hospitalised patients with confirmed COVID-19. These consist of Gilead's RNA polymerase inhibitor remdesivir, the antimalarials hydroxychloroquine and chloroquine, the HIV protease inhibitors lopinavir and ritonavir, and lopinavir and ritonavir in combination with the immunomodulatory agent interferon beta-1a. First results could be available within 12–16 weeks, insiders say.

Not only will the umbrella trial test multiple drugs at scale, but it also seeks to align the research community behind key clinical trial design features that can make the most of incoming data. By enrolling patients from around the world, the Solidarity trial might be able to answer questions more quickly than standalone trials can. Already, 70 countries have committed to joining up. Countries with the least developed health-care infrastructures can follow a backbone protocol, whereas those with better capabilities will launch "daughter" trials that will collect additional data.

"I like the Solidarity trial", says Zhi Hong, chief executive officer of the biotech Brii BioSciences and former head of infectious disease research and development at GlaxoSmithKline. Although the trial is not double-blinded, that is acceptable in a pandemic, he says. "You really want to make this as easy and simple as possible", says Hong, who is not involved in the trial. By enrolling as many and as diverse a population as possible, the data will be more likely to reflect real-world efficacy, he adds.

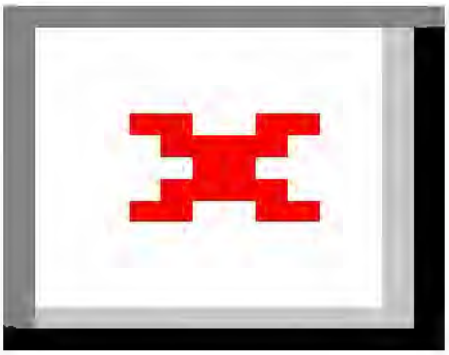


1. • Download : Download high-res image (280KB)
2. • Download : Download full-size image

Expectations for these agents, however, need to be tempered. "I don't want to set expectations too high", says Røttingen, who chairs the executive group and the international steering committee of the Solidarity trial. "I'm not saying these will be a cure for COVID-19", he adds. "But even if we can reduce the proportion of patients that need ventilators by, say, 20%, that could have a huge impact on our national health-care systems."

Marie-Paule Kieny, director of research at INSERM, which is taking part in Solidarity, and former assistant director-general at WHO, is also hedging her bets. "Will we have a magic bullet? Most likely not", she says. A 200-patient trial of the lopinavir plus ritonavir combination has already failed, Cao and colleagues reported in the *New England Journal of Medicine* in March, although subgroup analyses of the data suggest the drugs might still have efficacy.

Researchers have been finding preliminary antiviral efficacy signals with repurposed agents including hydroxychloroquine for decades, says Bausch. But these rarely translate into clinical success. "I have no optimism for hydroxychloroquine", adds Bausch. "I am not opposed to the study of hydroxychloroquine. But I am opposed to what I'm seeing around the world, with this drug being worked into clinical algorithms already."



1. • Download : Download high-res image (265KB)
2. • Download : Download full-size image

This leaves plenty of room—and need—for other agents. Beyond the traditional antivirals, a few candidates are already attracting attention. Virally targeted antibodies might be able to help the immune system to ward of infection, for example. There is also hope that anti-inflammatory agents might be able to keep overactive immune responses in check.

The Solidarity trial has been set up such that some of these other agents can be added in as new arms, as the trial progresses. But there is a trade-off here—and elsewhere throughout the COVID-19 drug development landscape—between speed and breadth. "If we add more arms, it will take longer to actually collect solid data on the therapeutic options that are in the existing arms", cautions Røttingen.

The different classes of agents might also be most useful in different stages of diseases. Antiviral agents, for example, might be most beneficial when used as early as possible in the course of disease, prophylactically even if possible. Anti-inflammatory agents might, by contrast, be harmful if used early on, if they dampen the immune response too much.

Many more trials, consequently, are going to be needed. WHO might yet start another Solidarity trial in an earlier disease setting. Other large trials to build up the evidence base include the UK's multiarm RECOVERY trial in hospitalised patients, which has already recruited 4 300 patients and is adding 400 more a day, and an international 40 000-patient prevention trial with chloroquine and hydroxychloroquine.

Industry sponsored trials will also be needed, both to prioritise which agents to test at scale and potentially to secure regulatory approvals. Gilead is aiming to recruit more than 3000 patients into its phase 3 trial of remdesivir, in addition to its collaborative efforts with WHO, the US National Institutes of Health, and others.

Having multiple parties and funders pursue their own favoured agents also provides a safeguard against groupthink, adds Kieny. "We shouldn't have a single approach, and it is absolutely fair to do more trials", she says. "But it would be good if other investigators look at what we have done with Solidarity, committing to a consortium to increase the likelihood of finding an answer to the most pressing scientific questions."

Bausch similarly urges for more coordination around clinical data collection. "If everyone has their own case-report forms to record the different clinical signs and symptoms of disease, they might record these in different ways", explains Bausch. "This makes it very difficult to later merge the databases and make sense of things across different trials."

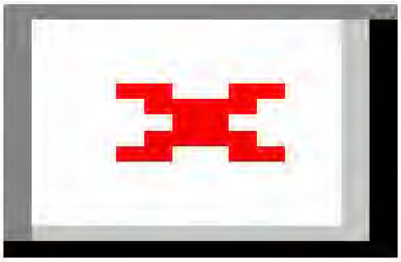
While finding effective drugs is no easy feat on its own, it is also only at best a single step on a long journey towards taming the COVID-19 beast. Manufacturing, regulatory approval, and supply and access decisions are also going to need collective solutions, as will vaccine and diagnostic development.

It remains to be seen how this will all play out. "There is a saying that everyone wants to see more coordination, but no one wants to be coordinated. I think that is an issue we are now seeing", says Røttingen.

Parsey nevertheless remains optimistic. "We are all working through different options and trying to help each other out", says Parsey. "It's really heartening."

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/20 18:42:06
Delivered Date:	2020/04/20 18:42:18
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Science: These drugs don't target the coronavirus—they target us
Date: 2020/04/02 13:25:37
Priority: Normal
Type: Note



Researchers will start to treat COVID-19 patients at Aarhus University Hospital with a drug named camostat mesylate that targets a human protein.
HENNING BAGGER/AFP via Getty Images

These drugs don't target the coronavirus—they target us

By Kai KupferschmidtApr. 2, 2020 , 11:10 AM

***Science*'s COVID-19 reporting is supported by the Pulitzer Center.**

In another example of the blinding speed at which science is moving during the pandemic era, researchers at Aarhus University will start a clinical trial of a drug named camostat mesylate tomorrow—barely 1 month after a *Cell* paper showed the compound can prevent the novel coronavirus, SARS-CoV-2, from entering human cells.

"If we are to have an impact on the rising epidemic, then we have to act right now," says Ole Søgaard, the infectious disease physician leading the study.

One reason the Danish researchers can act so fast is that camostat mesylate is already licensed in Japan and South Korea to treat pancreatitis, a potentially fatal inflammation of the pancreas. Enough safety data were available to convince an ethical panel to greenlight the trial.

The trial also illustrates a new approach to combatting the virus. Thousands of researchers around the world are investigating existing drugs as potential therapies for COVID-19, most of them looking at antivirals, such as remdesivir, developed to treat Ebola, or Kaletra, a combination drug against HIV. But Nevan Krogan, a molecular biologist at the University of California, San Francisco, sees another opportunity: "The virus can't live by itself, right? It needs our genes and proteins in order to live and to replicate." Camostat mesylate is one of several candidate drugs that block those interactions. They don't target the virus, but us, the host.

To identify these drugs, scientists study the complicated molecular dance that happens between a virus and its host cells. For instance, from past work, researchers know in detail how other coronaviruses—those that cause severe acute respiratory syndrome and Middle East respiratory syndrome—infect a cell. First, a protein on the viral surface called the spike attaches to a receptor on the human cell called ACE2. Then, another human protein, TMPRSS2, cleaves the spike protein, allowing the virus to fuse with the cell and start to replicate inside it.

Camostat mesylate blocks TMPRSS2; in the *Cell* paper, molecular biologist Stefan Pöhlmann of the German Primate Center and other researchers showed the drug kept SARS-CoV-2 from infecting lung cells in the lab. TMPRSS2's normal role in the human body is unclear, Pöhlmann says. Knocking out the gene in mice seems to leave them unaffected.

Patients in the Danish trial will be given two 100-milligram pills of the drug or a placebo three times a day for 5 days, the maximum dose given to patients with pancreatitis in Japan, and their symptoms will be monitored. Whether the drug will reach the lung cells that the virus targets is a big question. "We can only hope that is the case," Pöhlmann says.

The Danish researchers are planning to include 180 patients, with a first analysis planned after 108 have completed the study, including a 1-month follow-up. The team could know whether the drug is effective within 3 months, says Mads Kjølby, a researcher at Aarhus University who is also involved in the trial.

Krogan's lab is looking for other human proteins that the virus exploits. To find these proteins—potential drug targets—his lab does a kind of molecular fishing. The researchers attach a molecular handle to proteins from the virus. Then they put these proteins into human cells, using them as lures to pull out any human proteins they stick to, and retrieve them with the handle.

Krogan's lab started work on January, 2 weeks after the first SARS-CoV-2 genetic sequence became available. A few days later, when it became clear the virus was already spreading in California, Krogan realized time was running out. "I went into the lab and I told everybody to stop what they were doing and work around the clock on this," he says. The lab produced the last bits of data a few hours before his university shut down on 18 March. "It was a huge race against time."

In a preprint first posted on bioRxiv on 22 March, Krogan and a team of dozens of international collaborators presented their results: 332 human proteins that SARS-CoV-2 appears to target. "The virus gets its fingers in most of the major biological processes," Krogan says, including DNA replication, vesicle trafficking, and the cytoskeleton.

The virus can't live by itself, right? It needs our genes and proteins in order to live and to replicate.
Nevan Krogan, University of California, San Francisco

For many of the proteins, "There is no clear explanation why the virus would need them," says co-author Marco Vignuzzi, a virologist at the Pasteur Institute. Some may simply be false hits. But many human proteins have several functions, not all of which are known. "The virus might be using a secondary use for a protein or even hijacking it and making it do things it doesn't normally do," Vignuzzi says.

Scouring the literature and asking scientists around the world, the team also identified 69 drugs that act on 66 of these proteins. They include camostat mesylate and a closely related compound called nafamostat that also acts on TMPRSS2 but is given intravenously. Another one is chloroquine (and its sister compound hydroxychloroquine), a drug that has garnered a lot of attention but whose effectiveness against COVID-19 is as yet unproved. Chloroquine reduces the acidity in endosomes, compartments that cells use to ingest material from the outside and that coronaviruses can use instead of the ACE2 receptor to enter a cell.

Now, just over 1 week after Krogan's team assembled its list, scientists are starting to test all of the drugs in cell culture, including several cancer drugs and haloperidol, a compound used to treat schizophrenia. "It's an important dataset," says John Young, global head of infectious diseases, Roche Pharma research, and early development at Roche, which is funding some of Krogan's work. "Every

company in the world right now is looking at that data set and thinking about what it might mean for therapeutics."

Young cautions that host-directed drugs are more likely to do harm than therapies that target the virus directly. "Because you're hitting a host target, hitting a host function, there's an increased safety risk." Krogan hopes focusing on drugs already approved for other diseases, such as camostat mesylate, will largely bypass that problem.

On the other hand, the virus may be less likely to develop resistance to these therapies, because the targeted proteins are encoded in the human genome and not that of the virus. (Resistance is a major problem with antivirals for HIV, influenza, and other diseases.) If researchers manage to target a human protein that's central in coronavirus infections in general, it could even lead to a broader therapeutic, Krogan says. "Then you would also have a treatment for COVID-22 or COVID-24 or whatever virus comes."

If any leads look promising in the lab, they could soon enter clinical trials as well. Of the 69 drugs, 27 are already approved, 14 are in clinical trials, and 28 are in preclinical tests. Most of the newly identified drugs will probably hinder the virus, says Stanley Perlman, a coronavirus researcher at the University of Iowa. "That may be useful. But similar to remdesivir, they probably have to be used early during the infection, or they won't help much," he says.

Perlman says combining such drugs with another type of host-directed treatment that dampens the immune system may be the way to go. That approach may sound paradoxical, but the immune system itself may cause much of the damage to the lungs of COVID-19 patients as it fights the infection, says Susanne Herold, an expert on pulmonary infections at the University of Giessen. "If you knock down the virus without the host immune response, you may not change anything," Perlman says. "If you knock down the host immune response without the virus, you can enhance virus replication, which would be a problem."

Researchers are looking at several compounds to lessen the immune response. They are trying to find out, for instance, whether using antibodies to block interleukin 6 or complement component 5, two signaling molecules that play a role in the human immune defense, can help patients. The danger is that dampening the immune system could make patients susceptible for other infections, Herold notes—for instance bacterial infections of the lung.

Regardless of how many of these approaches will bear fruit, the spirit of collaboration and the speed of discovery have been a positive signal in dark times, says Krogan. "We [downloaded] the sequence on January 24, and two months later we are testing drugs in Paris," he says. "It's just surreal."

Posted in:

- Chemistry
- Health
- Coronavirus

doi:10.1126/science.abc0405

Kai Kupferschmidt

Kai is a contributing correspondent for *Science* magazine based in Berlin, Germany. He is writing a book about the color blue, to be published this autumn.

- Twitter

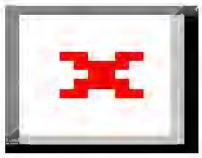
Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/02 13:25:10
Delivered Date:	2020/04/02 13:25:37
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: POLITICO: Trump: We'll 'slash red tape' to find coronavirus drugs
Date: 2020/03/19 13:34:30
Priority: Normal
Type: Note

Trump: We'll 'slash red tape' to find coronavirus drugs

The president suggested certain programs that the administration could use to get experimental drugs to people quickly outside of clinical trials.



Donald Trump
President Donald Trump speaks during press briefing with the coronavirus task force at the White House Thursday. | Evan Vucci/AP Photo

By SARAH OWERMOHLE
03/19/2020 01:01 PM EDT

President Donald Trump said he will "slash red tape like nobody has even done it before" in a bid to get unapproved coronavirus treatments to patients faster and identify effective drugs.

The president said Thursday he directed the Food and Drug Administration to "eliminate out-of-date rules and bureaucracy so this can go forward fast" — but he did not offer any details.

Instead, Trump and top health officials highlighted steps the government has taken in recent weeks to launch clinical trials of potential coronavirus treatments.

Trump's remarks came one day after he teased that an "exciting FDA announcement" was on the way — news that reportedly caught some in the health agency by surprise as they scramhled to finalize details, said three HHS officials.

> The president suggested certain programs that the administration could use to get experimental drugs to people quickly outside of clinical trials. One such route, known as "Right to Try," was established by a 2018 law that Trump and Vice President Mike Pence supported to help people who are seriously ill and have no other treatment options.
>
> "What we're talking about today is beyond Right to Try," Trump said, adding that the law "has been a tremendous success."

That program allows patients to appeal directly to drugmakers to use medicines that are still being developed and tested. Bioethicists and drug policy experts argue there are other ways to help people access experimental medicine — like the FDA's compassionate use route, also name checked by the president — and that Right to Try fuels false hope, while making it difficult to collect data on how well the drugs work.

The drugmaker Gilead has provided its experimental antiviral drug remdesivir to patients with coronavirus under compassionate use rules first established in 1987. The National Institutes of Health has also started a clinical trial of the drug in coronavirus patients.

Trump name-checked remdesivir at Thursday's briefing, along with two drugs that have been used for decades to treat malaria. He suggested that the malaria drugs, hydroxychloroquine and chloroquine, could be effective against coronavirus — but the data is still sparse.

It is unclear how many people have been treated under the federal Right to Try law for any condition. There are at least nine publicly reported cases. The libertarian Goldwater Institute, which spearheaded efforts to pass the legislation, says at least six of those involved people who received experimental brain cancer vaccine.

Goldwater this week pushed for Right to Try to be used amid the coronavirus outbreak.

Others are more skeptical about the program's usefulness during the current crisis. "A lot of these [drug] products are already being deployed through clinical trials as well as compassionate use or emergency use authorities," Steve Ubl, CEO of the drug lobby PhRMA, said Wednesday when asked about the Right to Try push. "I'll leave it at that."

Bioethicists were quick to sound the alarm when Goldwater floated the idea, arguing it would fuel false claims and panic around the outbreak.

“Right now, to push the Right to Try pathway seems really irresponsible and dangerous,” said Holly Fernandez Lynch, a bioethicist at University of Pennsylvania. “This is the type of thing that's critically important to preserve clinical trials for or we’re not going to be able to figure out whether this stuff works.”

Trump has urged manufacturers to get treatments and vaccines to patients qnickly even as other officials have warned that creating an effective vaccine, in particular, will take at least a year.

The FDA this week also let researchers alter clinical trials to keep subjects safe during the ontbreak and allow for scientists to assess patients remotely. "What's important is not to provide falsehood bnt provide hope," the agency's commissioner, Stephen Hahn, said Thnrsday.

Hahn instead appeared to lean on compassionate use rather than the newer Right to Try law. "The important thing about compassionate use — and that's what the president meant [with] this is beyond Right to Try — is that we get to collect the information," he said.

"At this point, the issues that we have been raising with the administration have been focused more on logistics and ensuring that we online to have the free flow of goods to make sure that we can meet patient needs," PhRMA's Ubl told reporters Wednesday when asked about the lobby's goals amid the government's response.

Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date: 2020/03/19 13:34:19
Delivered Date: 2020/03/19 13:34:30
Message Flags: Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>

Subject: Data on 53 Patients Treated With Investigational Antiviral Remdesivir Through the Compassionate Use Program Published in New England Journal of Medicine

Date: 2020/04/10 17:46:49

Priority: Normal

Type: Note

Data on 53 Patients Treated With Investigational Antiviral Remdesivir Through the Compassionate Use Program Published in New England Journal of Medicine

-- Remdesivir treatment resulted in clinical improvement in 68 percent of patients in this limited data set --

April 10, 2020 03:31 PM Eastern Daylight Time

FOSTER CITY, Calif.--(BUSINESS WIRE)--Gilead Sciences, Inc. (Nasdaq: GILD) today announced results from a cohort analysis of 53 patients hospitalized with severe complications of COVID-19 who were treated with the investigational antiviral remdesivir on an individual compassionate use basis. The majority of patients in this international cohort demonstrated clinical improvement and no new safety signals were identified with remdesivir treatment. Compassionate use data have limitations and multiple Phase 3 studies are ongoing to determine the safety and efficacy of remdesivir for the treatment of COVID-19. The detailed results of this analysis were published today in *The New England Journal of Medicine*.

Remdesivir is not yet licensed or approved anywhere globally and has not been demonstrated to be safe or effective for the treatment of COVID-19.

Nearly two thirds of patients (64 percent, n=34/53) in this cohort were on mechanical ventilation at baseline, including four patients also on extracorporeal membrane oxygenation (ECMO). Treatment with remdesivir resulted in an improvement in oxygen support class for 68 percent of patients (n=36/53) over a median follow-up of 18 days from the first dose of remdesivir. More than half of patients on mechanical ventilation were extubated (57 percent, n=17/30) and nearly half of all patients (47 percent, n=25/53) were discharged from the hospital following treatment with remdesivir. After 28 days of follow-up, the cumulative incidence of clinical improvement, defined as discharge from the hospital and/or at least a two-point improvement from baseline on a predefined six-point scale, was 84 percent according to Kaplan-Meier analysis. Clinical improvement was less frequent among patients on invasive ventilation versus noninvasive ventilation (HR: 0.33 [95 percent CI 0.16, 0.68]) and among patients at least 70 years of age (HR vs <50 years: 0.29 [95 percent CI 0.11, 0.74]). Compassionate use data have limitations due to the small size of the cohort, the relatively short duration of follow-up, potential missing data due to the nature of the program and lack of a randomized control group.

"Currently there is no proven treatment for COVID-19. We cannot draw definitive conclusions from these data, but the observations from this group of hospitalized patients who received remdesivir are hopeful," said Jonathan D. Grein, MD, Director of Hospital Epidemiology, Cedars-Sinai Medical Center,

Los Angeles, and lead author of the journal article. "We look forward to the results of controlled clinical trials to potentially validate these findings."

The overall mortality rate in this cohort was 13 percent (n=7/53). The mortality rate was higher in the subgroup of patients on invasive ventilation (18 percent, n=6/34), compared with patients on noninvasive oxygen support (5 percent, n=1/19). Factors associated with an increased risk of mortality included age greater than 70 years (HR vs <70 years: 11.34 [95% CI 1.36, 94.17]) and higher baseline serum creatinine levels (HR per mg/dL: 1.91 [95% CI 1.22, 2.99]), indicating reduced kidney function. Mild to moderate liver enzyme (ALT and/or AST) elevations (23 percent, n=12/53) were observed in this cohort. No new safety signals were detected during short-term remdesivir therapy.

Given the limitations of this data set and analysis, data from ongoing, randomized clinical studies of remdesivir are needed to provide a scientifically robust understanding of the clinical impact of remdesivir treatment.

"While the outcomes observed in this compassionate use analysis are encouraging, the data are limited," said Merdad Parsey, MD, PhD, Chief Medical Officer, Gilead Sciences. "Gilead has multiple clinical trials underway for remdesivir with initial data expected in the coming weeks. Our goal is to add to the growing body of evidence as quickly as possible to more fully evaluate the potential of remdesivir and, if appropriate, support broader use of this investigational drug."

Gilead is conducting two Phase 3 clinical trials of remdesivir, the SIMPLE studies, in countries with high prevalence of COVID-19. Data from the SIMPLE study in patients with severe disease are expected this month, followed by data from the SIMPLE study in patients with moderate disease in May. In addition, Gilead is supporting multiple clinical trials led by other organizations, including two studies conducted in Hubei Province, China. Gilead has been informed that the study in China in patients with severe disease was terminated early due to low enrollment; the company awaits the publication of these data to enable an in-depth review of the results. The study in China in patients with mild-to-moderate disease is ongoing. A global study of remdesivir led by NIAID continues to enroll patients and data from this study are anticipated in May. Finally, additional studies of remdesivir and other investigational treatments for COVID-19, based on a master protocol by the World Health Organization, have also begun to enroll patients in countries around the world.

About the Compassionate Use Cohort Analysis

Since January 25, 2020, Gilead has been providing emergency access to remdesivir for qualifying patients with severe complications of COVID-19 who are unable to enroll in ongoing clinical trials. More than 1,800 patients have been treated with remdesivir through individual compassionate use protocols. This cohort evaluated data from 53 patients in the United States, Europe, Canada and Japan who received at least one dose of remdesivir on or before March 7, 2020, through Gilead's compassionate use program. All patients were hospitalized with severe acute respiratory coronavirus 2 (SARS-CoV-2) infection and either an oxygen saturation of 94 percent or less, or a need for oxygen. The median duration of symptoms before initiation of remdesivir was 12 days. The majority of patients (75 percent) were men over the age of 60 years with comorbid conditions, including hypertension, diabetes, hyperlipidemia and asthma. Combined, all three of these factors have been associated with adverse outcomes of COVID-19.

The planned treatment was a 10-day course of remdesivir, consisting of a 200 mg loading dose administered intravenously on day 1, followed by 100 mg daily for the remaining nine treatment days. Of the 53 patients included in the analysis, 75 percent received the full 10-day course of remdesivir, 19 percent received 5-9 days of treatment, and 6 percent received fewer than 5 days of treatment. Follow-up continued through 28 days after initiation of remdesivir treatment. Four patients discontinued remdesivir prematurely, one due to worsening of pre-existing renal failure, one due to multiple organ failure and two due to elevated liver enzymes, including one patient with a maculopapular rash.

There were no prespecified endpoints for this program. As part of the analysis, rates of key clinical events were quantified, including change in oxygen support requirements, hospital discharge, reported adverse events leading to discontinuation of remdesivir treatment and mortality. In addition, the analysis evaluated the proportion of patients with clinical improvement, defined as live discharge from the hospital and/or a clinical improvement of at least two points from baseline on a six-point scale reflecting hospitalization and oxygen support status, as recommended by the World Health Organization R&D Blueprint Group.

About Remdesivir

Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity both *in vitro* and *in vivo* in animal models against multiple emerging viral pathogens, including Ebola, Marburg, MERS and SARS. *In vitro* testing conducted by Gilead has demonstrated that remdesivir is active against the virus that causes COVID-19. The safety and efficacy of remdesivir to treat COVID-19 are being evaluated in multiple ongoing Phase 2 and 3 clinical trials. Initial clinical trial data are expected in mid-April.

About Gilead Sciences

Gilead Sciences, Inc. is a research-based biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet medical need. The company strives to transform and simplify care for people with life-threatening illnesses around the world. Gilead has operations in more than 35 countries worldwide, with headquarters in Foster City, California.

For more information on Gilead's response to the coronavirus outbreak please visit the company's dedicated page: https://protect2.fireeye.com/url?k=0b70e4c5-5724fdb9-0b70d5fa-0cc47adc5fa2-576dca5030719e68&u=https://www.gilead.com/purpose/advancing-global-health/covid-19.

Forward Looking Statement

This press release includes forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks, uncertainties and other factors. Remdesivir is an investigational agent that has not been licensed or approved anywhere globally, and it has not been demonstrated to be safe or effective for any use, including for the treatment of COVID-19. There is the possibility of unfavorable results from clinical trials involving remdesivir and the possibility that Gilead may be unable to complete one or more of such trials in the currently anticipated timelines or at all. Further, it is possible that Gilead may make a strategic decision to discontinue development of remdesivir or that FDA and other regulatory agencies may not approve remdesivir, and any marketing approvals, if granted, may have significant limitations on its us. As a result, remdesivir may never be successfully commercialized. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. These risks, uncertainties and other factors could cause actual results to differ materially from those referred to in the forward-looking statements. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in Gilead's Annual Report on Form 10-K for the year ended December 31, 2019, as filed with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead, and Gilead assumes no obligation to update any such forward-looking statements.

For more information about Gilead, please visit the company's website at https://protect2.fireeye.com/url?k=422a6c2c-1e7e7550-422a5d13-0cc47adc5fa2-2183042b3f899ba7&u=http://www.gilead.com/, follow Gilead on Twitter (@GileadSciences) or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.

