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新型冠状病毒肺炎诱发肺纤维化的机制及相关治疗研究进展

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【摘要】 2019年12月暴发于中国武汉的新型冠状病毒肺炎（COVID-19）与2003年暴发于中国广州的严重急性呼吸综合征（SARS）是由同源性较高的高致命性冠状病毒导致的。新型冠状病毒传播性强、进展迅速，在全球范围内造成不良的社会影响和巨大经济损失，但目前尚无针对COVID-19的疫苗或特效药物。肺纤维化是一种进行性纤维化的肺部疾病，是导致SARS幸存者愈后肺功能障碍及生存质量下降的主要因素。大量流行病学、病毒免疫学及目前的临床证据支持肺纤维化有可能成为COVID-19患者的严重并发症之一。目前暂无关于COVID-19引发肺纤维化的机制的报道，本文就现有理论依据重点讨论COVID-19肺部持续损伤的可能机制、异常免疫机制在引发和促进肺纤维化中的关键作用以及相关治疗措施。

【关键词】 肺纤维化；　细胞因子类；　免疫系统；　新型冠状病毒肺炎；　急性呼吸窘迫综合征

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Advances in the research of mechanism of pulmonary fibrosis induced by Corona Virus Disease 2019 and the corresponding therapeutic measures

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[**Abstract**] The Corona Virus Disease 2019 (COVID-19) outbroke in Wuhan, China in December 2019 and the severe acute respiratory syndrome (SARS) outbroke in Guangzhou, China in 2003 were caused by highly pathogenic coronaviruses with high homology. Since the 2019 novel coronavirus has strong transmissibility and progress rapidly. It has caused negative social effects and massive economic damage on a global scale. While there is currently no vaccine or effective drugs. Pulmonary fibrosis is a pulmonary disease with progressive fibrosis, which is the main factor leading to pulmonary dysfunction and quality of life decline in SARS survivors after recovery. Extensive epidemiological, viral immunological, and current clinical evidences support the possibility that pulmonary fibrosis may be one of the major complications in COVID-19 patients. Although there are no reports on the mechanism of COVID-19 inducing pulmonary fibrosis, based on the existing theoretical basis, we focus on the possible mechanism of COVID-19 sustained lung damaging, the key role of abnormal immune mechanism in the initiation and promotion of pulmonary fibrosis, and the corresponding therapeutic measures.

[Key words] Pulmonary fibrosis; Cytokines; Immune system; Corona Virus Disease 2019; Acute respiratory distress syndrome

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On March 11, 2020, the World Health Organization (WHO) announced that the new coronavirus pneumonia (COVID-19) epidemic constituted a "global pandemic" [1]. According to the daily epidemic report on the WHO official website, as of March 14, 2020, COVID-19 had 142,539 confirmed cases worldwide, affecting 135 countries, territories and regions other than China [2], in the world Cause adverse social impact and huge economic losses . There is a lot of evidence to support COVID-19 can cause pulmonary fibrosis [3]. Most survivors of severe acute respiratory syndrome (SARS) have varying degrees of fibrosis in the lungs [4]. The cause of pulmonary fibrosis is currently unclear. The abnormal immune response caused by the new coronavirus, especially non-specific immunity, can Induced cytokine storm [5], lung injury caused by lung epithelial cells and microvascular endothelial cells damage, tissue cell damage caused by ischemia and hypoxia, combined with mechanical ventilation is the main treatment of severe COVID-19 complications ARDS Means may increase lung damage. If these causes cannot be cleared in time, it will lead to continuous inflammation and damage to lung tissue and the development of pulmonary fibrosis. Therefore, pulmonary fibrosis may become a complication after the outbreak of this outbreak. This article focuses on the analysis of the continuous lung injury during the course of COVID-19, which may be the main cause of pulmonary fibrosis. The abnormal immune response plays a key role in promoting pulmonary fibrosis. Fibroblasts (Fb) are the source and function of pulmonary fibrosis effector cells. Provide more ideas and strategies for the current treatment of COVID-19, guide physicians to formulate more beneficial treatment measures for patients, and reduce complications and mortality through early intervention.

1 Pulmonary fibrosis may be an important complication affecting the quality of life of patients with COVID-19

Pulmonary fibrosis is a pathological result of chronic inflammation in the lungs caused by different reasons. The pathophysiology is that abnormally activated alveolar epithelial cells produce cellular mediators to induce Fb recruitment and conversion into muscle Fb, causing lung tissue and airway contraction and reducing lung compliance. ; Excessive deposition of a large amount of ECM leads to progressive destruction of the lung structure and scar formation [6]. Idiopathic pulmonary fibrosis (IPF) refers to pulmonary fibrosis of unknown etiology and is the main manifestation of pulmonary fibrosis. The clinical manifestations of IPF are progressive current dyspnea. The terminal stage is characterized by severe pulmonary hypertension with pulmonary heart disease. About 40% of IPF patients eventually die of respiratory failure, and the 5-year survival rate (20%) is low [7]. In this epidemic, biogenic continuous lung injury from viruses and iatrogenic continuous lung injury from mechanical ventilation may be important causes of pulmonary fibrosis.

Viral pneumonia often causes IPF, the exact mechanism of which is not yet clear, and often leads to irreversible restrictive lung function deterioration and death. At present, the clinical manifestations and severity of the COVID-19 epidemic in China are very similar to SARS[1]. The new coronavirus has a certain affinity with SARS virus, the two share 79.5% of the gene sequence[2], and both target human spike protein recognition angiotensin converting enzyme 2 (ACE2) receptor as the target and enter human mucosal epithelium Cells are replicated[3]. Some scholars have observed in the lung specimens of two patients with lung adenocarcinoma undergoing lobectomy combined with novel coronavirus infection. The early pathological changes of COVID-19 lungs were manifested as viral interstitial pneumonia, and the lungs showed diffuse alveolar injury. Pulmonary edema is more prominent[4]. It is suggested that patients with mild COVID-19 with early infection, even after the condition improves and are discharged from the hospital, have the potential to further progress to pulmonary fibrosis. According to a meta-analysis of 50,466 COVID-19 hospitalized patients, 14.8% of COVID-19 patients had ARDS[5], which was lower than 20% of SARS patients[6]; ARDS survivors often had pulmonary fibrosis , And 36% and 30% of SARS patients develop pulmonary fibrosis 3 and 6 months after infection[7]. Therefore, patients with light and heavy COVID-19 have the potential to progress to pulmonary fibrosis.

In addition, a large number of COVID-19 patients with ARDS and SARS patients require mechanical ventilation to maintain respiratory function, and mechanical ventilation-related lung injury is a major adverse reaction caused by the ventilator to patients[8]. The harmful effects of mechanical ventilation are not only mediated by the systemic release of local inflammatory cytokines, but also the cellular molecular mechanisms of lung injury caused by mechanical stress. Gurkan et al[9] pointed out that the lung injury caused by mechanical ventilation can become the second blow secondary to acute lung injury (ALI), aggravating ALI and inducing pulmonary fibrosis. The underlying mechanisms of these changes may be epithelial-mesenchymal transition (EMT) and the release of pro-fibrotic mediators caused by cell stretching and mechanical ventilation[10].

2 Continued damage to lung tissue is the key cause of pulmonary fibrosis

Fb recruitment and collagen deposition are the body's inherent response to tissue repair and repair and protection against the invasion of potential foreign pathogenic microorganisms. When the cause of tissue damage cannot be removed in time, resulting in continuous tissue damage, tissue fibrosis will eventually develop. In addition to the lung damage caused by the virus itself, COVID-19 also plays an extremely important role.

2.1 Specific immune injury

The body-specific acquired immunity against virus clearance is mainly divided into the following two categories: humoral immunity based on B lymphocytes that produce high-potency specific antiviral antibodies and cells based on CD8 + T cells that kill virus-infected cells Immunization. Among them, specific humoral immunity prevents the virus from spreading by neutralizing the virus, and mediates the efficient killing of the virus by phagocytes. It is the most efficient mechanism for the body to directly remove the virus. Although specific cellular immunity cannot directly kill the virus, it is mainly responsible for removing the cells infected with the virus, which is an important mechanism for the body to completely remove the virus. Both humoral immunity and cellular immunity work together to eliminate viruses. If the cellular immune function is low, the patient will become an asymptomatic virus carrier; however, due to various reasons that cause the body's humoral immunity to the virus to be impaired or inadequate, the virus will continue to infect normal cells, resulting in continuous strengthening of cellular immunity, resulting in tissue Continuous damage. Some viruses can even escape the body's entire specific immune response attack. As observed in the study of SARS virus, SARS virus can effectively induce Th1 and Th2 type immune responses in in vitro cell culture experiments, which indicates that SARS virus uses a special mechanism Cellular and humoral immune escape and even suppression have occurred [· ·], which has increased the damage of non-specific immune response to tissues and increased the risk of tissue fibrosis, although the mechanism of this phenomenon is currently unknown.

2.2 Non-specific immune injury

Corresponding to acquired immune specific killing virus and virus-infected cells, the body's natural immune cells can directly kill the virus in two ways: one is to directly recognize, engulf, and kill the virus through non-specific receptors on the surface of the cell membrane. (Comparative antibodies mediate the phagocytosis of cells); the other is to secrete a large amount of active substances and inflammatory mediators to kill the virus and infect the cells indifferently, but this method will also damage normal tissue cells and cause tissue damage. Corresponding to acquired immunity, normal cell infection is blocked by specifically neutralizing virus particles. On the one hand, natural immune cells secrete inflammatory mediators to induce blood vessels around injured tissues to form thrombi to block viral bloodborne transmission, and on the other hand, induce Fb to affect affected tissues. It is partially wrapped to restrict the virus from quickly infecting other normal tissue cells, so as to gain time for the body to develop efficient and specific immunity. In the autopsy report of the COVID-19 deceased, transparent thrombosis in the alveolar septal vessels, hemorrhagic infarction in the lung tissue, and pulmonary interstitial fibrosis and other pathological changes can confirm this. When the specific immune response to virus clearance is low or obstacles, the body will

compensatively continue to strengthen the non-specific immunity with low virus removal efficiency, resulting in continuous tissue damage and increasing fibrosis [ ].

The new coronavirus combined with ACE2 quickly entered the cell for replication and proliferation [ ]. Generally, after the virus enters the human body, non-specific immunity will be initiated immediately before specific immunity, mainly mediated by natural immune cells such as macrophages, natural killer cells and γδT cells [ ], which can directly pass the pathogen-related molecular model (PAMP) Recognize viruses, TNF-α, γ interferon, LPS and other factors induce macrophage activation and secrete a large number of pro-inflammatory factors (such as TNF-α, IL-1β, IL-12, IL-23 and granulocyte-macrophage Colony stimulating factors, etc.), further induce the recruitment of circulating mononuclear macrophages and neutrophils to the lungs to amplify inflammation, by generating a larger amount of the above-mentioned proinflammatory factors and reactive oxygen species and other non-specific killing viruses, virus infection cells As well as normal tissue cells, causing secondary tissue damage, inducing pulmonary microvascular endothelial cells and alveolar epithelial cells and apoptosis [ ], strengthening Fb recruitment, muscle Fb transformation, collagen deposition, and airway remodeling [ ].

2.3 Cytokine storm damage

Although the mechanism by which COVID-19 triggers a cytokine storm is unclear, the specific immune killing function and the nonspecific immune response hyperactivity caused by the virus-specific immune response, especially the humoral immunity may cause the cytokine storm Plays a key role in [ ]. Huang et al. [ ] observed IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon-gamma-inducible protein 10, monocyte chemoattractant protein, macrophage in the plasma of COVID-19 patients in ICU The expression levels of cytokines, such as inflammatory proteins and TNF-α, increased significantly, showing a high level of non-specific immune response. Wan et al. [ ] observed low levels of CD4 + T cells and CD8 + T cells in COVID-19 severe patients , but higher levels of IL-6; Xu et al [ ] performed flow cytometry on peripheral blood of COVID-19 deceased Cytological examination should also confirm this. Although the patient's CD4 + T cells and CD8 + T cells were greatly reduced, they were abnormally activated, manifested by an increase in Th17 and excessive activation of CD8 + T cells, suggesting that the specific immune killer function is compensatory. Enhanced.

Therefore, the impact of the new coronavirus on the body mainly comes from the imbalance of the proportion of cytokines produced by the body in response to the abnormal immune response induced by the virus invasion. In this process, lung epithelial cells and alveolar microvascular endothelial cells become the target organs attacked by inflammatory mediators, causing the

characteristic damage of ARDS[ ]. First, the vasoconstriction after vascular endothelial cell damage and activation of inflammatory mediators increases capillary permeability and is the main site leading to leakage of blood and inflammatory factors[ ]; leaked protein-rich fluids enter the alveoli and Interstitial, causing interstitial and alveolar edema, destroying the permeability of the alveolar epithelial barrier, and reducing the alveolar surfactant, leading to alveolar collapse and atelectasis. During the above process, lung epithelial cells and vascular endothelial cells were largely destroyed. Second, tissue ischemia and hypoxia aggravate lung injury. Leakage of interstitial fluid leads to pulmonary alveolar and pulmonary interstitial edema, decreased alveolar surfactant, and then lung atrophy, resulting in reduced oxygen diffusion and impaired ventilation / blood flow ratio, which aggravates lung ischemia and hypoxia. Therefore, patients with severe COVID-19 generally show progressive hypoxemia, and a large amount of jelly-like mucus is observed in the lung pathological specimens of COVID-19 deceased[ ], which explains why a large number of patients even Flux mechanical ventilation is also difficult to improve hypoxemia[ ]. It has been reported that the hypoxic environment can also promote the progress of fibrosis through EMT[ ]. Furthermore, the hypoxic state not only directly causes lung tissue damage, but also aggravates inflammation and oxidative stress. Oxygen free radicals increase during inflammation, and the body cannot produce enough superoxide dismutase and catalase to remove them in time, thus aggravating the above-mentioned damage[ ]. In addition, mechanical ventilation promotes the release of local inflammatory factors throughout the body, and mechanical stress can also cause secondary lung damage through the inflammatory process. The above mechanism causes sustained lung damage before the condition improves. In the middle and late stages of ARDS, the lung tissue damage-repair mechanism is activated and fibrosis is formed. It has been reported that during the ARDS repair phase, collagen deposition and fibrosis-promoting levels increase, and Fb proliferates[ ].

3 Specific immunity and non-specific immunity play a key role in promoting pulmonary fibrosis

3.1 The role of specific immunity in pulmonary fibrosis

After the virus enters the lungs, it can activate CD4 · T cells through PAMP[ ] and bind to the Toll-like receptors of alveolar macrophages to differentiate them into Th cells and exert specific immune effects. Th cells are composed of two subgroups Th1 and Th2, and their characteristics are distinguished from different cytokine secretion patterns. Th1 secretes interferon-gamma, IL-2, TNF-o, granulocyte-macrophage colony-stimulating factor, etc., and promotes CD8 · T ceil activation to mediate cellular immunity. Th1-type cytokines are mainly pro-inflammatory cytokines, which are mainly responsible for specifically killing virus-infected cells in antiviral immunity. Th2 secretes IL-4,

IL-5, IL-6, IL-10, IL-13, etc. By inducing B lymphocytes to mature and mediate humoral immunity, it is mainly responsible for neutralizing and directly removing viruses in antiviral immunity. Th2-type cytokines have anti-inflammatory effects, of which IL-10 is an inhibitor of cytokine synthesis. These Th2 type cytokines such as IL-4, IL-6, and IL-13 can stimulate B lymphocytes to produce Ig, and also stimulate human Fb to synthesize collagen[ ]. In contrast, Th1-type cytokines such as interferon gamma and TNF-α inhibit Fb production of collagen in vitro[ ]. Under normal conditions, the two subgroups antagonize each other to form a negative feedback effect, keeping the cytokine network in a balanced state of low-level expression. Under pathological conditions, if Th1 / Th2 balance is at a high-level equilibrium state or biased to Th2, resulting in excessive Ig Increased deposition and fibroblast synthesis of collagen increase the risk of pulmonary fibrosis. Wallace et al.[ ]In 1995, the Th2 type immune response was observed to be dominant in the process of pulmonary fibrosis and the Th2 dominance theory of pulmonary fibrosis was proposed. Therefore, a high level of Th2-type immune response is an important factor that triggers pulmonary fibrosis.

In the antiviral immune response, Th2 helps B lymphocytes mature and secrete specific antiviral antibodies, effectively blocking the spread of the virus and efficiently mediated phagocytic cells to directly kill the virus, which is the most effective way for the body to remove the virus; while Th1 mainly activates CD8 + T cells, which effectively kill virus-infected cells, are an important means for the body to remove viruses hidden in cells. When the body develops a specific humoral immune deficiency or disorder against the virus, the virus transmission cannot be effectively controlled, resulting in the continuous enhancement of the cell killing effect mediated by the Th1 type immune response and continuous damage to the tissue. In order to cope with the continuous tissue damage and avoid the out-of-control Th1 type immune response, the body continues to passively compensate to enhance the antiviral and inefficient Th2 type immune response (it cannot induce effective antiviral humoral immunity). For example, serum levels of Th1 and Th2 cytokines can be significantly increased in the serum of patients with severe COVID-19[ ]. Therefore, the adverse reaction of Th2 cytokines to promote fibrosis has been significantly strengthened, and the risk of pulmonary fibrosis in patients with severe COVID-19 has been significantly increased.

3.2 The role of non-specific immunity in pulmonary fibrosis

After the new coronavirus comes into contact with ACE2, the nonspecific immune response mediated by macrophages participates in the first line of defense against the virus. Pulmonary macrophages are polarized into M1 macrophages under the induction of Th1 interferon and TNF-α, secreting IL-12, inducible NOS, TNF-α, IL-1β, IL-23, IL -6, chemokine ligand 10 (CXCL10) and other pro-inflammatory active substances and trace anti-inflammatory factor IL-10[ ]. These macrophages

have strong antimicrobial, degradative ECM, mediate tissue damage and trigger inflammation. If the M1 type response is not effectively controlled, the tissue will continue to be damaged.

Under the induction of IL-4, IL-10, IL-13 and other factors, the lung macrophages polarize into M2 macrophages [ ], which induces a Th2 type immune response while secreting a large amount of anti-inflammatory factor IL- 10. TGF-β, VEGF, platelet-derived growth factor. These anti-inflammatory factors can not only resist the pro-inflammatory effects produced by M1 macrophages, but also further promote the proliferation of Fb and make it secrete collagen, which promotes the progress of pulmonary fibrosis. Among them , the role of TGF-β_{1} is the most important. On the one hand, TGF-β_{1} can significantly induce the production of p3 - regulatory T cells of forkhead winged spiral transcription factor , inhibit Th1 / Th2 / Th17 type immune response and the secretion of related proinflammatory factors, Down-regulate the inflammatory response; on the other hand, TGF-β_{1} induces EMT, promotes the proliferation of lung tissue and EMT-derived Fb, and stimulates ECM deposition [ ]. Although circulating fibroblasts also have an effect on ECM deposition, circulating fibroblasts TGF-β_{1} exhibits resistance and cannot induce α-smooth muscle actin (α-SMA) after being induced by TGF-β_{1} Muscle Fb may not originate from circulating cells [ ]. Some scholars have observed elevated levels of pro-inflammatory factors IL-17, IL-6, and anti-inflammatory factors IL-10 and TGF-β_{1} in patients with COVID-19 [ ], Indicating that COVID-19 patients have high levels of pro-inflammatory factors and anti-inflammatory factors at the same time, and the body's cytokine network is at a high level of equilibrium. It is the main feature of the malignant outcome of severe COVID-19 patients and it is the cytokine storm. , The main cause of ARDS, MOF [ ]. Under normal conditions, the body's complex cytokine network has a strong buffering capacity, and sudden changes in a small number of cytokines will not affect the balance of the entire cytokine network; under certain pathological conditions, the body's entire cytokine network is at a high level The horizontal balance state may be that the sudden fluctuation of a certain cytokine will become the last straw to overwhelm the camel, breaking the balance and triggering a cytokine storm. Even if the balance is not broken, long-term exposure to this high-level cytokine balance will lead to pathological repair characterized by continuous damage to normal tissues and continuous repair of Fb, which eventually leads to tissue fibrosis.

4 Source and function of Fb during pulmonary fibrosis

At present, it is considered that the pathophysiological process of pulmonary fibrosis is an abnormal wound healing state. Abnormal Fb proliferation and accumulation of ECM proteins (such as collagen) have become the focus of recent research on pulmonary fibrosis [ ]. In the process of pulmonary fibrosis, Fb is its main effector cell, mainly derived from: (1) lung tissue itself [ ]. Fb in

lung tissue maintains the proliferation of lung epithelial cells by secreting derived factors, and epithelial cells control Fb proliferation through intercellular contact interaction. If the lung epithelium is severely damaged for a long time, it can lead to Fb proliferation and EMC deposition, which plays a major role in filling damaged tissues[ ]. (2) Peripheral circulation[ ]. Circulating fibrocytes transient state is a group of cells derived from the expression of CD14 + CD16 + of bone marrow stromal progenitor cells[ ]. In the case of inflammation, circulating fiber cells can be recruited to the affected area, converted into muscle Fb, and secrete ECM. Circulating fiber cells can act as antigen-presenting cells and angiogenic cells at the same time, participating in tissue inflammation and fiber repair processes. But the more important significance is that circulating fibroblasts are positively correlated with the degree of IPF fibrosis, which can reflect the degree of lung tissue fibrosis, indicating which IPF patients may face a greater risk of poor prognosis. Chemokine CXC subfamily receptor 4 (CXCR4) is the main chemokine receptor expressed on circulating fibroblasts in humans and mice. The levels of CXCL12 in the lung and plasma of patients with pulmonary fibrosis and the number of circulating pulmonary fibroblasts There is a direct correlation[ ]. Disruption of the phosphoinositide 3-kinase / protein kinase B / mammalian rapamycin target protein pathway inhibits the expression of lung-derived CXCL12 and fibroblast-derived CXCR4[ ]. Fibrosis provides some clues for intervention. (3) EMT. EMT refers to the transformation of fully differentiated epithelial cells into cells with mesenchymal morphology and function. In the process of pulmonary fibrosis, it refers to the mesenchymal transformation of alveolar epithelial cells. In a mouse model of bleomycin-induced pulmonary fibrosis, fibrotic lung tissue has up to 30% EMT-derived Fb[ ]. The transformed cell phenotype includes cell markers, reorganization of the skeleton, disappearance of adhesion, changes in ECM composition and migration ability. The main features of EMT are the decreased expression of epithelial phenotype proteins (such as mucin, epithelial cadherin, tight junction protein), and mesenchymal phenotype proteins such as fibroblast specific protein-1, neural cadherin, wave Protein, fibronectin and α-SMA increase[ ]. The EMT process, of TGF-beta] $_1$ plays an important role, which can be activated from EMT plurality of passages[ ]. In short, compared with Fb derived from lung tissue itself and peripheral circulating fibroblasts, EMT is more critical in the process of responding to inflammation and promoting fibrosis.

Fb apoptosis is essential for the outcome of pulmonary fibrosis. On the one hand, Fb apoptosis disorder leads to the continuous and dysregulation of lung tissue repair process, which eventually leads to tissue fibrosis; on the other hand, Fb apoptosis abnormality, collagen breakdown obstacles, normal lung epithelial progenitor cells can not proliferate to repair vacancies, restore tissue function. Although the current mechanism of this anti-apoptotic property is not yet clear, there is sufficient evidence to support this view. Compared with healthy people, the percentage of a-SMA

positive cells in the lung tissue cell suspension of IPF patients is higher, the expression level of type I collagen mRNA is higher, and the content of synthesized collagen is higher, and the growth rate of Fb decreases[ ]. After Moodley et al[ ] also observed a similar phenomenon, it was confirmed that Fb in IPF patients is resistant to Fas-induced Fb apoptosis compared with healthy people. Some scholars believe that the epithelial-mesenchymal interaction may induce some genetic or epigenetic changes, resulting in an anti-apoptotic Fb phenotype. Therefore, induction of Fb / muscle Fb apoptosis may be a target for the treatment of pulmonary fibrosis.

5 Treatment measures

In response to the above possible mechanism of COVID-19-induced pulmonary fibrosis, the author summarizes the following methods that can be used to prevent and treat pulmonary fibrosis while treating COVID-19, and provide a reference for physicians.

5.1 Cytokine inhibitory drugs

5.1.1 Tocilizumab (IL-6 inhibitor)

IL-6 is not only the main therapeutic target for the treatment of COVID-19 complicated with cytokine storm syndrome[ ], but also the profibrotic factor produced by Th2 type immune response. Studies have observed that Fb induces the conversion of Fb into muscle Fb by secreting IL-6, and promotes the development of pulmonary fibrosis[ ]. Tocilizumab is an IL-6 receptor antibody, and the "New Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Version 7)" (hereinafter referred to as "the program") issued by the National Health and Health Commission has used tocilizumab for the treatment of both lungs. People with extensive lesions and severe patients, and those with elevated IL-6 levels in the laboratory. However, there are many cytokines involved in the cytokine storm, and vigorously exploring other key cytokines is also a problem that researchers need to solve urgently. In addition, the "Proposal" recommends blood purification treatments such as plasma exchange, adsorption, perfusion, and blood / plasma filtration for heavy patients, which are also aimed at removing inflammatory factors to block the cytokine storm's damage to the body.

5.1.2 TGF-β_1 signaling pathway inhibitor

Pirfenidone is currently the only drug approved for treatment of IPF has worldwide, which reduces beta]-of TGF $_1$ expression, it is also possible by directly altering the expression of collagen, inhibit abnormal recruitment of ECM-producing cells and play Anti-fibrosis effect[ ]. Ifenidone, an analogue of pirfenidone, also entered Phase I clinical trials in 2017. Arsenic trioxide has been used as a medicine for the treatment of diseases such as ulcers, psoriasis and malaria for more than 2,000

years[ ]. Studies have shown that arsenic trioxide inhibits TGF-β 1 signaling by inhibiting the phosphorylation of Smad2 / Smad3 and protein kinase B. In a mouse model of bleomycin-induced pulmonary fibrosis, it was observed that low concentrations of arsenic trioxide can inhibit TGF-β 1 mediated Fb activation, proving that arsenic trioxide prevented the progression of pulmonary fibrosis to a certain extent[ ].

5.2 Antiviral drugs

The early use of antiviral drugs can reduce the possibility of malignant outcomes leading to pulmonary fibrosis. In the United States, according to the principle of sympathetic medication, the use of remuxivir in the treatment of a COVID-19 patient achieved significant results[ ]. The drug is a nucleotide analogue in the research and development stage, which can inhibit RNA synthase, thereby blocking the replication of the virus. It has been reported that in vitro and animal models, ramcivir is effective for SARS and MERS, and The drug has now completed Phase 2 clinical trials for the treatment of Ebola virus. However, in this report, the treatment target is only one case. Although the patient's condition improved after 1 day of treatment after dyspnea, further experiments are needed to determine its effectiveness and safety. The guanine riboline analogue ribavirin recommended by the "Proposal" and the virus assembly inhibitor lopinavir / ritonavir are also antiviral drugs, which have a certain inhibitory effect on the virus. The use of the two is Based on the treatment experience of SARS[ ], although the new coronavirus has many similarities with SARS, it is currently used to treat COVID-19 with limited experience, and as a RNA virus mutation rate is faster, used for diseases with faster virus replication The initial significance is greater than the middle and late stages with high levels of inflammatory factors, so it has limitations.

5.3 Other treatment methods

5.3.1 Mesenchymal stem cells (MSC)

MSCs are derived from early mesoderm and ectoderm and are stem cells with multi-directional differentiation potential. They can repair damaged alveolar epithelium, inhibit pulmonary fibrosis, and regulate abnormal immune responses. First, the lung is the first organ of intravenous infusion of MSC. After homing to the lungs, MSC differentiates into pulmonary vascular endothelial cells and alveolar epithelial cells, mainly type II alveolar epithelial cells[ ], repairing damaged alveolar epithelial cells And vascular endothelial cells, increase the secretion of alveolar surfactant, and initiate the repair of alveolar-epithelial cells; secondly, MSC reduces the expression of TGF-β, reduces collagen formation, and inhibits pulmonary fibrosis[ ]. Importantly, MSC can also regulate abnormal non-specific immunity and specific immunity to avoid excessive activation of the immune system[ ]. At present,

there are several clinical projects that use MSC in the treatment of ARDS, and its efficacy has been confirmed[ ], which indicates that it has a good application prospect for the treatment of severe COVID-19 and the prevention and treatment of pulmonary fibrosis[ ].

5.3.2 Lung transplantation

Lung transplantation is currently the only treatment that can improve the survival rate of patients with pulmonary fibrosis. IPF patients with varying degrees of single lung transplantation or double lung transplantation can improve symptoms, prolong life, and improve quality of life[ ]. As of March 13, 2020, China's Chen Jingyu team has taken the lead in successfully performing 3 cases of heavy-duty COVID-19 double lung transplantation with nucleic acid turning negative, of which 2 cases have entered perioperative management and the first patient can be out of bed Functional exercise[ ] highlights the superiority of lung transplantation in the treatment of severe COVID-19 with severely damaged lungs. However, factors such as postoperative rejection, high price, and the occurrence of complications make the operation safe and effective for COVID-19.

6 Summary

At present, the new coronavirus can be spread in a large area around the world through human-to-human transmission at least through droplets, contact, aerosols, etc. Although the current data shows that it has a lower mortality rate than SARS, COVID-19 severe patients have The type and severity of complications showed considerable similarity with SARS. Although it is still in a critical period of epidemic situation and there is little evidence of pulmonary fibrosis caused by COVID-19, there are still some early manifestations of COVID-10[ ], the outcome of ARDS patients[ ], epidemiological data of SARS The situation[ ] provides a possible basis for support—pulmonary fibrosis may become the most serious complication after the outbreak. No matter whether it is COVID-19 or pulmonary fibrosis, there is still a lack of effective targeted drug treatment. How to prevent and reduce the occurrence of pulmonary fibrosis in patients with COVID-19 is an urgent problem that medical workers need to solve in the current treatment. Although it is now possible to provide some potentially effective therapeutic drugs based on the currently available potential targets in the pathogenesis of COVID-19-induced pulmonary fibrosis, most of them still need time and scientific research to verify their effectiveness and safety. Therefore, for newly emerging highly pathogenic coronaviruses, strict and timely epidemiological measures are essential to curb the rapid spread, and early treatment methods to prevent pulmonary fibrosis are imperative.

Conflict of interest All authors declare that there is no conflict of interest

references

[1]

World Health Organization. WHO characterizes COVID-19 as a pandemic [EB / OL]. (2020-03-11) [2020-03-13]. Https://www.who.int/emergencies/diseases/novel-coronavirus -2019 / events-as-they-happen.

[2]

World Health Organization. Situation report-54 Coronavirus Disease 2019 (COVID-19) [EB / OL]. (2020-03-14) [2020-03-14]. Https://www.who.int/docs/default -source / coronaviruse / situation-reports / 20200314-sitrep-54-covid-19.pdf? sfvrsn = dcd46351_2.

[3]

Zumla A, Hui DS, Azhar EI, et al. Reducing mortality from 2019-nCoV: host-directed therapies should be an option [J]. Lancet, 2020,395 (10224): e35-36. DOI: 10.1016 / S0140- 6736 (20) 30305-6.

[4]

Venkataraman T, Coleman CM, Frieman MB. Overactive epidermal growth factor receptor signaling leads to increased fibrosis after severe acute respiratory syndrome coronavirus infection [J]. J Virol, 2017,91 (12): e00182-17. DOI: 10.1128 / JVI. 00182-17.

[5]

Chen Qian, Wang Yao, Jiao Fangzhou, et al. Discussion on the occurrence mechanism and intervention strategy of a new coronavirus pneumonia "inflammatory storm" [J / OL]. Chinese Journal of Infectious Diseases, 2020,38 (2020-02-26) .http: //rs.yiigle.com/yufabiao/1182703.htm. DOI: 10.3760 / cma.j.cn311365-20200221-00103. [Pre-published online].

[6]

Glasser SW, Hagood JS, Wong S, et al. Mechanisms of lung fibrosis resolution [J]. Am J Pathol, 2016,186 (5): 1066-1077.DOI: 10.1016 / j.ajpath.2016.01.018.

[7]

Spagnolo P, Maher TM, Richeldi L. Idiopathic pulmonary fibrosis: recent advances on pharmacological therapy [J]. Pharmacol Ther, 2015,152: 18-27. DOI: 10.1016 / j.pharmthera.2015.04.005.

[8]

Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology [J]. Semin Immunopathol, 2017,39 (5): 529-539. DOI: 10.1007 / s00281-017-0629-x.

[9]

Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin [J / OL]. Nature, 2020 [2020-03-13]. Https://DOI.org/10.1038 /s41586-020-2012-7.[published online ahead of print Feb 03, 2020] .DOI: 10.1038 / s41586-020-2012-7.

[10]

Zhu N, Zhang DY, Wang WL, et al. A novel coronavirus from patients with pneumonia in China, 2019 [J]. N Engl J Med, 2020,382 (8): 727-733. DOI: 10.1056 / NEJMoa2001017.

[11]

Tian SF, Hu WD, Niu L, et al. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer [J / OL]. J Thorac Oncol, 2020 [2020-03-11] .https: //pubmed.ncbi.nlm.nih.gov/32114094/. [published online ahead of print Feb 27, 2020] .DOI: 10.1016 / j.jtho.2020.02.010.

[12]

Sun PF, Qie SY, Liu ZJ, et al. Clinical characteristics of 50466 hospitalized patients with 2019-nCoV infection [J / OL]. J Med Virol, 2020 [2020-03-11] .https: //onlinelibrary.wiley. com / DOI / abs / 10.1002 / jmv.25735. [published online ahead of print Feb 28, 2020] .DOI: 10.1002 / jmv.25735.

[13]

Ngai JC, Ko FW, Ng SS, et al. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status [J]. Respirology, 2010,15 (3): 543-550. DOI: 10.1111 / j.1440-1843.2010.01720.x.

[14]

Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors [J]. Thorax, 2005,60 (5): 401 - 409. DOI: 10.1136 / thx.2004.030205.

[15]

Lionetti V, Recchia FA, Ranieri VM. Overview of ventilator-induced lung injury mechanisms [J]. Curr Opin Crit Care, 2005,11 (1): 82-86. DOI: 10.1097 / 00075198-200502000-00013.

[16]

Gurkan OU, O'Donnell C, Brower R, et al. Differential effects of mechanical ventilatory strategy on lung injury and systemic organ inflammation in mice [J]. Am J Physiol Lung Cell Mol Physiol, 2003,285 (3): L710- 718. DOI: 10.1152 / ajplung.00044.2003.

[17]

Cabrera-Benítez NE, Parotto M, Post M, et al. Mechanical stress induces lung fibrosis by epithelial-mesenchymal transition [J]. Crit Care Med, 2012, 40 (2): 510-517. DOI: 10.1097 / ccm.0b013e31822f09d7 .

[18]

Totura AL, Baric RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon [J]. Curr Opin Virol, 2012,2 (3): 264-275.DOI: 10.1016 / j.coviro.2012.04.004.

[19]

García-Sastre A, Biron CA. Type 1 interferons and the virus-host relationship: a lesson in détente [J]. Science, 2006,312 (5775): 879-882. DOI: 10.1126 / science.1125676.

[20]

Barron L, Wynn TA. Fibrosis is regulated by Th2 and Th17 responses and by dynamic interactions between fibroblasts and macrophages [J]. Am J Physiol Gastrointest Liver Physiol, 2011,300 (5): G723-728. DOI: 10.1152 / ajpgi. 00414.2010.

[twenty one]

He JH, Tao HY, Yan YM, et al. Molecular mechanism of evolution and human infection with the novel coronavirus (2019-nCoV) [J / OL]. BioRxiv, 2020 [2020-03-07]. Https: // www .biorxiv.org / content / 10.1101 / 2020.02.17.952903v1. [published online ahead of print Feb 21, 2020] .DOI: 10.1101 / 2020.02.17.952903.

[twenty two]

Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity [J]. Cell, 2006,124 (4): 783-801. DOI: 10.1016 / j.cell.2006.02.015.

[twenty three]

Goodman RB, Pugin J, Lee JS, et al. Cytokine-mediated inflammation in acute lung injury [J]. Cytokine Growth Factor Rev, 2003,14 (6): 523-535. DOI: 10.1016 / s1359-6101 (03) 00059-5.

[twenty four]

Kim YK, Oh SY, Jeon SG, et al. Airway exposure levels of lipopolysaccharide determine type 1 versus type 2 experimental asthma [J]. J Immunol, 2007,178 (8): 5375-5382. DOI: 10.4049 / jimmunol.178.8 .5375.

[25]

Chen Cheng, Zhang Xiaorong, Ju Zhenyu, et al. The mechanism of cytokine storm caused by novel coronavirus pneumonia and related immunotherapy research progress [J / OL]. Chinese Journal of Burns, 2020, 36 (2020-03-02) .http: // rs.yiigle.com/yufabiao/1183285.htm. DOI: 10.3760 / cma.j.cn501120-20200224-00088. [Pre-published online].

[26]

Huang CL, Wang YM, Li XW, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [J]. Lancet, 2020, 395 (10223): 497-506.DOI: 10.1016 / s0140-6736 (20) 30183-5.

[27]

Wan SX, Yi QJ, Fan SB, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP) [J / OL] .medRxiv, 2020 [2020-03-07]. https://www.medrxiv.org/content/10.1101/2020.02.10.20021832v1. [published online ahead of print Feb 12, 2020] .DOI: 10.1101 / 2020.02.10.20021832.

[28]

Xu Z, Shi L, Wang YJ, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome [J / OL]. Lancet Respir Med, 2020 [2020-03-07] .https: //pubmed.ncbi .nlm.nih.gov / 32085846. [published online ahead of print Feb 18, 2020] .DOI: 10.1016 / S2213-2600 (20) 30076-X.

[29]

Han SH, Mallampalli RK. The acute respiratory distress syndrome: from mechanism to translation [J]. J Immunol, 2015, 194 (3): 855-860.DOI: 10.4049 / jimmunol.1402513.

[30]

Gao Yuqi. Treatment strategy based on the pathophysiological mechanism of new coronary pneumonia [J / OL]. Chinese Journal of Pathophysiology, 2020 [2020-03-07].

Http://html.journal.founderss.cn/ZBLS/782/431/. [published online ahead of print March 01, 2020]. DOI: 10.3969 / j.issn.1000-4718.XXXX.XX.001.

[31]

Liu Youning. Thinking about new drugs for treating coronavirus infections [J / OL]. Chinese Journal of Tuberculosis and Respiratory Diseases, 2020,43 (2020-02-18) .http: //rs.yiigle.com/yufabiao/1182253.htm . DOI: 10.3760 / cma.j.issn.1001-0939.2020.0017. [Pre-published online].

[32]

Lin YT, Wu KJ. Epigenetic regulation of epithelial-mesenchymal transition: focusing on hypoxia and TGF-β signaling [J]. J Biomed Sci, 2020,27 (1): 39. DOI: 10.1186 / s12929-020-00632-3 .

[33]

Tikly M, Marshall SE, Haldar NA, et al. Oxygen free radical scavenger enzyme polymorphisms in systemic sclerosis [J]. Free Radic Biol Med, 2004,36 (11): 1403-1407. DOI: 10.1016 / j.freeradbiomed.2004.02 .079.

[34]

Silasi-Mansat R, Zhu H, Georgescu C, et al. Complement inhibition decreases early fibrogenic events in the lung of septic baboons [J]. J Cell Mol Med, 2015,19 (11): 2549-2563. DOI: 10.1111 / jcmm.12667.

[35]

Lee KY. Pneumonia, acute respiratory distress syndrome, and early immune-modulator therapy [J]. Int J Mol Sci, 2017,18 (2): 388. DOI: 10.3390 / ijms18020388.

[36]

Khalfaoui S, Eichhorn V, Karagiannidis C, et al. Lung infection by human bocavirus induces the release of profibrotic mediator cytokines in vivo and in vitro [J]. PLoS One, 2016,11 (1): e0147010.DOI: 10.1371 / journal .pone.0147010.

[37]

Wallace WA, Ramage EA, Lamb D, et al. A type 2 (Th2-like) pattern of immune response predominates in the pulmonary interstitium of patients with cryptogenic fibrosing alveolitis (CFA) [J]. Clin Exp Immunol, 1995,101 (3): 436-441. DOI: 10.1111 / j.1365-2249.1995.tb03131.x.

[38]

He X, Zhang L, Ran Q. Integrative Bioinformatics Analysis Provides Insight into the Molecular Mechanisms of 2019-nCoV. [J / OL] .medRxiv, 2020 [2020-03-07] .https: //www.medrxiv.org/ content / 10.1101 / 2020.02.03.20020206v1. [published online ahead of print Feb 05, 2020] .DOI: 10.1101 / 2020.02.03.20020206.

[39]

Shamaei M, Mortaz E, Pourabdollah M, et al. Evidence for M2 macrophages in granulomas from pulmonary sarcoidosis: a new aspect of macrophage heterogeneity [J]. Hum Immunol, 2018,79 (1): 63-69. DOI: 10.1016 / j.humimm.2017.10.009.

[40]

Mou FH, Mou CL. Necrostatin-1 alleviates bleomycin-induced pulmonary fibrosis and extracellular matrix expression in interstitial pulmonary fibrosis [J]. Med Sci Monit, 2020,26: e919739. DOI: 10.12659 / MSM.919739.

[41]

Hashimoto N, Jin H, Liu TJ, et al. Bone marrow-derived progenitor cells in pulmonary fibrosis [J]. J Clin Invest, 2004,113 (2): 243-252. DOI: 10.1172 / JCI18847.

[42]

Shochet GE, Wollin L, Shitrit D. Fibroblast-matrix interplay: Nintedanib and pirfenidone modulate the effect of IPF fibroblast-conditioned matrix on normal fibroblast phenotype [J]. Respirology, 2018,23 (8): 756-763. DOI: 10.1111 /resp.13287.

[43]

Habiel DM, Hogaboam CM. Heterogeneity of Fibroblasts and myofibroblasts in pulmonary fibrosis [J]. Curr Pathobiol Rep, 2017,5 (2): 101-110. DOI: 10.1007 / s40139-017-0134-x.

[44]

Hoyles RK, Derrett-Smith EC, Khan K, et al. An essential role for resident fibroblasts in experimental lung fibrosis is defined by lineage-specific deletion of high-affinity type II transforming growth factor β receptor [J]. Am J Respir Crit Care Med, 2011, 183 (2): 249-261. DOI: 10.1164 / rccm. 201002-0279OC.

[45]

Barron L, Gharib SA, Duffield JS. Lung pericytes and resident fibroblasts: busy multitaskers [J] .Am J Pathol, 2016,186 (10): 2519-2531. DOI: 10.1016 / j.ajpath.2016.07.004.

[46]

Pilling D, Tucker NM, Gomer RH. Aggregated IgG inhibits the differentiation of human fibrocytes [J]. J Leukoc Biol, 2006,79 (6): 1242-1251. DOI: 10.1189 / jlb.0805456.

[47]

Chow LN, Schreiner P, Ng BYY, et al. Impact of a CXCL12 / CXCR4 Antagonist in Bleomycin (BLM) Induced Pulmonary Fibrosis and Carbon Tetrachloride (CCl4) Induced Hepatic Fibrosis in Mice [J]. PLoS One, 2016,11 (3): e0151765. DOI: 10.1371 / journal.pone.0151765.

[48]

Tanjore H, Xu XC, Polosukhin VV, et al. Contribution of epithelial-derived fibroblasts to bleomycin-induced lung fibrosis [J]. Am J Respir Crit Care Med, 2009,180 (7): 657-665. DOI: 10.1164 / rccm.200903-0322OC.

[49]

Zavadil J, Böttinger E P. TGF-β and epithelial-to-mesenchymal transitions [J]. Oncogene, 2005, 24: 5764-5774. DOI: 10.1038 / sj.onc.1208927.

[50]

Bartram U, Speer CP. The role of transforming growth factor beta in lung development and disease [J]. Chest, 2004,125 (2): 754-765. DOI: 10.1378 / chest.125.2.754.

[51]

Ramos C, Montaño M, García-Alvarez J, et al. Fibroblasts from idiopathic pulmonary fibrosis and normal lungs differ in growth rate, apoptosis, and tissue inhibitor of metalloproteinases expression [J]. Am J Respir Cell Mol Biol, 2001,24 (5): 591-598. DOI: 10.1165 / ajrcmb.24.5.4333.

[52]

Moodley YP, Misso NL, Scaffidi AK, et al. Inverse effects of interleukin-6 on apoptosis of fibroblasts from pulmonary fibrosis and normal lungs [J]. Am J Respir Cell Mol Biol, 2003,29 (4): 490-498. DOI: 10.1165 / rcmb.2002-0262OC.

[53]

Zhao Fangzhe, Sang Xiaoqing, Zhu Yan, et al. Research on the action mechanism of IL-6 factor promoted by M2 macrophage on fibroblast activation [J / OL]. Journal of Pharmaceutical Sciences, 2020 [2020-03-14]. : //DOI.org/10.16438/j.0513-4870.2019-1044. [Published online ahead of print March 11, 2020]. DOI: 10.16438 / j.0513-4870.2019-1044.

[54]

Waxman S, Anderson KC. History of the development of arsenic derivatives in cancer therapy [J]. Oncologist. 2001,6 Suppl 2: S3-10. DOI: 10.1634 / theoncologist.6-suppl_2-3.

[55]

Luo FY, Zhuang Y, Sides MD, et al. Arsenic trioxide inhibits transforming growth factor-β1-induced fibroblast to myofibroblast differentiation in vitro and bleomycin induced lung fibrosis in vivo [J]. Respir Res, 2014,15 (1): 51 . DOI: 10.1186 / 1465-9921-15-51.

[56]

Li Hui, Wang Yeming, Xu Jiuyang, et al. 2019 new coronavirus antiviral therapy is available [J / OL]. Chinese Journal of Tuberculosis and Respiratory Diseases, 2020,43 (2020-02-05) .http: //rs.yiigle .com / yufabiao / 1179590.htm. DOI: 10.3760 / cma.j.issn.1001-0939.2020.0002. [Pre-published online].

[57]

Chu CM, Cheng VC, Hung IFN, et al. Role of lopinavir / ritonavir in the treatment of SARS: initial virological and clinical findings [J]. Thorax, 2004,59 (3): 252-256. DOI: 10.1136 / thorax .2003.012658.

[58]

Li Lang, Dong Liang, Gao Fei, et al. Experimental study on the effect of Hippo signaling pathway regulating mesenchymal stem cells on the repair of ARDS lung injury [J] .Chinese Journal of Critical Care Medicine, 2019,31 (3): 281-287. DOI : 10.3760 / cma.j.issn.2095-4352.2019.03.005.

[59]

Jahn A, Rio C, Montes A, Characterization of mesenchymal stem cells obtained from human lungs with and without idiopathic pulmonary fibrosis [J]. European Respiratory Society, 2019, 54 suppl 63. DOI: 10.1183 / 13993003.congress-2019.PA1281.

[60]

Mei SHJ, McCarter SD, Deng Y, et al. Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1 [J]. PLoS Med, 2007,4 (9): e269. DOI: 10.1371 / journal .pmed.0040269.

[61]

Horie S, Gonzalez HE, Laffey JG, et al. Cell therapy in acute respiratory distress syndrome [J]. J Thorac Dis, 2018,10 (9): 5607-5620. DOI: 10.21037 / jtd.2018.08.28.

[62]

Liu Guangyang, Zheng Libo, Wang Hao, et al. Research on mesenchymal stem cells in the treatment of new coronavirus pneumonia [J] .Pharmaceutical Evaluation Research, 2020,43 (3): 372-377.DOI: 10.7501 / j.issn.1674- 6376.2020.03.003.

[63]

Kumar A, Kapnadak SG, Girgis RE, et al. Lung transplantation in idiopathic pulmonary fibrosis [J]. Expert Rev Respir Med, 2018, 12 (5): 375-385. DOI: 10.1080 / 17476348.2018.1462704.

[64]

Surging news. Chen Jingyu once again lung transplanted for patients with new coronary pneumonia, both patients were detached from ECMO [EB / OL] .2020 [2020-03-14]. Https://www.thepaper.cn/newsDetail_forward_6491113.

[65]

Marchioni A, Tonelli R, Ball L, et al. Acute exacerbation of idiopathic pulmonary fibrosis: lessons learned from acute respiratory distress syndrome? [J]. Crit Care, 2018,22 (1): 80. DOI: 10.1186 / s13054-018 -2002-4.

[66]

Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors [J]. Chest, 2005,128 (4) : 2247-2261. DOI: 10.1378 / chest.128.4.2247.

Trends in Molecular Medicine

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REVIEWS

Review

COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives

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The recent outbreak of COVID-19 in Wuhan turned into a public health emergency of international concern. With no antiviral drugs nor vaccines, and the presence of carriers without obvious symptoms, traditional public health intervention measures are significantly less effective. Here, we report the epidemiological and virological characteristics of the COVID-19 outbreak. Originated in bats, 2019-nCoV/ severe acute respiratory syndrome coronavirus (SARS-CoV)-2 likely experienced adaptive evolution in intermediate hosts before transfer to humans at a concentrated source of transmission. Similarities of receptor sequence binding to 2019-nCoV between humans and animals suggest a low species barrier for transmission of the virus to farm animals. We propose, based on the One Health model, that veterinarians and animal specialists should be involved in a cross-disciplinary collaboration in the fight against this epidemic.

Highlights

The basic reproductive number (R_0) of 2019-nCoV is higher than R_0 of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). COVID-19 presents with asymptomatic infections, with potential to propagate and perpetuate this epidemic.

2019-nCoV isolated from patients shows limited sequence diversity, suggesting that the interspecies transmission event was very recent and that the source of the virus was focused, possibly a point-source event.

The amino acid sequence in the ACE2 receptor responsible for 2019-nCoV binding in farm animals and cats has only a few exchanges compared with the human receptor, suggesting that the species barrier for virus transmission is small.

Emergence of COVID-19

In December 2019, a cluster of pneumonia with unknown etiology appeared in Wuhan City, Hubei Province of China. Several of the initial patients visited a wet seafood market where other wildlife species were also sold. Subsequent virus isolation from human patients and molecular analysis showed that the pathogen was a new coronavirus (CoV), first named 2019-nCoV, and subsequently this disease was renamed by WHO as COVID-19. A study group of the International Committee on Taxonomy of Viruses (ICTV) proposed the name SARS-CoV-2, but this name remains to be officially approved [1]. This new CoV is now the seventh member of the *Coronaviridae* known to infect humans. With the explosive increase of confirmed cases, the WHO declared this outbreak a public health emergency of international concern (PHEIC) on January 30, 2020.

CoVs are a class of genetic diverse viruses found in a wide range of host species, including birds and mammals. Many CoVs cause intestinal and respiratory infections in animals and in humans [2–5]. CoV came into the spotlight in 2002–2003, when clusters of 'atypical pneumonia' were first reported in Guangdong Province, subsequently spreading to Hong Kong. Researchers in Hong Kong isolated a novel CoV virus (SARS-CoV) and the disease was later renamed **severe acute respiratory syndrome (SARS)** (see Glossary). Because of international travel, the virus spread from Hong Kong to the rest of the world and more than 8000 people in 26 countries became infected, with a case fatality rate of approximately 10% (https://www.who.int/csr/sars/country/table2004_04_21/en/). SARS posed a serious public health threat to the world at that time, with a significant negative impact on the economy in affected areas. Subsequent studies found that SARS-CoV originated from bats and interspecies transmission to humans took place via an intermediate host: Himalayan palm civets (*Paguma larvata*) or raccoon dogs (*Nyctereutes procyonoides*) [5–7]. Another well-known CoV of animal origin is **Middle East respiratory syndrome coronavirus (MERS-CoV)**, which has an even higher case fatality rate, but it is rarely transmitted between humans.

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As major natural reservoir species of *Alphacoronavirus* and *Betacoronavirus*, bats carry highly diverse SARS-like-CoVs. These bats are distributed in many provinces of China. The genetic diversity of these SARS-like-CoVs and their molecular evolution within their natural host species have been studied intensively [2,8–11]. Here, we review the recent but still very limited facts about the current epidemiology of COVID-19 and discuss viral characteristics of 2019-nCoV on the backdrop of our knowledge about the previous epidemic of SARS and MERS.

Epidemiology of COVID-19

As of 24:00 February 20, 2020 (UTC+8), there are a total of 75 995 confirmed cases, including 2239 fatalities in China (mainland: 75 891; Hong Kong: 68; Macao: 10; and Taiwan: 26), and 1200 confirmed cases, including eight fatal ones outside China, in all five continents (Figure 1). The epidemiology curve can roughly be divided into three phases.

i. The local outbreak by exposure in the aforementioned food wholesale market marks the first phase. From the first case in December 2019 to the emergence of new cases outside Wuhan by January 13, 2020, a total of 41 cases were confirmed. Epidemiologic analysis showed that already in this initial phase, person-to-person transmission had occurred by close contact [12].
ii. The second phase started on January 13, marked by rapid expansion and spread of the virus within hospitals (nosocomial infection) and by family transmission (close-contact transmission). In this phase the epidemic spread from Wuhan to other areas [12–18]. The first case outside of China was reported in Thailand on January 13, caused by a Wuhan resident travelling to this country. On January 19 cases were reported from outside Wuhan, in Beijing City, and in the Guangdong Province, indicating that the virus had spread within China, and the total number of confirmed cases rose to 205. Already by January 23, 29 provinces, plus six foreign countries, had reported a total of 846 confirmed cases, an approximately 20-fold increase from the first phase. Meanwhile, Wuhan city implemented a 'lock-down' (i.e., shutting down all movement within and out of the city). Unfortunately, this period coincided with the traditional mass movement of people, a form of 'home-coming', before Chinese New Year and thus more than 5 million people had already left Wuhan.
iii. The third phase started on January 26, which is marked by the rapid increase of cluster cases. On February 10, retrospective analysis showed that the number of clustered cases accounted for 50–80% of all confirmed cases in Beijing, Shanghai, Jiangsu, and Shandong [19]. On January 30, the number increased 240-fold, reaching 9826 confirmed cases, and the WHO declared this epidemic a PHEIC. By February 11, 44 730 confirmed cases and 16 067 suspected cases were reported in about 1386 counties and districts in China [20]. However, there were only 441 confirmed cases in 24 countries outside of China. The fatality rate remained high in China, with a total of 1114 deaths, but with just one fatality outside China, in the Philippines. By February 12, due to adoption of a new clinical definition for diagnosis in Hubei province, newly confirmed cases jumped to 14 840, of which 13 332 cases were based only on clinical diagnosis. By that time, 25 countries had reported 60 329 infections, with 1471 times the initial number (Figure 1A). Of note, February 3 seems to be a tipping point of the epidemic, from which time the daily number of confirmed cases outside Hubei began to decline. Whether it reflects a success of the 'Wuhan lock-down' and other public health measures, or virus transmission reduced for other reasons, remains unclear.