Contacts

Douglas Maffei, Ph.D., Investors
(650) 522-2739

Sonia Choi, Media
(650) 425-5483

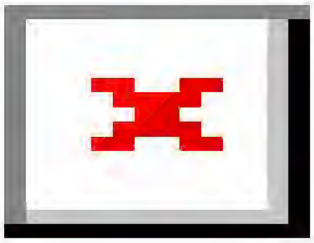
Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/10 17:46:06
Delivered Date:	2020/04/10 17:46:49

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: NPR: FDA Grants Experimental Coronavirus Drug Benefits For Rare Disease Treatments
Date: 2020/03/25 07:59:05
Priority: Normal
Type: Note

The Coronavirus Crisis

FDA Grants Experimental Coronavirus Drug Benefits For Rare Disease Treatments

• •
• • • March 24, 20207:26 PM ET
Sydney Lupkin



Gilead Sciences CEO Daniel O'Day (center) took part in a meeting of the White House Coronavirus Task Force on March 2.
Andrew Harnik/AP

The Food and Drug Administration gave an experimental medicine called remdesivir to treat COVID-19 what's called orphan drug status on Monday.

To qualify for an orphan designation, drug companies must show that their product will treat a population of fewer than 200,000 patients or that it would be unprofitable.

With more than 52,000 confirmed U.S. cases of COVID-19 reported as of Tuesday afternoon, the illness is under the technical threshold for a rare disease. But cases are rising quickly and it seems inevitable that they will surpass 200,000.

The agency's decision would provide lucrative incentives to the drug's maker, Gilead Sciences, and could keep lower-priced generic versions of the medicine off the market for several years if remdesivir is approved for use, public health advocates say.

Remdesivir is an intravenous, antiviral medicine that is being studied in clinical trials around the world as a possible treatment for COVID-19.

Clinical trials for remdesivir as a COVID-19 treatment got started in China in early February. Tests of the drug are now enrolling patients elsewhere, including the United States.

The FDA's granting of orphan status for remdesivir as a treatment for COVID-19 came with financial incentives for Gilead that include tax breaks, waiver of FDA fees and market exclusivity for seven years if the drug is approved. New drug molecules typically only get five years of this exclusivity.

The agency decision drew criticism from consumer advocates.

"FDA should not provide long-term financial incentives for a treatment that would be very widely used if it works," said Diana Zuckerman, who heads the National Center for Health Research, a consumer advocacy and research organization. The goal of the orphan drug program is to "make it more lucrative for a company to develop a treatment that won't have a lot of customers."

With more than 50,000 confirmed U.S. cases of COVID-19 reported as of Tuesday afternoon, the disease is under the technical threshold for a rare disease. The law states that the number of patients must be fewer than 200,000 "at the time of the submission of the request for orphan-drug designation."

The FDA told NPR that this is why remdesivir was given orphan status this week, adding that it met the "standard criteria for prevalence for designation."

In an emailed statement, a Gilead spokesperson wrote that when it sought the orphan designation, "only a small number of Americans were affected by COVID-19." A company spokesperson declined to say when this was. The drug company said it "has been making significant at-risk investments" to study remdesivir and increase its supply during the global health emergency.

If remdesivir is approved, Gilead's statement said, "we are committed to making the medicine both accessible and affordable to governments and patients around the world."

Advocates voiced concern that the FDA's decision paves the way for Gilead to charge a high price for remdesivir. Many orphan drugs are among the most expensive medications in the United States, in part because generic competitors are delayed.

"Gilead's pursuit of an orphan designation is unconscionable and could be deeply harmful," Peter Maybarduk, who directs Public Citizen's access to medicines program, wrote in a statement. "Remdesivir is one of relatively few medicines that may prove effective in treating COVID-19 this year. The government should be urgently concerned with its affordability for citizens."

Earlier this month, Public Citizen and 70 other organizations co-authored a letter to President Trump, urging his administration not to award monopolies to pharmaceutical companies working on COVID-19 vaccines and cures. The letter cited Public Citizen's report, which found that taxpayers had already spent $700 million on pharmaceutical research and development for coronaviruses since 2002.

During a congressional hearing in late February, Department of Health and Human Services Secretary Alex Azar declined to promise that coronavirus treatments would be affordable.

"We can't control that price because we need the private sector to invest," he said during the hearing with the House Committee on Energy and Commerce.

The decision to award remdesivir orphan designation as a treatment for COVID-19 also puzzled Ken Kaitin, who directs the Tufts Center for the Study of Drug Development. If the FDA's goal was to speed development, he said it could do that in other ways.

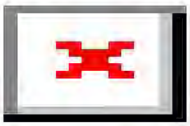
"I could see that Gilead would like that," Kaitin said of the orphan drug tax breaks and promise of seven years without generic competitors. "But at the same time, it's hard to imagine the FDA would say, OK, we're going to call it an orphan drug even though it's not [rare.]' "

The Government Accountability Office finished a yearlong investigation of the FDA's orphan drug program in 2018. It found that the agency wasn't always ensuring that the intent of the Orphan Drug Act was being met. Instead, FDA reviews that determined orphan designation were often inconsistent and incomplete.

The GAO report followed a Kaiser Health News investigation into manipulation of the orphan drug program that showed that many pharmaceuticals that received rare disease perks started off as blockbuster products with millions of customers.
Still, the National Organization for Rare Disorders, a patient advocacy group, said remdesivir's designation follows the letter of the law.
"It is important to remember that, under the Orphan Drug Act, FDA must make designation decisions based on available data at the time the application is submitted," Rachel Sher, the group's vice president of policy and regulatory affairs, said in a statement provided to NPR.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/25 07:57:46
Delivered Date:	2020/03/25 07:59:05
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Science: 'We thought she was going to pass away.' Did an experimental drug help a U.S. coronavirus patient?
Date: 2020/03/13 17:56:34
Priority: Normal
Type: Note



George Thompson
University of California-Davis Health

'We thought she was going to pass away.' Did an experimental drug help a U.S. coronavirus patient?

By Jon CohenMar. 13, 2020 , 1:30 PM

On 26 February, what seems like ages ago in the ongoing pandemic, the University of California Davis Medical Center in Sacramento finally got RNA test results confirming that a critically ill patient it had been treating for a week had coronavirus disease 2019 (COVID-19). (It took 4 days before the U.S. Centers for Disease Control and Prevention agreed to evaluate her samples because the woman did not meet the strict criteria the agency then had in place, and 3 more days for the result to come back.) The patient, who for privacy reasons has only been described as a woman by California's governor and state health officials, was the first likely case of U.S. community spread detected, meaning that the source of her infection was not known: She had had not traveled outside the United States to an infected area or been in known contact with a confirmed case.

The difficulty the medical center faced acquiring a test for its patient received widespread media scrutiny, but her fate largely escaped notice: After her condition declined, the UC Davis doctors secured what's known as compassionate use permission from the Food and Drug Administration to test an experimental drug on their patient outside of a clinical trial. The drug, remdesivir made by Gilead Sciences, is given by an intravenous drip. Several randomized, placebo controlled trials of remdesivir for COV-19 are now underway in China and the United States and everyone is looking for quick hints on whether the drug works—a new preprint out today on the drug's use in three COVID-19 patients is raising questions about its ultimate value.

Remdesivir cripples an enzyme called RNA polymerase that is used by many viruses to copy themselves; it does not specifically target SARS-CoV-2, the virus that causes COVID-19. But it worked well in test tube and animal studies of human coronaviruses, cousins of SARS-CoV-2 called severe acute respiratory syndrome and Middle East respiratory syndrome, that cause similar respiratory conditions. (Ebola also is

an RNA virus, but a test of remdesivir in the Democratic Republic of the Congo last year showed that it didn't work for that disease.)

George Thompson, an infectious disease specialist at the medical center, was on the team that cared for the California patient and spoke to *Science*Insider about her case. This interview has been edited for clarity and length; additional information added by *Science*Insider is in brackets.

Q: When did the patient start on remdesivir?

A: From diagnosis to therapy, about 36 hours, which is very short for emergency approval of an investigational drug.

Q: How sick was she?

A: We thought she was going to pass away.

Q: Did you do extracorporeal machine oxygenation (ECMO)? [This is a type of artificial lung that removes blood, pumps oxygen into it, and then returns it back to the body. It has been used extensively in China to save some critically ill COVID-19 patients.]

A: We had started those conversations to see how we would do it logistically, and she was very close to needing it, but her health started to turn around. We have some severe influenza cases every year that end up on ECMO, but nobody likes to do it. Those patients are so sick and they require a lot of time, a lot of resources. But we do it if we need to. And we were willing to do it for that patient.

Q: One truism of antivirals for acute diseases is that if you start them late, they don't work. Do you think that the point at which you gave her the treatment was early enough for it to have worked?

A: I think so. One requirement was that the patient had to have a positive test [showing the presence of SARS-CoV-2] right before starting the drug to make sure that she hadn't spontaneously already cleared the virus. The day after the infusion of the drug, she consistently got better. I can't prove it's related. I wish we had been able to do serial [polymerase chain reaction] PCR testing of her blood, but we couldn't because of lack of resources. With most investigational drugs tested in, say, macaque monkeys, there's a nice correlation between the administration of the drug and a drop in the amount of virus in the blood. That's what we hoped we could have seen in this patient.

[PCR can amplify a tiny amount of viral RNA so that it can be detected and is the basis of most SARS-CoV-2 tests.]

Q: What do you mean by a lack of resources?

A: The county only had 20 coronavirus tests for the whole county. That patient already had a confirmed infection and was not a priority for using them.

Q: Couldn't you take serial blood samples, store them, and look at them later?

A: We have all those samples saved in our local hospital and we're going to be able to do the testing next week from what I've been told. We finally have our own home-brewed [SARS-CoV-2] test up and running and I think that'll tell more of the story. If the drops in her viral loads are temporally related to remdesivir, it's a much more compelling argument than she lived, so it must have worked. But then again, I've heard stories that many COVID-19 patients just have the virus in their respiratory samples and not their blood.

Q: When would you expect to see that drop in viral load if it was due to remdesivir?

A: Within the first 24 hours you really want to see a [big drop]. But I think we've got a lot to learn about this disease.

Q: Has she been discharged?

A: To protect her privacy, let's just say she's doing well.

Q: Have you treated other patients at UC Davis Medical Center who have confirmed COVID-19?

A: Yes, but they had moderate disease and it was mild enough for them to go home. None would have qualified for compassionate use of remdesivir, which is only given to patients with severe disease.

Q: That's a conundrum though because remdesivir has the best chance of working in patients who are treated early, before the disease becomes severe.

A: For most any infectious disease, I think the earlier we start drugs the better. But it's a risk versus benefit question. What if this drug causes liver toxicity in 50% of the people, and we've given it to somebody who was probably going to do well without it?
[Clinical trials underway will look at all stages of disease.]
Q: Are you planning to test other experimental drugs for COVID-19?
A: We've already been contacted by a whole bunch of companies with different compounds. So, I think we'll be able to offer most anybody with confirmed COVID-19 some experimental protocol in a clinical trial. There's a lot of interest in chloroquine, and interferon with Kaletra.
[Chloroquine is an antimalarial, interferon is an immune system messenger, and Kaletra is a combination of two protease inhibitors used to treat HIV infection.]
Q: Was what you saw frightening?
A: Well, it can be severe. My research lab works on a pathogen, *Coccidioidomycosis* fungus, that must be studied in a BSL-3 [biosafety level 3] lab. So I'm pretty used to wearing all the gear. [BSL-3 is the second strictest level of containment.] There's a lot of fear in the hospital. Nurses need to talk a lot about it. And respiratory therapists want to talk a lot about what are you going to do for a patient who's on a nebulizer [a machine that turns liquid medicines into a mist].
Q: Many people talk about this disease with great authority based on reports they've read. My sense of this virus is it's really nasty for people who are older than 80, and for people who have heart conditions, diabetes, hypertension, but for most healthy people, it's going to be like a flu. It typically doesn't do much of anything to kids. Is that your perception of this having seen the disease?
A: That's my general perception based on the literature and what we know of the virology, but it's pretty early, right? We've had such poor testing capacity, I don't think we really have clinical experience with the breadth of the disease. Our first couple of patients have been, middle-age, healthy people. But again, you know, if you have some very minor version of it, you're probably not going to seek any care. So that side of the iceberg—I just don't think we'd have clinical experience with yet.
***Correction, 13 March, 4:30 p.m.:** Due to a transcription error, an earlier version of this story said Thompson studies coxsackievirus.*
doi:10.1126/science.abb7243

Jon Cohen

Jon Cohen
Jon is a staff writer for *Science*.

- Email Jon
- Twitter

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/13 17:56:22
Delivered Date:	2020/03/13 17:56:34
Message Flags:	Unread

From:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject:	Remarks by President Trump, Vice President Pence, and Members of the Coronavirus Task Force in Press Briefing / April 13, 2020
Date:	2020/04/14 16:25:50
Priority:	Normal
Type:	Note

Skip to content
Remarks

Remarks by President Trump, Vice President Pence, and Members of the Coronavirus Task Force in Press Briefing

Issued on: April 14, 2020

James S. Brady Press Briefing Room
April 13, 2020
5:49 P.M. EDT

THE PRESIDENT: Thank you very much, everyone. My administration will do everything possible to help those communities get back on their feet. We're speaking with the governors and representatives. FEMA is already on its way, and they got there — as soon as we heard the word, I said, "Get out there." So FEMA is there, and you know the great job that FEMA does. It's, really, something very special.

So we just want to say: Warmest condolences, and we're with you all the way. It's a tough deal. That was a bad, bed level five. That was a bad group. That's as high as it gets. It was a bad grouping of tornadoes. Something that's something incredible, the power — the horrible, destructive power.

America is continuing to make critical progress in our war against the virus. Over the weekend, the number of daily new infections remained flat nationwide. Flat. Hospitalizations are slowing in hotspots like New York, New Jersey, Michigan, and Louisiana. This is clear evidence that our aggressive strategy to combat the virus is working and that Americans are following the guidelines. It's been incredible what they've done.

You looked at the charts, and the charts are — and the models from early on — predictions were 100 [thousand] and 120,000 people look like. If they did well, they were going to unfortunately perish. And we're going to be, hopefully, way, way below that number. So that will be a sign of people doing things right, but it's still just a horrible thing all over the world. A hundred and eighty-four countries.

This is all a tribute to our wonderful healthcare advisors and experts who have been with us right from the beginning. We appreciate it so much. In fact, Dr. Fauci is here. Maybe I could ask Tony to say a few words before we go any further.

Thank you very much. Tony, please.

DR. FAUCI: Thank you, Mr. President. Just one — a couple of things, and then I just want to make a comment about something that happened yesterday.

You're going to hear from Dr. Birx soon about the numbers that we've been talking about and how things are starting to balance off. And I think the more, as we go by each day, I think we're going to see

— and again, I never like to get ahead of myself or of Dr. Birx, but it looks like even though we've had a really bad week last week — remember, when I was speaking to you before, I was saying this was really a bad week — there's still going to be a lot of deaths, but we're starting to see in some areas now that kind of flattening, particularly in a place that was a hotspot like New York. That's the first thing.
The second thing is that I had a really very, very productive conversation with the Congressional Black Caucus this morning, for about an hour, and they really wanted to know what exactly are we going to be doing in the immediate, as well as the long range, about the health disparities and the discrepancies both in infection and in poor outcome in the minorities in general, but specifically African American. And, I mean, I made it very clear to them that what we have to do is focus on getting the resources where the vulnerable are, to be able to get testing done, to be able to get the appropriate identification, where proper and where appropriate, to isolate and contact trace if we can, but also to help mitigate in a community that is suffering and suffering much more disproportionately.
So I just wanted to get that out of the way.
The other point I wanted to make is that I had an interview yesterday that I was asked a hypothetical question. And hypothetical questions sometimes can get you into some difficulty because it's what "would have" or "could have." The nature of the hypothetical question was: If, in fact, we had mitigated earlier, could lives have been saved? And the answer to my question was, as I always do — and I'm doing right now — perfectly honestly say, "yes." I mean, obviously. If you — mitigation helps.
I've been up here many times telling you that mitigation works. So if mitigation works, and you instigated and — you initiated earlier, you will probably have saved more lives. If you initiated it later, you probably would have lost more lives, if you initiated at a certain time.
That was taken as a way that maybe, somehow, something was at fault here.
So let me tell you from my experience — and I can only speak from my own experience — is that we had been talking, before any meetings that we had, about the pros and the cons, the effectiveness or not, of strong mitigations. So discussions were going on mostly among the medical people about what that would mean.
The first and only time that Dr. Birx and I went in and formally made a recommendation to the President to actually have a, quote, "shutdown" in the sense of — not really "shutdown" but to really have strong mitigation, we discussed it. Obviously, there would be concern by some that, in fact, that might have some negative consequences. Nonetheless, the President listened to the recommendation and went to the mitigation.
The next second time that I went with Dr. Birx in — to the President and said, "Fifteen days are not enough. We need to go thirty days," obviously, there were people who had a problem with that because of the potential secondary effects. Nonetheless, at that time, the President went with the health recommendations, and we extended it another 30 days.
So I can only tell you what I know and what my recommendations were. But, clearly, as happens all the time, there were interpretations of that response to a hypothetical question that I just thought it would be very nice for me to clarify because I didn't have the chance to clarify.
Thank you.
Q The date on that?
DR. FAUCI: Excuse me?
Q The date.
DR. FAUCI: You know, to be honest with you, I don't even remember what the date was. But I can just tell you the first and only time that I went in and said we should do mitigation strongly, the response was, "Yes, we'll do it."
Q And what did he do? Was that the travel restrictions?
DR. FAUCI: No. The travel restriction is separate. That was whether or not we wanted to go into a mitigation stage of 15 days of mitigation. The travel was another recommendation, when we went in

and said, "We probably should be doing that." And the answer was "yes." And then another time was, "We should do it with Europe," and the answer was "yes." And the next time, "We should do it with the UK," and the answer was "yes."
Q In this interview, you said there was pushback.
DR. FAUCI: Yeah.
Q Where did that pushback come from?
DR. FAUCI: No, it wasn't — that was the wrong choice of words. You know what it was? When people discuss, not necessarily in front of the President — when people discuss, they say, "Well, you know, this is going to have maybe a harmful effect on this or on that." So it was a poor choice of words. There wasn't anybody saying, "No, you shouldn't do that."
Q Are you doing this voluntarily? Or did the President —
DR. FAUCI: No, I'm doing it —
Q — or Vice President ask you to do this?
DR. FAUCI: Everything I do is voluntarily. Please. Don't even imply that.
Q So, Mr. President, the question is —
THE PRESIDENT: And, by the way, the travel ban, that was earlier. The travel ban was done earlier.
Q You couldn't give us a date when he talked to you.
THE PRESIDENT: And if you look at statistics — I happened to write a couple of them down. If you look at statistics — so, on January 6th — that's long before the dates you're talking about — there were — CDC issued a travel notice for Wuhan, China, a notice, before there was even a confirmed case of the virus in the United States. That's on January 6th. This is all documented. Because we have so much fake news, I like to document things. January 6th, long before the dates we're talking about, CDC issued travel notice to Wuhan — for Wuhan.
On January 11th, we have zero cases in the United States. Zero. We don't have any cases. So there are no cases reported that we know of. This is January 11th. The CDC issued a level one travel notice health — for health, while there were still no confirmed cases. So we had zero cases. People want me to act. I'm supposed to close down the economy — the greatest economy in the history of the world — and we don't have one case confirmed in the United States. That's January 11th.
On January 17th, the CDC began implementing public health entry screenings at three major U.S. airports that received the greatest volume of passengers from Wuhan, at my instructions. There was not a single case of the coronavirus in the United States. So on January 17th, there wasn't a case, and the fake news is saying, "Oh, he didn't act fast enough." Well, you remember what happened. Because when I did act, I was criticized by Nancy Pelosi, by Sleepy Joe Biden. I was criticized by everybody. In fact, I was called xenophobic. I was asking Biden to please define that for me. I was called other things by Democrats and some others — not too many others, actually. So that — by the media, definitely.
Now, on January 21st — this is long before the time we're talking, because when Tony is talking, I believe he's talking about the end of February. On January 21st, okay — still early — there was one case of the virus. At that time, we called it the "Wuhan virus," right? Wuhan. There was one case in the whole United States. We have one case. This is all documented. It all comes from you. A lot of it comes from you people.
On January 21st, the CDC activated an emergency operation center. There was just one case, one person. That's why that ad was such a phony. There was one person in the United States. You know they used the ad, "There's only one person..." That statement was made at that time. One case. In the whole United States, one case. I'm supposed to shut down the government? The biggest — the biggest economy in the history of the world. "Shut it down. We have one case."
Seven cases were on January 31st. Now, on January 21st, there was a case. Not one person had died. You heard that, Steve, right? Not one person.

So we have this massive country, the United States of America. We have the greatest economy in the world — bigger than China's, by a lot — right? — because of what we've done over the last three and a half years, prior to the virus, but including the virus. So we have the biggest economy, the greatest economy we've ever had; the highest employment numbers; the best employment numbers; best unemployment numbers also. The best of everything.

So, on January 31st — think of it — not one person has died. Not one. Nobody died. Not one, Jon. I don't think you'll find any. This is reported by CDC, confirmed by the news — which doesn't mean anything to me because they don't tell the truth. But CDC reported: January 31st, not one person has died.

And I issued a travel restriction from China. Think of it. So nobody died, and I issued. You can't get earlier than that.

So we have nobody died, and I said, "China, you can't come in. I'm sorry." Because I saw what was going on. It wasn't so much what I was told; it was that I saw what was going on and I didn't like it. But I didn't speak to Tony about it. Didn't speak to very many people about it. I didn't like it.

So what did I do? Ready? January 31st: In the United States, not one person had died because of the — again, the Wuhan virus. So I issued travel restrictions on that date, even though nobody died, and I got brutalized over it by the press because I was way too early; I shouldn't have done it. Brutalized by the press. But, you know, sort of — I've been brutalized for the last four years. I used to do well before I decided to run for politics. But I guess I'm doing okay because, to the best of my knowledge, I'm the President of the United States, despite the things that are said.

So, then, first mandatory quarantine in more than 50 years, we did. First mandatory in 50 years. The same restrictions that the Democrats and the media called "xenophobic." Now, Joe Biden said, "He's a racist." He called me a racist because I said, "We're shutting down entry from China. We're shutting it down." He called me xenophobic, and he called me racist and other things.

Since then, on a Friday night, two weeks ago, Joe Biden issued a state- — it wasn't him; he didn't write it. I'm sure he doesn't even know that it was issued. But the people from his campaign — who are smart. The people that write those little PR releases are pretty smart, reasonably good. Not the best, but they're not bad. But they issued a statement, saying that Joe Biden agrees that the Pres- — that President Trump was right to close it down to China. Now, he did that.

Now, he issued it on Friday night. We've all heard about that, Jon — Friday nights, right? In fact, his was later Friday night than I ever released mine on Friday night. Okay?

Q (Inaudible) seems pretty late.

THE PRESIDENT: So he did — he did it pretty late. I mean, you know, like at 11 o'clock in the evening or something. You know, that's pretty late. Anyway. So Joe Biden issued — and it's one of those things. But, in February, Nancy Pelosi said we should come to Chinatown. This is late February. "Come to Chinatown. We think it's very safe. Come here. Let's all have the big parade — Chinatown parade." Probably referring to San Francisco. And that's it.

But I took this action early. And so the story in the New York Times was a total fake. It's a fake newspaper and they write fake stories. And someday — hopefully in five years, when I'm not here — those papers are all going out of business because nobody is going to want to read them. But now they like them because they write about me.

Now, with that, I have a couple of interesting — we have a few clips that we're just going to put up. We could turn the lights a little bit lower. I think you'll find them interesting. And then we'll answer some questions. I'll ask you some questions because you're so guilty, but forget it. But most importantly, we're going to get back onto the reason we're here, which is the success we're having. Okay?

Please, you could put it on. Thank you.

(A video is played.)

So we could give you hundreds of clips like that from governors — including Democratic or "Democrat," as I call them, governors, which is actually the correct term. We could give you hundreds of clips just like

that. We have them. We didn't want this to go on too long, but I just want to say it's — you know, it's very sad when people write false stories like, in that case, I guess it was gotten mostly from the New York Times, which is a highly — I mean, if you had libel laws, they would have been out of business even before they'll end up going out of business. So it's too bad.

But we could have given you — you saw the statements. We have hundreds of statements. Hundreds of statements, including from Democrats and Democrat governors.

And if you look, they were all saying, "We need ventilators. We need..." You don't hear "ventilators" anymore. They have all the ventilators they need, which we were right about. We said, "You're asking for too many. You don't need that." And, in all fairness, these two people right here — Dr. Birx, Dr. Fauci — they said, "I don't think they need that many ventilators." And I said, "I agree."

At one point — and I'm not knocking New York for this, but they were asking — you remember? — 40,000 ventilators. And that's more than they have all over the country. And we got them a lot of ventilators, and nobody has complained.

We got them, as you know, beautiful — we built hospital rooms all over the country. The governor of Louisiana, John Bel Edwards, was very nice. He said, "You know what? You don't have to build a second hospital." Because good news is happening. They're not able to fill the beds. They needed two hospitals. We built one; it was perfect. We're getting — we're just starting the other. I called him up. I said, "Do you think we should build the second one? I don't think you're going to need it." He said, "Let me get back." He got back. We didn't need it.

With Governor Cuomo, in all good spirit and faith, he wanted to have the Jacob Javits Center done. And we built 2,900 incredible beds. Incredible. Then we make it — we made it COVID — and — or, to be exactly accurate, COVID-19, and — which was a lot of work. We had to change the ductwork. We had to seal up certain areas. We had to put areas of rooftop things over the beds. We did a lot of work. And we had it — but they never really had too much use for it.

And they called also — Mayor de Blasio, rightfully, he called. He said, "Would it be possible to get more medical help?" So, now, not only are we building facilities, we're — they're asking us for help because they're unable to man it. And we got him the help. We got Mayor de Blasio a lot of help.

Then, when the Javits Center wasn't used much — and then, as you know, the Mercy — and we took the Mercy and we took the Comfort, and we made them both — Los Angeles and New York — we made them COVID-adaptable, which was not easy to do. And we didn't get almost any people sent there. They didn't need them at the beginning because they didn't need it for anything but this because there were fewer accidents, fewer motorcycles, fewer everything.

And what we did was like an incredible job, but they didn't need them. It turned out — they were there. We were ready. You know the expression? They have an expression: "Ready, willing, and able." We were ready, willing, and able. What the Army Corps of Engineers did was a miracle. What — what FEMA did was a miracle. What the doctors did.

So I got a call two days ago from the mayor of New York. He said, "Could you help us even more with medical personnel?" And we sent — I think it was 448 doctors, nurses, and respiratory experts. Real experts. And I got a call from the mayor and he said, "I want to tell you: Incredible — these people are incredible." He said, "They lifted the spirits of the hospital workers from New York City like nothing I've ever seen." He's — he was unbelievable, what he said. It was really appreciated. And I let them know that. I let the military people — he said, "They went in there so brave, so incredible. They lifted the spirits of everybody."

We did all of this work, but when you read the phony stories, you — nobody — nobody acknowledges this. And it doesn't have to be acknowledged, from my standpoint, but it does have to be acknowledged from the great work that these doctors, nurses, the Army Corps of Engineers, FEMA — all these people, they've done this incredible job. And they shouldn't be abused because — you take a look at what's happened. Nobody is asking for ventilators, except outside of our country.

Outside of our country, they're calling me — every country. They're calling me. So many countries. And I'm going to try and help them because we have thousands of ventilators being built. But nobody is asking for ventilators. Nobody is asking for beds because we built hospitals. I think we built 20,000 beds in a period of a couple of weeks.

The job they've done is incredible. With all of that being said, I'm getting along very well with governors. And if I wouldn't, Mike Pence had a call today with the governors and it was like a 10. I said, "How was it?" He said, "It's a 10." He was one of my expressions, actually. But he said it was like a 10. And I'm sure you people were probably on the call, although you weren't supposed to be. But you were sitting in somebody's office listening to it, because every time we have these — and, you know, and you would know that for weeks those calls have been very good. But there wasn't a raised voice. There wasn't even a statement of like, "We think you should do this or that." I heard it was, like, just a perfect phone call. It might not be reported that way. They'll say, "I thought that somebody maybe slightly raised..." Didn't even raise a voice.

My only point of saying this, because I want to get back to why we're here: The press has not treated these incredible people who've done such a great job, they haven't treated them fairly. They're way off. We were way ahead of schedule.

And remember this — because the Times story was a fake — but everything — remember this: Everything we did, I was criticized because I was too early. If I waited longer, it would have been — you would have been critic- — if I went way early, if I went three months earlier, I would have been criticized — you know, criticized for being way too early.

So, with all of that being said, we understand it. I think I've educated a lot of people as to the press. And I would love to be able to say that we have a very honest press. Honestly, Jon, there'd be nothing I would be more proud of if the press would work — and I don't mind being criticized, but not when they're wrong. Not when people have done a great job.

Yes.

Q Can I just ask you about the video? Because I've never seen a video like that played in this room. It looks a bit like a campaign ad. Who — who produced that video for you?

THE PRESIDENT: That was done by a group in the office, and it was done just by — we just put some clips together. I could give you — I'll bet you I have over 100 more clips even better than them. They were just pieced together over the last two hours. That was just — oh, we have far better than that. That's nothing compared to some of them.

Q But this was produced here in the White House by —

THE PRESIDENT: Yeah, this was done by Dan and a group of people, and they just put it together in a period of probably less than two hours.

Q Why did you feel the need to do that?

THE PRESIDENT: Because we're getting fake news, and I like to have it corrected. They're saying what a great job we're doing, and the media — these are the governors of California, governor of New Jersey, governor of New York.

Look, in New York, we work very close with Andrew. In New York, ventilators — we're going to be probably — we didn't — they didn't have a problem We got them tremendous numbers of — thousands, but we got them a tremendous number of ventilator. You don't hear ventilators are a problem. Beds were going to be a problem. I mean, I'm happy about it. The Javits Center, which is incredible, is almost empty because they don't need them. That's good news, not bad news. I'm — you know, I'm not saying, "Gee, I wish more people were there." I don't want more people there.

We brought in the boat. We brought in the Comfort. And the Comfort was originally not supposed to be for this at all — the coronavirus. It was not supposed to be for that at all. They called, they said, "Could we have it?" That was a number of weeks ago. We said, "We don't think you need it, but if you need it, we'll do it." Then they said, "Could you get the medical personnel to run the Javits Center? Could you

get the medical personnel to run the ship?" We said, "If it's necessary, we will." And we did. There were military personnel. That's the ones that Mayor de Blasio was so great to, in terms of his statements. I mean, I really appreciated his statements. He was so impressed with them, and I am too. The level of genius and bravery. They're great people, the military people.

And we pieced that together — I would say it took less than two hours. It was done in house.

Steve?

Q But just to be clear, this was produced by government employees, by people here at the White House — this campaign-style video here?

THE PRESIDENT: I wouldn't use the word "produced." All they did was took some clips, and they just ran them for you. And the reason they did is to keep you honest. Now, I don't think that's going to work. It's not going to have any impact. But just think of it: You heard the clips, you heard what I said. They said I acted late on closing down the country.

Some people wish we never closed it down. Now, if we didn't, we would have lost hundreds of thousands of people. You know, interestingly — so I'm — I'm against that. We did the right thing. Everything we did was right. If we would have closed down —

Q You don't think you made any mistakes along the way here? You think everything you did was right?

THE PRESIDENT: Well — well, look, governors should have had ventilators; they chose not to have them. We were able to get them ventilators. You haven't heard — other than, you know, there was a lot of panic, a lot of screaming, "We want ventilators." They got the ventilators. You don't have that anymore. And the surge is supposed to be coming now. And if they do need ventilators, Jon, we've got almost 10,000 that are ready to rock. We have people standing with those ventilators right now. If you needed 2,000 in New York, which you don't, but if you did, we can have them here in less than 24 hours. We're ready to rock. This was a great — this was a great military — and beyond that — operation.

Let's get back to the regular. Shouldn't we get back to the regular? We could talk about this, but all I'm doing is this: I could have given you — like, those are four or five clips that we just played for you. I could have given you hundreds of people — I mean, Gavin was on television two days ago with one of your competitors, singing praises. He says, "Look..." You know, the question was asked in a negative way. He said, "Look, I know what you want to say but — want me to say, but he's been really good. It's hard for me to say that. In fact, it's impossible for me to say it." Gavin Newsom, the governor of California.

I have many clips from many — I have some clips from Anthony, that I didn't want to put up, which were really good. I think Anthony would be the first one to say, when I closed the country to China, when I closed the — the China ban, whatever you want to call it — Anthony said I saved a lot of lives by doing that. I mean, am I correct? I don't want to put words in Anthony's mouth, by the way, and I like him. Today, I walk in and I hear I'm going to fire him. I'm not firing — I think he's a wonderful guy.

Q But why did you tweet something that said "Fire Fauci"? Why did you —

Q You retweeted the hashtag #FireFauci.

THE PRESIDENT: I retweeted somebody. I don't know. They said "fire." It doesn't matter.

Q Did you notice that when you retweeted it?

THE PRESIDENT: Yeah, I notice everything.

Q So you retweeted it even though it said, "Time to fire Fauci"?

THE PRESIDENT: No, no, that's somebody's opinion. All that is is an opinion.

Q But you read it and you elevated it.

THE PRESIDENT: No, I was called about that. I said, "I'm not firing him." In fact, if you ask your friends in the office — in the public relations office, I was immediately called upon that. And I said, "No, I like him. I think he's terrific." Because this was a person's view. Not everybody is happy with Anthony. Not everybody is happy with everybody.

But I will tell you, we have done a job, the likes of which nobody has ever done. The mobilization, getting of equipment, all of the things we've done — nobody has ever done a job like this.
We have 50 governors — and territories, by the way. People don't ever mention that we have territories. We have 50 governors and territories, and many of those governors are Democrats, and they can't find anything to complain about. And honestly, many of them didn't do their jobs. I'll let you know someday — let's see what happens — but I may let you know who's not doing their job. I can tell you the ones that are good, both Republican and Democrat, and the ones who don't know what they're doing. But we help some of the ones that don't know what they're doing. They should have had their own stockpiles. And now, if they want, we can build them stockpiles of ventilators.
The hardest thing is a ventilator, because it's expensive, it takes a while to get. We got them, and nobody believed we did.
Now, many of the governors were asking for far too many. And we said they were asking for far too many. We talked and we said — you said very strongly that they just don't need that many. You said they don't need that many beds — Deborah.
So that's it. Steve, go ahead.
Q To be clear, you and Dr. Fauci are on the same page?
THE PRESIDENT: Yeah, we have been from the beginning. I don't know what it is exactly. But if I put somebody's opinion up — you know, I don't mind controversy. I think controversy is a good thing, not a bad thing. But I want it to be honest controversy.
Now, when I got a call — I got a call not very quickly; nobody, you know, saw that as being any big deal — they said, "How are you doing with Dr. Fauci?" I said, "I'm doing great." And I didn't talk to Dr. Fauci, even until we just got here. Dr. Fauci asked one of the people if he could get up and speak, and he did.
Q So he said that once you —
THE PRESIDENT: And they totally misinterpreted him. I saw what they did.
Q Can I — can I ask you? He said the question was hypothetical. But what he was just acknowledging is that lives would have been saved if the mitigation practices were put into place earlier. That seems obvious. Do you not agree with that?
THE PRESIDENT: Here's the thing. No, no. What he really is saying though: "But how could you have done it?" Look, I just went over stats with you. Right here. Right here.
How do you close it up? You have no deaths and no cases on January 11th. Doctor, would you recommend closing the United States of America?" "Oh, this must be terrible. How many cases do we have?" "None." How many deaths do we have?" "None."
January 17th — go back another week. On January 17th — this is 10 days before I did the — little bit less than 10 days before I did the ban. I did a ban on China. You think that was easy? I then did a ban on Europe. And a lot of people said that was an incredible thing to do, because you look at Spain — and, by the way, we're doing very well because when you look at all of those flat graphs and you add it all up, the United States is very low, and per capita we're very low. We're doing very well.
But how do you close up the United States of America? So, on January 6th, no deaths. On January 11th, no deaths. And no — no cases. On January 17th, no cases, no cases, no deaths. I'm supposed to close up the United States of America when I have no cases?
Q You didn't close down until the middle of March. "Should you have closed it down earlier?" — that's the question.
THE PRESIDENT: I closed down from China.
Q It's not about January.
THE PRESIDENT: Excuse me, I closed it down from China. And, by the way, some people think I should have waited longer and maybe ridden it out. I disagree with them. Okay? But it was thought of. I mean, that was an alternative. You know, there are a lot of people that would have said, "Let's ride it out." Now, I'll give you the good news. If I would have done that, it would have been, I think,

catastrophic because their numbers are, Anthony, 1.6 to 2.2 million people would have died if we tried to do that.

And I did this last time: Cut it in half. Don't say 2.2 million. Cut it in more than half. Say a million people died — well, that's much more than the Civil War. Cut it in half. Take the million and cut it in half; that's 500,000 people would have died. Now, that number we would have reached. Okay? That would have been easy to reach if we did nothing. So we did the right thing, and our timing was very good.

But here's the one thing — and you have to say this — when you ask me, "Why didn't you do this?" — how come when I did the ban on China and some very, very — instituted some very tough things, how come Nancy Pelosi, a month later, is in Chinatown, saying, "Let's all march. This is not going to happen"? How come we have many of the experts from CNN and many other networks — if you call CNN a network; I don't, personally. But we have CNN, we have many other places, and they're all saying, "He doesn't need to do it. He doesn't need to do it."

All I'm saying is this: How do you close down the greatest economy in the history of the world when, on January 17th, you have no cases and no death; when on January 21st, you have one case and no death? One case. Think of it. Now, we're supposed to close down the country?

But here's what happened: When, on January 31st, I instituted the ban, Joe Biden went crazy. He said, "You don't need the ban. You..." He didn't go crazy. Like, he has — he didn't even know what the hell the ban was. But he — so he didn't go crazy. But he did say —

Q Your ban bought you time.

THE PRESIDENT: He did call me xenophobic.

Q What did you do with that time?

THE PRESIDENT: Wait a minute. He called me xenophobic; he called me a racist because — he has since apologized and he said I did the right thing. So when you say, "Why didn't you do this?" Every Democrat thought I made a mistake when I did it. I saved tens of thousands, maybe hundreds of thousands of lives, by doing that.

Q But what did you do with that time that you bought? The argument is that you bought yourself some time and you didn't use it to prepare hospitals, you didn't use it to ramp up testing. Right now —

THE PRESIDENT: You're so — you're so —

Q — nearly 20 million people are unemployed.

THE PRESIDENT: You're so disgraceful. It's so disgraceful the way you say that.

Q Tens of thousands of Americans are dead.

THE PRESIDENT: Let me just — listen.

Q How is this sizzle reel —

THE PRESIDENT: I just went over it.

Q — or this rant supposed to make people feel confident —

THE PRESIDENT: I just went over it.

Q — in an unprecedented crisis?

THE PRESIDENT: Nobody thought we should do it. And when I did it —

Q But what did you do with the time that you bought?

THE PRESIDENT: You know what we did?

Q The month of February. That —

THE PRESIDENT: You know what we did?

Q That video has a gap. The entire month of February.

THE PRESIDENT: What do you do — what do you do when you have no case in the whole United States when you —

Q You had cases in February.

THE PRESIDENT: Excuse me. You reported it: zero cases, zero deaths on January 17th.

Q January.

Q January, February — the entire month of February.
THE PRESIDENT: January. I said in January.
Q Your video has a complete gap: the month of February.
THE PRESIDENT: On January 30th —
Q What did your administration do in February with the time that your travel ban bought you?
THE PRESIDENT: A lot.
Q What?
THE PRESIDENT: A lot. And, in fact, we'll give you a list — what we did. In fact, part of it was up there. We did a lot.
Q It wasn't in the video. The video had a gap.
THE PRESIDENT: Look. Look, you know you're a fake. You know that. Your whole network — the way you cover it — is fake. And most of you — and not all of you — but the people are wise to you. That's why you have a lower — a lower approval rating than you've ever had before, times probably three.
Q Twenty million people now are unemployed.
THE PRESIDENT: And when you ask me that questions —
Q Tens of thousands of people are dead, Mr. President.
THE PRESIDENT: Let me ask you this: Why didn't Biden — why did Biden apologize? Why did he write a letter of apology?
Q I don't think the unemployed people right now care about why Joe Biden didn't apologize to you, sir.
THE PRESIDENT: Why did the Democrats think that I acted too quickly? You know why? Because they really thought that I acted too quickly. We have done a great job.
Q So get us the list of what you did in February.
THE PRESIDENT: Now, I could've — I could've kept it open. And I could've done what some countries are doing. They're getting beat up pretty badly. I could have kept it open. I thought of keeping it open because nobody has ever heard of closing down a country, let alone the United States of America. But if I would have done that, we would have had hundreds of thousands of people that would right now be dead.
We've done this right. And we really — we really have done this right. The problem is the press doesn't cover it the way it should be.
Go ahead. One more question. Steve, go ahead.
Q There's a debate over what authority you have to order the country reopened. What authority do you have?
THE PRESIDENT: Well, I have the ultimate authority, but we're going to get into that in a minute. We're going to just finish this up. We're going to tell you about other things that we've done right.
But I will say this: Had we said, "Let's just keep going and let's not do a closing" — whether it's 2.2 that they, at one point, predicted as an outside or 1.6 at a lower number; you cut it all the way down to 6- or 7- or 800,000; take just a fraction of the number that could have happened, it literally would have been more than the Civil War. It would have been a disaster.
So, the minimum number was 100,000. And I think — I feel pretty good that we're going to be substantially below, Anthony, the 100,000. And I hope we will.
All right. So, today, the Department of Health and Human Services is announcing five new contracts to procure large numbers of additional ventilators under the Defense Production Act, which we used a lot, by the way — which you didn't like to talk about — in addition to the 1,300 we received today. We received, today, 1,300 additional ventilators. Now, we're probably not going to need them, but we can add that to our stockpile, which is very big, and we can move it around should the surge take place and should it be a very substantial surge. We're ready to — we're ready to rock.
The contracts are with General Electric, Hillrom, Medtronic, ResMed, and Vyaire, combined with the DPA contracts that we announced last week with General Motors and Philips and two other contracts

with Hamilton and ZOLL. We're adding 6,190 ventilators to the Strategic National Stockpile, of which we have a lot already — thousands — close to 10,000. But this will be added by May 8th, another 29,000 by the end of May. And more than 120,000 total we will have by the end of the year.

Now, we're going to help other countries. We're going to help states if they need it. We may help some states' stockpile. You know, they're supposed to buy their own stockpile. They have state stockpiles. They're supposed to be using that. And unfortunately, most of the states weren't there. And a lot of people didn't want to talk about it, but they weren't there. We will talk about it at the right time, if you want to. I — at this point, I'm more focused on getting past this nightmare of a epidemic or a pandemic — anything you want to call it. We got to get past it.

No one who has needed a ventilator has not gotten a ventilator. Think of that. You know, you heard all about ventilators, ventilators. "We need ventilators." Because they didn't have them. Because the states should have had them. No one who has needed a ventilator has not gotten a ventilator. No one who has needed a hospital bed has been denied a hospital bed. That's not even really our responsibility.

Now, if we can help, we're going to do it. But that's where the Army Corps of Engineers did such a great job. We built over 20,000 beds. In fact, we built thousands more than we've actually needed to be safe. We wanted to be safe and we really — they rose to this incredible occasion.

I mean, we built more beds than we thought. We thought, in Louisiana, we were going heavy. And again, when I called the governor, I said, "Maybe we shouldn't build that second hospital, because we don't want to build it if you don't need it." He called back, he said, "I don't think we're going to need it." They had 1,000 rooms, 1,000 beds, and they used a lot of them, but they didn't need the other one so we stopped it because we don't want to waste.

But we're prepared to build thousands more should we need it. I don't think we're going to need it because it looks like we're plateauing and maybe even, in many cases, coming down.

In addition, we've ordered a total of 60 mobile decontamidation [sic] — -contamination systems. So the decontamination system from Battelle, in Ohio, is an incredible thing because it takes the masks, and up to 20 times you can decontaminate a mask. And I've been asking from the beginning: "Why can't we sterilize and sanitize these masks?" And it turned out we can. And there was a great company in Ohio, they sent us some great equipment, and they're doing that now.

And now we're going to have more than 33 million N95 masks per week will be cleaned, decontaminated, and it'll be great. It's something that, frankly, I think people should have thought of a long time ago.

Five more flights landed today as part of the Project Air Bridge — our massive air lift operation to bring personal protective equipment into the United States, which has now delivered nearly half a million N95 masks, 370 million gloves, 25 million surgical masks, and 4.9 million gowns. So, we have millions of gowns, gloves, masks, all surgical equipment coming in should the states need it.

Now, the states — the states are supposed to be buying their own stuff. But should they need it, we are ready to give them, because we're building up our stockpile again like crazy.

Remember, I — and you saw the stories. I inherited — this administration — Mike, myself, the whole administration, we inherited a stockpile where the cupboards were bare. There was nothing. And I say it and I'll say it again: Just like we didn't have ammunition, we didn't have medical supplies, we didn't have ventilators, we didn't have a lot of things that should have been had. And you can read your own stories on that because you know what happened: They didn't want to spend the money. But we did.

To date, we've facilitated the supply of more than 38 million N95 masks nationwide. This week, we'll be sending 2 million N95 masks to the Commonwealth of Pennsylvania. The Vice President will go into more detail. He's got great detail on that, and I think it's a pretty amazing story. We have a lot of masks already in stock, and we have more coming.

We're further expanding hospital surge capacity in key areas of the opening, and we have a portion of certain VA hospitals and non-veteran coronavirus patients, including at the East Orange, New Jersey

Medical Center, as well as facilities in Manhattan and Brooklyn. They're ready. They're able. They're beautiful. Hopefully, we won't need too many of them because, frankly, we built everything that the governors wanted. And in many cases, it's too much. We told them it was too much, but we wanted to err on the side of caution.

The United States has now conducted nearly 3 million tests for the virus. Three million — the most of any nation. We are performing approximately 150,000 tests every single day and our rate of testing is especially high in areas hardest hit by the virus, if you look. And that's really — and it has hit some areas — the virus — very, very hard. For example, per capita testing in New York is higher than the rest of the world.

The NIH, CDC, and FDA are also currently validating several antibody tests that will allow us to determine whether someone has already had the virus and potentially become immune to infection. We're looking at that. The antibody tests are going to be very interesting, over the next short while. A lot of things are being developed, as we speak.

In the race to develop effective treatments, the drug company Gilead announced that its drug, remdesivir, has shown promising results — very promising — in compassionate use settings. In addition, the FDA has just granted emergency use authorization for a device that removes certain proteins from the bloodstream, possibly preventing a patient's immune system from overreacting to the virus and damaging vital organs, which is a big problem.

Furthermore, over the last seven days, my administration has deployed roughly 28 million doses of hydroxychloroquine from our National Stockpile. We have millions of doses that we bought and many people are using it all over the country. And just recently, a friend of mine told me he got better because of the use of that — that drug. So, who knows? And you combine it with Z-Pak, you combine it with Zinc — depending on your doctor's recommendation. And it's having some very good results, I'll tell you.

I think if anybody recommended it other than me, it would be used all over the place, to be honest with you. I think the fact that I recommended it, I probably set it back a lot. But it's a lot of good things that are happening with it. A lot of good tests.

Scientists are also pursuing a blood therapy known as convalescent plasma. Convalescent plasma. This therapy uses antibodies from the blood of recovered patients to treat those who are sick. And this is something that actually is a very old procedure, but it's done in a very modern way.

During this difficult time, we're also working to ensure that the 2020 Census is completed safely and accuracy. We may be asking for an extension because, obviously, they can't be doing very much right now. They wouldn't even be allowed to do it. So, the Census, we're going to be asking for a delay — a major delay, I think. How can you possibly be knocking on doors for a long period of time now?

The Census Bureau recently made the decision to temporarily suspend its field operation data-collection activities to help stop the spread. In addition, while millions of Americans continue to complete their questionnaire online, the Census Bureau has asked Congress for a 120 extension. I don't know that you even have to ask them. This is called "an act of God." This is called a — a situation that has to be — they have to give in. I think 120 days isn't nearly enough.

My administration is also taking bold action to help American workers. On Friday, Americans began receiving the cash payments authorized by a historic $2 trillion relief bill.

By the end of the week, nearly 80 million Americans will receive a total of $147 billion. And from what the Secretary of the Treasury tells me, that's very much on time and going very nicely. He'll be speaking in a moment. And payments — these payments go directly into the banks and the bank accounts of these people. Millions of additional payments will follow. The typical family of four will receive $3,400. That's for a family of four. That's something.

Additionally, through our Paycheck Protection Program –which is a tremendous success, and they should extend it and increase it. This has been a tremendous success. So successful that the banks are taking a little bit longer to distribute the money, but it's going rapidly.

We've now processed over $200 billion in loans to help small businesses retain their workers. Now we urgently need lawmakers to set aside the partisan agendas and to replenish this program with new funds because it's really something that has been an incredible success. And they need more money to keep it going to take care of these business and keep them — keep them open.

I want to thank the many governors, health professionals, scientists, and business leaders for their incredible hard work and input over the past month, and even long beyond a month, Mike, I would say. You know, we've been working together with a lot of for, it seems like, forever.

I've been having many discussions with my team and top experts, and we're very close to completing a plan to open our country, hopefully even ahead of schedule. And that's so important.

We will soon finalize new and very important guidelines to give governors the information they need to start safely opening their states. My administration's plan and corresponding guidelines will give the American people the confidence they need to begin returning to normal life. That's what we want. We want to have our country open. We want to return to normal life. Our country is going to be open, and it's going to be successfully opened. And we'll be explaining over a very short number of days exactly what is going to be.

We've also, as you probably heard, developed a committee. We're actually calling it a number of committees with the most prominent people in the country, the most successful people in the various fields. And we'll be announcing them tomorrow.

This weekend, the United States also helped facilitate an unprecedented agreement among the 23 nations of OPEC Plus — that's OPEC plus additional energy-producing nations — representing many of the world's largest oil-producing countries to stabilize oil markets. And we have, in fact — and I think you've seen a big stabilization over the last couple of days.

Together, countries around the world will cut oil production by approximately 20 million barrels. People are saying 10 million, but we think that the number that they'll actually hit is going to be closer to 20 million barrels a day. And that will help a lot with saving jobs all over Texas and Oklahoma and North Dakota and many of other — other of our big energy states.

This historic action will help nearly 11 million American workers who are supported by the U.S. oil and gas industry. It's a very monumental agreement. I want to thank Saudi Arabia and the King of Saudi Arabia, the Crown Prince of Saudi Arabia — both. I want to thank President Putin of Russia. And I want to thank a very good friend of mine — a man who's become a friend of mine: The President of Mexico showed great flexibility. President López Obrador. He showed great flexibility and — and tremendous intelligence doing what he did. It was not that easy for him. And I want to thank Mexico and the president. This is a very historic deal. Very historic. So we'll see how it all goes.

In this time and challenge — and we are certainly in a time probably like we haven't been in many, many decades — we are strengthened and sustained by the bonds of love and loyalty that unite all Americans. I'm so proud of the American people.

Everywhere you look, you see the patriotism of our people shining through and the courage of our doctors and nurses on the frontlines, and the dedication of our food supply workers, and in the commitment of every citizen to achieving victory over the virus. That's what's going to happen. It's going to happen sooner than people think. And we're going to be smart about it. Very, very smart about it. We're going to be safe about it. We're going to be listening also to the great doctors and medical professionals.

Together, we're beating back the invisible enemy and we're paving the way for great resurgence. Really, a great resurgence for American prosperity. Our country wants to go back. They want to go back to work. They're going to go back safely, and that's what we want.

I'd like now to ask Vice President Pence to say a few words, followed by Dr. Fauci and Dr. Birx. I think before we — before we do this — because I know there's an emergency where they want Steve to

come. So what I'll do is I'll ask Steve to come up — Secretary of the Treasury. You can talk a little bit and then maybe take a couple of questions about what's happening. Tell them the success we're having. Thank you very much.

SECRETARY MNUCHIN: Thank you, Mr. President and Mr. Vice President. As you announced, we are very pleased that we are ahead of schedule on delivering the economic impact payments. These are what was known as the checks in the mail that we want to deliver in direct — direct deposit.

This is ahead of schedule. We started processing those last Friday. We expect that over 80 million hardworking Americans will get the direct deposit by this Wednesday. And we know how important that is to all of those hardworking Americans, many of which are at home, not working at the moment.

If you do not receive them by Wednesday — on Wednesday, we will be launching at IRS.gov. Click on IRS.gov, go to "Get Your Payment." If you filed a tax return in 2018 and '19 — or '19 — have that information available. You'll be able to ID yourself, you'll be able to put in your direct deposit information, and within several days, we will automatically deposit the money into your account. We want to do as much of this electronically as we can. It's very important in this day and age. It's more secure, and you don't have to go to the bank.

If you're a Social Security beneficiary, you do not need to do anything. You will get a direct deposit. If you have not filed and did not need to file a 2018 and '19 return, you can go to IRS.gov now and enter your information and authenticate yourself. So again, we are very pleased that that is ahead of schedule.

I'd also like to announce the progress we're making on the new SBA program, the PPP. Let me just remind everybody: This is a brand-new program that is now one week old.

We have distributed and confirmed $230 billion of loans to over 4,600 lenders participating. That is multiples and multiples of anything that the SBA has ever done in — in one year, before. And I especially want to thank the broad-based community banks that are participating. Again, over 4,600 banks.

If you haven't had your loan processed, you will get it processed this week. As the President said, we've gone back to Congress and asked them for more money to make sure that every business has access to this.