Furthermore, 85.8% of 37 269 confirmed cases had either lived in or traveled to Wuhan, or had close contact with persons who had been to Wuhan [20,21]. Unfortunately, as of February 11, 1716 medical-related staff from 422 medical institutions were infected, of which 1688 confirmed

cases were analyzed. Among them, 64% were infected in Wuhan city and 23.3% in the rest of Hubei, excluding Wuhan [20]. The specific causes of the infection of medical staff and the failure of protection need further investigation.

Initial evaluation of COVID-19 transmission dynamics showed that the **basic reproductive number (R_0)** of 2019-nCoV is estimated to be 1.4–3.9 [12]. The R_0 of SARS-CoV in the absence of interventions was 2.3–3.7 [22,23]. Breban *et al.* estimated MERS-CoV R_0 to be 0.50–0.92 by analysis of 55 of the first 64 laboratory-confirmed cases [24]. With the implementation of rapid diagnosis, coupled with effective isolation of patients, the R_0 of SARS-CoV dropped to less than 1, explaining why the SARS-CoV outbreak could eventually be controlled [25–27]. However, it is worth noting that R_0 estimates may vary upon numerous biologic, socio-behavioral, and environmental factors, and must be interpreted with caution [28].

Clinical Phenotype of COVID-19

Major initial symptoms of COVID-19 include fever, cough, muscular soreness, and dyspnea. Some patients showed atypical symptoms, such as diarrhea and vomiting. However, the clinical phenotype is confounded by the fact that 25.2% patients had at least one other underlying medical condition [13,15,29–32]. The overall clinical characteristics of COVID-19 were also influenced by the different phases of this epidemic [12,13,21,29,33]. Patients in the first and second phase of the epidemic were older, more likely to be male, and likely to have exposure to the seafood market. Clinically, they had more bilateral patchy shadows, or ground glass opacity in the lungs [13,21,29,33–36]. In addition, the mortality rate of the first and second phases of the epidemic was 4.3–15% and thus significantly higher than the 1.36% determined for the later phase of the epidemic [13,21,29,33,34]. This higher mortality rate was either due to: (i) more people with underlying medical conditions, such as high blood pressure and diabetes [12,13,19,20,29,31,33]; (ii) during the early phase of this epidemic the virus was more pathogenic; or (iii) the lower mortality rate was skewed by a larger sample size at the later phase of this epidemic. Importantly, 889 asymptomatic or subclinically symptomatic infected cases were reported [20,37]. Asymptomatic infection was also documented in Germany: two asymptomatic patients' throat samples were tested positive by reverse transcription (RT)-PCR and by virus isolation, while both patients remained well and afebrile for 7 days [38]. Importantly, the asymptomatic manifestation jeopardizes the screening of infected people by temperature measurements or by overt signs and symptoms [12,13,19,20,29,31,33]. Virus infection is not selective in age, as it was reported even in a 1-month-old infant [20,21,37]. Of the 44 672 confirmed cases, 77.8% are between 30 and 69 years old and 51.4% are male [20]. Until now, there is no evidence for intrauterine infection by vertical transmission in women who developed COVID-19 during late pregnancy and no evidence that pregnant women are more susceptible compared with other adult patients [34,39]. Although currently the number of new infections is decreasing, the COVID-19 epidemic is still ongoing. The order to Chinese citizens to return to work, which is accompanied by massive population movement, will likely increase the risk of transmission again. Overall, the current mortality rate of COVID-19 in China is 2.9% and in foreign countries 0.7%. The overall mortality rate remains the highest in Hubei (3.4%), 4.9 times higher than in other provinces (0.7%). For comparison, SARS-CoV exhibited a case fatality rate of 9.6% (774/8096) and MERS-CoV had a fatality rate of 34.4% (858/2494) (https://www.who.int/csr/sars/country/table2004_04_21/en/; https://www.who.int/emergencies/mers-cov/en/). However, 2019-nCoV is more infectious than SARS-CoV or MERS-CoV [40,41].

Origin and Evolution of 2019-nCoV

As animal markets had been implicated in the SARS-CoV outbreak of 2002–2003, and initial 2019-nCoV infections are also related to the seafood market with wildlife trading, it was soon assumed that wild animals were also involved in the emergence of 2019-nCoV. Yet, from

Glossary

Avian influenza virus: influenza viruses that circulate in birds, mainly in water fowl, without causing clinical symptoms (low pathogenic influenza virus). Occasionally they are introduced into poultry, where they might acquire a polybasic cleavage site within their main glycoprotein hemagglutinin (HA). HA is then cleaved by the ubiquitous protease furin and the now highly pathogenic virus causes a systemic and hence deadly infection ('bird flu').

Basic reproductive number (R_0): an epidemiologic metric to describe the contagiousness or transmissibility of infectious agents. It refers to the expected number of secondary infections that one infected person generates on average in an entirely susceptible population. It allows estimation of the potential of an agent to cause an epidemic, the extent of transmission without control measures, and the efficiency of control measures to reduce transmission.

Enfuvirtide: antiviral drug (trade name Fuzeon), licensed for the treatment of HIV infection, that inhibits the membrane fusion activity of its glycoprotein and hence cell entry of the virus.

Middle East respiratory syndrome coronavirus (MERS-CoV): a highly lethal and zoonotic pathogen that was first identified in Saudi Arabia in 2012. Since 2012, MERS has been reported in 27 countries. Scientific evidence suggests that people are infected through direct or indirect contact with infected dromedary camels.

Plaque: a plaque is an area of dead cells within a cell monolayer. The plaque is caused by an infection of a single cell by one virus that then spreads to neighboring cells. Plaque assays are used to determine the number of infectious virus particles.

Severe acute respiratory syndrome (SARS): caused by SARS coronavirus (SARS-CoV), which first occurred in Guangdong province, China, and became a global epidemic disease in 2002–2003. The disease was reported by 26 countries, with a case fatality rate of approximately 10%. Studies showed that SARS-CoV originated from bats and was transmitted to humans via palm civets or raccoon dogs.

ZDHHC family: family of polytopic membrane proteins that are characterized by the amino acid motif DHHC, which is located within a cysteine-rich domain in one of its cytoplasmic loops. Many of the family

which species and under what circumstance the virus crossed the species barrier to infect humans remains to be clarified. Early investigations about the origin of COVID-19 suggested that the 2019-nCoV may have jumped from bats to human [42,43]. This is not unprecedented since bat viruses have been shown to 'jump' the species barrier frequently to infect new species [44–50]. However, since bats were in hibernation when the outbreak occurred, and it was uncertain whether bats were sold at the market, the virus is more likely to have been transmitted via

members have been shown to transfer long chain fatty acids to cysteine residues of cellular and viral proteins.

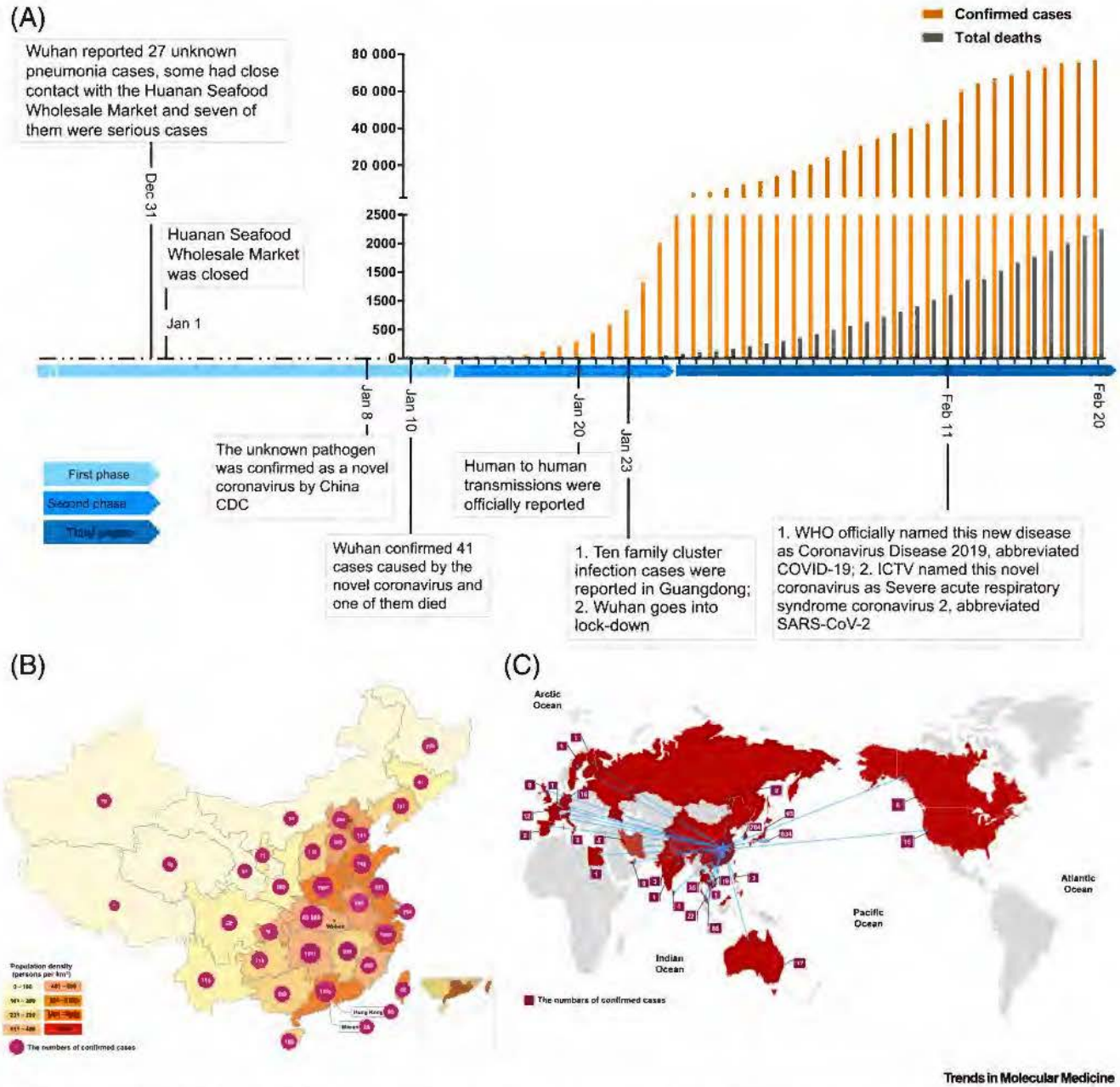

Figure 1. Spreading of the 2019-nCoV Epidemic. (A) Timeline of events during the 2019-nCoV epidemic. (B) Human confirmed cases of 2019-nCoV infection in China. (C) Human confirmed cases of 2019-nCoV infection in the world (Last update on 24:00 UTC+8, 20 February 2020). Abbreviations: CDC, Centers for Disease Control; ICTV, International Committee on Taxonomy of Viruses.

Box 1. Evolution Analysis Methods

Sequences analyzed: 18 betacoronavirus sequences and 95 full-length 2019-nCoV genomes kindly made available from GISAID (https://www.gisaid.org/) and from the National Center for Biotechnology Information GenBank (https://www.ncbi.nlm.nih.gov/) platforms. Some sequences were omitted, as they were too short, contained sequencing artefacts, resulted from resequencing of the same sample, or had insufficient annotations.

Sequence alignment and potential recombination analysis: sequences were aligned using MAFFT [83] and manually adjusted in MEGA7 [84]. The breakpoints were detected using the phylogenetic incongruence among segments in sequence alignments using GARD and are shown by using the Simplot version 3.5.1 and Kimura model. Slide windows were set as 1000 bp, with each step 500 bp.

Phylogenetic analysis: all ML trees were reconstructed using the general time reversible substitution model with gamma distributed rate heterogeneity and 1000 bootstraps by RAxML (v4.8.10) [85].

other species on the market. Genomic analyses of 2019-nCoV demonstrate a 96% nucleotide identity with a CoV isolated from a bat: BetaCoV/RaTG13/2013 [42]. Previous reports showed that species from the bat genera *Rhinolophus* in southern China are a rich pool of SARS-like-CoVs, which belong to the subgenera *Sarbecovirus*. These viruses exhibit rich genetic diversity and frequent recombination events, which may increase the potential for cross-species transmission [7,42,51–55]. Here, we reconstructed the evolutionary history of the 2019-nCoV cluster (Box

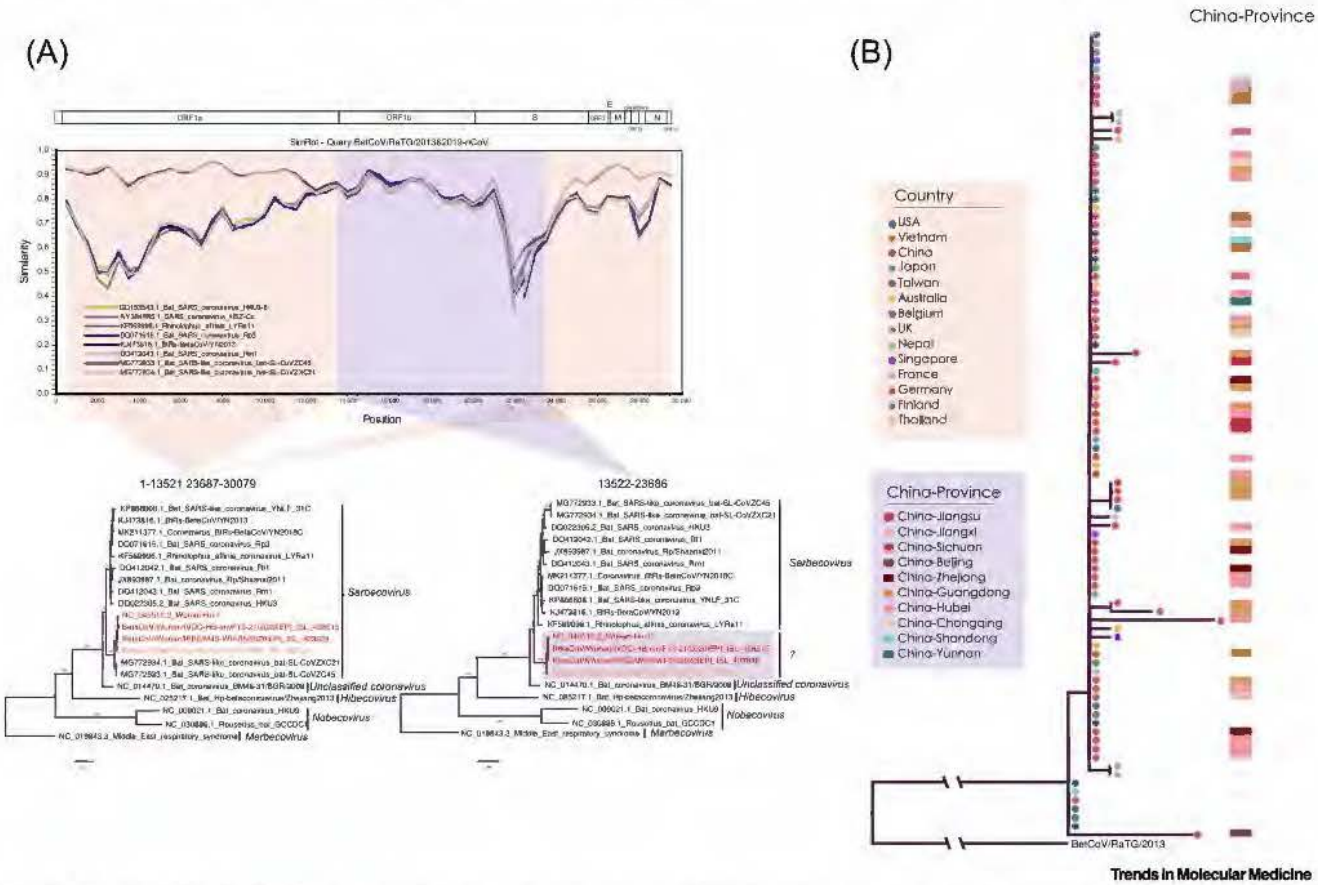

Figure 2. Structure of the 2019-nCoV Genome. (A) Recombination analysis of 2019-nCoV. A rescaled structure of the 2019-nCoV genome (top) and similarity recombination analysis with reference sequences using Simplot v3.5.1 (accession number BetaCoV/Wuhan/WIV02/2019|EPI_ISL_402127 EPI_ISL_402131, KJ473816, DQ071615, DQ412043, GQ153543, AY394995, KF569996, MG772933, MG772934). Sequences were separated based on potential recombination breakpoint on nucleotides 13 522 and 23 686. Maximum likelihood (ML) phylogenetic trees inferred for the pink and purple regions confirm different topologies and recombination. (B) ML tree of 2019-nCoV spike protein gene. The ML tree was reconstructed using the general time reversible substitution model with gamma distributed rate heterogeneity and 1000 bootstraps using RAxML (v4.8.10).

1). Based on recombination analysis and phylogenetic trees (Figure 2A), we found that 2019-nCoV shares a most recent common ancestor with BetaCoV/RaTG13/2013 (EPI_ISL_402131), because both viruses are in the same cluster. However, our results indicate that this cluster may be the result of convergent evolution or complex recombination events involving at least two virus species with differing evolutionary histories (Figure 2A). The two external segments of this clustered viral genome, encompassing nucleotide (nt) 1 to nt 13 521, and nt 23 687 to nt 30 079, are similar to bat CoVs ZC45 and ZXC21. The first segment includes ORF1a and the second segment includes the C terminus of the S protein, ORF3, E, M, ORF6, ORF7a, ORF8, N, and ORF10 (Figure 2A). This finding is also supported by reconstructing maximum likelihood (ML) phylogenetic trees, which reveal that segments from nt 1 to nt 13 521 and from nt 23 687 to nt 30 079 are clustered with *Sarbecovirus*. However, based on the ML tree result, the middle segment from nt 13 522 to nt 23 686 of 2019-nCoV genome and RaTG13 does not cluster with *Sarbecovirus*. It forms a new branch in the phylogenetic tree, located between *Sarbecovirus* and an Unclassified CoV. In addition, a recent preliminary report showed that the receptor-binding motif (RBM) of these two genomes shares a very low sequence similarity [56]. This divergence indicates a possible alternative source for the RBM encoding sequence in 2019-nCoV, as suggested by other preliminary reports [52,57]. Interestingly, Lam *et al.* found several putative pangolin CoV sequences with 85.5% to 92.4% similarity to 2019-nCoV [52]. Further preliminary studies showing the existence of multiple lineages of pangolin CoVs with genetic similarity to 2019-nCoV further support the hypothesis that pangolins served as a potential intermediate host [52,58]. The currently available data do not fully elucidate if the virus was directly transmitted from bats to humans or indirectly through an intermediate host, nor do they currently rule out convergent evolution as an alternative hypothesis to recombination to explain the discordant phylogenetic trees. Consequentially, more sequence data are needed to confirm the specific source and origin of the 2019-nCoV, which can only be achieved by enhanced collection and monitoring of bat and other wild animal samples.

The topology of a phylogenetic tree with all the currently available spike protein gene sequences of 2019-nCoV shows high similarities between human isolates (Figure 2B), indicating only minimal genetic variation, which is rather unexpected for fast evolving RNA viruses [42]. However, these similarities could be the result of a relatively recent common ancestor, suggesting that the emergence of the virus was a recent event. Furthermore, results are similar to the finding from other preliminary reports that indicate that the virus source of interspecies transmission was highly concentrated or limited, possibly a single event [14,42,43,59]. In addition, the high sequence similarity among the viruses isolated from patients indicates a recent introduction to humans [60]. In all, these results further support the role of Wuhan as the epicenter of the outbreak and there is no evidence for other sources of this 2019-nCoV.

Structure and Function of the Spike Protein of 2019-nCoV, the Major Determinant of Cell Tropism

The spike protein (S) is the major determinant of cell tropism and hence interspecies transmission of CoVs, since it binds the virus to a cellular receptor and subsequently catalyzes virus entry by membrane fusion. The 3D structure of the viral S of 2019-nCoV determined by electron microscopy (Figure 3A, [61]) revealed its similarity to S of other CoVs. This allows deduction of further features from other CoVs. S is a type I trimeric transmembrane protein with an N terminal cleavable signal peptide, one large and heavily *N*-glycosylated ectodomain (60–90 carbohydrates per trimer), a transmembrane region, and a cytoplasmic tail containing a cluster of *S*-acylated cysteine residues. The ectodomain is cleaved by proteases into the between genera highly variable S1 domain, carrying the receptor-binding activities, and the more conserved S2 domain that catalyzes membrane fusion. The S1 domain is further divided into

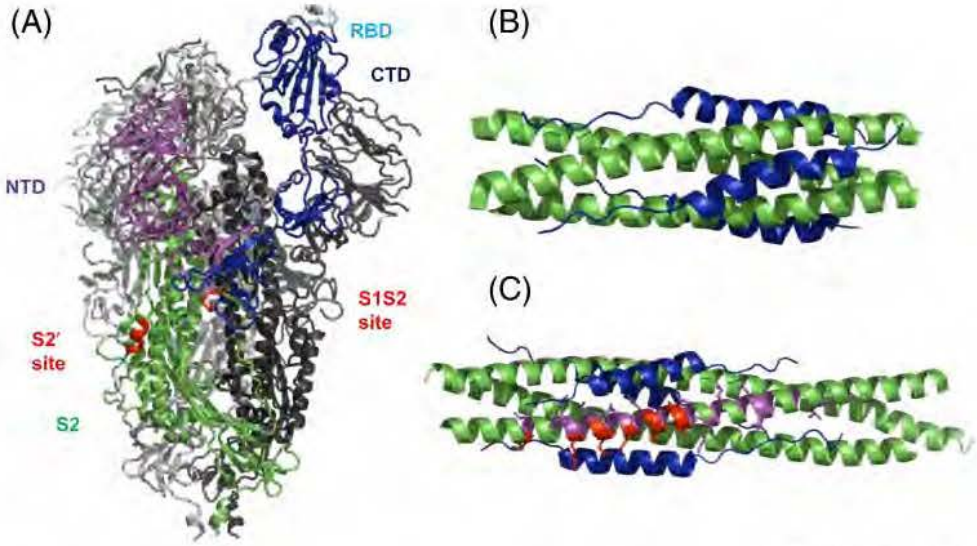

Figure 3. Structure of Spike Protein (S) Before and After Membrane Fusion. (A) Structure of the trimeric ectodomain of S from 2019-nCoV. The S2 subunit in one monomer is shown in green, the N terminal domain (NTD) of S2 in magenta, and the C terminal domain (CTD) of S2 in blue. The CTD is in the 'up-conformation', exposing the binding domain for the angiotensin-converting enzyme 2 (ACE2) receptor (cyan). The S1/S2 and S2' cleavage sites are indicated in red. The figure was created with Pymol from Protein Data Bank (PDB) file 6VSB. (B) Structure of the heptad repeat (HR) domains of S from severe acute respiratory syndrome coronavirus (SARS-CoV). Heptad repeat region 1 (HR1) is labeled green and repeat region 2 (HR2) in blue. Formation of this six-helix bundle is supposed to drive membrane fusion. The figure was created with Pymol from PDB file 1ZV8. (C) Structure of the HR1 of S from SARS-CoV (green) bound to the pan-coronavirus peptide inhibitor EK1 (blue). The amino acids in S essential for binding to EK1 are shown as magenta sticks in one helix. The amino acids in S from 2019-nCoV not conserved in S from SARS-CoV are shown as red sticks. Since the nonconserved amino acids are apparently not required for binding to EK1, the fusion inhibitor is likely to prevent cell entry of 2019-nCoV. The figure was created with Pymol from PDB file 5ZVM. Abbreviations: RBD, receptor-binding domain.

an N terminal domain (NTD) and a C terminal domain (CTD). The NTD exhibits a structural fold as human galectins, galactose-binding lectins, and hence, in most CoVs, a sugar present at the cell surface serves as an attachment factor. The CTD is responsible for binding to the host receptor angiotensin-converting enzyme 2 (ACE2) in the case of SARS-CoV and 2019-nCoV. The CTD contains two subdomains: a core structure (a five-stranded antiparallel β-sheet) and the actual RBM, which determines the receptor binding specificity. The recently released structure of the RBM ACE2 complex (Figure 4A) revealed that most S residues contacting ACE2 are identical between SARS-CoV and 2019-nCoV. However, some are unique, including an important salt bridge that involves different amino acids in ACE2 to bind S of SARS-CoV and 2019-nCoV. These slight differences might explain the more efficient binding of S from 2019-nCoV to ACE2, but this has not been observed in other preliminary studies [61,62].

The CTD of S has basically the same folding in other CoVs, even if they use different host receptors, such as dipeptidyl peptidase 4 for MERS-CoV. The diversity of receptor usage is an outstanding feature of CoVs and (assuming that they all have derived from a common ancestor) already indicates that they have changed their receptor binding specificity multiple times during evolution [63–65].

After binding to its receptor, S catalyzes fusion of the viral and cellular membrane to allow access of the viral genome to the cytosol. A prerequisite for this activity is the cleavage of S into subunits, a process called priming. The first cleavage site is located at the S1/S2 boundary

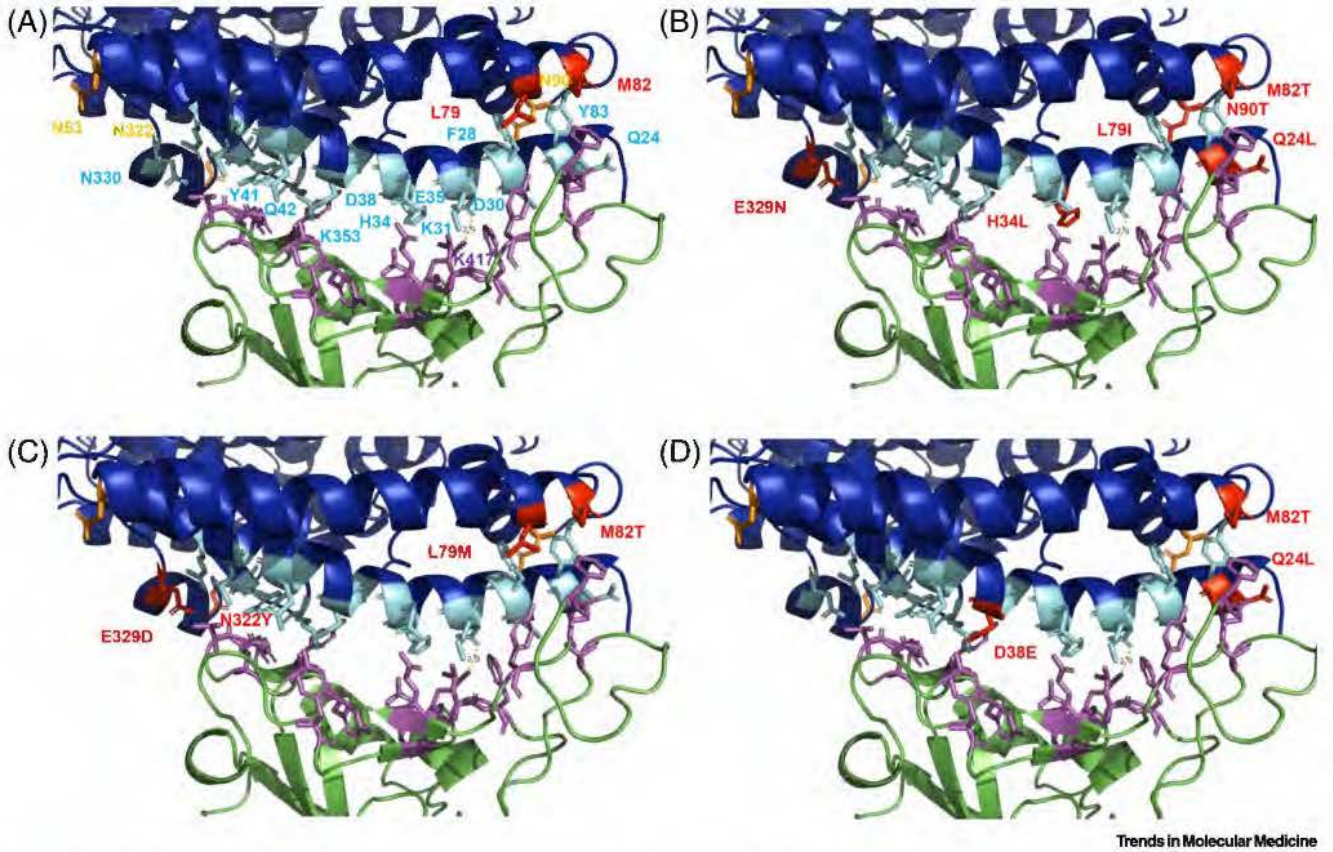

Figure 4. Spike Protein (S) and Its Receptor. (A) Structure of the receptor-binding domain of S from 2019-nCoV (green) bound to human angiotensin-converting enzyme 2 (ACE2) (blue). Most amino acids involved in binding are highlighted as magenta (S) and cyan (ACE2) sticks. Asparagine (N) that are *N*-glycosylation sites (motif N-X-S/T) in human ACE2 are shown as orange sticks. Amino acids in human ACE2 that are involved in binding, but encode a potential *N*-glycosylation site in ACE2 from other species, are shown as red sticks. The dotted line indicates the salt bridge between D30 and K417 (generated with Pymol from Protein Data Bank file6VSB). (B) Amino acid exchanges between human ACE2 and pig ACE2. Amino acid exchanges in ACE2 from pig compared with human ACE2 are highlighted in red. The exchange N90T destroys the *N*-glycosylation site in human ACE2. (C) Amino acid exchanges between human ACE2 and cattle ACE2. Amino acid exchanges in ACE2 from cattle compared with human ACE2 are highlighted in red. The exchange N322Y destroys the *N*-glycosylation site in human ACE2. ACE2 from sheep exhibits identical amino acid exchanges. (D) Amino acid exchanges between human and cat ACE2. Amino acid exchanges in ACE2 from cat compared with human ACE2 are highlighted in red. All relevant glycosylation sites in human ACE2 are conserved.

and another site (called S2') within S2. CoVs have evolved multiple strategies for proteolytic activation of S, and a large number of host proteases, such as furin, trypsin, trans-membrane protease/serine (TMPRSS), and cathepsins have been identified to process the spike protein. As a rule, furin cleaves S at a polybasic cleavage site (minimal motif R-X-X-R) during its biosynthesis in the trans-Golgi compartments or during virus entry in endosomes. Cleavage by trypsin and TMPRSS family members occurs at monobasic cleavage sites and likely takes place in the extracellular space and at the cell surface. Cathepsins, ubiquitous lysosomal enzymes with a rather broad substrate specificity, cleave S during virus entry [66]. For 2019-nCoV, it was shown that TMPRSS 2 primes S, the cathepsins B and L are only required in the absence of this protease [67]. Interestingly, S of 2019-nCoV has acquired a polybasic motif at the S1/S2 boundary, which is not present in S of the bat CoVs and SARS-CoV [68]. Preliminary data showed that S of 2019-nCoV is cleaved by furin during its biosynthesis [69]. This is reminiscent of low-pathogenic **avian influenza viruses**, which, if introduced into a poultry farm, may acquire a polybasic cleavage motif that causes a deadly outbreak of highly

pathogenic virus. S of MERS-CoV has a similar motif, which is cleaved by furin during biosynthesis of S. The availability and activity of the proteases in a certain cell, tissue, and host species regulates the tropisms of CoVs. However, the fact that S can easily acquire new protease cleavage sites and that various (some of them ubiquitous) proteases can fulfil the same task suggests that CoVs are naturally equipped or can easily adapt to multiply in several cell types.

Cleavage at the internal S2′ site occurs just upstream of the sequence S-F-I-E-D-L-L-F, which is highly conserved between S proteins of CoVs. It likely functions as a fusion peptide that inserts into the cellular membrane once the conformational change that catalyzes membrane fusion has been initiated. What triggers the refolding of S is unclear; the low pH prevailing in the endosome during virus entry is only required to activate cathepsins and binding to the receptor causes only minor conformational changes, but might be required to expose a previously hidden proteolytic cleavage site. The structure of parts of the S2 subunit from SARS-CoV in the postfusion conformation (Figure 3B) revealed a six helix bundle between two heptad repeats (a motif of seven amino acids in which amino acid 1 and 4 are hydrophobic), which is a typical feature of class I fusion proteins, such as hemagglutinin (HA) of influenza virus and Gp160 of HIV. However, the six helix bundle formed by S is longer, indicating its formation released more energy that drives the fusion of two lipid bilayers [70,71]. In summary, an amazingly large number of experimental data have already been worked out for S of 2019-nCoV and these models are still evolving.

Molecular Differences in the ACE2 Receptor between Human and Animal Species

The identification of the contact residues between the receptor-binding domain of S from 2019-nCoV and human ACE2 allows estimation of whether 2019-nCoV could infect other species (Figure 4A) [72]. To do so, we aligned all available ACE2 amino acid sequences with human ACE2. We placed emphasis on the presence of *N*-glycosylation motifs near the binding site, since they might affect attachment of S. Human ACE2 is glycosylated at N53, N90, and N322 (Figure 4A, orange sticks). N53 is conserved in all species. N90 is not a glycosylation site in ACE2 of mouse, pig, *N. procyonoides*, raccoon, civet, ferret, fox, *E. telfairi*, and chicken. N322 is not a glycosylation site in ACE2 of mouse, rat, cattle, sheep, *E. telfairi*, and pangolin. However, ACE2 of some species contain an additional glycosylation motif in this region. Residue L79 is a potential *N*-glycosylation site in chicken and M82 is a potential glycosylation site in *Rhinolophus sinicus*, pangolin, and rat. Notably, glycosylation of residue 82 has been show to prevent binding of S from SARS-CoV to rat ACE2 [73].

Some amino acids in ACE2 affect binding to S of 2019-nCoV are depicted for various species in Table 1. The S binding site of ACE2 from macaque and chimpanzees is identical to human ACE2. ACE2 from other species revealed eleven (chicken), nine and ten (rodents), or only three (cat) amino acid differences compared with human ACE2. Of special interest are ACE2 proteins from farm animals and a pet cat, since they might become another possible reservoir for 2019-nCoV. ACE2 from pig contains six exchanges, but they are mostly located at the periphery of the binding site (Figure 4B). N90T causes the loss of the glycosylation site. E329 forms a salt bridge with R426 in S of SARS-CoV, but S of 2019-nCoV forms a salt bridge with another residue (D30) in ACE2. Thus, the exchange of E329 by N in porcine ACE2 might affect binding to S of SARS-CoV, but not to S from 2019-nCoV. A similar pattern emerges for amino acid differences between human and cattle ACE2 (Figure 4C) and cat ACE2 (Figure 4D). The few exchanges are also located peripheral to the core of the binding region and thus their exchange might not represent a large obstacle for infection of cells from these species with 2019-nCoV.

Table 1. Comparison of Some Important ACE2 Residues among Different Species That Affect Binding to 2019-nCoV Receptor-Binding Domain (RBD)

Species	Amino acids (19) in different species ACE2 that affect binding to 2019-nCoV RBD, corresponding positions are based on human ACE2 numbering																			Similarity to human ACE2 (based on 19 amino acids)	GenBank accession number
	24	31	34	35	38	41	42	53	79	82	83	90	322	325	329	330	353	652	710		
Human	Q	K	H	E	D	Y	Q	N	L	M	Y	N	N	Q	E	N	K	R	R	19/19	AAT45083.1
Pig	**L**	K	**L**	E	D	Y	Q	N	**I**	**T**	Y	**T**	N	Q	**N**	N	K	R	R	13/19	XP_020935033.1
Cat	**L**	K	H	E	**E**	Y	Q	N	L	**T**	Y	N	N	Q	E	N	K	R	R	16/19	XP_023104564.1
Macaque	Q	K	H	E	D	Y	Q	N	L	M	Y	N	N	Q	E	N	K	R	R	19/19	XP_011733505.1
Chimpanzee	Q	K	H	E	D	Y	Q	N	L	M	Y	N	N	Q	E	N	K	R	R	19/19	XP_016798468.1
Mouse	**N**	**N**	**Q**	E	D	Y	Q	N	**T**	**S**	**F**	**T**	**H**	Q	**A**	N	**H**	R	R	9/19	ABN80106.1
Rat	**K**	K	**Q**	E	D	Y	Q	N	**I**	**N**	**F**	N	**Q**	**P**	**T**	N	**H**	R	R	10/19	AAW78017.1
Rhinolophus sinicus	**E**	K	**T**	**K**	D	**H**	Q	N	L	**N**	Y	N	N	**E**	**N**	N	K	R	R	12/19	AGZ48803.1
Horse	**L**	K	**S**	E	**E**	**H**	Q	N	L	**T**	Y	N	N	Q	E	N	K	R	R	14/19	XP_001490241.1
Cattle	Q	K	H	E	D	Y	Q	N	**M**	**T**	Y	N	**Y**	Q	**D**	N	K	R	R	15/19	XP_005228485.1
Sheep	Q	K	H	E	D	Y	Q	N	**M**	**T**	Y	N	**Y**	Q	**D**	N	K	R	R	15/19	XP_011961657.1
Nyctereutes procyonoides	**L**	K	**Y**	E	**E**	Y	Q	N	L	**T**	Y	**D**	N	Q	E	N	**R**	R	R	13/19	ABW16956.1
Raccoon	**L**	**N**	**N**	E	**E**	Y	Q	N	**Q**	**T**	Y	**D**	N	Q	E	N	K	R	R	12/19	BAE72462.1
Camel	**L**	**E**	H	E	D	Y	Q	N	**T**	**T**	Y	N	N	Q	**D**	N	K	R	R	14/19	XP_031301717.1
Civet	**L**	**T**	**Y**	E	**E**	Y	Q	N	L	**T**	Y	**D**	N	Q	E	N	K	R	R	13/19	AAX63775.1
Ferret	**L**	K	**Y**	E	**E**	Y	Q	N	**H**	**T**	Y	**D**	N	**E**	**Q**	N	K	R	R	11/19	BAE53380.1
Fox	**L**	K	**Y**	E	**E**	Y	Q	N	L	**T**	Y	**D**	N	Q	E	N	K	R	R	14/19	XP_025842513.1
Echinops telfairi	Q	**T**	**N**	E	**N**	Y	Q	N	L	**K**	**F**	**D**	**P**	Q	**D**	**K**	**L**	R	R	9/19	XP_004710002.1
Chicken	**E**	**E**	**V**	**R**	D	Y	**E**	N	**N**	**R**	**F**	**D**	N	**E**	**T**	N	K	R	R	8/19	XP_416822.2
Pangolin	**E**	K	**S**	E	**E**	Y	Q	N	**I**	**N**	Y	N	**K**	Q	E	N	K	R	R	13/19	XP_017505752.1

Potential Drug Targets in S of 2019-nCoV

No approved antiviral agents are available against the current outbreak, but convalescent sera or monoclonal antibodies inhibit SARS-CoV or MERS-CoV *in vitro* or in animal models. However, sufficient sera and antibodies can hardly be produced during a large outbreak. Moreover, monoclonal antibodies neutralizing SARS-CoV are not (or only poorly) reactive against 2019-nCoV, indicating that the antibody epitopes are highly variable [74]. Inhibitors of the proteases that prime S for fusion also have antiviral activity. However, since S can use various proteases for priming, more than one inhibitor is required.

More promising are drugs directed against the highly conserved S2 subunit, such as peptides that inhibit membrane fusion. The proof of principle is **enfuvirtide**, a 20 amino acid peptide that is identical in sequence to a part of the heptad repeat region 2 (HR2) that forms a six helix bundle with heptad repeat region 1 (HR1). The peptide binds to HR1, which saturates the binding site for HR2, thereby preventing the conformational change that catalyzes membrane fusion. Peptides with a similar mode of action have been developed for the S2 subunit of SARS-CoV and MERS-CoV. They inhibit virus entry, reduce formation of **plaques** *in vitro*, and had beneficial effects in a mouse model. The

most promising peptide is called E1, which binds with high affinity to the HR1 region of S from SARS-CoV [75]. Sequence comparison between HR1 of S from SARS-CoV and 2019-nCoV shows various amino acid exchanges, but none of them is involved in binding to E1 (Figure 3C), indicating that E1 could also be effective against 2019-nCoV.

Another potential drug target might be the cellular enzyme(s) that attach fatty acids to a cluster of cysteines in the cytoplasmic tail of S. The fatty acids are required for S to fuse with the host cell and affect virus assembly, similar to what has been described for other spike proteins, such as HA of influenza virus. Enzymes that attach acyl chains to S have not been identified, but cellular proteins are acylated by one or several of the 23 members of the **ZDHHC family**, which have distinct, only partly overlapping substrate specificities. If only a few of them might acylate S in airway cells of the lung, their blockade might result in suppression of viral replication, while acylation of cellular proteins will not be (or very little) compromised. Although more research is required, targeting acyltransferases might be promising, since the cluster of cysteines is present in S from all CoV genera, regardless of their origin. Acylation might thus be required for a very basic function of S, arguing that even newly emerged CoVs probably will also rely on this modification of S to replicate efficiently [76]. However, since key proteins of the innate immune response are also palmitoylated, acylation inhibitors might be limited if the proteins of the innate immune response are modified by the same enzymes as viral proteins.

Concluding Remarks

Previous studies showed that CoVs genomes display a high degree of plasticity in terms of gene content and recombination. Furthermore, the relatively large CoV genome increases the probabilities for adaptive mutations, with it being relative easy for the spike protein to exploit multiple cellular receptors for virus attachment and entry [52,77–79]. These features are likely the cause of this alarming propensity of CoVs for host-species expansion. Unfortunately, China has seen a number of interspecies transmissions by CoV in recent years [80–82]. Whether this current COVID-19 epidemic 'frizzles out' or expands into a full-blown pandemic remains to be seen. It might also be desirable to monitor farm animals and pet cats for infection with 2019-nCoV, since their ACE2 receptor responsible for 2019-nCoV binding differs in only a few amino acids from human ACE2. Surveillance might prevent the virus establishing itself in another animal species that is in close contact to humans. In addition, in light of the fact that there are multiple species of CoVs circulating in wildlife species and that these animals are constantly interacting with each other, host-species expansion or interspecies transmission of new CoV to humans seems to be inevitable. Major knowledge gaps regarding the emergence of 2019-nCoV remain exists but worldwide scientists are working with unprecedented speed to investigate the virus, rushing to develop targeted therapeutics (see Outstanding Questions). Notwithstanding, a global surveillance network involving veterinarians and animal biologists is urgently needed to monitor, and possibly to predict, potential sources for the emergence of another highly pathogenic CoV. We propose the concept of 'One Health' to facilitate scientific exchange across disciplines, sharing of data, and coordinated efforts in order to prevent future outbreaks.

Outstanding Questions

When and how did COVID-19 emerge? What is or are the natural and intermediate host species for 2019-nCoV? What is the distribution of 2019-nCoV in different mammalian species? Will it infect farm animals or pets?

From surveillance and evolutionary studies on animal viruses, can their zoonotic potential be identified before interspecies transmission occurs?

What are the key interactions between the spike protein (S) of 2019-nCoV and its receptor angiotensin-converting enzyme 2 (ACE 2)? Which amino acids in ACE2 determine whether S can bind? Is efficient binding to ACE2 the only determinant that decides whether an animal species can be infected?

Is expression of the trans-membrane protease/serine another decisive factor for infection of a cell? Is the newly acquired polybasic cleavage site in S associated with cross-species transmission of 2019-nCoV?

What are the similarities and differences of COVID-19 epidemiology in comparison with SARS and MERS? What is the basic reproductive number (R_0), the real incubation period, and the morbidity and mortality rate? Can COVID-19 develop into an endemic or seasonal infectious disease, like the flu?

With the experience of mitigating the outbreaks of SARS and avian influenza, what strategies can be applied in mitigating COVID-19 and future CoV outbreaks? Should veterinarians play more important roles in the prevention and control of emerging zoonoses in the future?

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References

1. Gorbalenya, A.E. *et al.* (2020) Severe acute respiratory syndrome-related coronavirus: the species and its viruses – a statement of the Coronavirus Study Group. *bioRxiv*. Published online February 11, 2020. https://doi.org/10.1101/2020.02.07.937862
2. Resta, S. *et al.* (2018) Isolation and propagation of a human enteric coronavirus. *Science* 4717, 978–981
3. Arabi, Y.M. *et al.* (2017) Middle East Respiratory Syndrome. *N. Engl. J. Med.* 376, 584–594
4. Zhong, N.S. *et al.* (2003) Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet* 362, 1353–1358
5. Drosten, C. *et al.* (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N. Engl. J. Med.* 348, 1967–1976
6. Guan, Y. *et al.* (2003) Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 302, 276–278
7. Song, H.D. *et al.* (2005) Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. *Proc. Natl. Acad. Sci. U. S. A.* 102, 2430–2435
8. Cohen, J. *et al.* (2019) New SARS-like virus in China triggers alarm. *Science* 6475, 234–235
9. Woo, P.C. *et al.* (2012) Discovery of seven novel mammalian and avian coronaviruses in the genus *Deltacoronavirus* supports bat coronaviruses as the gene source of *Alphacoronavirus* and *Betacoronavirus* and avian coronaviruses as the gene source of *Gammacoronavirus* and *Deltacoronavirus*. *J. Virol.* 86, 3995–4008
10. 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
11. He, B. *et al.* (2014) Identification of diverse alphacoronaviruses and genomic characterization of a novel severe acute respiratory syndrome-like coronavirus from bats in China. *J. Virol.* 88, 7070–7082
12. Li, Q. *et al.* (2020) Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *N. Engl. J. Med.* Published online January 29, 2020. https://doi.org/10.1056/NEJMoa2001316
13. Wang, D. *et al.* (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. Published online February 7, 2020. https://doi.org/10.1001/jama.2020.1585
14. Chan, J.F-W. *et al.* (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 395, 514–523
15. Yang, Y. *et al.* (2020) Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. *medRxiv*. Published online February 21, 2020. https://doi.org/10.1101/2020.02.10.20021675
16. Kang, M. *et al.* (2020) Evidence and characteristics of human-to-human transmission of SARS-CoV-2. *medRxiv*. Published online February 17, 2020. https://doi.org/10.1101/2020.02.03.20019141
17. Liu, Y.-C. *et al.* (2020) A locally transmitted case of SARS-CoV-2 infection in Taiwan. *N. Engl. J. Med.* Published online February 12, 2020. https://doi.org/10.1056/NEJMc2001573
18. Chang, D. *et al.* (2020) Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. *JAMA*. Published online February 7, 2020. https://doi.org/10.1001/jama.2020.1623
19. Li, L. *et al.* (2020) An update on the epidemiological characteristics of novel coronavirus pneumonia (COVID-19). *Zhonghua Liu Xing Bing Xue Za Zhi* 41, 139–144
20. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (2020) The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi* 41, 145–151
21. Guan, W.-j. *et al.* (2020) Clinical characteristics of 2019 novel coronavirus infection in China. *medRxiv*. Published online February 9, 2020. https://doi.org/10.1101/2020.02.06.20020974
22. Lipsitch, M. *et al.* (2003) Transmission dynamics and control of severe acute respiratory syndrome. *Science* 300, 1966–1970
23. Riley, S. *et al.* (2003) Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. *Science* 300, 1961–1966
24. Breban, R. *et al.* (2013) Interhuman transmissibility of Middle East respiratory syndrome coronavirus: estimation of pandemic risk. *Lancet* 382, 694–699
25. Chowell, G. *et al.* (2004) Model parameters and outbreak control for SARS. *Emerg. Infect. Dis.* 10, 1258–1263
26. Swerdlow, D.L. and Finelli, L. (2020) Preparation for possible sustained transmission of 2019 novel coronavirus: lessons From previous epidemics. *JAMA*. Published online February 11, 2020. https://doi.org/10.1001/jama.2020.1960
27. Park, J.E. *et al.* (2018) MERS transmission and risk factors: a systematic review. *BMC Public Health* 18, 574
28. Paul, L.D. *et al.* (2019) Complexity of the basic reproduction number (R_0). *Emerg. Infect. Dis.* 25, 1–4
29. Chen, N. *et al.* (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395, 507–513
30. Pongpirul, W.A. *et al.* (2020) Journey of a Thai taxi driver and novel coronavirus. *N. Engl. J. Med.* Published online February 12, 2020. https://doi.org/10.1056/NEJMc2001621
31. Bastola, A. *et al.* (2020) The first 2019 novel coronavirus case in Nepal. *Lancet Infect. Dis.* 20, 279–280
32. Holshue, M.L. *et al.* (2020) First case of 2019 novel coronavirus in the United States. *N Engl. J. Med.* Published online January 31, 2020. https://doi.org/10.1016/S1473-3099(20)30067-0
33. Huang, C., *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497-506
34. Chen, H., *et al.* Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 20, 30360-30363
35. Xu, X. *et al.* (2020) Imaging features of 2019 novel coronavirus pneumonia. *Eur. J. Nucl. Med. Mol. Imaging*. Published online February 14, 2020. https://doi.org/10.1007/s00259-020-04720-2
36. Lin, X. and Gong, Z. (2020) Novel coronavirus pneumonia outbreak in 2019: computed tomographic findings in two cases. *Korean J. Radiol.* 21, 365–368
37. Wei, M. *et al.* (2020) Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA*. Published online February 14, 2020. https://doi.org/10.1001/jama.2020.2131
38. Hoehl, S. *et al.* (2020) Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. *N. Engl. J. Med.* Published online February 18, 2020. https://doi.org/10.1056/NEJMc2001899
39. Zhu, H. *et al.* (2020) Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl. Pediatr.* 9, 51–60
40. Anderson, R.M. *et al.* (2004) Epidemiology, transmission dynamics and control of SARS: the 2002-2003 epidemic. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 359, 1091–1105
41. Chowell, G. *et al.* (2015) Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study. *BMC Med.* 13, 210
42. Zhou, P. *et al.* (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. Published online February 3, 2020. https://doi.org/10.1038/s41586-020-2012-7
43. Wu, F. *et al.* (2020) A new coronavirus associated with human respiratory disease in China. *Nature*. Published online February 3, 2020. https://doi.org/10.1038/s41586-020-2008-3
44. Li, G. *et al.* (2018) Origin, genetic diversity, and evolutionary dynamics of novel porcine circovirus 3. *Adv. Sci. (Weinh)* 5, 1800275