Let me also comment for the states. We are distributing out half the money, this week, to the states. That's a week ahead of time. And we'll deliver the other half of the money to the states next week.

And then let me just finally comment, we've been very — working very closely with the Federal Reserve. Last week, we announced expanded facilities and new facilities that total $2.3 trillion of liquidity. And in particular, I'd just like to highlight a Main Street lending facility that will be for companies between one worker and 10,000 people — so mid-sized businesses — and also, a municipal facility for states and local governments to be able to access funds given the shortages that they have.

So with that, I'm happy to answer any questions

THE PRESIDENT: You have any questions for Steve, please?

Q Secretary Mnuchin, thank you, sir. Both Speaker Pelosi and Minority Leader Schumer have said that they're in negotiations with you right now on additional funding for these small-business loans, for that package. Leader McConnell, though, has said that nothing should be added to the package. They should just be specific to small-business loans. What is the opinion of your administration? Should there be some sort of horse-trading here or should it just be small business loans?

SECRETARY MNUCHIN: Well, the President's view and the Vice President's and my view is this was a bipartisan program. This SBA program, it wasn't a Republican program, it wasn't a Democrat program; it was a bipartisan program. We've committed to small businesses. We should top up that program now. I know the Democrats want to talk about more money for hospitals and states. Right now, we're just sending the money out to the hospitals and states. They haven't come close to using that money. And I

know the President and Vice Presidents have said once we get the SBA done, we can go into another funding bill.
The President has talked about potentially adding infrastructure and other things. We think there is a likelihood we will need more money, and we will — we will sit down and try to get a bipartisan bill. But this is important we deliver on small businesses. Fifty percent of the people work for small businesses.
Q Thank you, sir.
Q What's the emergency that the President said you had to go for? The President said you had an emergency meeting —
THE PRESIDENT: Negotiation.
Q Over this bill?
SECRETARY MNUCHIN: Yeah, well — or because we don't want to run out of money. We've used about $220 billion of the $350 billion. We don't want to run out of that money. We don't want to create panics that people won't get it. So that's why we want to — we want to top that up, and we've asked for another $250 billion for that program.
And again, let me just remind you, every dollar we spend in this program, we save a dollar of unemployment insurance. So even though we're asking for $250 billion, it really won't cost that much.
Q Could I follow up?
Q What are your — do you have concerns about lifting the guidelines too soon? And what's the economic impact? I understand the economic argument for getting people back to work, obviously. But what's the economic risk of lifting them too early and seeing then a spike in cases again?
SECRETARY MNUCHIN: Well, of course there's economic risks in both directions. We reviewed with the President today a very broad list of over 100 business people that are going to help advise the President on what needs to be done to reopen the economy.
We want to make sure — and again, the combination of economic impact payments, small-business payments, enhanced unemployment insurance — the President made very clear, we want to make sure that hardworking Americans have liquidity while we wait to reopen the government.
Q So do you believe the government should be re- — or that the country, excuse me, should be reopened on May 1?
SECRETARY MNUCHIN: I've had discussions with the President. I know he's considering it, and I believe he's going to make a decision later in the week.
THE PRESIDENT: We have to do — everything has to be safe. We want safe.
Q What is your advice to the President?
SECRETARY MNUCHIN: My advice is: As soon as it's ready to open and based upon the medical professionals, and — and again, we're working very closely with the President and outside business leaders to develop a plan.
Q I just wonder — I wanted to ask you, Mr. President, what you think — what — if you could sketch for us what reopening the economy looks like. Do you think it's going to be everything open? Or do you think —
THE PRESIDENT: Well, I'll be doing that over the next few days because we'll probably be making a statement about that and exactly what it looks like.
I know what that looks like, but I also want to get the advice, in a sense. We have some of the — the biggest from every business on this council. We're actually setting up a number of different councils or committees, I guess you could call them. And we have a lot of smart people. I think that they will give us some also good advice. But, no, we want to be very, very safe. At the same time, we got to get our country open.
Q Yeah, I understand that, Mr. President. Do you think there is a possibility then that what you do is you open it incrementally? Do you think people will go back to restaurants, to concerts, the cinema?
THE PRESIDENT: I do think so. Eventually, they will. Yeah.

Q And let me ask one final —
THE PRESIDENT: I think eventually they will do that. And I think we're going to — boom — I think we're going to — I think it's going to go quickly. Our people want to get back to work, and I think there's a pent-up demand like there hasn't been in a long time.
And that's why — and that's why you see the stock market — I mean, to think that the stock market is at the level it is right now, with all that this world and this country has gone. And look at the European Union, how badly decimated they've been. Look at other countries. Look at China, by the way. I've seen the numbers. Look at China. Look at how these countries have been just decimated by this.
And to think that the stock market is at this tremendously high number. Not that much — you know, it was looking a little bleak for a while, but it — it hit a certain point and then started going up. I think that's a great tribute to the fact that there's a demand.
Yeah.
Q Mr. President, thank you, sir. In regards to some of your tweets earlier today, and I think it was Steve's question, my question to you is: What provision in the Constitution gives the President the power to open or close state economies? And then —
THE PRESIDENT: Numerous provisions. We'll give you a legal brief if you want.
Q And then — we'll be looking forward to that, sir. But following up: What happens if you say, for instance, "We want states to reopen but California or New York do not open"? What would you do then?
THE PRESIDENT: Well, I think everybody wants to open. I mean, I guess, you know, that could happen, but I don't think that would happen.
Go ahead please.
Q It's been states that have closed, ordered schools closed. It's been states that have ordered businesses like restaurants and bars closed.
THE PRESIDENT: That's because I let that happen because I would have preferred that. I let that happen. But if I wanted to, I could have closed it up. But I let that happen and I like the way they've done it. And the seven that remained really in sort of a semi-lockdown — if you look at those states, they've really done a very good job. They're very much different from a New York or from other places where they've been hit very hard.
Q So you're prepared then to bigfoot states and say, "I order you to open your schools, I order to force kids to be able to go"?
THE PRESIDENT: Go ahead, please. Yeah.
Q Yes, Mr. President. Following up on that, there are two consortiums of states today — California, Oregon, and Washington on the West Coast; Northeastern states — totally representing about 100 million people, who have said they're going to cooperate and decide when to reopen those states.
THE PRESIDENT: Well, they can decide, but —
Q Does that undermine what you're trying to do?
THE PRESIDENT: No, not at all. Let me just tell you — very simple. I'm going to put it very simply: The President of the United States has the authority to do what the President has the authority to do, which is very powerful. The President of the United States calls the shots.
If we weren't here for the states, you would have had a problem in this country like you've never seen before. We were here to back them up. And we're backing — and we've more than backed them up. We did a job that nobody ever thought was possible. It's a decision for the President of the United States. Now, with that being said, we're going to work with the states because it's very important. You have local governments, they're pinpointed. It's really — you talk about — it's like a microchip. They are pinpointed. We have local government that hopefully will do a good job. And if they don't do a good job, I'd step in so fast. But no, they can't do anything without the approval of the President of the United States.

Q But, Mr. President —
THE PRESIDENT: Go ahead, please.
Q So if some states refuse to reopen and you order them to, the 10th Amendment of the Constitution says all powers that don't reside in the President or Congress reside in the states. How do you overcome that?
THE PRESIDENT: Well, if some states refuse to open, I would be — I would like to see that person run for election. They're going to open. They're going to all open.
Q So that's a valid (inaudible).
THE PRESIDENT: I think that's something that's not going to happen. They want to open. They have to open. They have to get open. Every one of those states, the people want to go and they want to — Now, some will be — are in a different situation. You have — I won't name states now, but I will over the next two or three days. I'm going to be very specific. But you have some states where this is not the kind of a problem than it is in New York or Louisiana or Michigan or other places that got hit very hard. Illinois got hit very hard. But all states want to open and they want to open as soon as possible. But they want to open safely and so do I.
Yeah, please.
Q Thank you, Mr. President. Today, the French President Emmanuel Macron said that he will keep the shutdown in France until the middle of May. Does that mean that the U.S. will keep the ban from flights from —
THE PRESIDENT: No, France got hit very hard. France got hit very hard. And again, he has to do what he has to do. He's a friend of mine. But France — Spain has just been decimated. You look at what's happened in Italy, it's a very well-known fact, what happened in Italy. No, they were hit very hard.
Q Question for Secretary Mnuchin: Has everybody that you would like to have — the 100 business people on the Economic Council — have they all been invited already? Have they all agreed to be —
SECRETARY MNUCHIN: They ha- — they haven't been invited yet. We've just reviewed the names with the President —
THE PRESIDENT: It's a group.
SECRETARY MNUCHIN: — today, for him to sign off on.
Q And are they from all sectors? Energy —
SECRETARY MNUCHIN: Yes, there's — basically, there's verticals. So every single area of the economy we wanted to be represented.
Q Great. One other thing. Is there anything else that needs to be done to work on industry — oil industry jobs — to save oil industry jobs after the deal this past weekend?
SECRETARY MNUCHIN: Well, I think there's always things. So we're working with Larry Kudlow. I mean, we have —
Q Anything specifically that needs to be done?
SECRETARY MNUCHIN: We have — we have economic plans for every single part of the economy. Obviously, in the case of the oil industry, they've been hit especially hard because you've had both the supply issue and you've had the demand issue.
Q Have you — have you figured out the bailout money for the airlines, with the allocations for the airlines?
SECRETARY MNUCHIN: So I'm pleased to say we've worked very hard. I think, as you probably have seen, we've put out a press release that we have now had discussions with almost all the airlines. I've personally had discussions with all the major airlines' CEOs. We specifically created an exception for small airlines that we could process very quickly. And I think you'll see, very quickly, decisions coming out. I'm very pleased with the discussions we've had.
THE PRESIDENT: We've had very good dis- — really just good discussions.
Q Mr. Secretary?

SECRETARY MNUCHIN: Yes.
Q Do you still see a need for a phase four stimulus? Or is this push to reopen —
THE PRESIDENT: Steve, I just want to say we have had —
Q — the economy in lieu of that?
THE PRESIDENT: — discussions — wait, excuse me. One second, please. We've had very good discussions with the airlines. Very good discussions.
Q And is it possible to reopen the economy on May the 1st?
THE PRESIDENT: I don't want to say that. You'll be hearing over the next few days.
Q Mr. President —
Q Is phase four going to be later than that, Mr. President?
SECRETARY MNUCHIN: Let me — let me just comment — I'm going to answer your question.
Q Mr. Secretary, do you see a need for a phase four? Or is this push in lieu of another stimulus?
SECRETARY MNUCHIN: Okay. So again, let me just comment — I mean, Congress, on a bipartisan basis, approved an unprecedented amount of money to help American workers and American business because it was no fault of their own that business was closed down. We had been very diligently executing on that. You know, everybody said it was going to take months to get people money. We are executing very quickly. We created a whole new SBA program in a week.
Our job right now is to execute the $2.3 billion, which we can add several trillion dollars with the Fed. The one area we are particularly concerned about is the Small Business program. Quite frankly, it's even more incredibly popular and successful than we anticipated. So the President wants to be very clear: We have money for that. And once we get done with that, we will review with the President. If there is more money that needs to be — to support this economy, to support hardworking Americans — we will work with Congress to get that in time.
THE PRESIDENT: And, Steve, do you want to talk about phase four?
SECRETARY MNUCHIN: So, phase four, the President has talked about infrastructure for a long period of time. We've talked about — to the extent that the hospitals need more money because of the medical issues, we'll monitor that. We want to make sure there are incentives for restaurants, entertainment — people to get back to those types of things. So we'll be looking at, very specifically, provisions to stimulate parts of the economy. Some of them may be money issues. Some of them may be regulatory issues.
Q Mr. President, just to clarify your understanding of your authority vis-à-vis governors — just to be very specific: For instance, if a governor issued a stay-at-home order —
THE PRESIDENT: When you say "my authority" — the President's authority. Not mine, because it's not me.
Q If I could just ask the question —
THE PRESIDENT: This is — when somebody is the President of the United States, the authority is total, and that's the way it's got to be.
Q It's total? Your authority is total?
THE PRESIDENT: It's total. It's total.
Q Your authority is total?
THE PRESIDENT: And the governors know that.
Q So if a governor —
THE PRESIDENT: The governors know that. No, you have —
Q If a governor issues a stay-at-home order, you —
THE PRESIDENT: — a couple of bands of — excuse me. Excuse me. You have a couple —
Q Could you rescind that? Could you rescind that order?
THE PRESIDENT: You have a couple of bands of Democrat governors, but they will agree to it. They will agree to it.

Q What if it was a Republican governor?
THE PRESIDENT: But the authority of the President of the United States, having to do with the subject we're talking about, is total.
Yeah, please, go ahead.
Q Mr. President, one of the things you —
THE PRESIDENT: Go ahead, please.
Q One of the things you — one of the things you spoke — we saw in your video about was the travel ban from Europe. As part of reopening America, do you want to reopen the borders so that people from Europe, from the UK —
THE PRESIDENT: At the right time.
Q How soon do you think we are from —
THE PRESIDENT: And a very good question, actually.
Well, I'm going to have to take a look. I wouldn't say Italy is doing great right now, and I wouldn't say Spain is doing great right now. And we just heard that France is extending its stay-inside order, right? Their stay — they've extended it — I just see that — and, I think, for a short period of time.
But no, when they're back. We want to do it very quickly, but we want to make sure everything is good. No, right now we have a very —
Q Weeks, months?
THE PRESIDENT: Right now we have a very strong ban. We're going to keep it that way until they heal.
Q Weeks, months? What would you —
THE PRESIDENT: Well, I can't tell you that. I can't tell you that. I have to see: How are they doing? I mean, France just went for another two days — for another two weeks. We have to see.
Jon.
Q So Dr. Fauci said that you took his advice on the question of mitigation. He made the recommendation. You accepted it. You put into place. As you make this next decision, which, as you have said —
THE PRESIDENT: Well, I'm not sure who — Jon, I'm not sure who really gave me advice on the ban. I think I took —
Q No, not on the ban. I'm talking about the mitigation.
THE PRESIDENT: I think I took my own advice on the ban. I don't know.
Q — the social — the social distancing, I'm talking about. The shutting down.
THE PRESIDENT: Okay.
Q Not of travel, but of activity. So my question is: As you make this next decision, which you have said may be the most difficult or important decision of your presidency, will you assure the American people that you will again take the advice of the doctors — of Dr. Fauci, of Dr. Birx? Will you take the advice of the health experts before you do that?
THE PRESIDENT: I will and many other people also. But I will absolutely take their advice.
Q But would you go against them?
THE PRESIDENT: Please go ahead.
Q Yes, Mr. —
Q Would you go against their recommendation? If they say you need another 15 or 30 days, would you —
THE PRESIDENT: I don't think it would be likely because I think we're not very far from being on the same page.
Please.
Q Yes, Mr. President, one thing that Governor Cuomo said today is that states do not have the capacity to do the mass COVID-19 testing ahead of a reopening as —
THE PRESIDENT: Well, they have to do it. Look, they're supposed to be doing it.

Q He says he can't purchase the diagnostic tests or equipment —
THE PRESIDENT: Yeah, I know. I know.
Q — and needs federal help. So will the states get that?
THE PRESIDENT: Well, they — they may need help, but —
Q Will they get it?
THE PRESIDENT: But they're there. They're on ground. They've got local mayors, local representatives. They have people that do it.
Q But he needs the supplies.
THE PRESIDENT: And what we did last time is unprecedented. We literally rebuilt tests. We — we rebuilt a whole industry because we inherited nothing. What we inherited from the previous administration was totally broken, which somebody should eventually say. Not only were the cupboards bare, as I say, but we inherited broken testing. Now we have great testing.
I just left the top executives at Abbott. Who would have thought that would have happened, where they have such a great test as that?
And, in fact, what I'll do — I think, unless you have any further questions for the Secretary of the Treasury — do you have anybody for Steve? Anybody?
Q Mr. Secretary Mnuchin —
THE PRESIDENT: Is that for the Secretary of the Treasury or for me?
Q For Secretary Mnuchin, yeah. Yes, sir.
THE PRESIDENT: Because if it's for me, we can wait.
Q It's for Secretary Mnuchin.
THE PRESIDENT: We have to get him back to work, okay?
Q Yes, sir. For Secretary Mnuchin, a question —
SECRETARY MNUCHIN: Yes.
Q — from one of my colleagues who's not able to be in the room. They're curious about the SBA rule that prevents small casinos from getting some of this relief. Is that something that you're taking a look at? Is there going to be a change to the —
SECRETARY MNUCHIN: So, no — not small casinos, but there are such things as small taverns and restaurants that have literally, you know, small gaming things. And we are coming out with some additional guidance on that. But I want to be clear: It's not small casinos.
Q Thank you, sir.
Q Secretary Mnuchin?
Q Secretary?
SECRETARY MNUCHIN: Yes.
Q There was a letter that some House Republicans sent this weekend, about the liquidity for a mortgage servicers.
SECRETARY MNUCHIN: Yes.
Q Are — can you explain what you're looking at on that front?
SECRETARY MNUCHIN: Sure. So I think I commented on this a week or so ago. We had a subcommittee task force at FSOC that specifically studied this issue. We have all the appropriate people on it. Ginnie Mae has automatically taken some action. We've had conversations with the FHFA as to what they're going to do for Fannie and Freddie. And we've said that to the extent they need certain authorities from the Treasury, we will accommodate that.
So we're — we're very aware of the issue. Quite frankly, we've been studying this issue way before COVID and had concerns about some of these non-bank servicers not being well capitalized. But we're going to — we're going to make sure that the market functions properly.
Q Thank you, sir. We have seen, in a number of these relief bills, that Democrats and Republicans have been able to push forward different non-coronavirus-specific funding priorities. Are you trying to keep

funding specific to coronavirus? And then, if there are going to be other additions — for instance, a change to labor rules is something that many on the left wanted. Some of the right are wondering if they should also — if you should also be pushing for, you know, their preferred add-ons.
SECRETARY MNUCHIN: Well, I think our expectation has always been this is COVID related. Some people have a rather broad view of what "COVID related" is, because it has impacted almost every single business. I mean, I think, we've — the President has talked about the Kennedy Center, which is a good institution. Obviously, that was not the major priority in the bill, but they were hit with COVID related. So — but, no, the President has instructed we want to be very specific in the next bill. It's COVID-related items.
Q It's been reported —
THE PRESIDENT: Well, we didn't want to do the Kennedy Center, just so you understand. And that that was done — the Democrats wanted it in. We didn't want that, but they wanted it in. And we had to agree in order to get something done for the workers. But we want this to be for the workers and for companies that employ the workers. That's what we're looking for. We're not looking for extraneous nonsense.
Q It's been reported that you argued, at the time the China ban was being discussed, that that was too disruptive to the global economy. Is that accurate?
SECRETARY MNUCHIN: Let me be clear: I had nothing to do with the China ban. I wasn't on the task force at the time. I'm not even sure I was — I think I was traveling at the time. But I never had any — I was not part — I did become very active, and after the China ban, but that report in the New York Times was not accurate.
Q You did not weigh in beforehand?
SECRETARY MNUCHIN: I was not part of the task force at that time, and I was — I was not involved. As a matter of fact, I think I may have been traveling.
Q Secretary Mnuchin, there's a proposal made by Senator Hawley to get direct payments to employers to pay people who have been laid off and to keep people on payroll. Does the administration support that proposal?
SECRETARY MNUCHIN: Well, again, that is the PPP. The PPP is basically sending money to small business — 50 percent of American workers — to keep those people paid. And it's the most efficient way. Every dollar, as I said, we do through that, it's one less dollar of unemployment. And more importantly, we want those people to have — be associated with the business. So as soon as the President is ready to open up the economy, those businesses are together. We don't want those businesses to fall apart. That's why this is such a successful program, and we want Congress to put more money in.
THE PRESIDENT: But are you talking about unemployment? You're talking about the unemployment?
Q (Inaudible) Senator Hawley.
THE PRESIDENT: Sending it indirectly to the states? We would have preferred that it was sent directly to the people. The Democrats wanted it to be sent through the unemployment system. And, you know, I've talked to you about it: We have 40-year-old equipment in many of those systems. They're run by the state. But I'm hearing they're getting the money out anyway.
SECRETARY MNUCHIN: So, some — some of them are, and some of the states aren't, and we encourage — you know, we're working with the states to try to update their computers, but it's a — it's a long haul.
THE PRESIDENT: Okay? Thank you, Steve.
SECRETARY MNUCHIN: Thank you. Thank you, Mr. President.
THE PRESIDENT: Phase four, Steve. Phase four. Come on, Steve.
Q A quick question about something you just said. You said, "When someone is President of the United States, their authority is total." That is not true. Who — who told you that?
THE PRESIDENT: Okay. So you know what we're going to do? We're going to write up papers on this. It's not going to be necessary, because the governors need us one way or the other, because ultimately it

comes with the federal government. That being said, we're getting along very well with the governors, and I feel very certain that there won't be a problem.
Yeah, please. Go ahead.
Q Has any governor agreed that you have the authority to decide when their state opens back up?
THE PRESIDENT: I haven't asked anybody because I don't — you know why?
Q Because no one has — no one has said that.
THE PRESIDENT: Because I don't have to.
Go ahead, please.
Q But who told you the President has the total authority?
THE PRESIDENT: Enough. Please.
Q You mentioned the Vice President's call with the governors today. Governor Hogan of Maryland has urged your administration to ask Congress for $500 billion to help stabilize budgetary shortfalls created by coronavirus.
THE PRESIDENT: It's nice of Governor Hogan, very much. We appreciate Governor Hogan's statement.
Q Governor Cuomo said the CARES Act ignored state government shortfalls.
THE PRESIDENT: Cuomo.
Q Do you support that request?
THE PRESIDENT: Which one? What did he say?
Q He said the CARES Act ignored the budgetary shortfalls.
THE PRESIDENT: Well, they're looking at things in phase four, where they have — you know, where they talk about states, and they're also talking about hospitals. They're talking about states who have been battered, and they're also talking about hospitals. And we're certainly willing to look at that.
Q Will you urge Congress on their behalf?
THE PRESIDENT: You know, we'll see what we all come back with. But they are talking about states and they're talking about hospitals.
OAN.
Q Thank you, Mr. President. The Governor of Michigan, Gretchen Whitmer, has on Thursday signed an executive order banning the sale of non-essential goods. If other states follow —
THE PRESIDENT: The sale of what?
Q Non-essential goods. She has banned the sale of non-essential goods. Many are calling this draconian, unconstitutional. As President, do you think that if other states were to follow her example in the coming weeks, that the federal government should intervene?
THE PRESIDENT: Well, I don't think that's going to happen. I think it's very extreme. But she's doing it, and I think it's going to be over a long way before we have to start thinking about it too much. It is strong. It's a very strong position to take. But they're making a lot of progress in Michigan, so let's see how it all works.
Q What is the status of the funding for the World Health Organization?
THE PRESIDENT: We're going to be talking about that very soon. I'm getting a full report. I'm not happy with the World Health Organization. I'm not happy with the World Trade Organization either. We've been ripped off by everybody.
And we have — this country, for so many years, has been ripped off by everybody, whether it's a World Health or World Trade. And they're like — I call them the "Bobbsey Twins." They'd look at our country — for years and years, we had people that did nothing about it. We're doing a lot about it. So we'll have a report.
And we'll also — we're also talking about the World Trade Organization. But we've made a lot of progress there. We're now winning cases for the first time, because they know I'll leave if we don't get treated fairly.

This country — our country — was at a point where we rarely, if ever, won the lawsuits within the World Trade Organization. But now we're winning a lot of them, because they know I'm not — I'm not playing games. We will pull out if we have to. We just won a 7-billion-dollar lawsuit, which was very nice.
Q Do you expect a decision this week on cutting funding for the WHO?
THE PRESIDENT: Uh, yeah. I would say, by the end of the week, I'm going to make a decision on that. Yeah. There's a lot of — right now, there's a lot of things happening.
Q On China — why are there no consequences for China, for the misinformation that they shared?
THE PRESIDENT: How do you know there are no consequences?
Q Because you've said. Well, you've been asked, and it appear that there were no —
THE PRESIDENT: How do you know there are no consequences?
Q What are the consequences, Mr. President, for the misinformation —
THE PRESIDENT: I wouldn't tell you. China will find out. Why would I tell you?
Q But people are concerned that they stonewalled, that they gave misinformation —
THE PRESIDENT: No, you started off by saying, "Why are there no consequences?"
Q Because you've been asked this a few times, so I'm following up on your response. Why are there no consequences for China?
THE PRESIDENT: How do you know there are no consequences?
Q Because we've asked you —
THE PRESIDENT: You're going to find out.
Q — and you've said — you've said that didn't want to have an consequences because you suggested trade.
THE PRESIDENT: I wouldn't tell you. You'd probably be the last person on Earth I'd tell.
Q So you're saying there will be consequences?
THE PRESIDENT: Go ahead. Uh, yeah, please.
Q Mr. President — actually, this is a question for Mr. Vice President. Do you agree with the President's statement and his understanding of federalism, that his power is total — like in the way he described it? Is there anything you'd like to add or any context you'd like to add to the way he was discussing that?
THE VICE PRESIDENT: I support the President's leadership under the national emergency declaration that he signed.
And we're standing before you today, the first time in American history, when all 50 states have issued emergency declarations, and the territories. This is an unprecedented time in the life of the nation. And fortunately, as the President has reflected and our health experts will continue to reflect, because the American people have heeded the President's Coronavirus Guidelines for America; because state governors have taken those and implemented them, even in states where there was not a significant outbreak; and implemented additional measures as we provided them with data about cases and best practices — we're making real progress as a country.
Q But it sounds like you think his power is a little bit more circumscribed than totally.
THE PRESIDENT: Well, make no mistake about it: In the long history of this country, the authority of the President of the United States during national emergencies is unquestionably plenary. And you can look back through times of war and other national emergencies. And as the President said, we'll happily brief that.
But in the days ahead, what the President has charged us to do is to work with our health experts. We're going to bring together an extraordinary group of American business leaders to counsel the President. And then, working with the CDC, we're going to produce new guidelines, based upon the data, for every state and territory in this nation. We're going to give them guidance. And, as the President has indicated, we'll continue to respect the leadership and partnership that we forge with every governor in America.

But this is an unprecedented time. But I have to tell you: When you look at the fact — despite the heartbreaking loss of more than 22,000 Americans — when you look at the fact of what the health experts told us this could be, I think I only can feel a sense of gratitude to the American people, gratitude to the extraordinary team that has counseled this President, the steps that President Trump has taken, the policies that governors have implemented all across America.

I mean, we were discussing today, at the task force, that when you look at the European Union as a whole, they have nearly three times the mortality rate that the United States of America has today. And that is a tribute to our extraordinary healthcare workers, their dedication, their tireless work. But it's also a tribute to the fact that the American people put into practice the mitigation efforts that the President counseled the nation to do on the advice of our best scientists, now more than a month ago, and our hospitals were not overwhelmed and are not overwhelmed at this hour.