45. Huang, Y.-W. *et al.* (2013) Origin, evolution, and genotyping of emergent porcine epidemic diarrhea virus strains in the United States. *mBio* 4, e00737-00713
46. Tao, Y. *et al.* (2017) Surveillance of bat coronaviruses in Kenya identifies relatives of human coronaviruses NL63 and 229E and their recombination history. *J. Virol.*, e01953-16
47. Yang, L. *et al.* (2019) Broad cross-species infection of cultured cells by bat HKU2-related swine acute diarrhea syndrome coronavirus and identification of its replication in murine dendritic cells in vivo highlight its potential for diverse interspecies transmission. *J. Virol.* 93, e01448-19
48. Karakus, U. *et al.* (2019) MHC class II proteins mediate cross-species entry of bat influenza viruses. *Nature* 7746, 109–112
49. He, W. *et al.* (2019) Genetic analysis and evolutionary changes of porcine circovirus 2. *Mol. Phylogenet. Evol.* 139, 106520
50. Chen, W. *et al.* (2005) SARS-associated coronavirus transmitted from human to pig. *Emerg. Infect. Dis.* 11, 446–448
51. Hu, D. *et al.* (2018) Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats. *Emerg. Microbes Infect.* 7, 154
52. Lam, T.T.-Y. *et al.* (2020) Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China. *bioRxiv*. Published online February 18, 2020. https://doi.org/10.1101/2020.02.13.945485
53. Menachery, V.D. *et al.* (2015) A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat. Med.* 21, 1508–1513
54. Paraskevis, D. *et al.* (2020) Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. *Infect. Genet. Evol.* 79, 104212
55. Luk, H.K.H. *et al.* (2019) Molecular epidemiology, evolution and phylogeny of SARS coronavirus. *Infect. Genet. Evol.* 71, 21–30
56. Wong, M.C. *et al.* (2020) Evidence of recombination in coronaviruses implicating pangolin origins of nCoV-2019. *bioRxiv*. Published online February 13, 2020. https://doi.org/10.1101/2020.02.07.939207
57. Xiao, K. *et al.* (2020) Isolation and characterization of 2019-nCoV-like coronavirus from Malayan pangolins. *bioRxiv*. Published online February 20, 2020. https://doi.org/10.1101/2020.02.17.951335
58. Liu, P. *et al.* (2020) Are pangolins the intermediate host of the 2019 novel coronavirus (2019-nCoV)? *bioRxiv*. Published online February 20, 2020. https://doi.org/10.1101/2020.02.18.954628
59. Lu, R. *et al.* (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 395, 565–574
60. Hui, K.P. *et al.* (2017) Tropism and innate host responses of influenza A/H5N6 virus: an analysis of ex vivo and in vitro cultures of the human respiratory tract. *Eur. Respir. J.* 49, 1601710
61. Wrapp, D. *et al.* (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. Published online February 19, 2020. https://doi.org/10.1126/science.abb2507
62. Sun, C. *et al.* (2020) SARS-CoV-2 and SARS-CoV spike-RBD structure and receptor binding comparison and potential implications on neutralizing antibody and vaccine development. *bioRxiv*. Published online February 20, 2020. https://doi.org/10.1101/2020.02.16.951723
63. Li, F. (2016) Structure, function, and evolution of coronavirus spike proteins. *Annu. Rev. Virol.* 3, 237–261
64. Cui, J. *et al.* (2019) Origin and evolution of pathogenic coronaviruses. *Nat. Rev. Microbiol.* 17, 181–192
65. Lu, G. *et al.* (2015) Bat-to-human: spike features determining 'host jump' of coronaviruses SARS-CoV, MERS-CoV, and beyond. *Trends Microbiol.* 23, 468–478
66. Millet, J.K. and Whittaker, G.R. (2015) Host cell proteases: critical determinants of coronavirus tropism and pathogenesis. *Virus Res.* 202, 120–134
67. Hoffmann, M. *et al.* (2020) The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *bioRxiv*. Published online January 31, 2020. https://doi.org/10.1101/2020.01.31.929042
68. Coutard, B. *et al.* (2020) The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antivir. Res.* 176, 104742
69. Walls, A.C. *et al.* (2020) Structure, function and antigenicity of the SARS-CoV-2 spike glycoprotein. *bioRxiv*. Published online February 20, 2020. https://doi.org/10.1101/2020.02.19.956581
70. Deng, Y. *et al.* (2006) Structures and polymorphic interactions of two heptad-repeat regions of the SARS virus S2 protein. *Structure* 14, 889–899
71. Heald-Sargent, T. and Gallagher, T. (2012) Ready, set, fuse! The coronavirus spike protein and acquisition of fusion competence. *Viruses* 4, 557–580
72. Lan, J. *et al.* (2020) Crystal structure of the 2019-nCoV spike receptor-binding domain bound with the ACE2 receptor. *bioRxiv*. Published online February 20, 2020. https://doi.org/10.1101/2020.02.19.956235
73. Li, F. *et al.* (2005) Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* 309, 1864–1868
74. Zumla, A. *et al.* (2016) Coronaviruses - drug discovery and therapeutic options. *Nat. Rev. Drug Discov.* 15, 327–347
75. Xia, S. and Yan, L. (2019) A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. *Sci. Adv.* 5, eaav4580
76. Gadalla, M.R. and Veit, M. (2020) Toward the identification of ZDHHC enzymes required for palmitoylation of viral protein as potential drug targets. *Expert Opin. Drug Discov.* 15, 159–177
77. Wang, N. *et al.* (2019) Structural definition of a neutralization-sensitive epitope on the MERS-CoV S1-NTD. *Cell Rep.* 28, 3395–3405
78. Letko, M. *et al.* (2018) Adaptive evolution of MERS-CoV to species variation in DPP4. *Cell Rep.* 24, 1730–1737
79. Zhang, S. *et al.* (2018) Structural definition of a unique neutralization epitope on the receptor-binding domain of MERS-CoV spike glycoprotein. *Cell Rep.* 24, 441–452
80. Su, S. *et al.* (2016) Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol.* 24, 490–502
81. Zhou, P. *et al.* (2018) Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature* 556, 255–258
82. Hu, B. *et al.* (2017) Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLoS Pathog.* 13, e1006698
83. Katoh, K. *et al.* (2002) MAFFT: a novel method for rapid multiple sequence alignment based on fast Fourier transform. *Nucleic Acids Res.* 30, 3059–3066
84. Kumar, S. *et al.* (2016) MEGA7: molecular evolutionary genetics analysis version 7.0 for bigger datasets. *Mol. Biol. Evol.* 33, 1870–1874
85. Stamatakis, A. (2014) RAxML version 8: a tool for phylogenetic analysis and post-analysis of large phylogenies. *Bioinformatics* 30, 1312–1313

16 Years

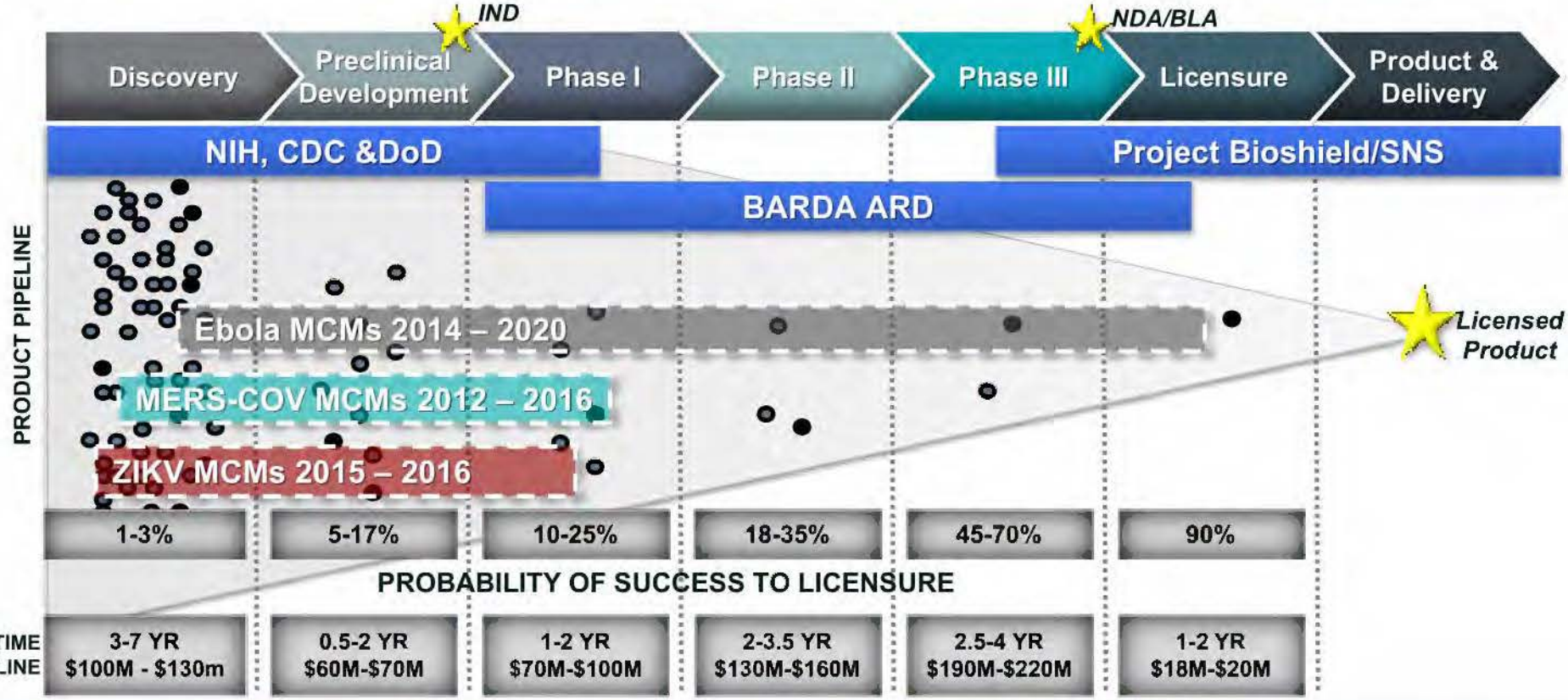
3rd Coronavirus Outbreak

No Licensed products

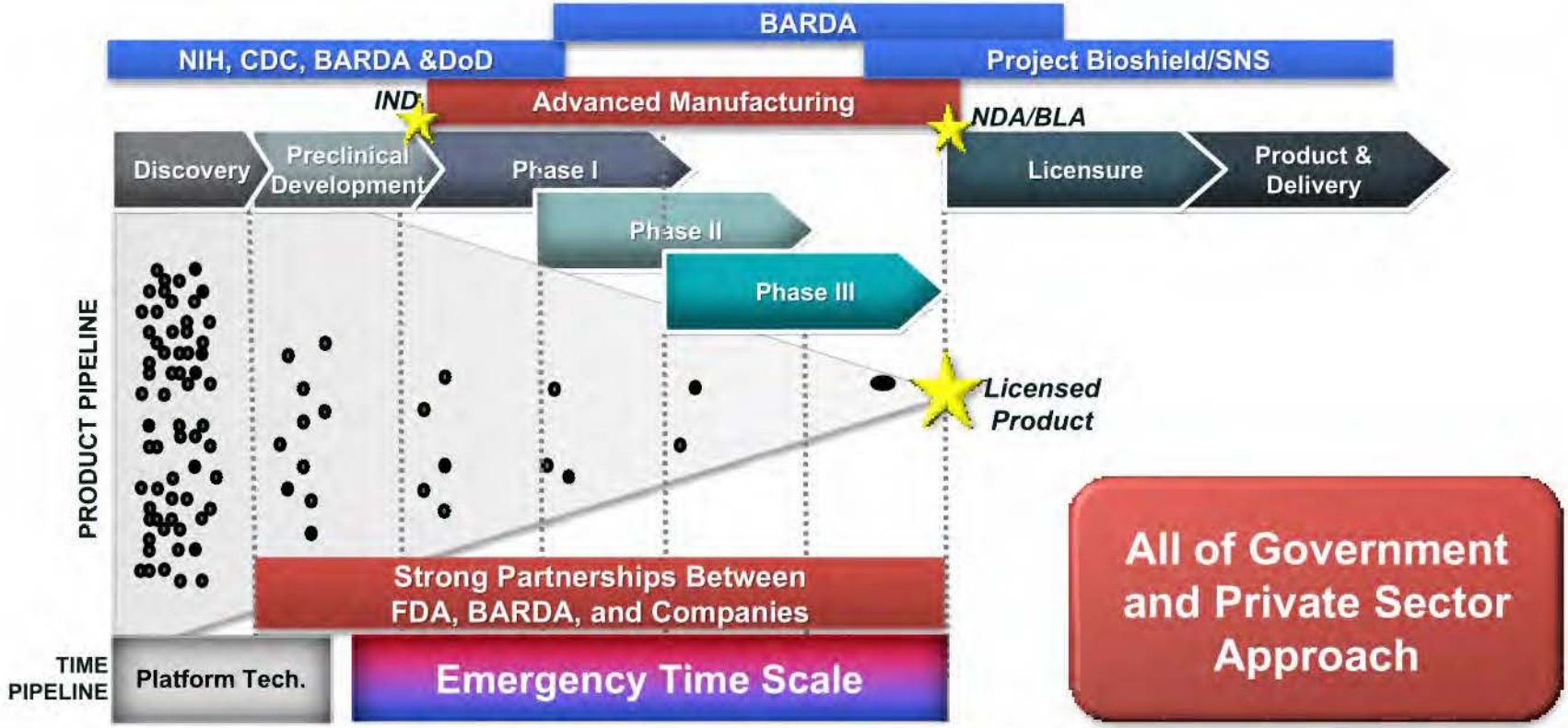
2019-nCoV Medical Countermeasures Task Force

Align MCM development across Interagency partners to avoid duplication of effort, identify opportunities for synergy, and fill potential gaps

Vaccine & Drug Development is Expensive, Risky and Lengthy



Emergency Vaccine & Drug Development



COVID-19 MEDICAL COUNTERMEAUSRE DEVELOPMENT STRATEGY

ACCELERATE DEVELOPMENT

- Platform technologies
- Repurpose licensed products
- Parallel, not sequential, activities

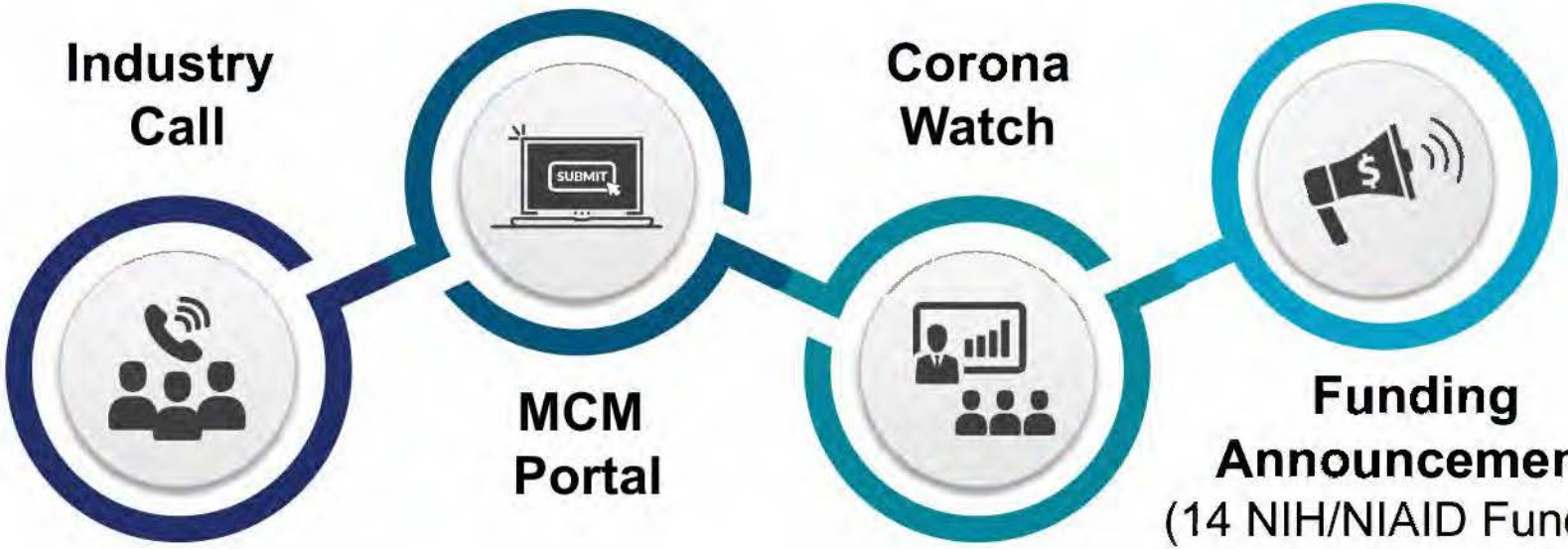
MITIGAGE RISK

- Multiple technologies
- Multiple targets
- Redundancy

DOMESTIC MANUFACTURING

- Scale Up & Scale Out
- Raw materials and supply chains
- Leverage existing facilities

Agency-Wide Engagement with Developers



COVID-19 Market Research Portal Submissions

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BARDA COVID-19 Submissions Report - Overview - EZ-BAA Review - Detailed Tables - Maps

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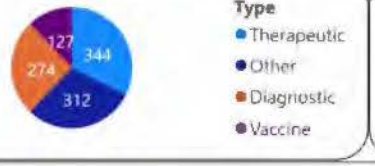
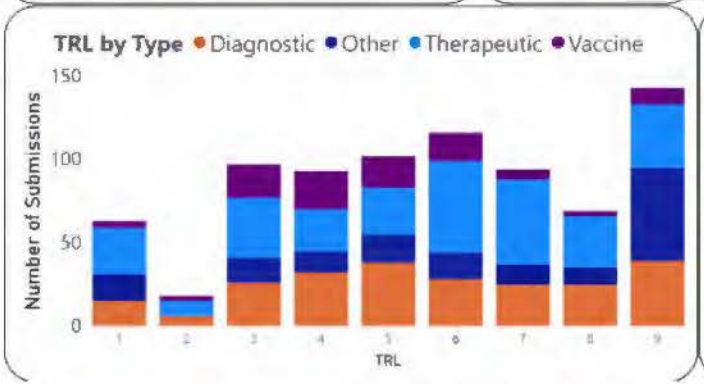
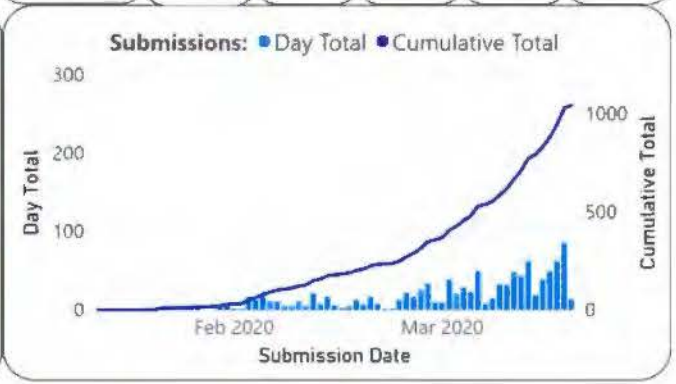
Last Refreshed

Total Submissions	Market Research Submissions	BAA Submissions	EZ-BAA Submissions
1057	1000	7	50



Mkt Research Contacts	Total	Dx	Tx	Vx	Other
All Contacts	1000	231	341	124	304
TWs Held	91	33	21	18	19
TWs Scheduled (not held)	1	-	1	-	-





Therapeutics Development

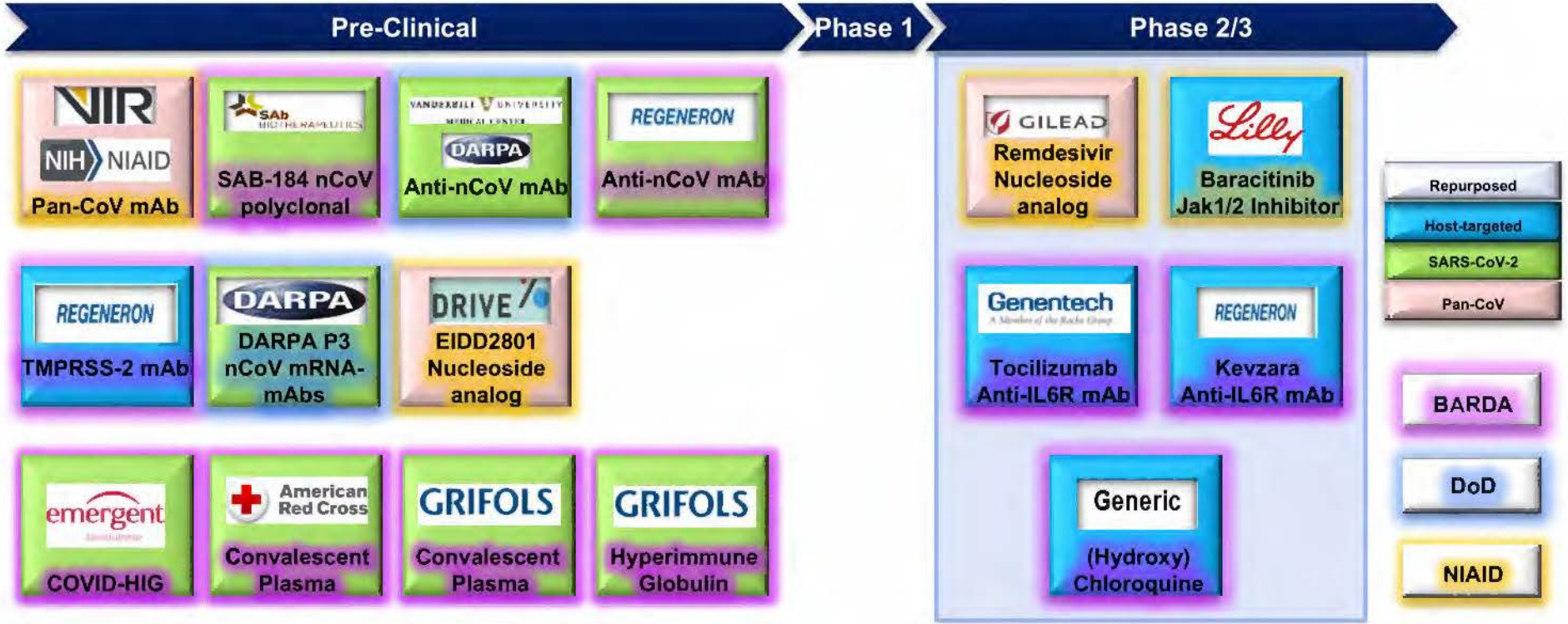
FDA-approved therapeutics licensed for other indications
- Ready for immediate clinical testing

e.g., inhibitors of viral activation, host pathway modulators

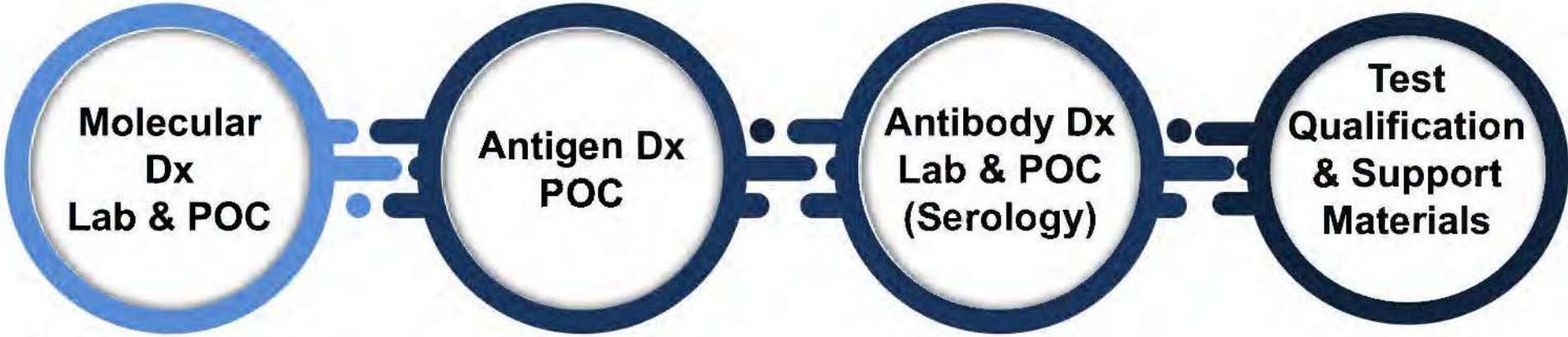
e.g., 2019-CoV specific monoclonal antibodies, small molecule antivirals, and immunoglobulins

Leverage existing infrastructure for rapid MCM generation and production through partnerships (contracts and OTA) including other USG agencies

USG-Supported SARS-CoV-2 Therapeutics



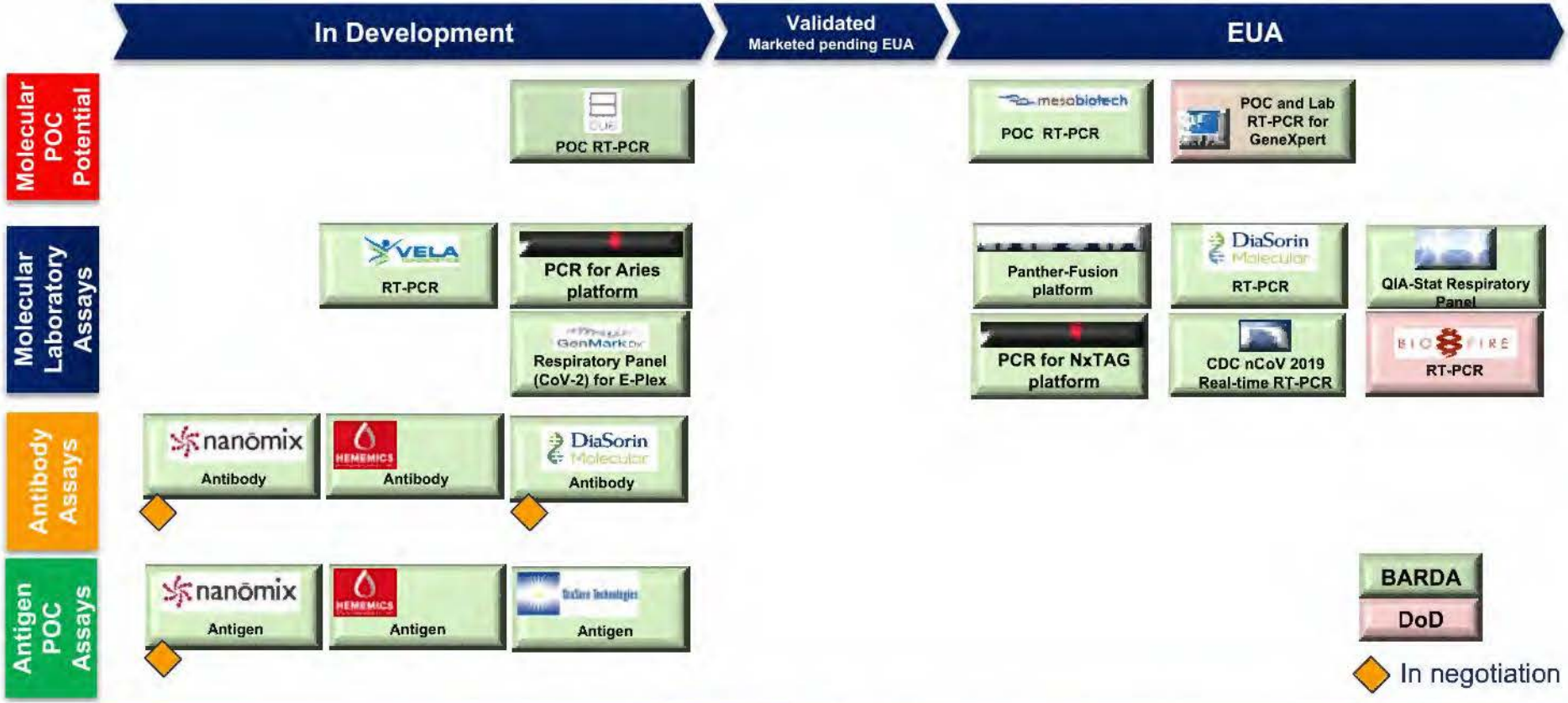
Diagnostics Development: Four-Pronged Approach



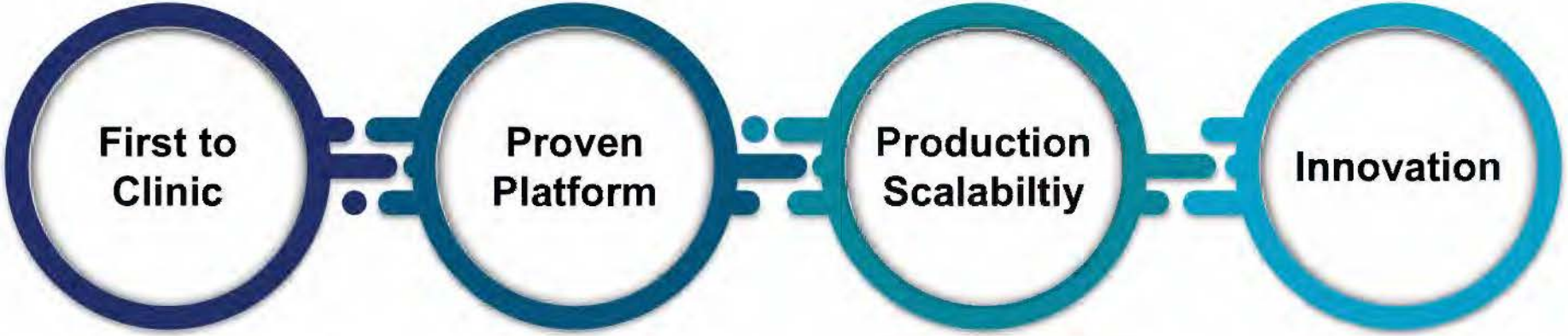
Leverage existing Laboratory Infrastructure & Equipment
Leverage Existing & Complete In-Development POC Equipment

04/02/20

USG-Sponsored SARS-CoV-2 Diagnostic Tests



Vaccine Development



e.g., mRNA based vaccines that allow rapid early development

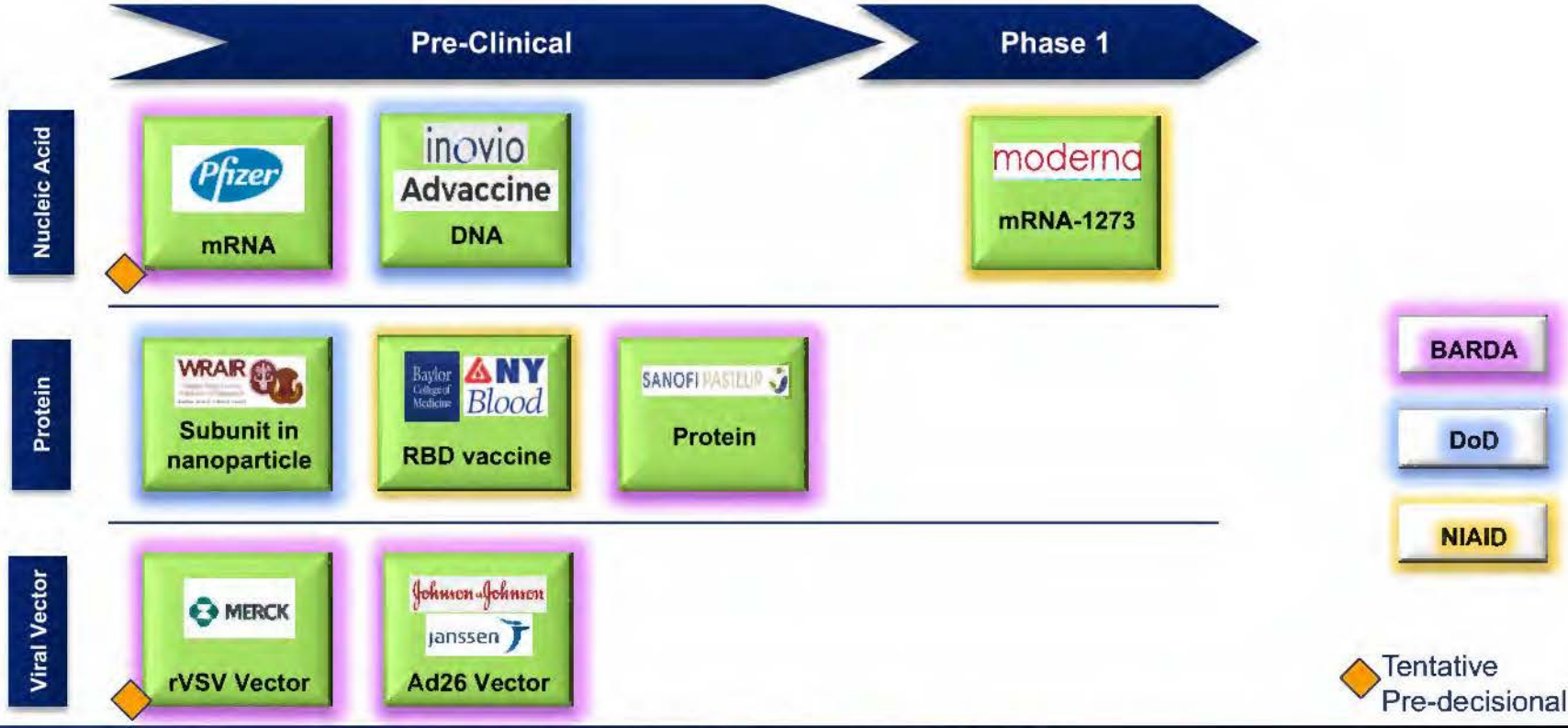
e.g., viral vectors with demonstrated safety and efficacy

e.g., Existing or readily amenable to large scale manufacturing, including experienced workforce

e.g., novel platforms, delivery approaches, or new thinking to transform the field

Leverage existing infrastructure for rapid MCM generation and production through partnerships (contracts and OTA) including other USG agencies

USG-Supported SARS-CoV-2 Vaccines



VACCINE APPROACH

Accelerate Development

Rapid Vaccine Platform Approaches
- Nucleic Acid
- Vectors
- Recombinant protein

Repurpose Licensed Products
- Viral Vector
- Recombinant Protein

Parallel Activities
- Overlapping clinical trials
- Scale up in parallel with clinical development

Mitigate Risk

Multiple Technologies
- Address potential yield risks
- Address potential dose risk

Multiple Targets
- Disease enhancement mitigation
- Alternative routes of delivery

Redundancy
- Take multiple products through large scale clinical trials
- Multiple manufacturing facilities for each product

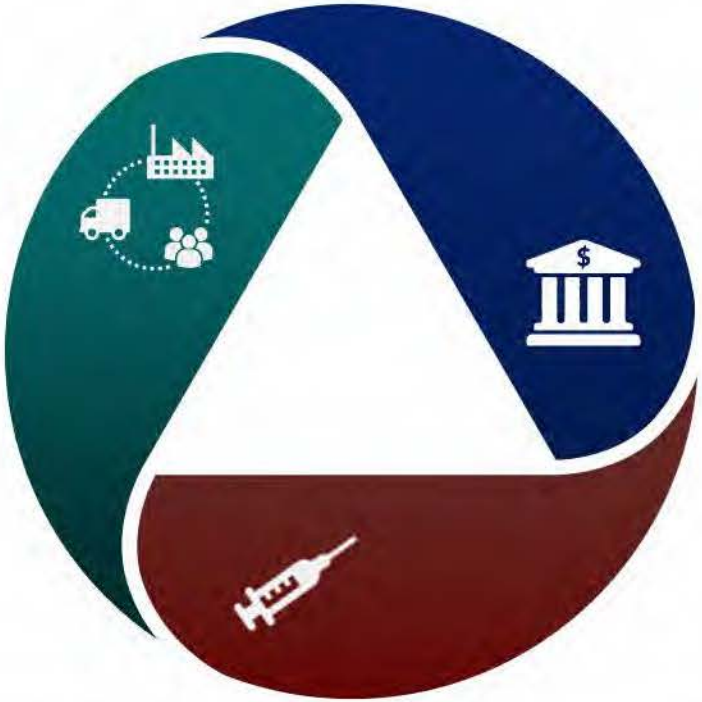
Domestic Manufacturing

Scale up & Scale out
- Validate larger scale process (i.e. larger tanks)
- Multiple
- Technology Transfer to more facilities
- Increase fill/finish capacity

Raw Materials Supply Chains
- Remove bottlenecks
- Establish stockpiles

Leverage Existing Facilities
- **CIADMs**
- Facilities of large pharma partners
- CMOs

Moderna



DEVELOPMENT

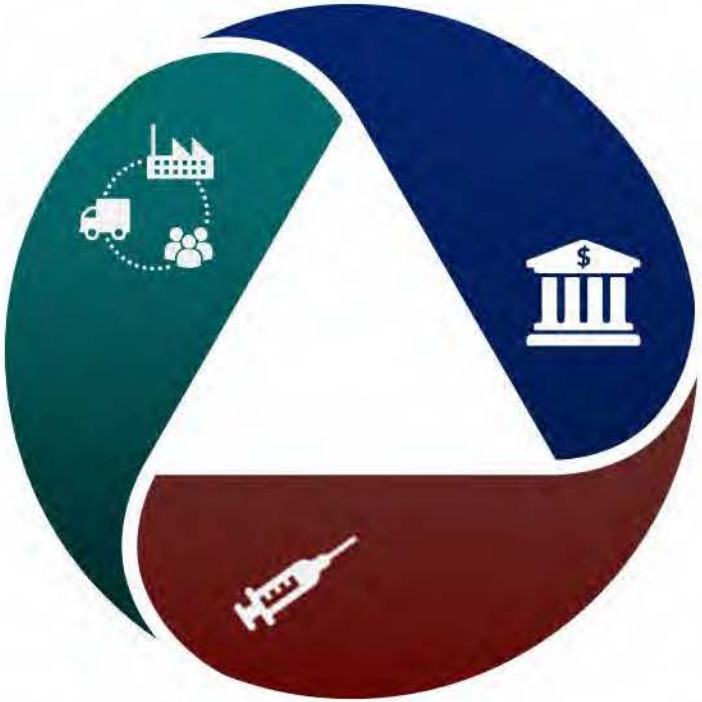
- First to clinic (1Q 2020)
- Phase 2 (2Q 2020)

(b)(5)

DOMESTIC MANUFACTURING

- Scale up (limited) and out
- Secure supply chain

Janssen



DEVELOPMENT

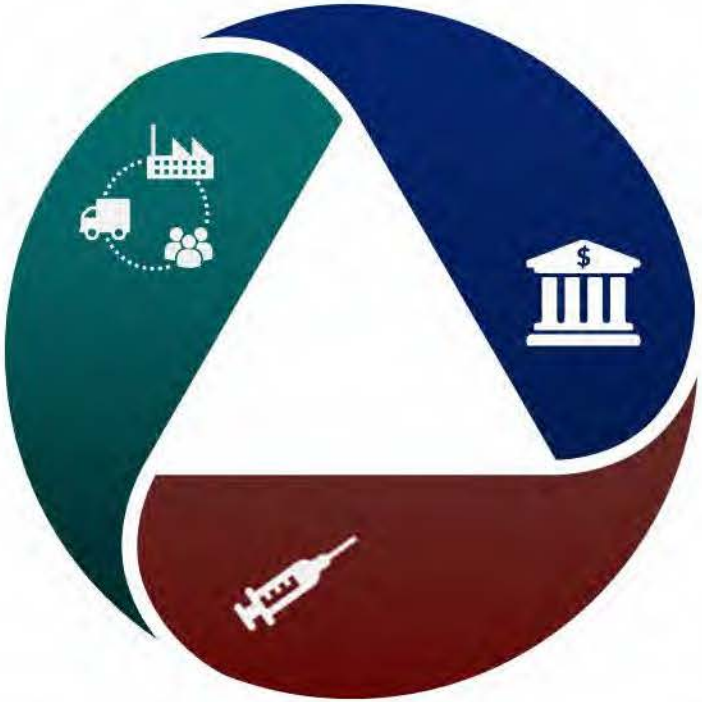
- Parallel Work Streams
- Robust preclinical screening
- Phase 1 by 3Q2020

(b)(5)

DOMESTIC MANUFACTURING

- Technology transfer to domestic facility
- Significant manufacturing experience mitigates risk

Sanofi Pasteur



DEVELOPMENT

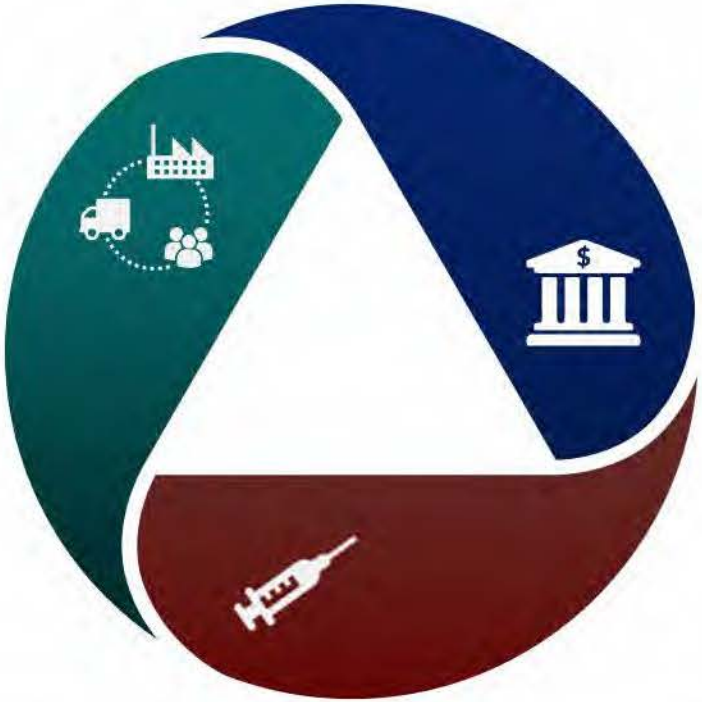
- FDA-licensed vaccine platform
- Parallel Work Streams
- Phase 1 by 3Q2020

(b)(5)

DOMESTIC MANUFACTURING

- Licensed manufacturing facility available
- Production levels likely to be robust
- Experienced manufacturing team

Merck



DEVELOPMENT

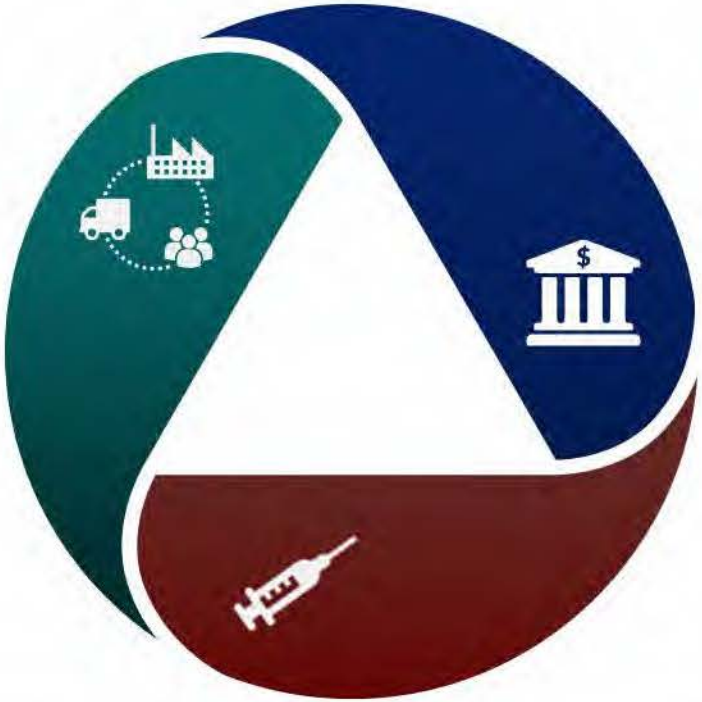
- Parallel Work Streams
- FDA-licensed platform (VSV-vectored Ebola vaccine)

(b)(5)

DOMESTIC MANUFACTURING

- Scale Up or Out
- Experienced workforce
- Domestic facilities available

Pfizer



DEVELOPMENT

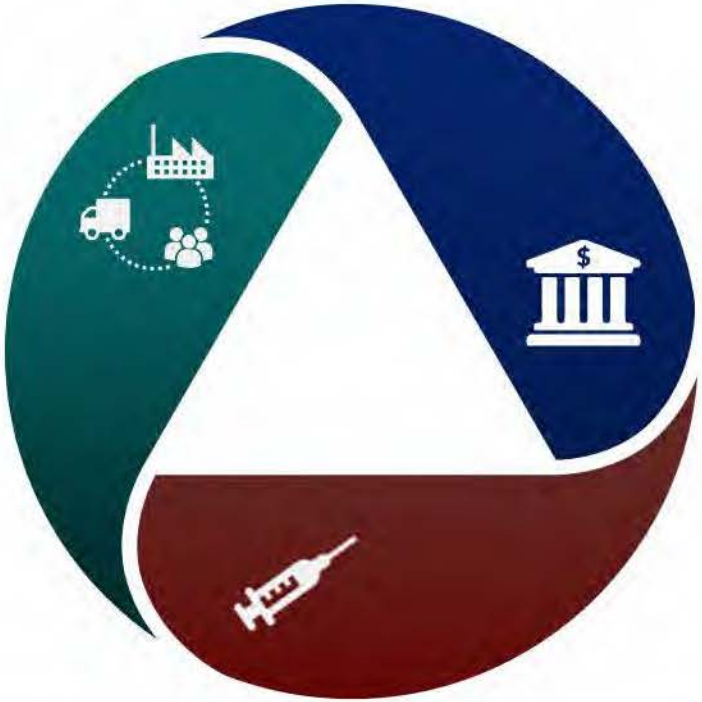
- Parallel work streams
- Phase 2 by 2Q 2020

(b)(5)

DOMESTIC MANUFACTURING

- Technology transfer to United States
- Large domestic facilities and experienced staff readily available
- Raw Materials Supply Chains

Innovation



AREAS OF INTEREST

- Product yield enhancement
- Faster time to protection
- Operational improvements

(b)(5)

TARGETED STRATEGY

- Initial 'seed' funding to assess feasibility
- Flexible funding approaches
- Cost Share

COVID-19 MEDICAL COUNTERMEASURE UPDATE

April 5, 2020

Brief to HHS Secretary Azar and HHS COVID-19 Advisory Panel, including NIH, FDA, CDC, ASPR, ASFR Leadership

FOUO- FOR OFFICIAL USE ONLY- PRE-DECISIONAL

16 Years

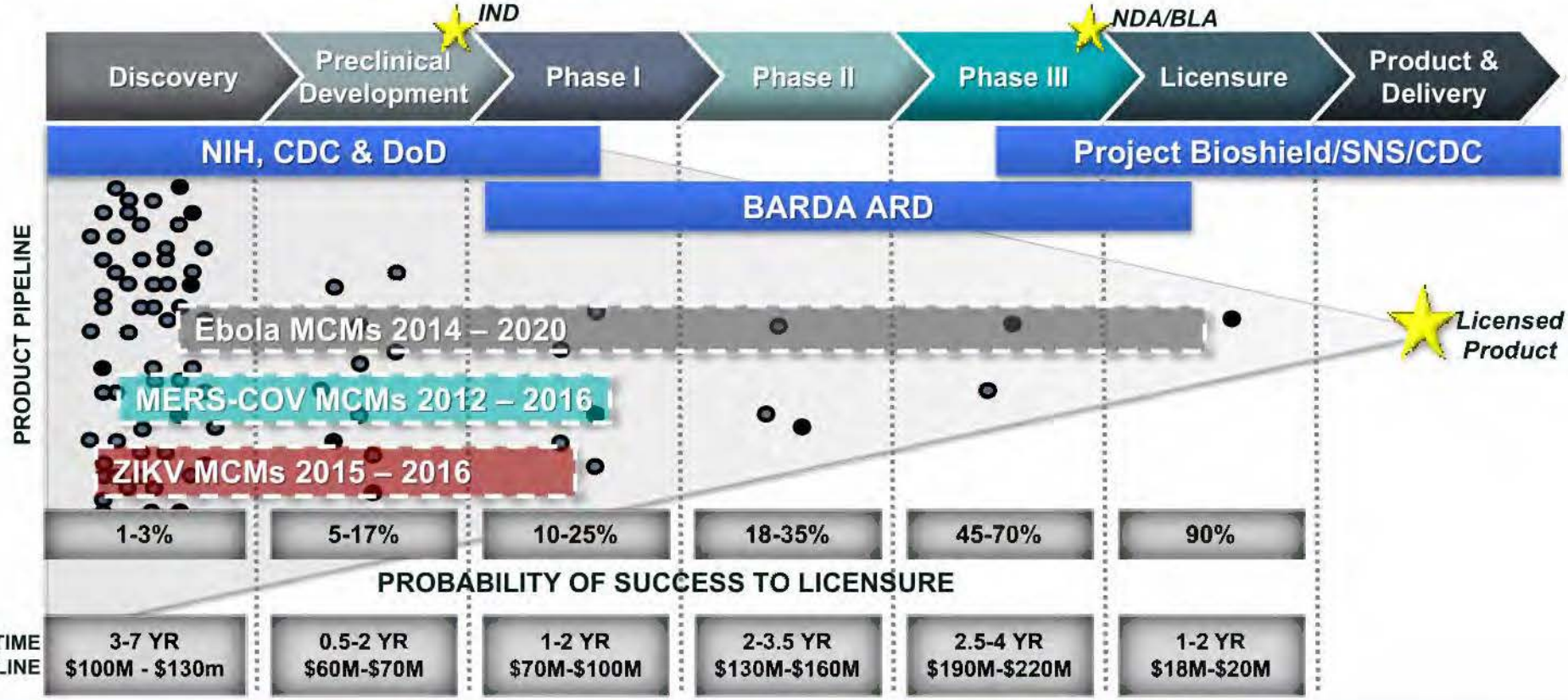
3rd Coronavirus Outbreak

No Licensed products

2019-nCoV Medical Countermeasures Task Force

Align and prioritize MCM development across Interagency partners to avoid duplication of effort, identify opportunities for synergy, and fill potential gaps

Vaccine & Drug Development is Expensive, Risky and Lengthy



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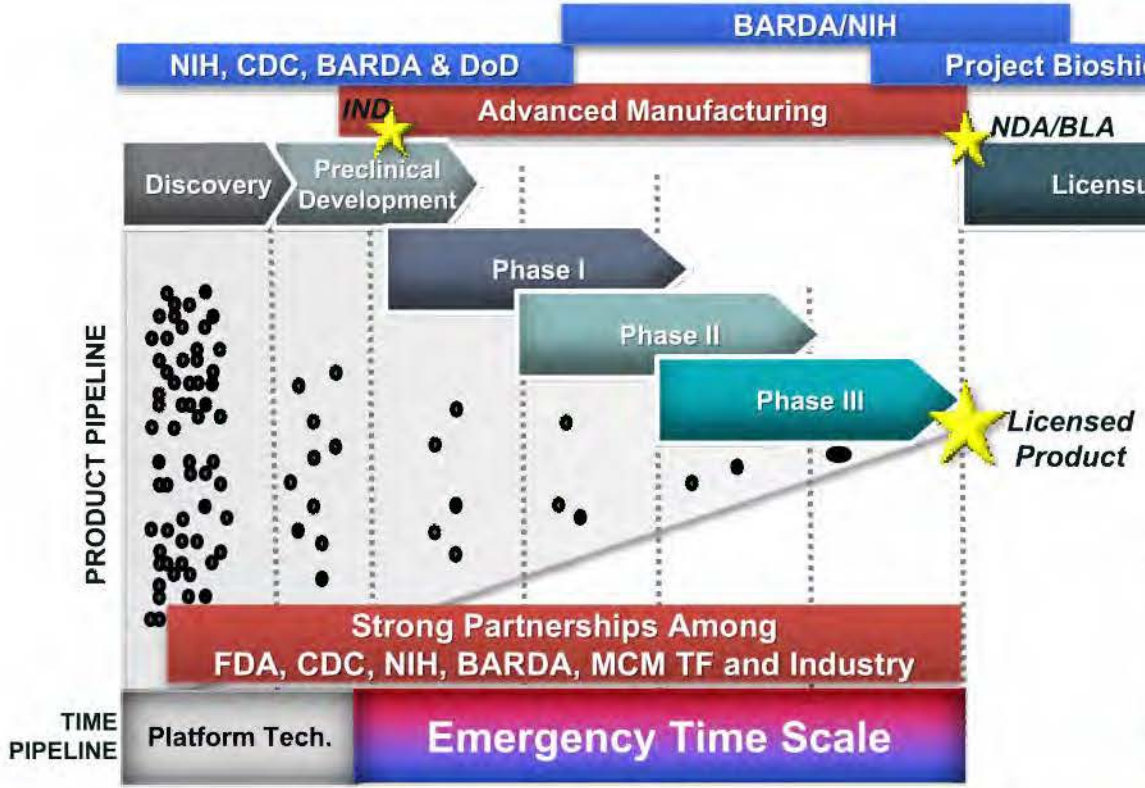


All of Government and Private Sector Approach

COVID-19 MEDICAL COUNTERMEAUSRE DEVELOPMENT STRATEGY

ACCELERATE DEVELOPMENT

- Platform technologies
- Repurpose licensed products
- Parallel, not sequential, activities

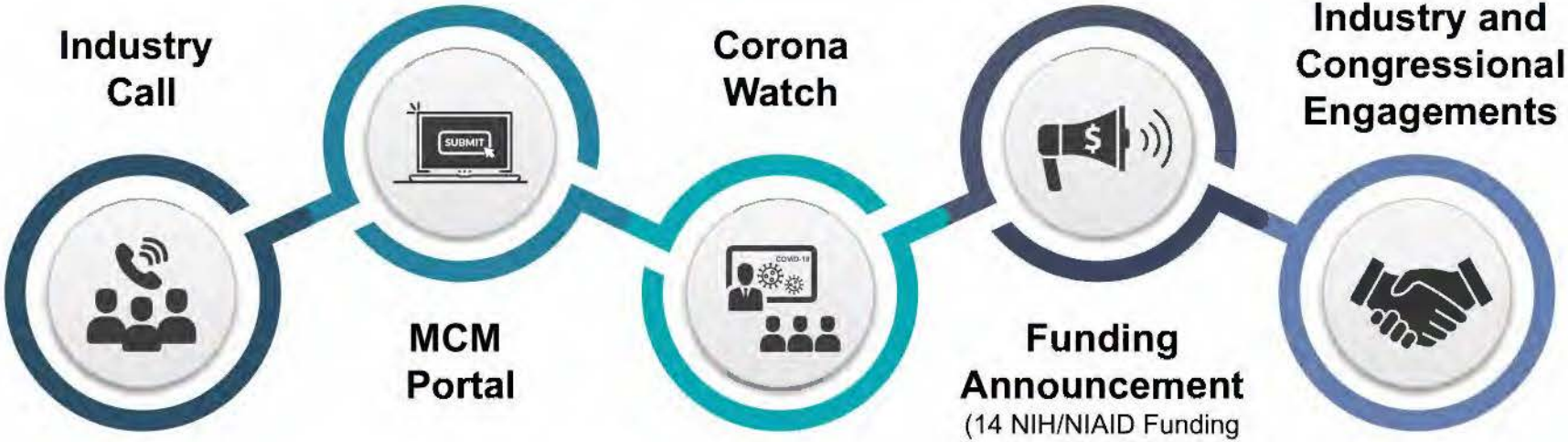
MITIGAGE RISK

- Multiple technologies
- Multiple targets
- Redundancy

DOMESTIC MANUFACTURING

- Scale Up & Scale Out
- Raw materials and supply chains
- Leverage existing facilities

Agency-Wide Engagement with Developers



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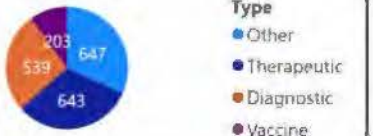

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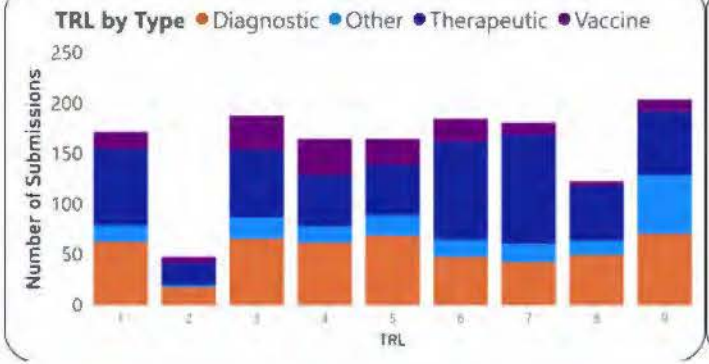