And I have to tell you that standing here today, I couldn't be more proud to stand alongside this President and to be a part of this team that has served the American people during this challenging hour.

And I just say to you: To every American looking on, as we see the numbers leveling and maybe even beginning to go down, I just encourage you to keep doing what you're doing. Because of the sacrifices that Americans and American families have made through these mitigation efforts, you're saving lives and you're seeing our nation through this time.

THE PRESIDENT: Go ahead.

Q Sir, did the states tell you — you've been talking to the governors quite a bit — did those coalitions of states on the West Coast and in the Northeast, did they tell you what they are going to be announcing before they announce it?

THE VICE PRESIDENT: Governor Phil Murphy and the governor of Connecticut expressed today that they were going to be speaking on a — and discussing on a regional basis what their recommendations would be. And we assured them today —

Q Did they alert the White House about that, though, sir?

THE VICE PRESIDENT: We assured them today on our conference call with, I think, 48 governors that were with us today for the better part of an hour and a half — we told them that what the President would be producing — has directed to be produced are additional guidelines for the states, certified by the CDC, that would inform those governors and local communities and mayors about the best way forward, based on the unique circumstances that those states and those communities are facing.

I think what's clear is the American people have seen the experience in Washington State, where this really all began for us; and in California; and now, the extraordinary challenges in the Greater New York City area, including New Jersey and Connecticut; the challenges in New Orleans and Louisiana and Detroit, still Chicago, parts of Houston.

But they're also seeing that, in each one of those cases, that the mitigation efforts are truly working. And so we'll — we'll work with those — we'll work with those states. And in some cases, it'll make perfect sense for them to work together on a regional basis.

Q Any idea why they didn't let you know ahead of time what they were planning?

THE PRESIDENT: Well, you don't know that. You don't know that.

THE VICE PRESIDENT: But — but the President — the President will be —

Q (Inaudible.)

THE PRESIDENT: You don't know that. I'm sorry.

THE VICE PRESIDENT: I'm sorry, I didn't hear your question.

Q Mr. President, can you tell us? Did they let you know?

THE PRESIDENT: You don't know that. No, you made a statement. You don't know that.

THE VICE PRESIDENT: I didn't hear your — I didn't hear your statement. I'm sorry.

THE PRESIDENT: And we would — and we would like to have their cooperation. And we are going to have their cooperation. They will cooperate perfectly. Watch.
THE VICE PRESIDENT: I — and let me just affirm what the President said. We heard it again today in what I think was our ninth conference call with governors is: I think every American would be proud to see the partnership that this President has forged with governors across the country. I mean, it is an extraordinary statement.
And you'll see some data when Admiral Polowczyk gets up in just a few moments, but the flow of resources from around the world that we've moved into areas that have faced challenges — I mean, this President has directed us to ensure that every state has what they need, when they need it. And the spirit that I heard again from Republicans and Democrat governors today was reflective of that partnership.
And as we move forward to the President's goal of reopening America, we expect the same kind of partnership in the interest of the nation.
THE PRESIDENT: All right, go ahead, with the face mask. Go ahead.
Q Sir, if you can hear me through the mask —
THE PRESIDENT: Barely.
Q Can — can you —
THE PRESIDENT: I hear you well, actually.
Q — the — the District of Columbia argues that they were shortchanged in the most recent funding bill because they were treated as a territory instead of as a state. Will that be made right in phase four?
THE PRESIDENT: Well, we're looking at that certainly. I heard that complaint, but the mayor seems to be very happy with everything we've done.
THE VICE PRESIDENT: She was on today.
THE PRESIDENT: I mean, she's actually — and she was on today, saying very good things.
Okay, yeah. Go ahead in the back.
Q Mr. President, you talked about this being the most difficult decision that you are going to have to take about whether to reopen the economy. I wonder how much it weighs on your mind the thought that if there is a second wave, you've reopened the economy and you might have to shut things down again.
THE PRESIDENT: It does. And I hope that won't happen. I certainly hope that won't happen, but it does weigh on my mind.
Okay, in the back, go ahead. You had one. Go ahead.
Q Mr. President?
THE PRESIDENT: Go ahead, please.
Q Thank you. Okay, thank you. A question for one of my colleagues who wasn't able to be here. China deployed an aircraft carrier into the South China Chi [sic] — South China Sea this weekend, amid claims by Chinese state media that COVID has reduced U.S. military readiness in the region. What kind of responses are you thinking of? Will you have a response to this action?
THE PRESIDENT: China has their own difficulties. We have a relationship with China that — we're not happy with certain things that happened over the last period of time, as you know, and I've been very explicit on that. But we know all about that.
And, no, China is — we've seen what they did. We've seen many other things that they've done, both pro and con. And we'll be just fine.
Q On Abbott, you said something earlier, where you said that you're putting together the economic task force and that you thought that the recommendations were happening earlier than expected. Did you mean to suggest that it could be before May 1st that you start recommending that states open?
THE PRESIDENT: I don't want to say that, but we're going to be putting out guidelines and recommendations fairly quickly. In a few days.

Q You're not ruling out that it would be before?
THE PRESIDENT: I'm not going to say. But, look, certain states are doing very well. Certain big parts of the country are doing very well. They're doing, really, very well. And so we're going to be putting out recommendations and guidelines very soon.
Steve?
Q And would these new guidelines be -- would they fit each area or would they be a uniform set of guidelines?
THE PRESIDENT: Well, you're going to see. I — I don't want to tell you now, but right now we have a very strong indication that we know, pretty much — we have some good ideas.
I also do want to get — I want to have — we'll have video conference or at least a conference call with a lot of very good people, having to do with certain fields, whether it's energy or whether it's entertainment and restaurants, et cetera, et cetera.
We have to get people back into restaurants. We have to do what we have to do. Whether it's deductibility or not, we'll see, but it should be deductibility. You'll get them back so fast. I mean, they used to have deductibility. The restaurant business, it — it was one of the hot businesses. And then they ended it a long time ago, many years ago. But we may need that to get people back into the restaurants.
Please.
Q Yeah. Michelle Obama, today, got behind mail-in voting nationwide as a possible solution to the — on states. She said it shouldn't be a partisan issue. Have your advisors told you that that could save lives? And (inaudible)?
THE PRESIDENT: Absentee ballot, are you talking about? Absentee ballot?
Q Yeah, and on a massive scale because of the coronavirus.
THE PRESIDENT: Well, I don't know what she did. I mean, I didn't see that. When did that happen? Today?
Q Yeah, she's part of — that's a nonpartisan group.
THE PRESIDENT: Well, I wish her luck. I wish her a lot of luck.
Please, go ahead.
Q On Abbott Labs, you said you had long —
Q Yes, Mr. President. There's a little bit of confusion about your phone calls yesterday with President Putin. The Kremlin is saying that you discussed current issues of ensuring strategic security. That wasn't referred to in the White House
readout. Can you enlighten us —
THE PRESIDENT: We discussed many things. We did discuss China. We discussed many different things, but we — it was primarily a call on the oil, as you can imagine. And they were very helpful in getting a stabilization price, a stabilization of the number of barrels. I think the number is going to be closer to 20 — maybe 15, but closer to 20 than it is going to be to 10. And I think it was a very important call.
I also spoke with the King of Saudi Arabia and that was a very important call. And the bottom nine is OPEC Plus. It's called OPEC Plus because there are other states also, other nations. We came to a very good agreement.
Please.
Q You have —
THE PRESIDENT: Go ahead.
Q What was the part about strategic security? Was that —
THE PRESIDENT: I would say mostly we were talking about China. We were talking about their borders. And we're talking about our borders a little bit — our borders with Mexico. Because, as you know, Mexico is a big part of the deal. And Mexico really — it was very complex from the standpoint of Mexico. It was not an easy deal for Mexico. And the President — we appreciated a certain amount of flexibility. But we talked about borders, we talked about China, we talked about Mexico.

Q But "strategic security" sounds more like arms treaties.
THE PRESIDENT: Well, I mean, I — we did talk about the arms. Yes, we did. That was a very important part of the call actually. Yeah, good point.
Please.
Q So, on Abbott Labs, you said testing is going great. We know that they have — these machines have been sent to some of the governors, but some of them are saying they don't have the materials to actually conduct the tests.
THE PRESIDENT: Well, they have to get the material. You know, the governors have to get the material.
Q The cartridges.
THE PRESIDENT: Now, if they can't get it, they're going to see us.
Q The government is — the federal government is distributing those cartridges.
THE PRESIDENT: I'm talking about the local governments. I'm talking about governors have to get the material. Now, they have machines. In fact, we — we're going to go into — I'd ask Mike to go into it as soon as I leave. They have very powerful machines that they don't know they even have. I'm not talking about Abbott; I'm talking about the governors. They have machines that are used for this —
Q The hospital labs.
THE PRESIDENT: You know what I'm talk- — do you know what I'm referring to?
Q Yeah, they have the two different machines.
THE PRESIDENT: Very big, very powerful machines where, in a certain state's case, they're only using 10 percent of their capacity and they didn't know it. That happens to be Illinois.
Jon, please.
Q Okay, well, real quick. Real quick. These 15-minute tests that you've sent out, these new ones that you had in the Rose Garden, they say — including Governor Sununu in New Hampshire — that they don't have the cartridges to actually conduct the test. So when will they get those cartridges?
THE PRESIDENT: What do you think the answer to that is?
THE VICE PRESIDENT: We're rapidly — we're rapidly increasing the numbers, Mr. President.
THE PRESIDENT: Rapidly increasing the numbers.
THE VICE PRESIDENT: And Deb will speak to (inaudible).
Q Can we look into when?
THE PRESIDENT: Rapidly increases. Well, pretty quickly.
Q They can — they can do 50,000 a day, right?
THE PRESIDENT: Well, you have other machines where they can really work.
Q Can they go up beyond that?
THE PRESIDENT: And a lot of the states have the big machines that can do a lot. They didn't even know they had them. They didn't even know that they had them. And Mike is going to be talking about that.
Q And you remember you mentioned, several weeks ago, the — that Google was putting together that website
where they would handle the drive-through testing?
THE PRESIDENT: Yeah. Google and Apple.
Q Have you — have you given up on —
THE PRESIDENT: You mean Google and Apple combination.
Q Have you — have you moved past that, because you said —
THE PRESIDENT: No. A lot of people don't like it from the standpoint of constitutional rights. I mean, a lot of people don't like it and some people think it's great. No, they are working on that, as I understand.
Q How about the testing website? Remember you said a website for Google and —
THE PRESIDENT: Yeah, no, I know that. I know that. I know.
Q And it's only operating in, I think, five counties in California right now. Is that —

THE PRESIDENT: That's right. No, Google is looking at it, but Google is also working with Apple or looking at something. We have the greatest companies in the world looking at things that, in a year from now, everything that we're looking at now is going to be obsolete. That's how good it is.
We have things happening that are unbelievable. I saw a presentation today that I can't talk about yet, but it's incredible. Plus, I think they're doing — Tony — I think they're doing very well in the vaccines. They're working hard on the vaccines and I think you'll have an answer for vaccines. I believe that there's some great things coming out with respect to that. Now you need a testing period, but you're going to have some great things.
Please.
Q Sir, on the contact tracing that Google and Apple are doing — so a different subject, on the contact —
THE PRESIDENT: No, no. This is — this is the Google and Apple. I don't know if it's a partnership or what, but they're working on some —
Q Correct. So there was the one —
THE PRESIDENT: They're working on more than one element. They're working on a couple of different things, Google and Apple. Google is also working on something, as you know, having to do with testing. I believe they're doing that in a singular fashion.
Q So my question is not about the drive-through testing website. Not that.
THE PRESIDENT: Okay.
Q On Google and Apple's contact tracing that they want to —
THE PRESIDENT: Yeah. Yeah.
Q — they've got this process now where they can put, you know, contact tracing on your phone.
THE PRESIDENT: I know.
Q If you opt in, you can be alerted if you've been —
THE PRESIDENT: That's right.
Q — in contact with someone with the coronavirus. Do you — how do you feel about that?
THE PRESIDENT: Well, it's an amazing thing, but a lot of people have some very big constitutional problems with it. You know that. It's an amazing thing and it would be — actually, as you know, other countries are thinking about using something similar but not as good.
Q Which other countries are thinking about something similar?
THE PRESIDENT: I hear Singapore is. Singapore is. No, Singapore had a little bit of a setback because they had a –they had a break. You know that, and — but they'll take care of it. I know — I know the folks in Singapore. They're doing a great job and they're going to put it back very quickly. But Singapore and other countries are looking at other things, and some countries are doing other things.
Q Would you prefer that Americans use some other system?
THE PRESIDENT: Well, I don't want to get into that because we have a whole constitutional thing. We have more of a constitutional problem than a mechanical problem, but we will be making a determination on that. That's something we're going to be discussing with a lot of people over the next four weeks. That would be a very accurate way of doing it, but a lot of people have a problem with it.
Yeah, please. Go ahead.
Q A testing question, maybe for Dr. Fauci as well. Can you talk about where the antibody test is and how quickly that will be (inaudible)?
THE PRESIDENT: Well, it's moving along. I think I can speak because I — I have to leave. Moving along quickly, moving along well. It's a test that's been going along for many, many years, except now we have very modern, very incredible versions of it. But that's moving on. The antibody test have — moving along very well.
Okay, anymore COVID-19? COVID-19?
Yeah, Steve.

Q One soldier on the Theodore Roosevelt has died. Has — have you determined the status of Captain Crozier, the former commander?
THE PRESIDENT: Well, that's going through the Navy, as I understand it. The Navy is going to be making decisions on all of that. And they had a break in — I don't think the ship should have been stopping in Vietnam when you have a pandemic, to be honest with you. You know, I don't think the captain should have been writing letters. He's not Ernest Hemingway, as I said before, and he shouldn't have been writing letters.
And I don't think — I don't know who gave the orders to stop in Vietnam. But they stopped in Vietnam and all of a sudden they get on, and now you have over 500 sailors and — and people on the ship that are affected. I don't know whose idea that was, but that wasn't such a good idea in the middle of a pandemic.
Yes, please. Jon. Go ahead, Jon.
Q Just one last — on this question of constitutionality, I'm just wondering what changed your view because —
THE PRESIDENT: Nothing changed it. No, no, I know exactly what you're going to say. Nothing changed it. The fact that I want to rely on states or maybe will or maybe have, and the fact that we've gotten on — that's one thing. The fact that I don't want to use the power is another thing. Look —
Q But you said from the standpoint of the Constitution —
THE PRESIDENT: Yes, Constitution.
Q — you thought it should be up to the governors.
THE PRESIDENT: Constitutionally. You can look at constitutionally. You can look at federalism. You can look at it any different way. Jon, the fact that I don't want to exert my power is much different. We have the power.
You asked, "Does the federal government have the power?" The federal government has absolute power. It has the power. As to whether or not I'll use that power, we'll see. I would rather —
Q So if New York wants to stay closed down, you can —
THE PRESIDENT: Jon, I would rather work with the states, because I like going down to a local government. That's why with — I guess it's now seven states not eight that — because South Carolina did — you know, they went away from what we discussed the last time. So that's why I looked at the individual states; they're doing a very good job. They're really doing a very good job. I'd rather have them make the decision.
Now, the fact that I'd rather have — that's fine. But I have the absolute right to do if I want to. I may not want to. We have a very good relationship. Now, we'll see what happens.
If you notice, the few states you're talking about, they're all with Democrat governors. But if governors are doing a good job and they control it better — because you don't have somebody in Washington saying, "Set up a testing site in the parking lot of a Walmart." And we're in Washington and they're in a state that's very far away. That's really — it should be and it should have always been. And I've always said it was.
But the relationship we have now with the states and governors is very good. And we'll be announcing, over the next very short period of time, exactly what we're going to be doing.
Okay, a couple of more. Go ahead.
Q On coronavirus and Joe Biden: He's the presumptive Democratic nominee. Do you have any plans yet on when you'll start sharing, or when the White House will start sharing some of that information about the coronavirus? Your presidential daily brief?
THE PRESIDENT: Well, nobody has called about coronavirus, about — from their standpoint. Look, they had the H1N1, which is swine flu, and that was a big failure. That was a tremendous failure. They had a lot of failures. And you take a look at what — you take a look at the history. And, you know, 17,000

people died. And you talk about late? They were so late — they were late like it never even existed. That was a — that was a big problem. Caused a lot of other people a big problem too.
So, you know, if Joe Biden would like a briefing, I'd certainly get him a briefing. I don't know what he'd do with it.
Yeah, please.
Q So, are Jared and Ivanka on — serving on the new task force? And how are you going to balance —
THE PRESIDENT: No.
Q What?
THE PRESIDENT: No, they're not. No.
Q Okay.
THE PRESIDENT: Yeah. Yes, go ahead, please.
Q I just want to clarify. So, in earlier conversation, there was a description of multiple different councils or tasks — task forces. Can you just explain exactly what the structure is and who is going to be on it?
THE PRESIDENT: Well, you have Mike's task force, which is the White House Task Force, which really brought us up to this point brilliantly, I must say. Dealt with governors and dealt with governors all the way through. And I was on many of those calls. And every call got better and better and better. It was hostile at the beginning. By the time we finished — I mean, today's call was a very good call, a very friendly call. I think everyone is online.
And again, you don't have anybody driving you crazy, saying they're not getting ventilators, they're not getting all of the different things, they need more beds. They have a lot of beds right now.
Q (Inaudible) hospitals who — doctors who say they don't have the supplies that they need.
THE PRESIDENT: And we always err — and I think it's important for you know — we always erred on the sake of "Give them more." Even when we didn't think — we didn't think New York needed the beds that they were asking for. We didn't think they needed the ventilators that they asked for. And we were right.
Now, on ventilators, we're ready to march. I told you this: We're ready to march. We have 10,000 ventilators. We're ready to move them anywhere in the country when we need them, if we need them. We're also building a lot of ventilators, and that's going to be used at some point, I believe. You know we're going to have stockpiles, including state stockpiles if they want to work out some kind of an arrangement with us. But we're also going to help other countries, whether it's Italy, or Spain, or other — France is having a big problem. They all desperately need — Germany too — they need ventilators. So we're going to have a lot of ventilators. We have a lot — you heard the numbers — we have a lot coming next week. Next week, we have a tremendous amount coming.
Okay, final question. Steve.
Q And on the task force — I'd asked for the task — how the task force is going to be structured. Is it one —
THE PRESIDENT: No. Then we have — in addition to that, we have a number of committees. We'll have a transportation committee. We're going to have a manufacturing committee. You'll see it tomorrow. We're also having a religious leaders committee. We have a great group of religious leaders. We're having committees with religious leaders. You've been seeing what's going on with the churches, and all of that. And we're going to have a faith leaders committee.
And so we have — we're going to have a few committees. I'll call them "committees," and then ultimately we're going to make decisions. So we're going to make decisions fairly quickly, and I think they're going to be the correct decision. I hope so.
Steve.
Q So you form the economic task force tomorrow. When do you want them to have recommendations for you?
THE PRESIDENT: Soon. Soon. And they already know what I want.

Q Next week or —
THE PRESIDENT: And so, when we form — when you say "form," I don't have to give them instructions. These are very sophisticated people. These are the best people in their fields. So I don't have to say, "Gee, let's — we just met and we're going to meet in two weeks and here's what we're..." I said, "Here's what I want." We've already told them. And they're the —
Q What did you tell them you want?
THE PRESIDENT: — the best names in the various businesses and professions and religions. I mean, they're — these are the greatest names. The people that, I think, probably know the best.
So, we've called them and we're going to be speaking to them very soon. And we want them to have — if it's questions, or statements, we want them to have that for us. And we will have either a response, or maybe — I mean, ideally we're going to be learning from them. And we'll be able to do that and put them — put everything we learned from those calls into our new guidelines.
So we're going to have new guidelines coming soon. I think it's going to be very good. I think it's going to be very smooth. And I hope it's going to be very safe.
Thank you all very much. Thank you. Thank you.
Q Any thoughts on Stanley Chera, sir? Any thoughts on Stanley Chera —
THE PRESIDENT: Stanley Chera is a friend of mine for a long time. He's a great real estate person — passed away. Was a great real estate person. Great. Great. Sort of a legend in New York real estate.
He called me a couple of weeks ago, said he tested positive. Stanley is in his early- to mid-80s, I guess. And Stanley went to the hospital and he never came out. He went into a coma. He was unconscious for a long period of time and he never made it. A great man. He left — very charitable, really a great philanthropist. A very, very successful person in Manhattan, in the real estate business. So I got to know him a lot.
He was so excited when his friend from New York became the President of the United States. He was like — like a young boy. And he was not a young boy, but he was like a young boy. He was so excited. He thought we'd do such a good job and he was so happy. And he — he was very proud of what we've done in this administration.
But he was tested positive, and unfortunately he — he didn't make it. It's a very — to me, it's a very sad thing.
Thank you all very much. Thank you.
Q Thank you.
THE VICE PRESIDENT: Thank you, Mr. President. As the President mentioned, the task force today spoke to 48 of the nation's governors. On that call, we reflected on the fact that all — all 50 states had emergency declarations in place, which was a first for American history; $5.2 billion had been distributed to the states under the Stafford Act. And it was a productive call and reflective of President Trump's ongoing direction for us to work closely with the states to make sure the states in the areas most impacted by the coronavirus have what they need, when they need it.
We spoke about the issue of testing and supplies. And I'm going to ask Dr. Deborah Birx to come forward, as well as Admiral Polowczyk, to reflect on both of those topics for you. Dr. Birx has been leading an effort from the task force from early on, on rapidly expanding testing.
It was early on that the President formed that public-private partnership with commercial labs. And as we stand here today, more than 2.5 million tests have been performed. And when we add in the estimates of labs that we have to assume, with reasonable protections — projections have not yet reported into the CDC, we think that number could be closer to 3 million tests that have been performed.
As has been mentioned, the new 15-minute test, we are — we are working closely with Abbott Laboratories — that the President and our team met with today here at the White House — to rapidly increase the availability of cartridges. Abbott is producing roughly 50,000 cartridges a day. FEMA

acquired an initial supply of that and distributed those to the states, but we're working with the states to not only distribute what's being made, but also work with other suppliers to create additional cartridges.

A point that I'll ask Dr. Birx to expand on in just a moment is the fact that -- beyond the new 15-minute test by Abbott Laboratories; beyond what we expect to be a new antibody test, which may well be approved by the FDA in just a matter of days; and an antibody test that would be produced at the rate of 20 million tests a month -- the reality is that those commercial laboratories that the President brought in here, the better part of two months ago, and initiated that public- and private-partnership with have been producing hundreds of thousands of tests every single week.

But as Dr. Birx and our team have apprehended, we believe, at this point in time, that of the Roche equipment that is out there that does the high-speed testing — and we informed governors of this today — we think that that some 20 percent of that capacity is not being used.

And with regard to the Abbott m2000 systems, we told the governors today that we think 75 percent of that laboratory capacity that exists in the United States today is not being utilized by our governors. So we sent a very clear message to governors today to reach out to their hospitals, reach out to their labs to identify the presence of the Roche Amplicor 500 and the Abbott m2000 to get those activated.

We literally estimate that, although we're doing over 110,000 tests a day in the United States, that if our — if our governors and state labs would simply activate the machines that are already there, we could double the amount of testing in the United States literally overnight. And so, I know that governors' teams watch these briefings, and we'll remind them very respectfully again to identify those labs. And we have a — we have a team that now is deploying, reaching out to labs to see if we can activate all of those labs.

Secondly, on the subject of supplies — I've said it a couple of times from this podium today, but let me say it one more time: President Trump's direction to us, in dealing with the states on personal protective equipment and ventilators, has been to make sure that states have what they need, when they need it. And we recognize that while we all watch the overall curve of the coronavirus in America — understandably, the national numbers — the reality is this outbreak has taken place in its own individual curves: first, on the West Coast; then the New York City area; then Louisiana, Michigan; and now we continue to contend with it in Chicago and Houston and other metropolitan areas. It has given us the opportunity to ensure that personal protective equipment and ventilators are made available on a critical basis.

And I have to tell you: We're incredibly proud of the effort and the partnership with states that has us standing here today that no one who has required a ventilator has been denied a ventilator in the United States of America.

At this point, we have just short of 7,000 ventilators in the Strategic National Stockpile. But as — as Admiral Polowczyk will detail, we're already beginning to receive newly manufactured ventilators. We'll get another thousand in this week. By the middle of May, we'll literally have another 8,000 ventilators available for deployment around the country.

I'm going to let him describe to you the specific detailing of those resources. But — but I want to — I want to share these numbers, most especially for our healthcare workers around the country in the areas most impacted by the coronavirus, so that you know the resources are surging into the hospital systems at the point of the need, and we will continue to do just that.

So let me recognize Dr. Birx to reflect on the data and also on, maybe, some comments on testing. And then Admiral Polowczyk, if you can step up and then you'll describe the supplies. We'll hear from Dr. Fauci again, and then take a few questions.

DR. BIRX: Great. Thank you, Mr. Vice President. I don't know if we can get the first slide on cumulative cases? Yes, thank you so much.

I wanted to show you a different way of looking at it today. Obviously, we look at case counts per 100,000 Americans in each of our states and metro areas, but I wanted you to see, in absolute numbers, how much the New York, New Jersey metro area dwarfs all other metro areas.

And so you can't even see Chicago, Detroit, or Boston. All of those metro areas are under 25,000 cases. You can see that the New York, New Jersey metro area is about almost 250,000 when you bring those cases together — almost a log more. And that's why you hear us talking a lot about the metro area of New York and New Jersey; and the counties of Rockland and Westchester and Suffolk and Nassau and Bergen, New Jersey; and why we're so focused on getting resources to that metro area.

If I could see the next slide, then. So if I take New York and New Jersey metro area out, this is the other metro areas that we have been tracking very closely. I wanted to show this to you so that you could see how those curves are already starting to plateau.

So, if you look at Detroit, if you look at Philadelphia, if you look at Louisiana — Louisiana is in green. Detroit is in gray. You can see across the board, across these metro areas — across metro areas with — have a higher concentration of individuals, this is what the American people in these large cities have done, where it is more difficult often to socially distance. And we're just really impressed by the work of the mayors and the governors to make this happen.

I also wanted you to see this because you can clearly see Chicago and Boston. And so, Chicago is in the orange and Boston is in the yellow. They are crossing Detroit. And that's why we have been very much focused on the needs of those areas. And there is one — and Providence is also in that category. It's difficult for them to — for you to see you them because they're much further down on the slide.

But the highest — if you look at the axis on this slide — it's 25,000. The axis on the last slide was 300,000. And so that's why I really want people to understand each of these epidemics, minor — these small epidemics in each of the metro areas — we're tracking independently, as well as any epidemics and outbreaks that are happening in some of our other states.

So I just wanted you to have that perspective of how significant the New York, New Jersey issue is and why we've been tracking that so closely. But I also wanted to assure all of the other states that we're tracking them also very closely and really working with the governors and mayors and across — and that's why I wanted you to see that not only are the curves flattening in some of those major metropolitan areas, but they're starting to decrease. And this is what we're very excited about. These are cases. We also know that mortality will lag. And so we're really tracking also the number of individuals who have succumbed to the COVID-19.

I also wanted to really note here that, yes, our mortality is less when you combine European countries equal to the size of the United States. And I think this is really two things: One, it's the incredible work of the American people, that it's also the incredible work of our healthcare providers, and the system of each of these hospitals that have the resources and the ability to respond to the needs of the COVID-19 patients. And I think you can really see the superb healthcare delivery that is happening by the low mortality.

Just to mention really quickly about testing — because you've heard me before talk about it, and then it was a little bit misquoted and misaligned — but there are multiple Abbott machines, so I'm going to be very clear, having spent years in the laboratory. The high-throughput machines, which are the Roche 6800 and the 88- — I think it's the 8800 on Roche — and the Abbott M2000 — these are the machines that run between 500 and 1,000 assays at a time.

The Abbott company worked really hard, three weeks ago, in getting a million tests out there to be utilized. And they can make a million tests a week for all of our laboratories that have these platforms. And, so far, to date, somewhere around 250,000 tests have been utilized in three weeks' worth of work. And that's why we've really been appealing to the — to the laboratory directors to really bring all those machines on.

Last week, Dr. Fauci and his incredible team of researchers have agreed to really reach out and find additional Roche and Abbott high-throughput machines that are in research institutions and doing critical research work, to bring them online also to supplement the other laboratories' work, to create a mosaic and a complete strategy that brings together the high-throughput platforms, with the medium-throughput platforms, with what are the low-throughput but rapid platforms -- which is this ID NOW. ID NOW is not going to be the answer to the number of tests that we need over the next few weeks. Those run a test every 15 minutes, and we can get about 55,000 cartridges a day.

But I just got done saying that these other machines -- of which we have hundreds of -- can run 500 to 1,000 in a single timeframe. And so we need to bring all of these assays together. And a team has been created to call every single laboratory and every single research institution across the United States to define the complete capacity in every single state. Because it shouldn't be our expectation that every governor understands exactly everything that's in his state, but we have to understand everything in every state in order to be able to meet the needs of the American people as we increase testing.

Now, I know you all know that, in three weeks, we went from 300,000 tests total to 3 million tests total, in three weeks. We know that we have to further increase that. That has been done really by HHS and Admiral Giroir and the team up there. And we're going to supplement that team to really bring on all of the additional resources and platforms that we have in the United States of America, just like we did with ventilators to bring all of the capacity to bear so that we can also continue to increase testing.

Also, of course as these epidemics are si- — decrease, you can also be able to use more and more testing for surveillance. But I do want to call out the 19 states that aren't ever represented in these graphics in — by and large. The states have been continuing to do containment and outbreak investigation.

And I've been able to talk to many of those states. And I just remind all of us, when I talked to each one of these state health officials, where they are finding outbreaks are in nursing homes. And so we really knew to — need to continue to protect and we continue to test in nursing homes, because we know that that's a particularly vulnerable group and it's a group we're often — now that we're beginning to understand asymptomatic transmission.

No one is intending to pass the virus on to others, but we know, in essential workers around the United States, people are unknowingly infected and then passing the virus on. And so those are the ones that were very interested in finding. And you might say, "Well, how do you find them because they don't have symptoms?" And so this is where we really have to increase surveillance in a very deliberative and understand way.

And so we're really looking what are sentinel surveillance sites. I think we can see where there's outbreaks, because once people have symptoms, you can see them. But where do you do sentinel surveillance so that you find them before they have symptoms. This is what we have done for decades in HIV, and it's what's allowing us right now to really control the HIV/AIDS epidemic in Sub-Saharan Africa, because we're finding people when they're asymptomatic and treating them when they're asymptomatic. So this is something we know how to do and it's something we're working very closely with CDC and others on to make sure that we can bring that full capacity to the American people.

So these are just some insights and what we're working on. We're continuing, obviously, to track every single county and community.

And then, finally, I'm going to call on one additional group. There's a group out there of our HIV/AIDS activists and community workers that understand these tests that I've been talking about, these DNA — these RNA-based tests. Because they often get viral loads in HIV. But they will know how to explain this to the community, about sampling and what it means to run those assays. They are essentially virologists. They understand all of these assays. They also understand the antibody assays, because it's the antibody assays that they counsel and utilize in HIV testing across the United States.

And maybe it will be our translator to the American public and to their local mayors. They understand these tests. They're — essentially understand all the virology and all the immunology. And I'm really asking all of them to help us communicate what these tests are so the community is ready for them. Because antibody tests measure something very different than the viral load in the front of your nose that we're using for diagnosis. And so, really being able to understand all of those tests, when to use them, how to use them will be really critical. But the great thing is, in the United States of America, we have these community groups that understand these tests very well, and we'll be able to discuss them at every level with their community.

THE VICE PRESIDENT: I'm going to call Admiral Polowczyk up in a minute, but I have to call on Dr. Tony Fauci.

Let me — let me — let me just say something really straight from my heart, if I can. I lost my dad 32 years ago today. April 13th is always a tough day for our family. And this morning, when my brothers and sisters were sending around pictures of dad, like we always do, I just thought of the families of the more than 22,000 Americans that we've lost.

And I just want to tell you that you're on our hearts, and you're in the prayers of millions of Americans as you — as you deal with this heartbreaking loss, as well as families that have family members that are struggling with serious illness.

But let me just encourage everyone that, in the midst of that loss, because the American people have been putting these mitigation measures into practice, there are families that are still together today. And I just want to encourage you here at roughly the halfway point of "30 Days to Slow the Spread," to take — take that to heart. In no way minimize the losses that we've experienced as a nation and as families, but — but to be encouraged to know, when you see those numbers on the vast majority of states, that because of what the American people are doing, it's working.

And Dr. Fauci and Dr. Birx, and the entire team, continually asked us to remind the American people, and we do so again today: Keep doing what you're doing with the "30 Days to Slow the Spread," and we will hasten the day that we heal our land.

Dr. Fauci?

DR. FAUCI: I just want to make one comment that related to a question that was asked, and then we'll have questions. I don't want to take too much time. The idea about how we would evaluate, from a purely public health standpoint, about what I call reentry into some sort of normality. As health people, I don't know anything about, nor do I ever claim to know anything about, economics. There are going to be people that know a lot more than I do, who are going to give advice about all of the committees that the President was talking about.

But the one thing we do know as health people, as physicians and scientists and public health people — as I mentioned, I think over the weekend, on one of the shows, is that some people may think it's going to be like a light switch, on and off. You know, we're either out and we're in. It's just not going to be that way because we have a very large country and there are different impacts. As you see, New York is very different from other parts of the country, from the Midwest, from the mountain region, California and Washington, different than New Orleans.

So as we discuss and consider the public health aspects, it likely would be something that I refer to as sort of like a rolling reentry. It's not going to be one size fits all. So I don't know what it's going to be yet because we still have time to look at it.

Dr. Birx, who does an amazing job with showing you the data and the charts — that's going to likely influence some of the recommendations that we will make. But I can assure you there will be recommendations that will be based purely on public health. And the President will get a lot of other input from others, but we'll give the honest, public health recommendation.

THE VICE PRESIDENT: Thank you, Tony. Admiral? Admiral Polowczyk will give an update on supplies and then we'll take a few questions.

REAR ADMIRAL POLOWCZYK: Thank you, Mr. Vice President. Can I have the ventilator slide back up? I'll just start from there. All right, thank you.

So you start with what's in the stockpile this morning. And then here's the contracts that we'll be delivering over the next few weeks. And we added 8,600 ventilators to the pool we already had. That's the — that's the math that you — that you get there. That's a — that's included the DPA action with GM.

And we'll say that we've also issued what would be called "rated orders" with all of these vendors to allow them front-of-the-line privileges, so to speak, with — within their supply chain. So these — there's — we've, you know, written the contract. This is the 100,000-plus ventilators we're talking about, and then continue to work with them to ensure that the ventilators actually show up. So there's a continue to work there. And as we did that, we realized that downstream supply chains needed some additional Defense Production Act work as well.

If you go out to the air bridge — 80 flights scheduled, 37 complete, 43 on the — on the horizon. And you can see the numbers of material that's been brought in to supplement the volume that's needed.

Now, I'm going to go through a series of slides of New York first. So, Dr. Birx provides me what I will call as a geographic reference to align the supply chain. So all of those cities — you'll see a little bit of a theme here. I'll be talking about a lot of the — a lot of the cities and geographic areas.

I aligned the supply chain to those geographic areas to try to get as much there, while we realize the rest of the nation needs supplies as well. And then we aligned to the supply chain to site of care: public hospitals, VA, private hospitals, nursing homes, first responders, acute care, and on down the line.

So the last business week — so, Monday of last week through Friday, Saturday of the past week — these are the mass materials that came into the New York, New Jersey metro area, and you can see the volumes there.

So if you go to Detroit, we talked about their hotspot. Here's the volumes of deliveries going into Detroit for that same time period.

If you can go to Chicago. And I'm going to run through this kind of quick, but you can see that the geographic alignment, the places that Dr. Birx has talked about is where we're concentrating supplies.

You can go to New Orleans, to give you an understanding. Washington D.C., right? So now I can talk about that. Today was a — you know, a very, kind of, early entry into the Washington, D.C., Baltimore — right? — positioning supplies ahead of need, we hope, in Washington.

Go to Baltimore, and you can see trying to — the volumes there, trying to get ahead of that. And then Philadelphia is next.

And then now the next slide is a nine-city roll-up. And so to save a little time, I did not include Boston and Houston in there. So you can see the volume of material flowing through a commercial network air bridge, their supplies, into geographic regions and then — and then further prioritize to site of care.

Now, final topic: N95 masks. So the Department of Defense announced a DPA action this weekend. That came over from DOD on Friday, into the White House, approved on Saturday. And contract awarded today $131 million, five companies: 3M, Honeywell, Owens &Minor, Moldex, and Draeger.

You know, the CARES Act was signed before the — before March was end — towards the end there. So essentially two weeks from that money being put into the Title III authority for DOD. This action takes us from a baseline of what — what was being produced domestically of about 30 million masks upwards to, as we go through the fall into the end of the winter, 120 million masks domestically.

So, currently, we're filling some of that demand from overseas sources. Right? And so the additive masks here, through this, will ramp up, lower dependence on overseas sources, and that — that will essentially secure a big piece of the supply chain.

Five companies, six — six cities: Smithfield, Rhode Island; Phoenix, Arizona; Del Rio, Texas; Lexington, North Carolina; Sheboygan Falls, Wisconsin; and Aberdeen, North Dakota — all either producing more fabric or increasing production facilities to have that ramp up.

THE VICE PRESIDENT: Great. Great job. Thank you, Admiral.
And can we put that slide — I guess it's still up. This is for just the week ending April 11. We have distributed or directed the distribution of 5.3 million N95 masks, 5.5 million surgical masks, 110 million gloves. We shared that mostly just to make sure our healthcare workers know that the resources are flowing, we're going to continue to flow them, but this is just the numbers for this week and don't include, for instance, what the President announced.
I was able to tell Governor Tom Wolf of Pennsylvania today that, next week, they'll be receiving 2 million N95 masks to support some of the healthcare challenges that they're facing in the broader Philadelphia area.
So, with that, we'll be happy to take a couple of questions. Go ahead.
Q Thank you so much. One for the Admiral and then one for Dr. Fauci, if you don't mind.
THE VICE PRESIDENT: Yeah. Please.
Q Admiral, wouldn't it have been useful, as you're going through, you know, all of those supplies that are now making their way into the system — you talked about having to buy foreign products, you know, as we're catching up and making it — wouldn't it have been useful if it hadn't taken until mid-March for the government to start placing bulk orders for these kinds of supplies?
REAR ADMIRAL POLOWCZYK: Okay so, I came over from the Pentagon the 20th of March, so I'll speak from the 20th March on now. We're using the Defense Production Act. I think you'll see much more use of that as we go forward. You know, we make —
Q Sir, but my question is about the timing here and that lost time that the President earlier today denied.
REAR ADMIRAL POLOWCZYK: I know. And I'm not — I'm not equipped to talk about — other than from about the 20th of March forward. I just — I wasn't — I was over at the Joint Staff. I wasn't involved.
THE VICE PRESIDENT: Okay.
Q And I wanted to ask Dr. Fauci —
THE VICE PRESIDENT: Dr. Fauci.
Q — you know, you said that you'd be, you know, giving the President your recommendations, you and Dr. Birx, coming up with a plan that you guys are comfortable with. Are you willing, once the President has made his decision, are you willing to come here and tell us, tell the American public, what you actually had recommended to him and whether he followed through with what you recommended?
DR. FAUCI: I'm not really — what do you mean? Like —
Q So when the President stands up here, whether it's, you know, May 1st — whatever day it is — and outlines his plan, are you willing to stand up here after him and tell us all, tell the American public, what it was that you had recommended he do if there is a difference?
DR. FAUCI: You know, I have to think about that because, you know, when you have conversations with the President, sometimes they really should be confidential in what you give him because he's going to have to make his own choice.
I'd have to think about that.
Q So that way we would know whether he was actually listening to the health advice that he's being provided.
DR. FAUCI: Right. Yeah. He is. I mean, he — I can tell you one thing: He'll listen. But I think what's going to happen — you know, I don't know for sure — is that he will get input from a number of individuals representing a number of aspects of society; one of them will be health. The only thing that I can tell you is that I will give him the advice based on evidence, my observation of what the best public health approach would be.
Q Dr. Fauci?
DR. FAUCI: Yeah.

Q Just to go back to where we started today, which was with the President's seeming frustrations with some of the reporting about his early decision-making process in January and February.
As I'm sure you know, the reason we, in the press, do that kind of reporting is so that the next President that comes along, has to deal with a pandemic, can learn some of these lessons.
What — having watched this unfold up close, what do you think were the mistakes that were made early on that a future President could learn from? With the benefit of hindsight, of course.
DR. FAUCI: You know, I —
Q Because no President gets everything right, obviously.
DR. FAUCI: I understand. I don't want to use the word "mistakes," because when you're in the — in the fog of war when you're doing something, you have to make decisions. You get input from a number of individuals. It's always a moving target. And I just don't want to be — have anything taken out of context because I already had one of those already in the last couple of days — (laughs) — so I don't want to go through it again.
I wouldn't say "mistake." Could things have done better? Of course. I mean, nothing is perfect. And you could always do better. But, I mean, I hesitate to say something is a "mistake."
Q But with the benefit of hindsight, with that caveat, what could have been done better?
DR. FAUCI: Well, I mean, I can't — I can't comment about anything outside of my own field. But the thing that, when I think back on, was evolving, in my mind, was something that was a virus that was much worse than what I had thought it was going to be, based on what we had learned early on, when it was first felt to be something that just jumped from an animal to a human, and really didn't have much capability of going human to human. And then, all of a sudden, you find out that not only was it not just animal to human, but there were a lot of — that's probably the way it started.
But then, as you go back and you realize there were probably a lot of infections, that maybe if we had dealt into that a little bit more, we could have learned that not only is it affecting human to human, but it's transmitting really efficiently.
When I question myself — I'm not perfect; maybe I — I wouldn't say made "mistakes," but maybe I should have really tried to delve into that a little bit more about what was going on, but the information wasn't as forthcoming as I would have liked.
And then, all of a sudden, when you find out that you're dealing with something that is not only what had been your worst nightmare — because people ask me that: "What is your worst nightmare?" — a brand-new virus that's respiratory transmitted, that has a high degree of transmissibility, that has a high degree of morbidity and mortality. You know, is that a mistake? Maybe I should have been able to realize that earlier. I'm not sure it was a mistake; it was just an evolving thing that we finally realized and said, "Whoa, this is really worse than we could have imagined."
AIDE: All right. Last one, guys.
Q When you met with Abbott Laboratories today, what did you ask them to do? What did they say they could do?
THE VICE PRESIDENT: Well, we spoke with Abbott Laboratories today about how we can increase significantly the production of cartridges for the 15-minute test. Because, remember, we're — we are — we're not only scaling to rapidly expand testing across the country today. And it's one of the reasons why you heard me and Dr. Birx say that we are — we have an entire team now that's going to be working with governors and with laboratories around the country to identify the machines that already exist today and that could be activated in doing tests.
But we also — we also want to work with Abbott Laboratories for the longer term. Because if the current trend lines hold — and I hope and I literally pray that we will soon find ourselves on the downslope of the coronavirus in this country — this epidemic, in its current form, will come to an end. But as we make decisions in the days ahead to reopen America, what President Trump also wants to do is have a policy in place to stay open. And having the kind of surveillance testing available around the

country so that CDC can do the immediate contact tracing, when you have a positive test, so that we can deploy resources like the new Abbott 15-minute test specifically to nursing homes.
We spoke today to Governor Baker in Massachusetts, to Governor Hogan in Maryland, both of whom who have been very innovative implementing federal guidelines for preventing the spread of infectious disease at nursing homes, and we commend them for that. But being able to increase the manufacture of those devices so they can be deployed going forward in the months ahead is also a focal point of our efforts.
So, rapidly continuing to expand testing today. And the governor of Louisiana told me today that they had tested at the highest per capita — according to his numbers — of any state in the union. And we congratulate him for that. But making sure that, going forward, we'll have the infrastructure of testing all across America to deal with the coronavirus should it return in the future.
With that, let me — let me bid you all a good evening. And we will be back tomorrow. And —
Q Mr. Vice President —
THE VICE PRESIDENT: Okay. Go ahead.
Q I just have a question about these cartridges and this timeline because the New Hampshire governor says the federal government is in charge of distributing those — FEMA is. So what is the timeline for when they'll have enough of them? Because they say they don't have enough. Illinois said they didn't have enough. So what's the timeline that you're working with?
THE VICE PRESIDENT: Yeah, let me — let me let Dr. Birx address that. But there's a — there was an initial tranche that we purchased. There's some 18,000 Abbott Laboratory machines around the country, and FEMA acquired a certain amount that were immediately distributed across the states.
But now Abbott Laboratories is literally producing some 50,000 a day, and those are available in the open market. And we're also going to be working with Abbott and with the states to deploy those resources.
And we're also working with other manufacturers to increase the production of cartridges. But if there's more to that that you want to add, Deb, we'll make it the last.
DR. BIRX: No, that was perfectly said. I just want to — sometimes you ask those questions, and I always want to make sure that people understand.
So, a third of them went specifically to Indian Health Service and to these states that have smaller epidemics. Two thirds of it went into the public market, mostly targeted to the places where there is high disease. But only two thirds went that way so that people could purchase them directly, and one third went to the Indian Health Service and to the smaller states that really need these.
And so I think what we're trying to do now is balance the entire testing framework of medium-, low-, and high-throughput machines to give everyone the maximum flexibility, state by state, based on what the needs are at that moment.
If there's an outbreak and you have to do 5,000 tests, you're not going to do them on an ID NOW machine that takes 15 minutes for every negative, but you're going to do it on your high-throughput machine. So making sure everybody knows where everything is and what is being run will be really critical moving forward, because we can't leave anything not on –everything has to be on the table in order for us to be able to dramatically increase testing yet another — we went up by a log in three weeks. So if we're going to increase again, it's going to have to be getting every piece of equipment on
THE VICE PRESIDENT: Let just again say thank you all for your time and attention. And thanks to every American who's joined us tonight.
I just want to encourage you we're going to continue to lean into this effort, to expand testing across the country, to deploy supplies to our incredible healthcare workers that have done such an amazing job in the midst of the coronavirus epidemic.
But my last word, on behalf of the President, on behalf of our entire task force is: It's "30 Days to Slow the Spread." And I know we're almost at the halfway point, and I know it's been a month of these

mitigation strategies, but I hope as you look on, as you see the progress that's made on the West Coast, the beginnings of real progress in the Greater New York City area, Louisiana, Detroit, and elsewhere — I hope it will only steel your resolve to continue to do your part to slow the spread, because we'll get through this, but it'll take all of us to continue to do it.
So thank you to the American people for all your efforts, and we'll see you tomorrow.
END

• •

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/14 16:15:13
Delivered Date:	2020/04/14 16:25:50
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: VUMC team aids development of potential antiviral drug for COVID-19
Date: 2020/04/06 22:46:16
Priority: Normal
Type: Note

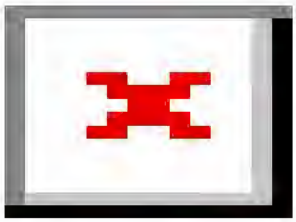
VUMC team aids development of potential antiviral drug for COVID-19

Apr. 6, 2020, 1:59 PM

by Bill Snyder

Researchers at Vanderbilt University Medical Center are playing a key role in the development of a potential new antiviral drug to treat COVID-19.

The drug, named EIDD-1931, was developed at the Emory Institute for Drug Development in Atlanta. In November, Mark Denison, MD, and colleagues at VUMC reported that EIDD-1931 blocked replication of a broad spectrum of coronaviruses in laboratory tests and prevented these viruses from developing resistance against it.



The drug study team includes (back row from left) Jim Chappell, MD, PhD, Andrea Pruijssers, PhD, Mark Denison, MD, (front row from left) postdoctoral fellow Maria Agostini, PhD, graduate student Jennifer Gribble Bowser, and senior research specialists Laura Stevens, MS, Tia Hughes, MS, and Xioatao Lu, MS. Current lab members also include research fellow Jordan Anderson-Daniels, PhD, and research assistant Amelia George, MS. (photo was taken last year)

Andrea Pruijssers, PhD, research assistant professor of Pediatrics and the lead antiviral scientist in Denison's lab, provided the first evidence of the drug's potent activity against SARS-CoV-2, the virus that causes COVID-19.

The VUMC researchers also contributed to a subsequent animal study conducted at the University of North Carolina at Chapel Hill.

That paper, published online April 6 by the journal *Science Translational Medicine*, includes data from cultured human lung cells infected with SARS-CoV-2, as well as mice infected with the related coronaviruses SARS-CoV and MERS-CoV.

The study found that EIDD-2801, a form of EIDD-1931 that can be taken orally, prevented severe lung injury in infected mice. When given 12 or 24 hours after infection had begun, the drug reduced the degree of lung damage and weight loss in mice.

If clinical studies in humans, expected to begin later this spring, are successful, EIDD-2801 could not only help stop the spread of SARS-CoV-2, but it also could control future outbreaks of other emerging coronaviruses, said Denison, an internationally known authority on coronavirus biology.

"We are amazed at the ability of EIDD-1931 and -2801 to inhibit all tested coronaviruses and the potential for oral treatment of COVID-19," Pruijssers said. "This work shows the importance of ongoing National Institutes of Health (NIH) support for collaborative research to develop antivirals for all pandemic viruses, not just coronaviruses."

The inter-institutional collaborators, supported by an NIH grant through the University of Alabama at Birmingham, also performed the preclinical development of remdesivir, another antiviral drug currently in clinical trials of patients with COVID-19.

In the paper published today, Maria Agostini, PhD, a postdoctoral fellow in Denison's lab, demonstrated that viruses showing resistance to remdesivir are more highly inhibited by EIDD-1931.

Since 2014 Denison and his colleagues have investigated the antiviral drug remdesivir, a potential COVID-19 treatment now in clinical trials in the United States and China. Pruijssers has also demonstrated that remdesivir is effective against SARS-CoV-2.

Currently no antiviral drugs have been approved to treat SARS-CoV-2 or any of the other coronaviruses that cause human disease. Since early January when the outbreak was first reported in China, SARS-CoV-2 has infected more than 1.3 million people worldwide and caused nearly 74,000 deaths.

Denison's lab also will be involved in a phase 1 clinical trial that is testing antibody responses to a potential vaccine against SARS-CoV-2 designed and produced by Massachusetts-based biotechnology firm Moderna Inc.

Denison, the Craig-Weaver Professor of Pediatrics, directs the Division of Pediatric Infectious Diseases in the Department of Pediatrics.

The VUMC research is supported by National Institutes of Health grants AI109680, AI142759, AI112541, AI133952 and GM065086.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/06 22:46:05
Delivered Date:	2020/04/06 22:46:16
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Texas A&M chemists working on drugs To treat COVID-19
Date: 2020/04/07 10:27:50
Priority: Normal
Type: Note

6-Apr-2020

Texas A&M chemists working on drugs To treat COVID-19

Wenshe Ray Liu's laboratory has refocused solely to combat the pandemic
Texas A&M University

In the wake of the novel coronavirus pandemic, Texas A&M University chemist Wenshe Ray Liu and his research team have focused their lab solely on searching for drugs to treat COVID-19.

The Liu group was the first to identify the antiviral drug remdesivir as a viable medicine to treat COVID-19 in a research study published in late January. The drug was originally developed in response to the 2014 Ebola pandemic.

As a chemical biologist specializing in medicinal chemistry, Liu's primary research target is cancer. But the lockdown of Wuhan and the first two diagnosed cases in the U.S. prompted him to refocus his lab on coronavirus.

"The motivation that drove us was the rush against time to find alternative medicines that might be put in use to fight against the virus when it spread to the U.S," Liu said.

The researchers are working to develop drugs that can prevent SARS-CoV-2 - the virus that causes COVID-19 - and other coronaviruses from replicating once inside human cells. They're also exploring how to counteract the effect of the viruses in human plasma.

Liu said his group has made significant progress in a very short time toward their ultimate goal: to push a COVID-19 drug candidate to preclinical trials and clinical testing before the pandemic subsides.

"There is sufficient scientific knowledge for this group of viruses, and we will be able to find cures," he said.

Remdesivir is being tested in at least five large-scale clinical trials around the world and also has been delivered to some patients, including the first known U.S. case confirmed Jan. 21 in Washington. That patient recovered after compassionate use of remdesivir.

While Liu said he remains convinced it's the right treatment, he cautioned that success shouldn't be viewed as a one-shot approach, given such a swift-moving target as COVID-19.

"Remdesivir is still the best and probably the only option to target the virus directly in patients," he said.

With the U.S. clinical trial set to finish this week, Liu is optimistic that the final results released next week will speak for themselves. However, with remdesivir poised to be the only approved drug to treat COVID-19, its large-scale use will occur, and some drug-resistant virus strains will evolve.

"At this stage, the scientific community needs to prepare for the worst and work to bring other treatment options to the forefront," he said, adding that while there have been positive results from tests of hydroxychloroquinine, additional options are needed.

When it comes to viral mutations and reports that multiple strains of the virus exist, Liu deferred to clinicians, but acknowledged that it has become more virulent.