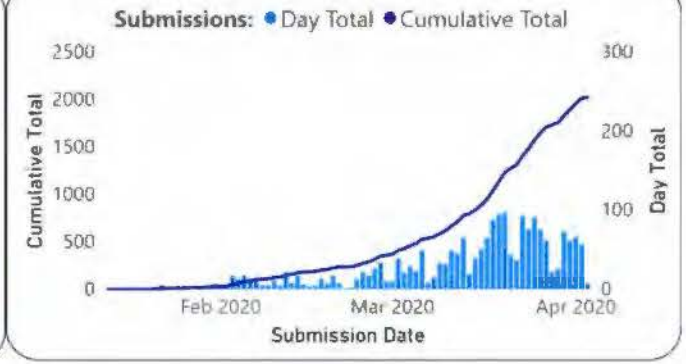

Therapeutics Development

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e.g., inhibitors of viral activation, host pathway modulators

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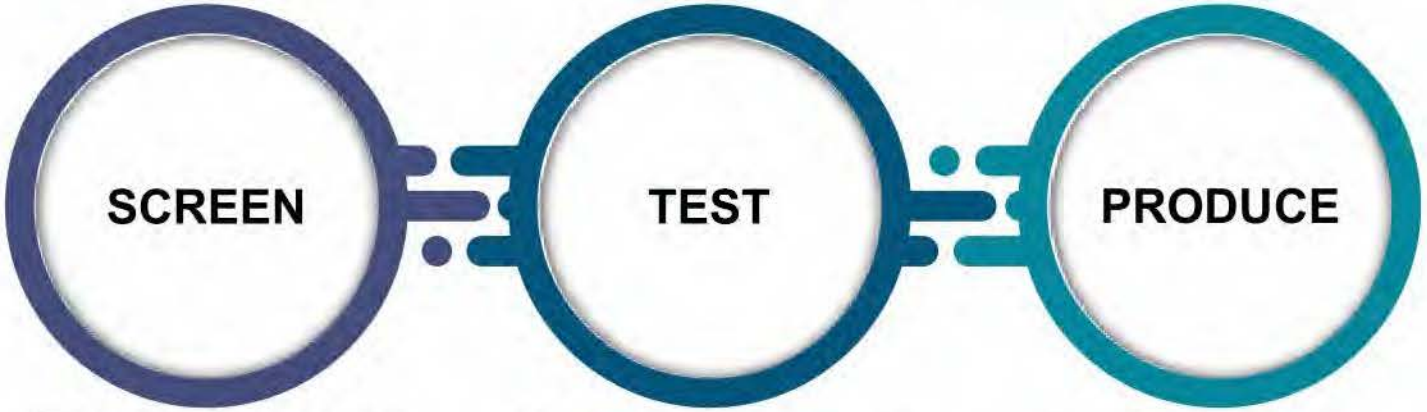
Repurposed Therapeutics



Thousands of compounds currently being screened-low cost/high impact
Many candidates identified and undergoing clinical evaluation

Allows rapid advancement to clinical trials (i.e. IL-6 monoclonal antibody trial started 2-weeks after identification)

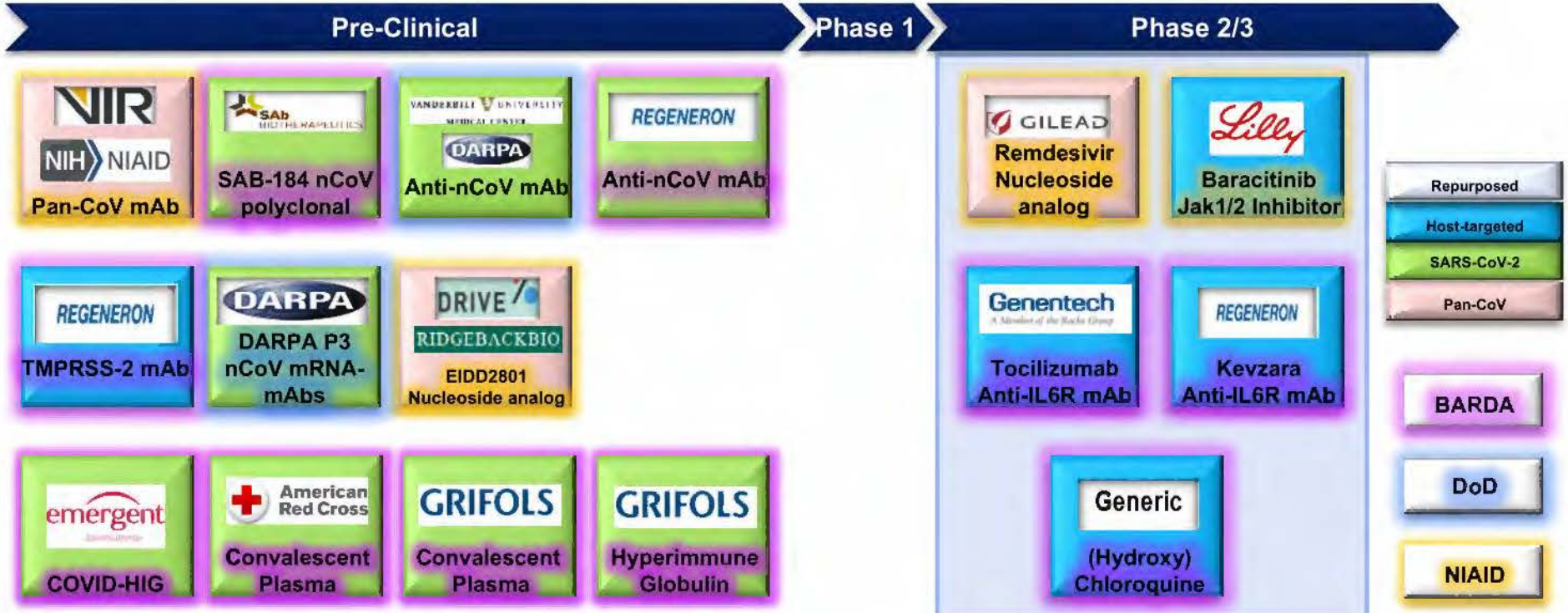
Utilize existing facilities for production;
Expand capacity through partnerships with large pharmaceutical partners

BARDA seeking to leverage existing infrastructure for rapid clinical trial initiation

Therapeutics Clinical Studies: US & ROW Summary

Product Type	US Trials	US + International Trials
All therapeutics	30	231
Remdesivir	4	12
HCQ/CQ	7	46
Sarilumab (Kevzara)	1	6
Tocilizumab (Actemra)	1	10

USG-Supported SARS-CoV-2 Therapeutics



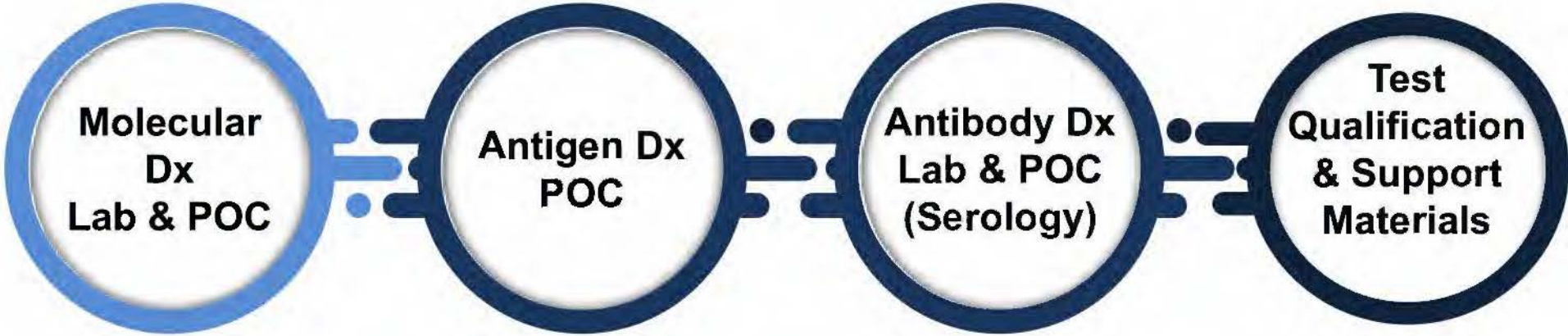
BARDA COVID-19 Therapeutic Investments

(b)(5)

BARDA / DoD / NIAID Supported Studies

Product Type	Product (Developer)	ClinicalTrials Identifier	Primary Endpoint	Target Enrollment	Current Enrollment	Number of Sites	Notes
Therapeutic	Remdesivir (Gilead)	NCT04280705	Clinical status assessed at Day 15 using 8-point ordinal scale	440 initially; increased to 700	426	49	Adaptive COVID-19 Treatment Trial; can add new candidates
Therapeutic	Sarilumab (Regeneron & Sanofi)	NCT04315298	Phase 2: Time to resolution of fever for 48h Phase 3: Time to improvement (2 points) using 7-point ordinal scale	400	730	51	Adaptive Phase 2/3 design; began enrolling March 19 and will enroll through 400th patient follow up and data analysis
Therapeutic	Tolilizumab (Genentech & Roche)	NCT04320615	Clinical status assessed at Day 28 using 7-point ordinal scale	330	2	2	Phase 3 study; Scheduled to begin enrollment during the week of April 3
Vaccine	mRNA-1273 (Moderna)	NCT04283461	Safety & Immunogenicity at 25µg, 100µg & 250µg	45	30	2	Second cohort (100µg) dosed and in monitoring phase; dosing of 250µg expected to begin Apr 8
Observational	n/a	n/a	Observational study to collect pathological data on COVID-19	n/a	32	5	Department of Defense's "EPiCC" Study; complementary studies in planning phases

Diagnostics Development: Four-Pronged Approach



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04/02/20

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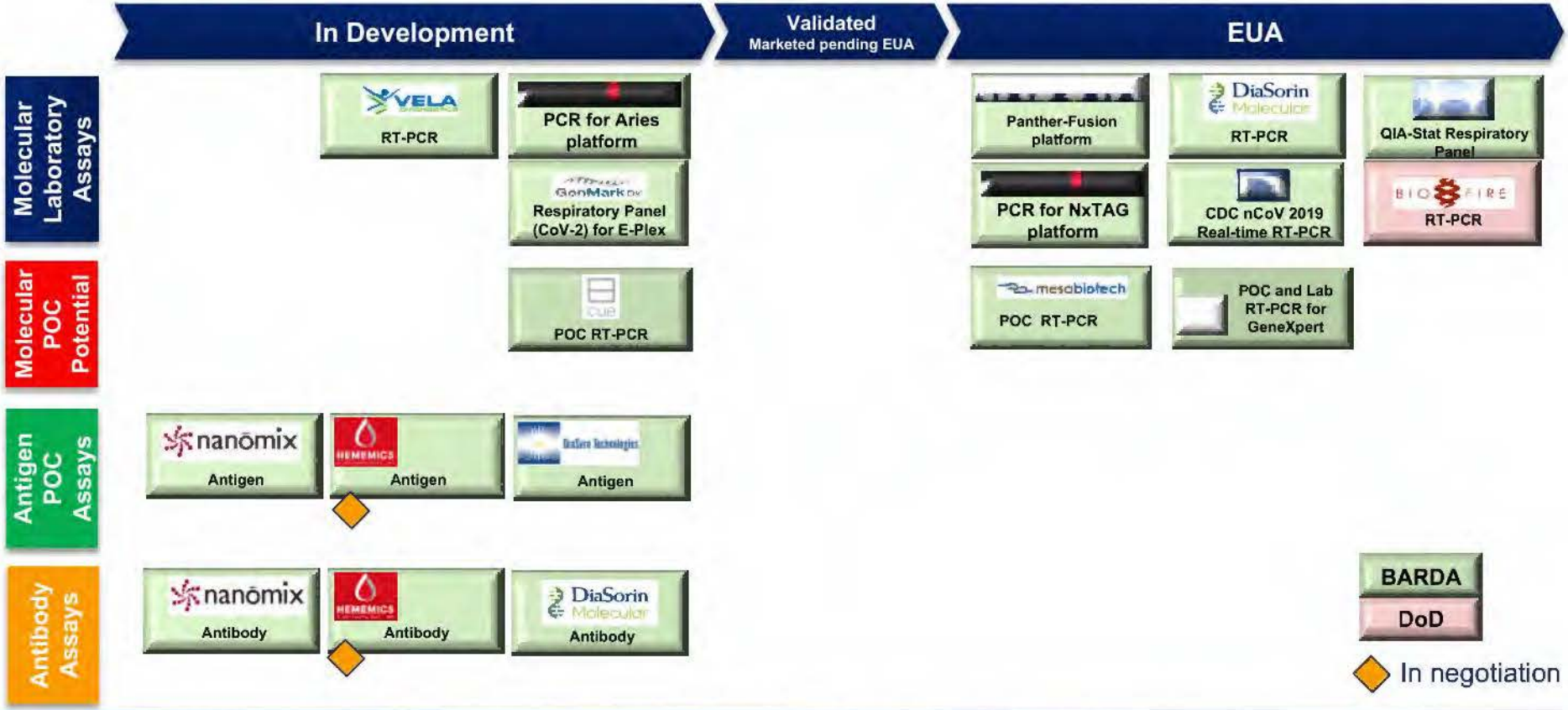

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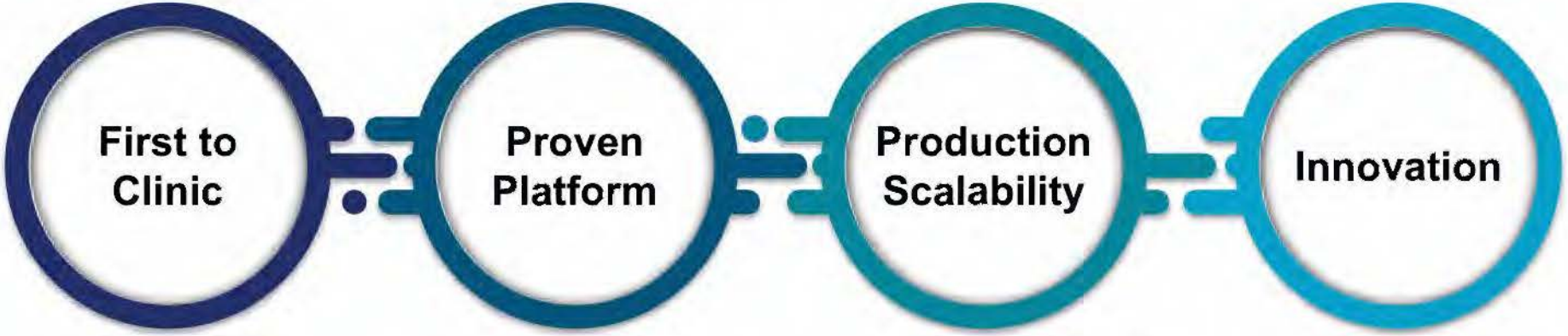

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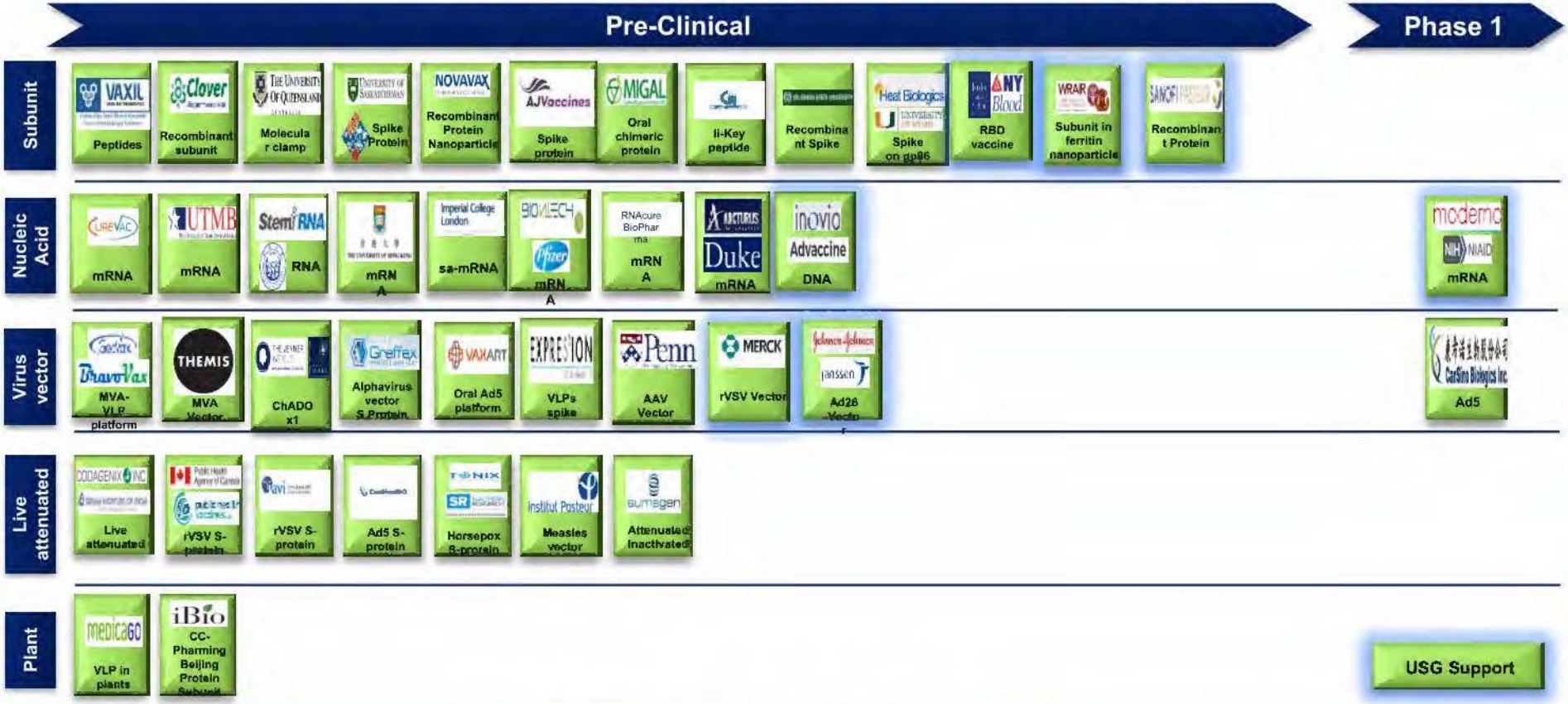
SARS-CoV-2 Vaccine Landscape



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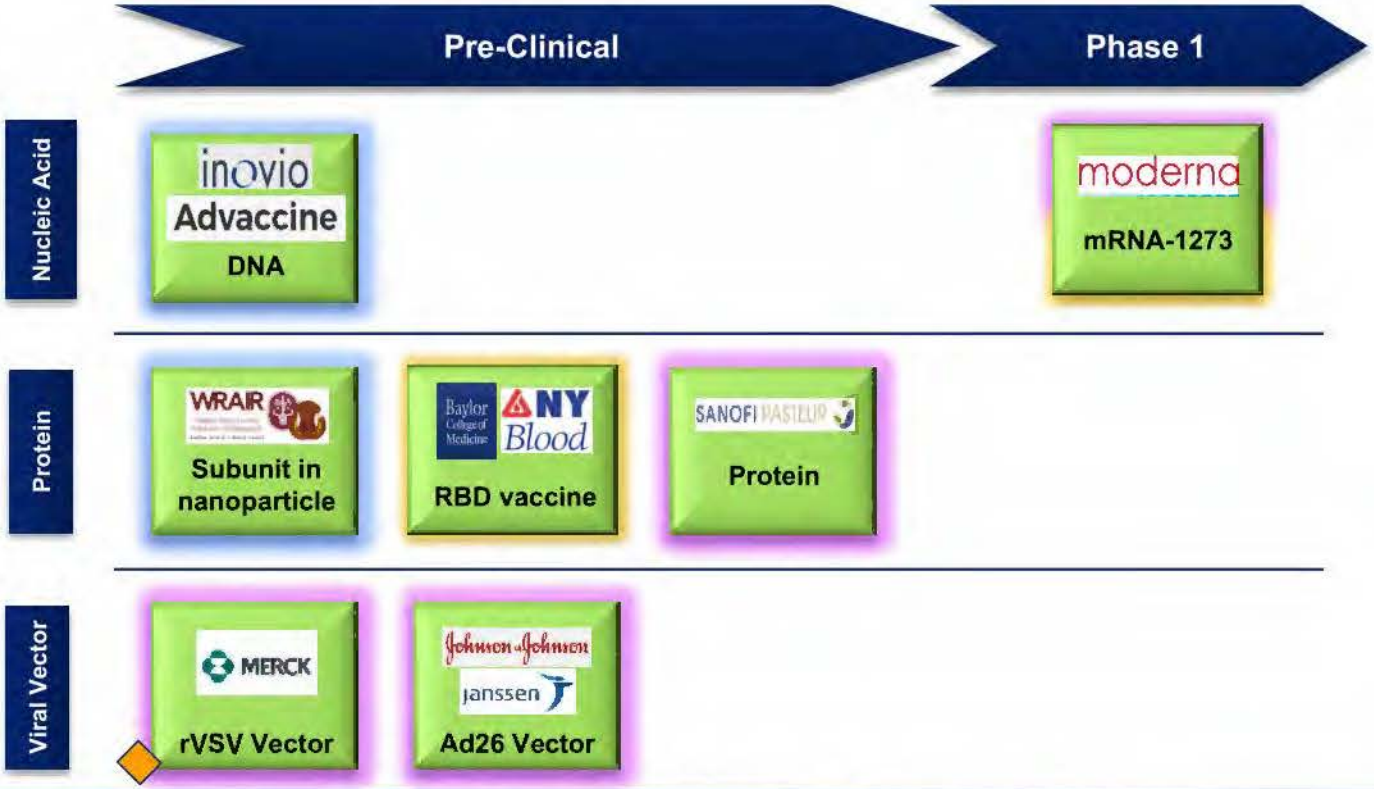

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Moderna

DEVELOPMENT

- First to clinic (1Q 2020)
- Phase 2 (2Q 2020)

(b)(5)

DOMESTIC MANUFACTURING

- Scale up (limited) and out
- Technology transfer to domestic facility – CIADM
- Secure supply chain

Janssen

DEVELOPMENT

- Parallel Work Streams
- Robust preclinical screening
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(b)(5)

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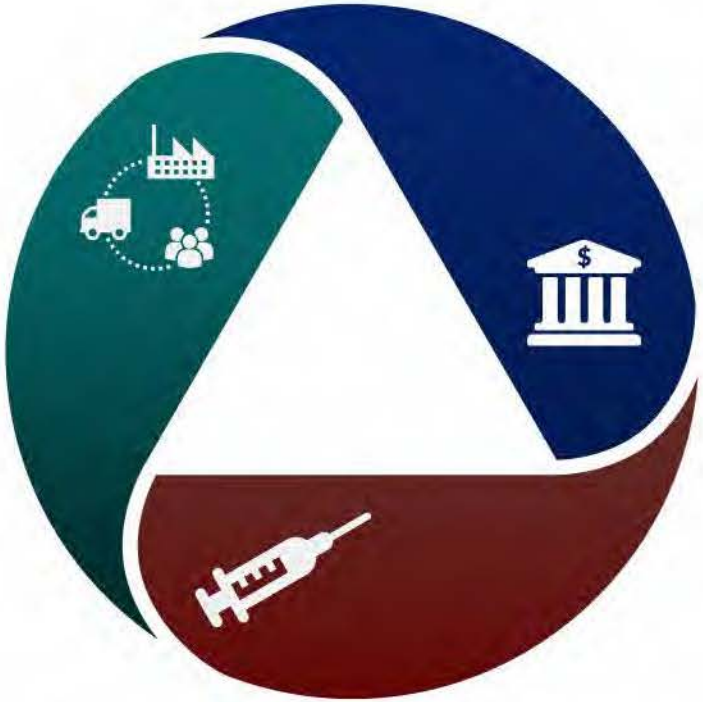

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(b)(5)

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Estimated Vaccine Development Timelines

(b)(5)

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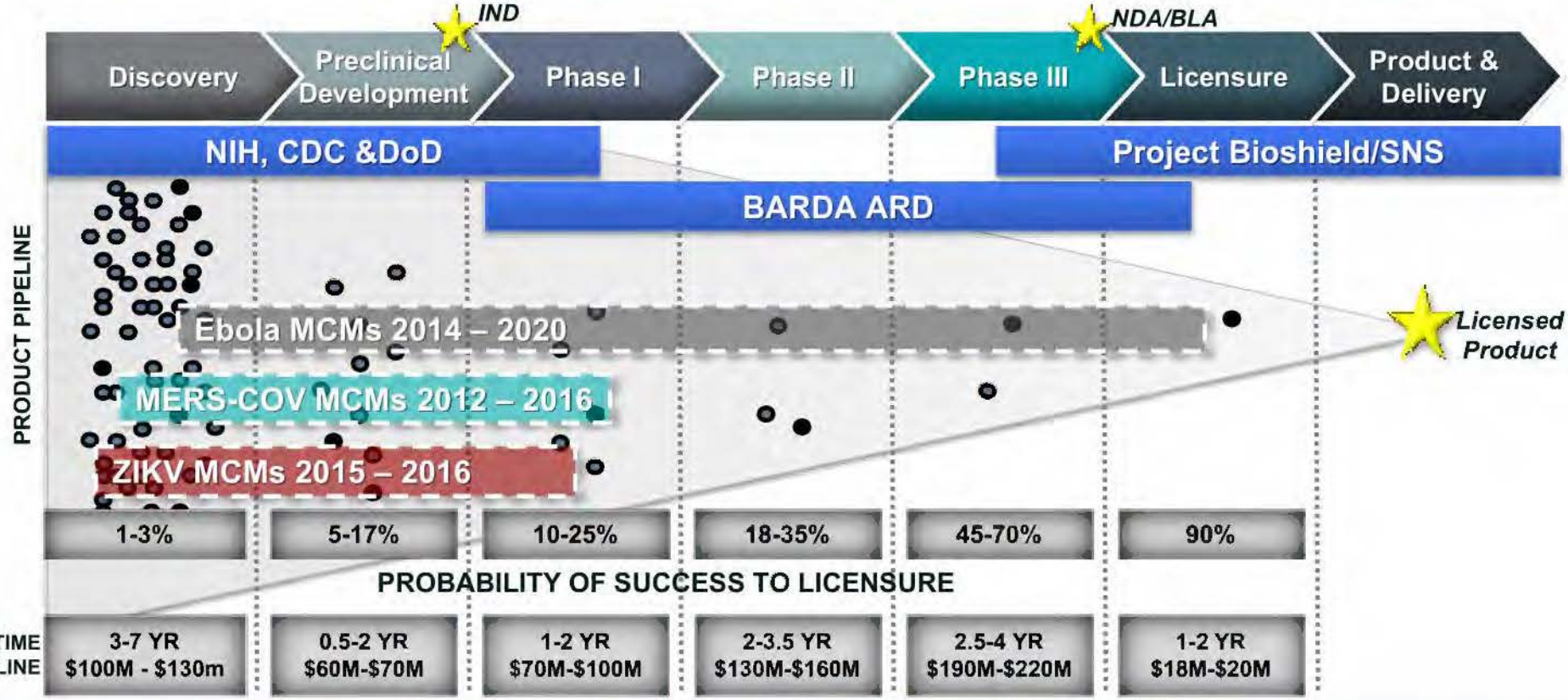