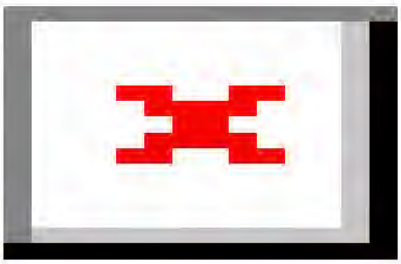
"The infectivity of the original strain shown in Wuhan was not as high as what we have observed for the current strain in the U.S.," he said.

###

Liu is joined in his work by several additional collaborators in the Department of Chemistry and across the Texas A&M campus, including Distinguished Professor of Chemistry and 2017 National Academy of Sciences member Marcetta Y. Darensbourg, Texas A&M Provost and Executive Vice President Carol A. Fierke, who is an X-ray crystallography expert, and noted Texas A&M biochemist Thomas Meek.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/07 10:27:21
Delivered Date:	2020/04/07 10:27:50
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Science: To streamline coronavirus vaccine and drug efforts, NIH and firms join forces
Date: 2020/04/18 12:01:32
Priority: Normal
Type: Note



National Institutes of Health Director Francis Collins
Tom Williams/CQ Roll Call via AP Images

To streamline coronavirus vaccine and drug efforts, NIH and firms join forces

By Jocelyn KaiserApr. 17, 2020 , 7:45 PM

***Science*'s COVID-19 reporting is supported by the Pulitzer Center.**

More than 100 treatments and vaccines are in development to stem the COVID-19 pandemic, and some onlookers have worried that this sprawling and potentially duplicative effort is wasting time and resources. Hoping to bring order to the chaos, the National Institutes of Health (NIH) and major drug companies today announced a plan to stage carefully designed clinical trials of the drugs and vaccines they have decided are the highest priorities for testing and development.

The public-private partnership involves NIH, other U.S. government agencies, 16 pharma companies and biotechs, and the nonprofit Foundation for the National Institutes of Health (FNIH). It aims to develop "an international strategy" for COVID-19 research, a press release states. However, NIH Director Francis Collins told reporters during a press call today that, "It is primarily a U.S. focused effort."

The initiative, called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), aims to make efficient use of NIH funding and its clinical trial networks by working with companies to evaluate data on early candidates, selecting those that have the most promise and are not already part of rigorous human tests.

NIH is stepping in partly because of concerns that some potential treatments, such as hydroxychloroquine/chloroquine, are being touted by some researchers as effective based on poorly designed trials. "We need the best research standards," says former NIH director and Sanofi executive

Elias Zerhouni, who sits on FNIH's board. "To me, the whole effort is to create a synergy between all of the players."

Collins said NIH began discussions with companies just 1 month ago, and plans gelled at a 3 April meeting. There was "unanimous agreement that the time has come to put aside any of the obstacles ... [to] such a public-private partnership and bring all the full resources and ideas together in a variety of ways that neither sector could do alone," Collins said.

Joining forces

ACTIV is partly modeled on a long-established FNIH-organized program called the Accelerating Medicines Partnership, in which companies join forces with NIH to generate shared data, such as biomarkers in Alzheimer's disease. Its goals include giving companies access to animal models and drug screening programs in high-security biosafety labs, as well as developing a "master protocol" and setting clinical standards for assessing a drug's efficacy that would be shared across trials. Companies will also share data on immune responses to candidate vaccines. Although focused on the United States, NIH says ACTIV is also working with the European Medicines Agency.

NIH is assembling working groups of scientists who will inventory drugs and vaccines at different stages of development, and then decide which are most promising for future testing and not already in well-designed studies. In making that list, the experts will also consider which untested compounds can most quickly move into human trials, and which could be manufactured in large quantities. The top-rated compounds will get priority for the $1.8 billion Congress gave NIH for COVID-19 research as part of pandemic recovery bills, and preferred access to NIH's dozen or more clinical trial networks.

Collins noted that once ACTIV has started coordinating clinical trials, it might become easier to rapidly start, end, or redesign trials to focus on the most promising candidates. As an example, he noted that NIH easily recruited 800 patients, 300 more than needed, to test the drug remdesivir (results are expected soon). If an additional candidate compound was available, he noted, NIH could have offered those 300 patients the option of becoming involved in a different trial instead.

NIH and its partners say they have put off, for now, deciding how to answer potentially thorny questions about intellectual property (IP) ownership and the pricing of any new treatments developed under the partnership. That's a reasonable strategy given the urgency, says science policy specialist Robert Cook-Deegan of Arizona State University, Tempe. "It's pretty clear that they're aware the IP could get complicated," he says. And he doubts that pricing issues "will play out the way it usually does, with companies pricing to maximize and government passively going along," if only because there is likely to be intense public scrutiny of the effort.

Collins pointed out that companies are unlikely to be motivated by profits after seeing their own clinical trial efforts shut down by COVID-19. Executives are "desperate" to get their businesses running again and "therefore willing to do whatever it takes both altruistically and practically," he predicted.

Growing efforts to coordinate

The NIH project joins numerous other COVID-19 research coordination efforts around the world. In the United Kingdom, for example, a trial testing several drugs called RECOVERY is being led by the University of Oxford and tapping nearly 1000 patients at 132 hospitals run by the country's National Health Service. Although the U.S. effort has been slower than some others to get started, "no doubt when the NIH gets going, it will be a ... very efficient study," says Mene Pangalos, executive vice president of bioPharmaceuticals R&D at AstraZeneca. "Hopefully, they won't do the same molecules they are doing in the U.K., and between us all, we'll learn faster." NIH says its working groups include representatives from efforts such as RECOVERY to avoid such duplication.

One global health leader is noticeably absent from the list of ACTIV's partners: the World Health Organization (WHO). It, too, has been coordinating COVID-19 research, organizing a global trial of several drugs called SOLIDARITY.

WHO chief scientist Soumya Swaminathan said her agency welcomes the NIH effort. But for vaccines, she contends that WHO is well-positioned to coordinate the field with an expert group that's now being formed. "The best and most efficient way would be to consider one large global study which would look at different vaccine candidates," she says.

Collins says NIH is keeping tabs on WHO's efforts as it makes its own plan. And infectious disease expert Daniel Bausch of the London School of Hygiene &Tropical Medicine says WHO does not have the capacity to launch the effort NIH has in mind. "It will be important, however, to have NIH and WHO coordination, especially to ensure equitable participation in the conduct of the trials and access to the products that they might produce," Bausch says.

Richard Danzig, former secretary of the U.S. Navy who is heavily involved in international vaccine planning, says that while "the NIH effort is commendable," it doesn't directly take on another challenge once a vaccine has been developed: how to make enough to vaccinate the world's population. "We need also," Danzig says, "to prepare global manufacturing for vaccine production."

With reporting by Jon Cohen and David Malakoff.

Posted in:

- Health
- Scientific Community
- Coronavirus

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/18 12:01:21
Delivered Date:	2020/04/18 12:01:32
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Vanity Fair: "I Take That as a Threat": Big Pharma Is Meddling in the Race for a COVID-19 Treatment
Date: 2020/04/24 10:03:15
Priority: Normal
Type: Note

"I Take That as a Threat": Big Pharma Is Meddling in the Race for a COVID-19 Treatment

A Yale researcher poised to start a crucial clinical trial received an ominous email from a pharmaceutical company. "There is undoubtedly a financial motivation," he said—and there could be millions on the line.

By Diana Falzone
April 24, 2020

Scientists are at work in the VirPath university laboratory in France as they try to find an effective treatment against...
Scientists are at work in the VirPath university laboratory in France, as they try to find an effective treatment against the coronavirus.By JEFF PACHOUD/AFP/Getty Images.

The race to develop a COVID-19 vaccine is well underway, but given its extended timeline—12 to 18 months—the search for an existing drug to treat the virus is almost equally pressing. For many on the right, including the president, the method of choice was hydroxychloroquine, a malaria drug initially thought to combat the infection. But with a damning study out showing the drug is basically ineffective, and in fact may lead to increased death rates, even Fox News has quietly dispensed with that theory.

In New Haven, meanwhile, **Dr. Joseph Vinetz,** an infectious disease doctor at Yale School of Medicine, is seeking to launch a clinical study of the drug camostat mesylate, a generic medication approved in Japan to treat chronic pancreatitis that he hopes can be approved and marketed to treat COVID-19. If the trial succeeds, he said, this could be "a total game changer." But the process is proving fraught. Within hours of registering his trial on a National Institutes of Health website on April 20, he received an email from a large U.S. pharmaceutical company. "They are trying to take my project and engulf it for their proprietary [financial] gain," Vinetz told me. "I take that email as a threat."

Unlike hydroxychloroquine, camostat is a drug researchers believe may have promising effects on COVID-19. It's also being studied in countries including Germany and Denmark. "The virus that causes COVID-19 requires a protein to get inside of the cells that line the respiratory tract," Vinetz explained. In test tubes and in mice, he said, camostat has been shown to inhibit an enzyme that allows the virus to enter those cells. Another published experiment showed that camostat prevented mice from dying of the SARS virus. As of yet, there's no data that shows how it could impact the novel coronavirus in humans. But if Vinetz's study is successful, he hopes camostat can be administered both to infected COVID-19 patients and as a preventative.

The drug is manufactured in Japan; Ono Pharmaceutical, a massive company headquartered in Osaka, has committed to providing enough camostat pills for 300 patients over the course of Vinetz's study. All he needs is FDA approval for the trial and his staff can begin testing. "We will be enrolling patients to come in daily for a swab test, receive medication, provide a symptom survey to ensure safety, and to look at any improvement [or lack thereof] after the drug or placebo is given," he explained. "We will be closely following all participants, including looking at their oxygen levels by pulse oximeter to make sure that they do not need to be hospitalized."

The email Vinetz received on April 20, after he registered the trial, threatened to throw a wrench in proceedings. In the email, a copy of which was reviewed by the Hive, a representative for a large pharmaceutical company wrote that the company was itself "exploring the opportunity with BARDA," the Biomedical Advanced Research and Development Authority, "and others to conduct clinical trials testing camostat mesylate in COVID-19," and noted that it has an "open IND," essentially a permission slip from the FDA to conduct a clinical trial. The email proposed that Vinetz, who has applied for an IND but has not yet received it, would need access to data the company has received through its IND, and that he'd need a letter of authorization from the company to get it. "We would appreciate gaining a better understanding of your study," the email continued, proposing a call to discuss the matter.

Vinetz said he interpreted the email to mean "you have to go through us." "They seem to want me to have to work under their authorization," he said. "I viewed it as a threatening email," he reiterated. "There is undoubtedly a financial motivation." He theorized that the company might be hoping to get camostat designated as an orphan drug. The Orphan Drug Act, which Congress passed in 1983, uses financial incentives to encourage the development of drugs that treat rare diseases. Among other things, said **Dr. Marion Mass,** a Philadelphia-based pediatrician and cofounder of Practicing Physicians of America, the act gives drug makers seven-year market exclusivity (meaning no other company can advertise the same version of the drug), a 50% tax credit on the cost of conducting clinical testing, and access to grants to conduct that testing.

In addition, a company studying a drug that's been granted orphan status can apply for a voucher to speed up the FDA approval process by several months, getting the drug on the market faster—a prospect that lets companies turn a profit sooner. A company with a voucher can auction it off to other pharmaceutical companies, selling it to the highest bidder. "These [vouchers] are highly valuable and have been...worth tens or even more than $100 million," Vinetz said. "I have a feeling that this pharma company wanted to do what Gilead did [with remdesivir] by applying for orphan drug status for camostat."

U.S. pharmaceutical giant Gilead Sciences managed to get remdesivir, a broad-spectrum antiviral drug initially used to treat Ebola, designated as an orphan drug in March, when COVID-19 was still considered a rare disease. Some physicians say the drug initially showed promise in treating COVID-19 patients, but they caution that studies are inconclusive. As COVID-19 cases mounted, Gilead faced enormous public backlash for its handling of remdesivir, particularly after reports surfaced that it was difficult for critically ill COVID-19 patients to obtain the drug after Gilead halted its compassionate-use access. Later that month, Gilead posted a statement announcing that it "has submitted a request to the U.S. Food and Drug Administration to rescind the orphan drug designation" and "is waiving all benefits that accompany the designation."

"There was a rapid, vociferous, and powerful public outcry because the implications for possible profiteering were concerning," Vinetz said of Gilead. **Dr. Purvi Parikh,** an immunologist and allergist in New York City, noted that "Those are bad optics for the company during a pandemic, to have a monopoly on a lifesaving drug."

A biotech venture capitalist told me that, while they do not have direct evidence that big pharma is meddling in trials of drugs to treat COVID-19, "I have heard from several sources that they are muscling in and sequestering patients and trial sites. Pharmas have a lot of money and political clout to monopolize the infrastructure for clinical trials." In fact, they noted, innovative drugs just as often come from small biotech labs and universities, not pharmaceutical companies. But in most cases, funding goes to "politically connected players and big businesses rather than...the small firms and even nonprofit entities that could achieve a lot with even a small slice of that financial pie."

Mass, the Philadelphia-based pediatrician, said pharma uses "perverse incentives and mountains of existing cash to seize the sole source control of an arena," citing Gleevec, Novartis's best-selling leukemia treatment, funded by U.S. taxpayers through National Institutes of Health grants and support from the Leukemia &Lymphoma Society. "This daily medication is the difference between life and death for so many people, but only if they can afford the $97 per pill for the name-brand version," Mass said. "Other companies are likely doing research; they got to the finish line first." She noted that some pharmaceutical companies do a lot of good, but "the quasi monopoly circle has been built by decades of perverse incentives created in Washington, D.C."

Dr. Jennifer Bryan, a Mississippi-based doctor and chairman of the board of trustees for Mississippi State Medical Association, listed a myriad of problems with big pharma's vice grip on the industry, such as overseas drug production, which in some cases has led to recall, and monopoly patents, meaning companies can ratchet up the prices of drugs for consumers. "It's disheartening to learn that this disruptive influence may be happening at the level of trying to intimidate research and corner a market on potential COVID-19 therapies," she said, "but it isn't surprising."

Regardless of the hurdles, Vinetz said he's willing to go to the mat to protect the camostat trial. "Maybe they thought I was naive," he said. "I have the entire clinical trial regulatory machine of Yale behind me."

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/24 10:00:55
Delivered Date:	2020/04/24 10:03:15
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: EMA Recommends Remdesivir for Treatment of COVID-19 Under Compassionate-Use Rules
Date: 2020/04/04 12:14:44
Priority: Normal
Type: Note

EMA Recommends Remdesivir for Treatment of COVID-19 Under Compassionate-Use Rules

Accessing the experimental antiviral treatment outside of clinical trials just got easier in the European Union.

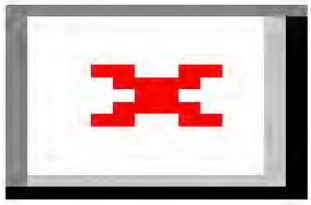
Cory Renauer
Cory Renauer
(TMFang4apples) Fool.com
Apr 3, 2020 at 1:51PM

The European Union's health regulator on Friday took an unusual step and increased access to an experimental drug that might be effective against SARS-CoV-2, the coronavirus that causes COVID-19. **Gilead Sciences'** (NASDAQ:GILD) antiviral treatment remdesivir is now indicated for the treatment of adults unable to breathe due to COVID-19 as part of a compassionate-use program, said the European Medicines Agency.

Not a full approval

The EMA has not approved remdesivir for COVID-19 or any other indication, but the drug has been taken by dozens of Ebola patients and it didn't appear to have dangerous side effects. Remdesivir is supposed to prevent infected cells from producing copies of just about any virus, but there are only anecdotal reports so far of it being successful as a COVID-19 treatment. And, worth noting, it failed in clinical trials as an Ebola treatment, though there is speculation that may have been due to how late in the progression of the disease patients were given the drug.

The EMA would prefer for COVID-19 patients to receive remdesivir by participating in one of nine clinical trials that are ongoing at the moment or expected to begin soon. However, given the extremely poor prognosis for COVID-19 patients who have already lost the ability to breathe properly on their own, waiting around for a drug trial to begin isn't always an option.



Healthcare worker holding a coronavirus sample.
Image source: Getty Images.

What to look for

During the PALM study in 2018 and 2019, 681 Ebola virus patients were randomized into groups that received remdesivir or one of three other experimental antiviral drugs. After an interim analysis, patients in the remdesivir group were switched over to groups with lower mortality rates.
In April, Gilead Sciences expects to release interim results from a controlled clinical trial of remdesivir in COVID-19. And this summer, **Regeneron** (NASDAQ:REGN) could begin clinical trials in which it treats COVID-19 patients with REGN-EB3, a cocktail of three monoclonal antibodies that outperformed remdesivir during the PALM study.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/04 12:14:13
Delivered Date:	2020/04/04 12:14:44


4th Interim

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: BMJ: Remdesivir in covid-19 /A drug with potential—don't waste time on uncontrolled observations
Date: 2020/04/22 21:23:35
Priority: Normal
Type: Note

Editorials

Remdesivir in covid-19

BMJ 2020; 369 doi: https://doi.org/10.1136/bmj.m1610 (Published 22 April 2020) Cite this as: BMJ 2020;369:m1610

Robin E Ferner, honorary professor of clinical pharmacology1,

1. • Jeffrey K Aronson, clinical pharmacologist2
Author affiliations

1. • Correspondence to: R E Ferner r.e.ferner@bham.ac.uk

A drug with potential—don't waste time on uncontrolled observations

The recent publication of an industry sponsored, open, non-randomised study of remdesivir in a heterogeneous patient population has added to the confusion surrounding the drug treatment of covid-19.1

The SARS-CoV-2 virus that causes covid-19 has potential therapeutic targets similar to those of other RNA coronaviruses such as SARS-CoV-1, which causes severe acute respiratory syndrome (SARS), and MERS-CoV, the cause of Middle East respiratory syndrome.

Coronaviruses enter host cells by binding to and fusing with cell membranes. Once inside, they subvert the host cell's machinery to replicate, using the virus's RNA dependent RNA polymerase (RdRp).2 This non-structural protein is highly conserved among different strains, making it a potentially attractive drug target. The principle of using synthetic analogues of nucleosides and nucleotides to inhibit RdRp has led, for example, to sofosbuvir, a successful treatment for hepatitis C infection.3

Remdesivir is a pro drug. Its active analogue enters and accumulates in cells, inhibiting viral RdRp4 and stopping viral replication. Coronaviruses have a "proofreading" enzyme (exoribonuclease) that corrects errors in the RNA sequence, potentially limiting the effects of analogues,56 but remdesivir is able to evade this proofreading.47 In the laboratory, viral mutation can lead to resistance to remdesivir, but the mutant viruses are less infective.5

Animal studies

In animal studies, pretreatment with remdesivir protected rhesus monkeys from MERS-CoV infection and reduced the severity of lung damage when given after exposure to MERS-CoV.8 It protected African green monkeys when given 24 hours after infection with Nipah virus, a cause of fatal encephalitis,9 and when given intravenously in a dose of 10 mg/kg for 12 days it prevented rhesus monkeys dying from Ebola disease even when treatment started three days after infection.7

A preprint of a randomised, well masked, controlled trial in 12 rhesus monkeys infected with SARS-CoV-2 reported that a course of remdesivir administered from 12 hours after inoculation attenuated respiratory symptoms and lung damage.15

However, efficacy in vitro or in animals does not inevitably predict outcomes in humans. When remdesivir was compared with three different antibody treatments in a randomised controlled trial in 681 patients with Ebola, mortality in the 175 treated with remdesivir was 53%, significantly worse than the 35% mortality in 174 patients treated with the most active antibody.10 Patients in the remdesivir group may have been "somewhat sicker" at baseline, according to the authors.

Use in covid-19

Initial reports of the use of remdesivir in humans with covid-19 were either anecdotal cases or small, uncontrolled case series lacking any information on outcomes.1112 Short term outcomes have now been reported for 53 of 61 patients with covid-19 treated in over 20 hospitals on three continents.1 Patients received at least one dose of a 10 day course of intravenous remdesivir as part of a compassionate use programme organised by the manufacturer, and not as part of a clinical trial. Thirty were being ventilated and four treated with extracorporeal membrane oxygenation (ECMO) at the start of remdesivir treatment. After a median of 18 days, 25/53 patients (47%) had been discharged from hospital and seven (13%) had died. Mortality was 5% among patients who were not ventilated. The overall probability of improvement by 18 days was 68% (95% confidence interval 40% to 80%).
Thirty two (60%) patients in this study had at least one adverse event; 12 (23%) experienced serious adverse events. The most common adverse events were abnormal liver function, diarrhoea, rashes, renal impairment, and hypotension. As the authors stated, "Interpretation of the results of this study is limited by the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on eight of the patients initially treated, and the lack of a randomized control group."
The existence of a compassionate use programme for remdesivir does not mean that its benefits outweigh its potential harms. That balance is still unknown. Compassionate use of remdesivir is reminiscent of the early compassionate use of penicillin for acute infective endocarditis13 but with important differences. The mortality from covid-19 is low compared with the mortality from acute infective endocarditis and differs across countries. Also, the criteria for mechanical ventilation are partly subjective. An open, uncontrolled trial cannot determine whether a treatment is beneficial overall.

Better evidence, faster

The mechanism of action of remdesivir makes it potentially useful in the treatment of covid-19. We shall *find out for certain only if patients are recruited to well powered*, adequately masked, randomised controlled trials. At least 23 studies of remdesivir are currently listed on various trial registers, intending to study 23 500 patients, but fewer than a quarter are double blind, and some are uncontrolled observational studies. The use of standard protocols prepared in expectation of future urgent needs would help. So too would wider adoption of adaptive trial protocols, such as platform trials,14 which allow the evaluation of several treatments at once and permit interim analyses after which treatments may be discarded or introduced.

Footnotes

- • Competing interests: We have read and understood BMJ policy on declaration of interests and declare that JKA is a member of the Centre for Evidence-Based Medicine in Oxford, which jointly runs the EvidenceLive Conference with the BMJ and the overdiagnosis conference with some international partners, which are based on a non-profit model. He is an associate editor of *BMJ Evidence Based Medicine* and was until recently vice president publications for the British Pharmacological Society. REF was until recently a member of the Birmingham, Sandwell and Solihull Area prescribing committee, is a series editor of *The BMJ*'s Therapeutic Series, and has an honorary position at University College London.

- Provenance and peer review: Not commissioned; externally peer reviewed.

References

1. ↵
    1. Grein J,
    2. Ohmagari N,
    3. Shin D,
    4. et al

    . *Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med2020. [Epub ahead of print.] . doi:10.1056/NEJMoa2007016 pmid:32275812*
    CrossRefPubMedGoogle Scholar

2. ↵
    1. Amirian ES,
    2. Levy JK

    . *Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic aptions for coronaviruses. One Health2020;9:100128. doi:10.1016/j.onehlt.2020.100128 pmid:32258351*
    CrossRefPubMedGoogle Scholar

3. ↵
    1. Xie Y,
    2. Ogah CA,
    3. Jiang X,
    4. Li J,
    5. Shen J

    . *Nucleoside inhibitors of hepatitis C virus NS5B polymerase: a systematic review. Curr Drug Targets2016;17:1560-76. doi:10.2174/1389450117666151209123751 pmid:26648061*
    CrossRefPubMedGoogle Scholar

4. ↵
    1. Gordon CJ,
    2. Tchesnokov EP,
    3. Feng JY,
    4. Porter DP,
    5. Götte M

    . *The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem2020;295:4773-9; [Epub ahead of print.]. doi:10.1074/jbc.AC120.013056 pmid:32094225*
    Abstract/FREE Full TextGoogle Scholar

5. ↵
    1. Agostini ML,
    2. Andres EL,
    3. Sims AC,
    4. et al

. *Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio2018;9:e00221-18. doi:10.1128/mBio.00221-18 pmid:29511076*
CrossRefPubMedGoogle Scholar

6. • ↵
    1. • Pruijssers AJ,
    2. • Denison MR

. *Nucleoside analogues for the treatment of caronavirus infections. Curr Opin Virol2019;35:57-62. doi:10.1016/j.coviro.2019.04.002 pmid:31125806*
CrossRefPubMedGoogle Scholar

7. • ↵
    1. • Warren TK,
    2. • Jordan R,
    3. • Lo MK,
    4. • et al

. *Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature2016;531:381-5. doi:10.1038/nature17180 pmid:26934220*
CrossRefPubMedGoogle Scholar

8. • ↵
    1. • de Wit E,
    2. • Feldmann F,
    3. • Cronin J,
    4. • et al

. *Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acod Sci USA2020;117:6771-6. doi:10.1073/pnas.1922083117 pmid:32054787*
Abstract/FREE Full TextGoogle Scholar

9. • ↵
    1. • Lo MK,
    2. • Feldmann F,
    3. • Gary JM,
    4. • et al

. *Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. Sci Transl Med2019;11:eaau9242. doi:10.1126/scitranslmed.aau9242 pmid:31142680*
FREE Full TextGoogle Scholar

10. • ↵
Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. biorXiv 2020.04.15.043166. [Preprint.] doi:10.1101/2020.04.15.043166
Abstract/FREE Full TextGoogle Scholar

11. • ↵
    1. • Mulangu S,

2. • Dodd LE,
3. • Davey RT Jr.,
4. • et al.,
5. • PALM Writing Group,
6. • PALM Consortium Study Team

. *A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med2019;381:2293-303. doi:10.1056/NEJMoa1910993 pmid:31774950*
CrossRefPubMedGoogle Scholar

12. • ↲
    1. • Holshue ML,
    2. • DeBolt C,
    3. • Lindquist S,
    4. • et al.,
    5. • Washington State 2019-nCoV Case Investigation Team

    . *First case of 2019 novel coronavirus in the United States. N Engl J Med2020;382:929-36. doi:10.1056/NEJMoa2001191 pmid:32004427*
    CrossRefPubMedGoogle Scholar

13. • ↲
    1. • Bhatraju PK,
    2. • Ghassemieh BJ,
    3. • Nichols M,
    4. • et al

    . *Covid-19 in critically ill patients in the Seattle region — case series. N Engl J Med2020. doi:10.1056/NEJMoa2004500 pmid:32227758*
    CrossRefPubMedGoogle Scholar

14. • ↲
    1. • Dolphin A,
    2. • Cruickshank R

    . *Penicillin therapy in acute bacteriol endocorditis. BMJ1945;1:897-901. doi:10.1136/bmj.1.4408.897 pmid:20786144*
    FREE Full TextGoogle Scholar

15. • ↲
    1. • Park JJH,
    2. • Siden E,
    3. • Zoratti MJ,
    4. • et al

    . *Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials2019;20:572. doi:10.1186/s13063-019-3664-1 pmid:31533793*
    CrossRefPubMedGoogle Scholar

View Abstract

Article tools

PDF0 responses

- Respond to this article
- Print
- Alerts &updates
- Citation tools
- Request permissions

- Author citation

- Add article to BMJ Portfolio

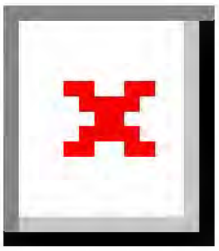
Email to a friend

- UK jobs
- International jobs

University Hospitals of Leicester NHS Trust: Consultant in Palliative Care
Cygnet Health Care: Regional Medical Director
Brighton and Sussex University Hospitals NHS Trust: Consultant Palliative Medicine
University Hospitals of Leicester NHS Trust: Consultant in Palliative Care Medicine
Spring Hill Medical Centre: Salaried/Salaried with a view to Partnership GP position
View more

Altmetric

Who is talking about this article?



Article has an altmetric score of 19
See more details

Tweeted by **31**

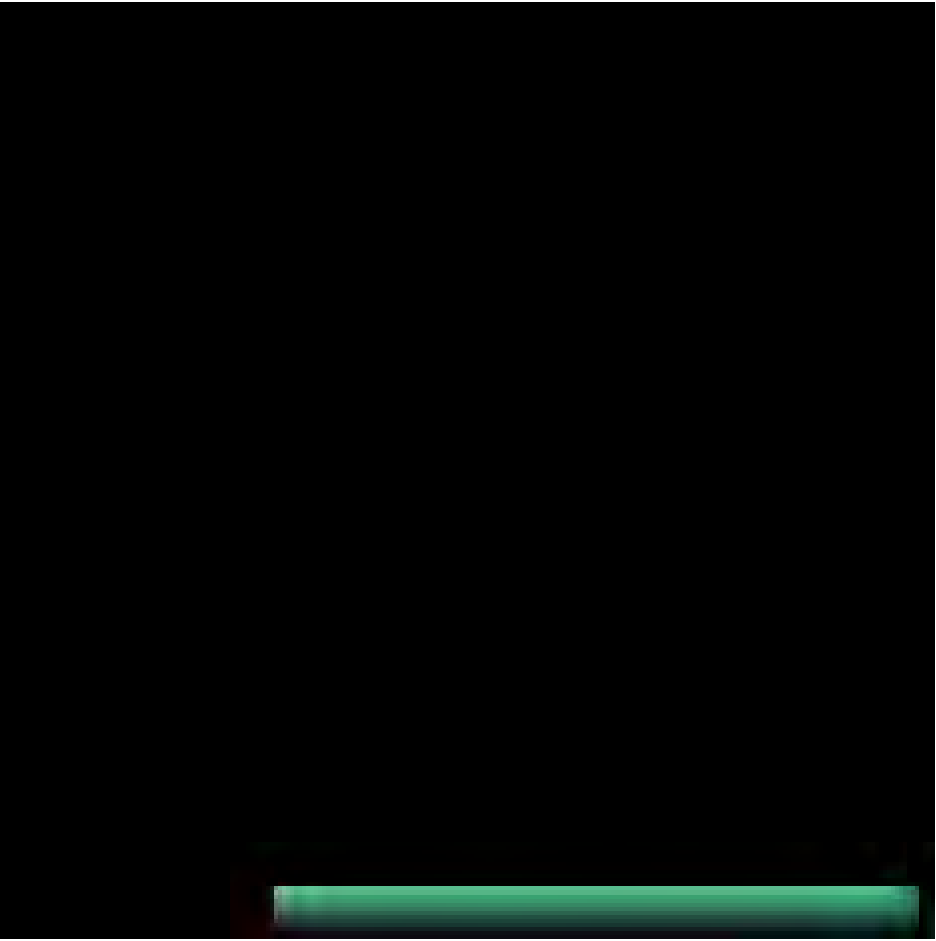
This week's poll

Should we give priority care to healthcare workers in the covid-19 pandemic?
Yes
No
VoteView Results
Read related article
See previous polls
Back to top

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/22 21:21:54
Delivered Date:	2020/04/22 21:23:35
Message Flags:	Unread


Airmetric
489


4th Interim Re



From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Putting remdesivir to the test for COVID-19
Date: 2020/04/08 17:18:50
Priority: Normal
Type: Note

8-Apr-2020

Putting remdesivir to the test for COVID-19

American Chemical Society

As the coronavirus pandemic claims lives and overwhelms health care systems throughout the world, scientists are closely watching several late-stage trials of the antiviral drug remdesivir. Developed to treat Ebola, remdesivir is now being tested against COVID-19. However, many infectious disease experts caution that the trials are unlikely to yield clear-cut results, according to an article in *Chemical &Engineering News* (C&EN), the weekly newsmagazine of the American Chemical Society.

Gilead Sciences discovered remdesivir during the 2014 Ebola outbreak in West Africa. Although the drug was not effective in treating late-stage Ebola, it was shown to be fairly safe, Senior Correspondent Lisa Jarvis writes. Remdesivir blocks an enzyme called RNA polymerase that the Ebola virus -- and other RNA viruses, including SARS-CoV-2 -- uses to replicate. Scientists have already shown in lab experiments and animal studies that the drug can help treat and prevent infections of the coronaviruses that cause SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome). Despite hints that remdesivir could also kill SARS-CoV-2, results from current clinical trials will likely be difficult to interpret, experts say.

Of the five Phase III studies testing remdesivir against COVID-19, two began in China in early February, one in the U.S. in February and two more in the U.S. in March. Because four of the five studies enrolled patients with moderate-to-severe diseases, which are more difficult to treat than milder cases, a failure of the drug in these trials doesn't necessarily mean it wouldn't work for patients treated earlier in the course of infection. Although the U.S. Food and Drug Administration typically takes 6-12 months to approve new drugs, the process will likely be expedited if results from these clinical trials look promising, according to experts.

###

The article, "What can initial remdesivir data tell us about tackling COVID-19?," is freely available here.

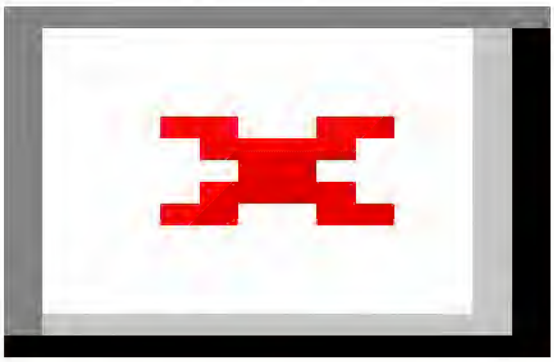
Disclaimer: Any third-party material in this email has been shared for internal use under fair use provisions of U.S. copyright law, without further verification of its accuracy/veracity. It does not necessarily represent my views nor those of NIAID, NIH, HHS, or the U.S. government.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/08 17:18:41
Delivered Date:	2020/04/08 17:18:50
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Novartis Launches Phase III Study of Hydroxychloroquine in COVID-19 Patients
Date: 2020/04/20 09:43:04
Priority: Normal
Type: Note

Novartis Launches Phase III Study of Hydroxychloroquine in COVID-19 Patients

Published: Apr 20, 2020 By Alex Keown



Hydroxychloroquine Pills

Swiss pharma giant **Novartis** will **launch a Phase III trial** assessing hydroxychloroquine for the treatment of hospitalized patients with COVID-19 disease. The trial will be conducted at more than a dozen sites across the United States.

Novartis said this morning that it plans to begin study enrollment of the 440 patient trial over the next few weeks and is committed to reporting results as soon as possible. Novartis' generic subsidiary Sandoz manufactures hydroxychloroquine for use as a treatment for malaria, lupus and rheumatoid arthritis and will supply the drug for the trial. Hydroxychloroquine is a drug that has been touted by President Trump as a "game-changer" in the fight against COVID-19, the disease caused by the novel coronavirus supported by anecdotal evidence of patient response to the drug. As a result of the anecdotal evidence and the hope that the drug will benefit patients, Novartis earlier this year agreed to donate up to 130 million tablets of hydroxychloroquine to support other studies of the drug, as well as compassionate use programs in hospitals. To achieve broad access to hydroxychloroquine as quickly as possible in these extraordinary circumstances, Novartis said it will make any intellectual property within its control that

relates to the use of hydroxychloroquine in COVID-19 available through non-exclusive voluntary licenses, appropriate waivers, or similar mechanisms.

John Tsai, chief medical officer at Novartis and head of its Global Drug Development program, said the company recognizes the importance of clinically determining whether or not hydroxychloroquine will be beneficial for patients with COVID-19 disease.

Novartis is not the only company or organization running a clinical trial for hydroxychloroquine against COVID-19. The University of Minnesota and the University of Washington are **conducting studies**, as is the National Institutes of Health. Last week, a **study in China** showed that hydroxychloroquine did not help patients clear the virus better than standard care.

In the Novartis study, patients will be randomized into three groups. The first group or arm will receive hydroxychloroquine. The second group will receive hydroxychloroquine in combination with azithromycin, an antibiotic therapy that has been given to many COVID-19 patients along with the malaria drug. The third group will receive a placebo. Patients in all treatment groups are receiving standard of care for COVID-19.

Other companies are also studying older medications against COVID-19, including Roche, Gilead Sciences, Incyte and more. On Friday, BioSpace reported that there were signs from a study of Gilead's remdesivir, an Ebola drug, which was effective in treating COVID-19. While the study was small and caution has been urged about reading too much into the results, the drug **appeared to benefit** the COVID-19 patients in a small University of Chicago study.

In addition to the Phase III hydroxychloroquine study for COVID-19, Novartis plans to sponsor or co-sponsor clinical trials to study Jakafi (ruxolitinib), a drug co-developed with Incyte, and Ilaris (canakinumab) for hospitalized patients with COVID-19 infections. **Incyte** told BioSpace this morning that Jakafi will specifically be studied in patients with COVID-19 associated cytokine storm, a severe immune response where the immune system begins to attack the body and healthy cells rather than the virus.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/04/20 09:41:07
Delivered Date:	2020/04/20 09:43:04
Message Flags:	Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: Houston Chron: UTMB once helped defeat Ebola. Can it replicate that success with coronavirus?
Date: 2020/04/02 09:43:33
Priority: Normal
Type: Note

UTMB once helped defeat Ebola. Can it replicate that success with coronavirus?

Photo of Nick Powell

Nick Powell April 1, 2020 Updated: April 1, 2020 6:13 p.m.

Dr. Scott Weaver is the director of the Institute for Human Infections & Immunity at University of Texas Medical Branch at Galveston. He is currently tasked with managing nearly two dozen research projects dedicated to the novel coronavirus outbreak.

1of76Dr. Scott Weaver is the director of the Institute for Human Infections &Immunity at University of Texas Medical Branch at Galveston. He is currently tasked with managing nearly two dozen research projects dedicated to the novel coronavirus outbreak.Photo: University of Texas Medical Branch at Galveston

Dr. Scott Weaver is the director of the Institute for Human Infections & Immunity at University of Texas Medical Branch at Galveston. He is currently tasked with managing nearly two dozen research projects dedicated to the novel coronavirus outbreak. 2of76Dr. Scott Weaver is the director of the Institute for Human Infections &Immunity at University of Texas Medical Branch at Galveston. He is currently tasked with managing nearly two dozen research projects dedicated to the novel coronavirus outbreak.Photo: University of Texas Medical Branch at Galveston

3of76People observe various degrees of social distancing along Buffalo Bayou, Wednesday, April 1, 2020, at Eleanor Tinsley Park in Houston.Photo: Mark Mulligan, Staff photographer

• •

• ••

•• •• •• •• •• •• •• •• •• •• •• •• •• Two years after Ebola ravaged parts of West Africa, the deadly virus in 2018 was making a comeback in the Democratic Republic of the Congro.
Researchers at the University of Texas Medical Branch in Galveston sprang into action, reverse engineering the construction of a new vaccine and delivering 7,500 doses of it to the central African country for widespread use, all within 72 hours.
It was, in the words of Ben Raimer, interim president of UTMB, a "proud" moment for the university system, a collaborative effort that yielded life-saving results. Raimer cautioned, however, against the unrealistic expecations the Ebola success may have created for university researchers now grappling with the nuances of the far more complex novel coronavirus.

"We're not a 72-hour virus maker here at UTMB," Raimer said. "We've done it one time for Ebola, but it's not likely for this virus until we get a better understanding on how it functions in its various forms."
Public health experts generally predict that a coronavirus vaccine will take much longer and won't be ready for at least 12 to 18 months from the first known infection in late December. Whilemore than 20 vaccine candidates are in development, most are in the early stages, well before clinical trials.
Uncertainty over the timeline has led to an unquenchable thirst for any morsel of good news regarding progress researchers have made in understanding how the virus attacks humans.
Scott Weaver understands this reality better than most. As the director of UTMB's infectious disease research programs, Weaver is tasked with helping manage nearly two-dozen projects related to the coronavirus, from macro initiatives like vaccine and antiviral treatment to more nuanced efforts such as why the virus affects people who smoke or vape more acutely.
For now, vaccine development is moving at a slower pace than Ebola, Weaver said, though he is hopeful that a previously developed SARS vaccine will prove effective.
One of the primary projects capturing the attention of UTMB scientists is testing antiviral drugs to treat the symptoms of the coronavirus, Weaver said. The drugs currently being tested were developed for other viral infections or non-infectious diseases, such as remdesivir, which was used to combat Ebola infections.
Both President Trump and the World Health Organization have highlighted remdesivir as a promising coronavirus treatment, though clinical trials are still ongoing to determine how effective the drug can be. UTMB has a clinical trial set up in the coming weeks to test remdesivir in Galveston County coronavirus patients.
"In the middle of an outbreak like this, there are going to be so many people who are hospitalized and eligible for these clinical trials that we'll learn very quickly whether (remdesivir) has efficacy or not," Weaver said. "I think that's really the best prospect for an improvement in patient care in the near future."
Tapping into funding sources to continue vaccine research is a bigger problem. One of the major differences between Ebola in 2018 and coronavirus that contributed to how quickly UTMB was able to develop a vaccine was the sustained funding for Ebola research. Besides the SARS outbreak in the early aughts and MERS in 2012, coronaviruses typically don't attract the same interest.
"It's much harder to get funding, especially commercial interest, in the coronavirus vaccine," Weaver said. "Unfortunately, that means we don't have as much to start from. There were some vaccines that were developed. They never went very far down the pipeline towards clinical trials, but at least we're not starting completely from scratch."
Now more than ever people need to be aware of COVID-19 symptoms and the proper way to treat the illness. Take a look at how to differentiate coronavirus vs. allergies, and hear a few words of advice from Dr. Peter Hotez with the Baylor College of Medicine.
Video: Laura Duclos/Houston Chronicle
The SARS vaccine, developed by researchers at Baylor College of Medicine and UTMB researchers, effectively protected mice against SARS, or severe acute respiratory syndrome, the pneumonia-causing virus from the same family a coronavirus that spread in the early 2000s. The vaccine never progressed to human testing because manufacturing of it wasn't completed until 2016, long after SARS had burned out.
Weaver noted two key challenges to completing work on the SARS vaccine: the genetically-altered laboratory mice used to test this vaccine had to be recreated from scratch; and funding sources, particularly from commercial interests, are hard to come by.
UTMB has cleared one hurdle. The transgenic mice embryos used for the original vaccine were recently implanted into female and male mice, and the first offspring were born several weeks ago. Of course,

even after these mice are used to test vaccine candidates, those vaccines will have to be tested on non-human primates before the FDA will consider permission for clinical trials in people.
But even if UTMB does not win the vaccine arms race, the university's coronavirus research has already made a significant difference in understanding the virus's complexities.
"We have here three virologist faculty scientists who focus their work on coronavirus, so we were well prepared to gear up very quickly to do research on this virus," Weaver said.
Indeed, at the outset of the viral outbreak, UTMB developed a reverse genetic system to manipulate the virus genome. The Galveston National Laboratory at UTMB, a high-security biocontainment lab, was one of three labs in the country to get the coronavirus isolate in February after the Centers for Disease Control worked on the first virus sample in Washington state and cultured it in Atlanta.
Pei-Yong Shi, a professor of human genetics at UTMB, led this effort, which allows scientists to essentially recreate the virus from scratch.
"We can understand the mutations and history of the virus. We will be able to manipulate the virus, to understand which regions are causing the disease so we can make vaccines and therapeutics," Shi said.
The UTMB genetic system played a vital role in helping develop badly needed diagnostic tests. The university's World Reference Center for Emerging Viruses and Arboviruses stockpiled the viral RNA — the genetic material needed to optimize tests for federal approval.
"There was a time period in late February where we were literally the only laboratory in the world providing these RNA samples for diagnostic (test) development," Weaver said. A lot of the big companies that you see now are starting to scale up diagnostics - like LabCorps and Quest and many of the big hospitals including some in Houston and here in Galveston - we provided that critical RNA to them so they could get their tests up and running as quick as possible."
But for as much work is being done behind the scenes in the race to cure and treat the coronavirus, Weaver said the immediate outcome and toll of this pandemic will be determined by public health measures such as social distancing.
"One person on average transmits the virus to 3 or 4 additional people and if one of those is a high-risk person, they may die, if one of those is a healthcare worker, they may spread it to many more people," Weaver said. "I just hope that everyone takes this very seriously."
nick.powell@chron.com

Sender: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date: 2020/04/02 09:42:58
Delivered Date: 2020/04/02 09:43:33
Message Flags: Unread

From: Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Subject: GHTC COVID-19 R&D Tracker https://bit.ly/2JfQ0zH
Date: 2020/03/25 17:23:59
Priority: Normal
Type: Note

...

US Government R&D Efforts

Soon after the virus was isolated, scientists in China sequenced its genome and made that sequence accessible for researchers around the world. Almost immediately, the US government stepped into action, investing in R&D and establishing partnerships to develop diagnostics, therapeutics, vaccines, and other tools to counter COVID-19. GHTC is tracking these efforts in the table below. Click here to access a full version of this table sortable by type of product, funder, etc.

1 COVID-19: US Government-supported R&D Efforts : Tracker

2 BARDA	Diagnostic	Accula COVID-19 point-of-care test	Anticipated EUA consideration in May	Mesa Biotech	BARDA is funding the final stages of Mesa Biotech's diagnostic before the company submits an EUA to FDA. The Accula COVID-19 diagnostic "requires minimal sample handling and a 30-minute sample-to-result time."	3.18.2020
3 BARDA	Diagnostic	Simplexa COVID-19 Direct Assay (anticipating EUA consideration by end of April)	Anticipated EUA consideration by end of April	DiaSorin Molecular	DiaSorin Molecular's test will use a nasopharyngeal swab and will used Diasorin Molecular's Simplexa Direct technology, which is FDA-cleared for influenza and RSV tests. The	3.13.2020

						test would run on an instrument that is in use across commercial and hospital laboratories across the country.	
4 BARDA	Diagnostic	QIAstat-Dx RPS2	Anticipated EUA consideration by June	QIAGEN		The QIAstat-Dx RPS2 diagnostic will run on the QIAstat-Dx Respiratory Panel, which is used to run FDA-cleared tests for 21 respiratory pathogens. The test is anticipated to only take an hour and will distinguish SARS-CoV-2 from other pathogens.	3.13.2020
5 BARDA	Diagnostic	High-throughput coronavirus molecular diagnostic	In development	Hologic		Hologic is using its Panther Fusion system, which has FDA-cleared tests for other respiratory infections, to develop a rapid diagnostic capable of processing up to 1,000 samples per day with results in less than three hours.	3.11.2020
6 BARDA	Therapeutic	Monoclonal antibody-based treatment	Pre-clinical (trials expected in	Regeneron/Sanofi		Based on the same technology that	3.17.2020

			early summer)		Regeneron used to develop antibodies that were effective against Ebola virus. Kevzara was approved by FDA in 2017 to treat severe rheumatoid arthritis and	
7 BARDA	Therapeutic	Kevzara (sarilumab)	Phase II/III	Regeneron/Sanofi	has entered a clinical trial with 400 patients to look for efficacy against COVID-19.	3.16.2020
8 BARDA	Therapeutic	Treatment	Pre-clinical	Janssen Pharmaceuticals (Johnson &Johnson)	Janssen is working with BARDA and other partners to screen its library of antiviral molecules to look for potential treatments.	2.11.2020
9 BARDA	Vaccine	S protein (baculovirus production)	Pre-clinical	Sanofi Pasteur (Protein Biosciences, biotech acquired by Sanofi)	Sanofi Pasteur previously worked to develop a SARS vaccine, and is using the recombinant DNA platform that is already used to manufacture its flu vaccine.	2.18.2020
10BARDA	Vaccine	Recombinant adenoviral vector vaccine	Pre-clinical	Janssen Pharmaceuticals (Johnson &Johnson)	The partnership will use Janssen's AdVac and PER.C6	2.11.2020

						technology that was used to develop and manufacture Janssen's investigational Ebola Vaccine and its Zika, RSV, and HIV vaccine candidates (source).	
11	CDC	Diagnostic	CDC 2019-nCoV Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel	Developed	FDA	CDC submitted an EUA package to FDA on Feb 3, 2020 before shipping the diagnostic to public health labs across the country. Many labs experienced issues validating the test, and CDC has worked closely with FDA to resolve these issues.	
12	DoD/DARPA	Antibody-based prevention technology	Antibody-based preventative technology	Pre-clinical	n/a	This antibody-based health technology is based on antibodies from patients who have survived the virus would provide temporary protection (several months) to at-risk individuals while a vaccine is still in development.	3.05.2020

13	DoD/WRAIR/USAMRIID	Vaccine	S protein	Pre-clinical	n/a	The development of this vaccine is based on previous research for Middle East Respiratory Syndrome.	3.13.2020
14	FDA	All	Regulatory Approval	n/a	Many	FDA is working closely with US agencies, the private sector, and the public sector to provide EUAs as quickly and safely as possible. See this link for updates on what FDA is doing for Coronavirus.	
15	NIAID	Diagnostic	RT-PCR diagnostic	Protocol available	University of Hong Kong	CEIRS researchers at the University of Hong Kong developed this RT-PCR test. The protocol is now publicly available through WHO.	3.03.2020
16	NIAID	Diagnostic	Enzyme-linked immunosorbent assay	In development	n/a	NIAID scientists are developing reagents for this type of assay.	3.03.2020
17	NIAID	Therapeutic	Remdesivir	Phase II	University of Nebraska Medical Center	Remdesivir is a broad-spectrum antivral compound originally developed by Gilead Sciences as an Ebola and	2.25.2020

18NIAID	Therapeutic	AT-100	Pre-clinical	Airway Therapeutics	Marburg virus treatment. AT-100, also known as recombinant human surfactant protein D (rhSP-D), has been shown effective against a range of respiratory diseases and is now being evaluated against COVID-19.	3.14.2020
19NIAID	Therapeutic	Monoclonal antibody (mAb)-based treatment	Pre-clinical	Vir Biotechnology Inc.	Vir will work with NIAID to identify and optimize antibody combinations against several coronaviruses, including SARS-CoV-2.	3.11.2020
20NIAID	Therapeutic	PCR-based assays	In development	n/a	NIAID-supported investigators are developing PCR-based assays for preclinical studies and product development.	3.03.2020
21NIAID	Therapeutic	SAB-301	Phase I (for MERS)	n/a	SAB-301 is an "experimental MERS treatment developed from cattle that make human antibodies," and might be	1.31.2020

22NIAID	Therpeutic	Kaletra and interferon-beta	Pre-clinical	n/a	used to treat COVID-19. NIAID is evaluating Kaletra, also known as lopinavir and ritonavir, and interferon-beta for their activity against COVID-19.	1.31.2020
23NIAID	Vaccine	SARS recombinant protein vaccine	Pre-clinical	Baylor College of medicine	This experimental SARS (SARS-Cov) vaccine is being evaluated for efficacy against SARS-CoV-2	3.03.2020
24NIAID	Vaccine	REGN3048 and REGN 3051 combination	Phase I (for MERS)	n/a	The REGN3048 and REGN 3051 combination is in phase I clinical testing and might be used to treat COVID-19.	1.31.2020
25NIAID	Vaccine	RNA vaccine	Pre-clinical	University of Washington	RML researchers are collaborating with the University of Washington to do early-stage testing of an RNA vaccine	3.03.2020
26NIAID/CEIRS	Diagnostic	mRNA-1273	Phase I	Moderna, CEPI, and KPWHRI	NIAID scientists began development on mRNA-1273, an LNP-encapsulated mRNA vaccine, within days of receiving the SARS-CoV-2 genetic	3.16.2020

					sequence. The Phase I study was launched 65 days after research began, a record speed.
27NIAID/RML	Vaccine	ChAdOx1	Pre-clinical	University of Oxford	Chimpanzee adenovirus-vectored vaccine. Platform also used for influenza, TB, Chikungunya, Zika, MenB, plague.

Acronyms: **BARDA** (Biomedical Advanced Research and Development Authority); **CEPI** (Coalition for Epidemic Preparedness Innovations); **DoD** (Department of Defense); **EUA** (FDA Emergency Use Authorization); **FDA** (Food and Drug Administration); **KPWHRI** (Kaiser Permanente Washington Health Research Institute); **NIAID** (National Institute for Allergy and Infectious Diseases); **NIH** (National Institute of Health); **RML** (Rocky Mountain Laboratories; **WRAIR** (Walter Reed Army Institute for Research); **USAMRIID** (US Army Medical Research Institute of Infectious Diseases)

US government agencies and their partners are coordinating closely to develop new tools against this pandemic. This efficient R&D coordination and collaboration is based on a global health R&D ecosystem strengthened by years of US government investment. Within this ecosystem, each US agency lends unique expertise to the development of new tools to diagnose, treat, and prevent global health diseases, including COVID-19:

- • The National Institute of Health (NIH), and specifically the National Institute of Allergy and Infectious Disease (NIAID), is taking the lead role in COVID-19 R&D efforts. Thanks to research investments into the SARS and MERS outbreaks, NIAID scientists and partners are better prepared to develop diagnostics, therapeutics, and vaccines against COVID-19.
- • The Centers for Disease Control and Prevention (CDC) is the world's lead organization in outbreak tracking and response. In record time, CDC rapidly developed a diagnostic test that has been shipped to public health labs across the US and continues to lead diagnostic efforts.
- • The Biomedical Advanced Research and Development Authority (BARDA) is designed to bridge the "valley of death" between basic science and clinical development of new products, partnering with the private sector to develop and bring new tools to market. BARDA has created a centralized portal for organizations looking to partner to develop new tools for COVID-19.
- • The Department of Defense (DoD) works across the R&D pipeline, from basic research to late-stage development. It has the unique flexibility to make high-risk, high-reward investments.
- • The US Agency for International Development (USAID) has created product-development partnerships to develop new tools for low- and middle-income countries. Over the last decade, USAID has invested in lab capacity strengthening, infectious disease surveillance networks, and

global health security around the world, preparing countries for a pandemic like the one we're facing.

Sender:	Folkers, Greg (NIH/NIAID) [E] <gfolkers@niaid.nih.gov>
Sent Date:	2020/03/25 17:23:12
Delivered Date:	2020/03/25 17:23:59
Message Flags:	Unread