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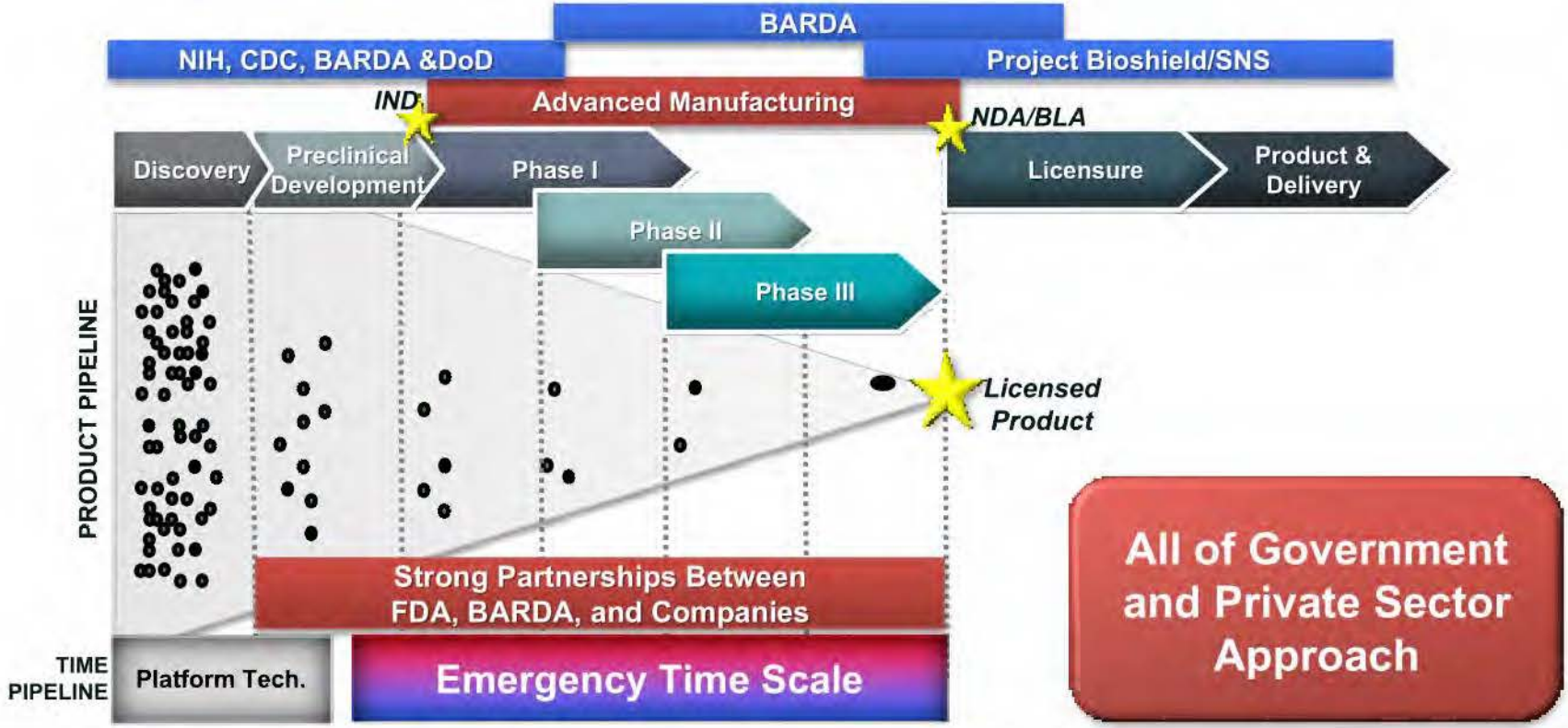

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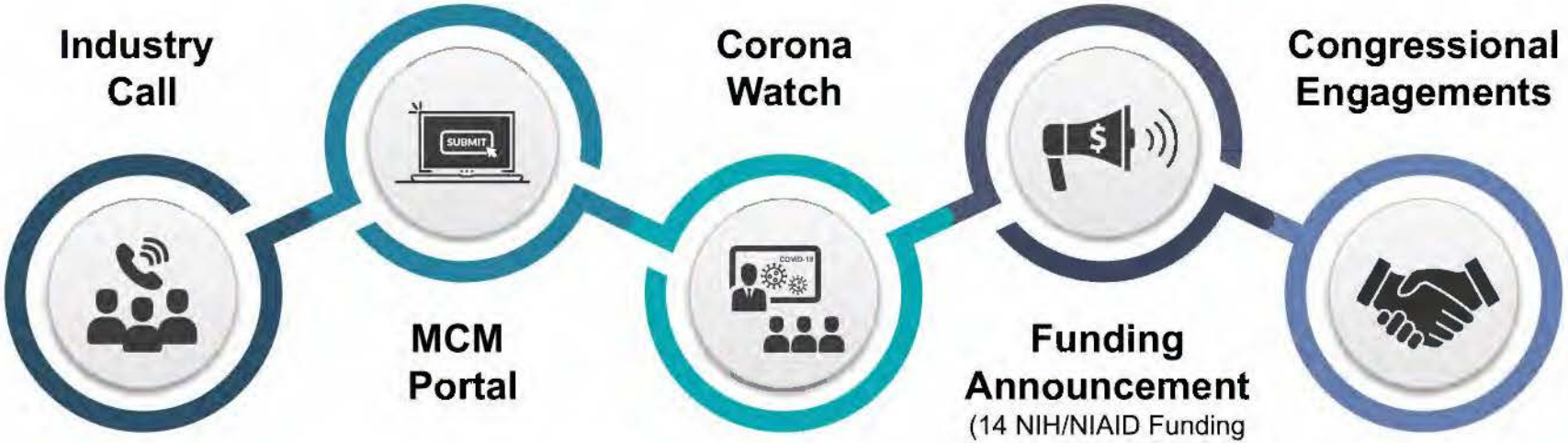

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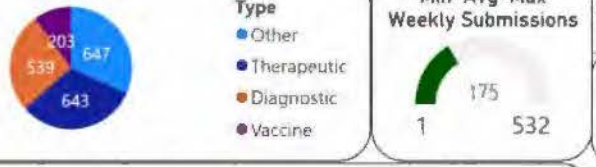

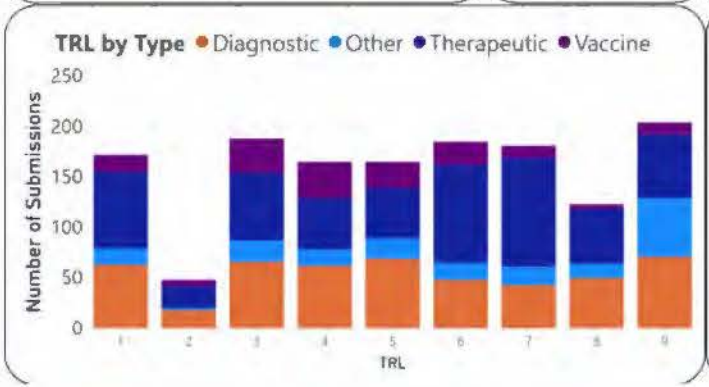

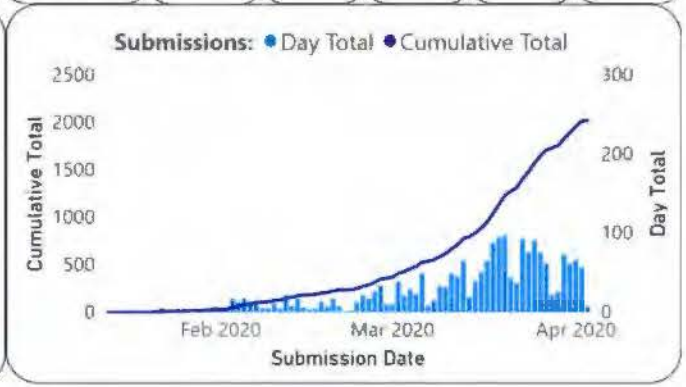

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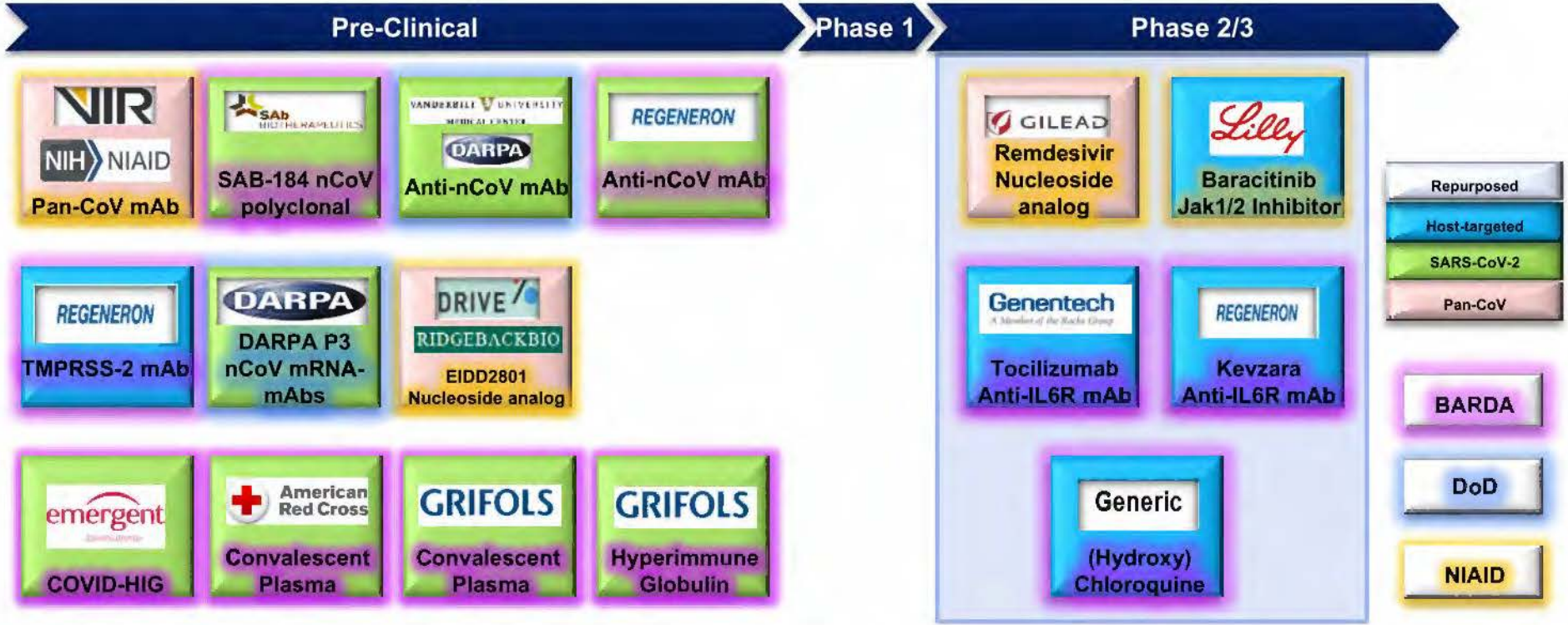

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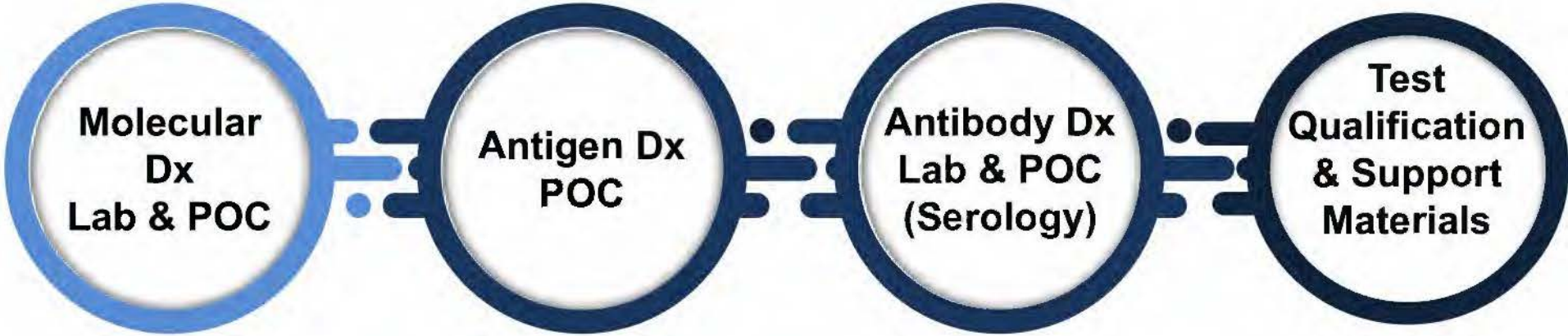

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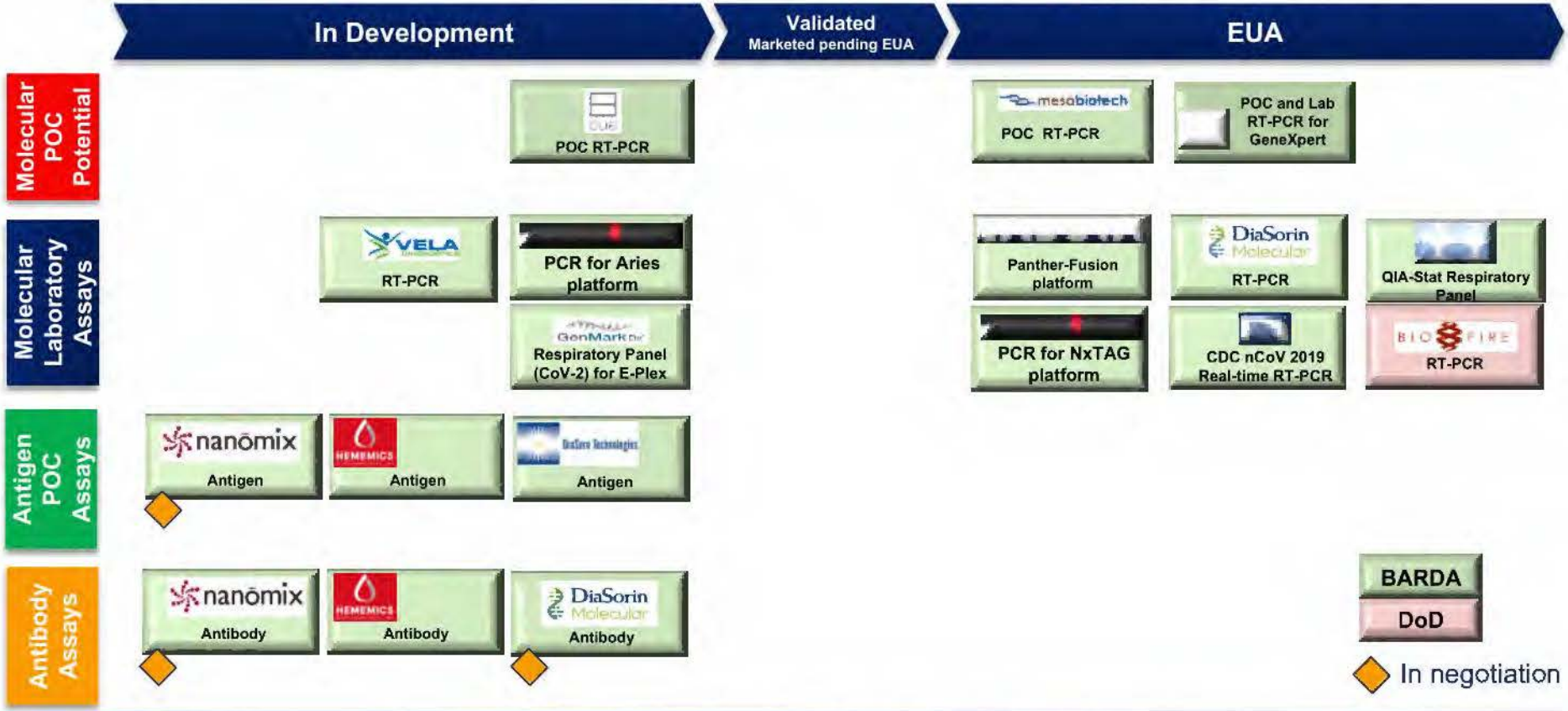

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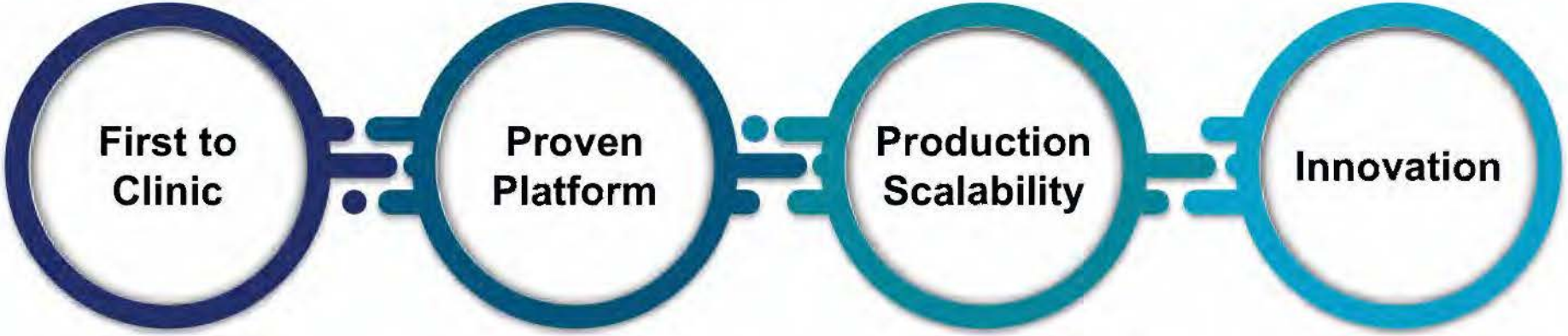

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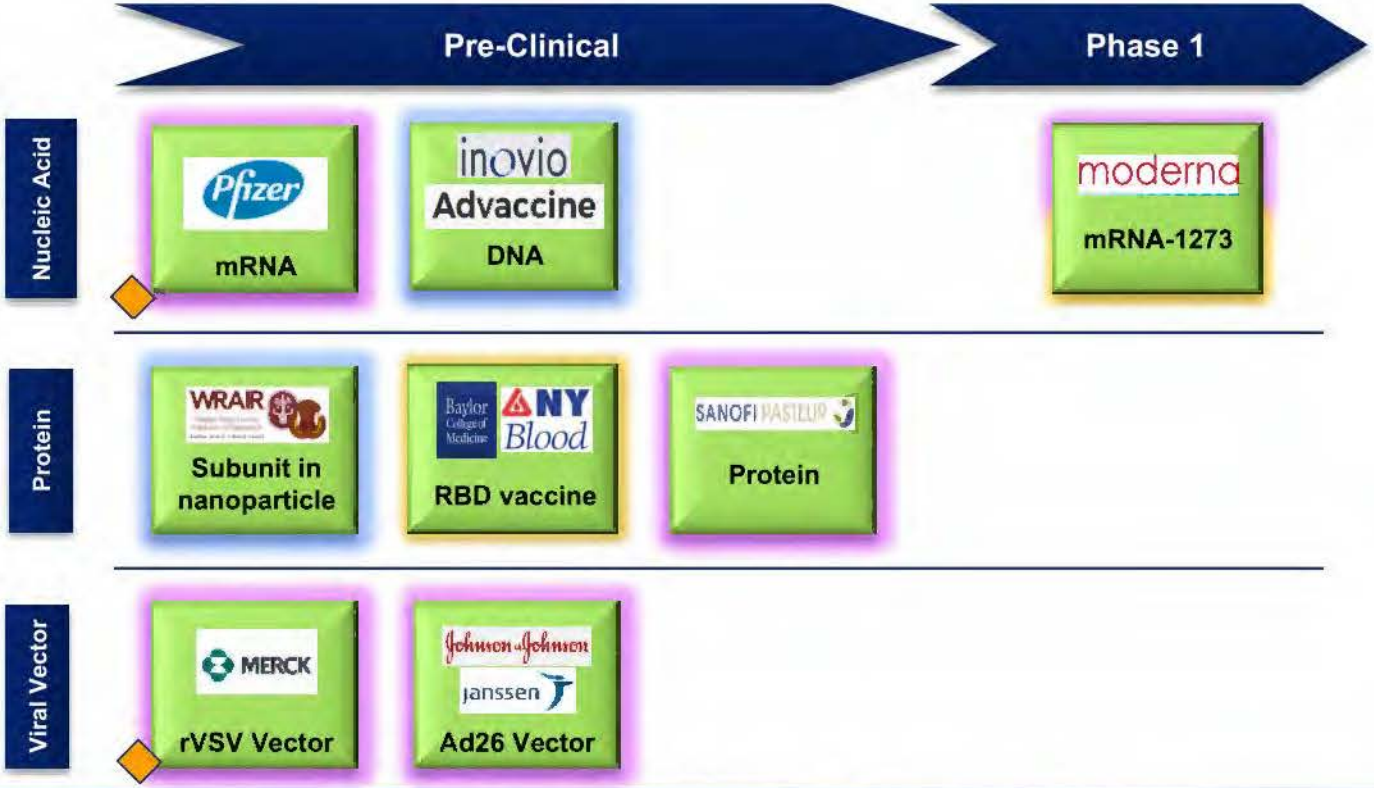

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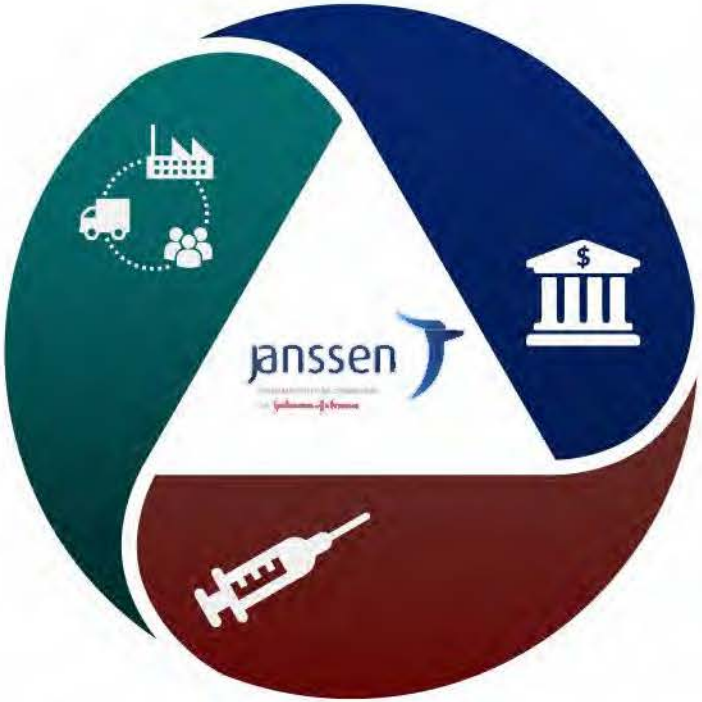

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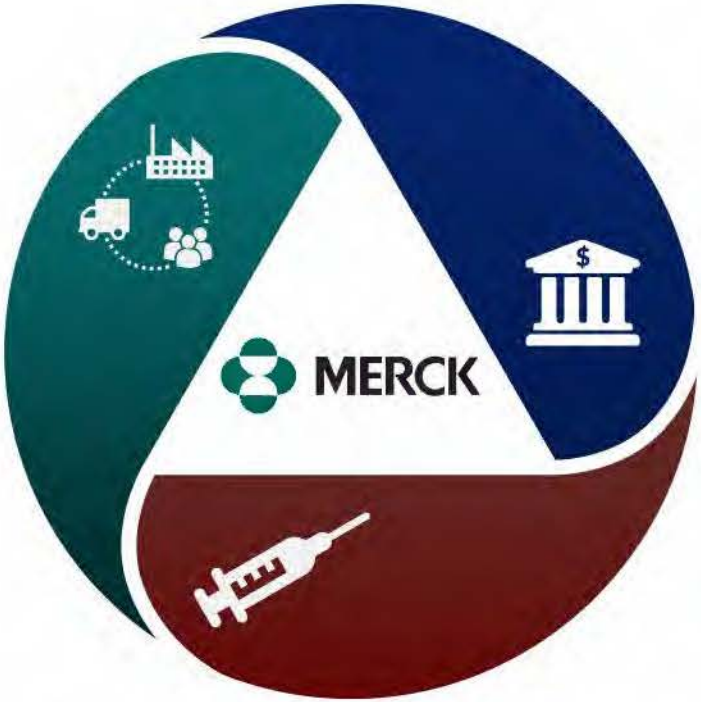
Merck



DEVELOPMENT

- Parallel Work Streams
- FDA-licensed platform (VSV-vectored Ebola vaccine)

(b)(5)

DOMESTIC MANUFACTURING

- Scale Up or Out
- Experienced workforce
- Domestic facilities available

Pfizer

DEVELOPMENT

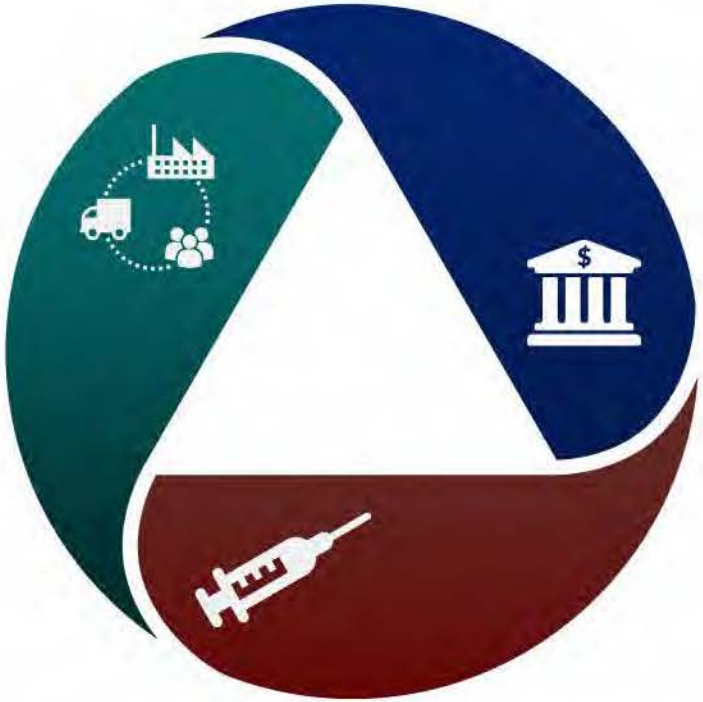
- Parallel work streams
- Phase 2 by 2Q 2020

(b)(5)

DOMESTIC MANUFACTURING

- Technology transfer to United States
- Large domestic facilities and experienced staff readily available
- Raw Materials Supply Chains

Innovation



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April 5, 2020

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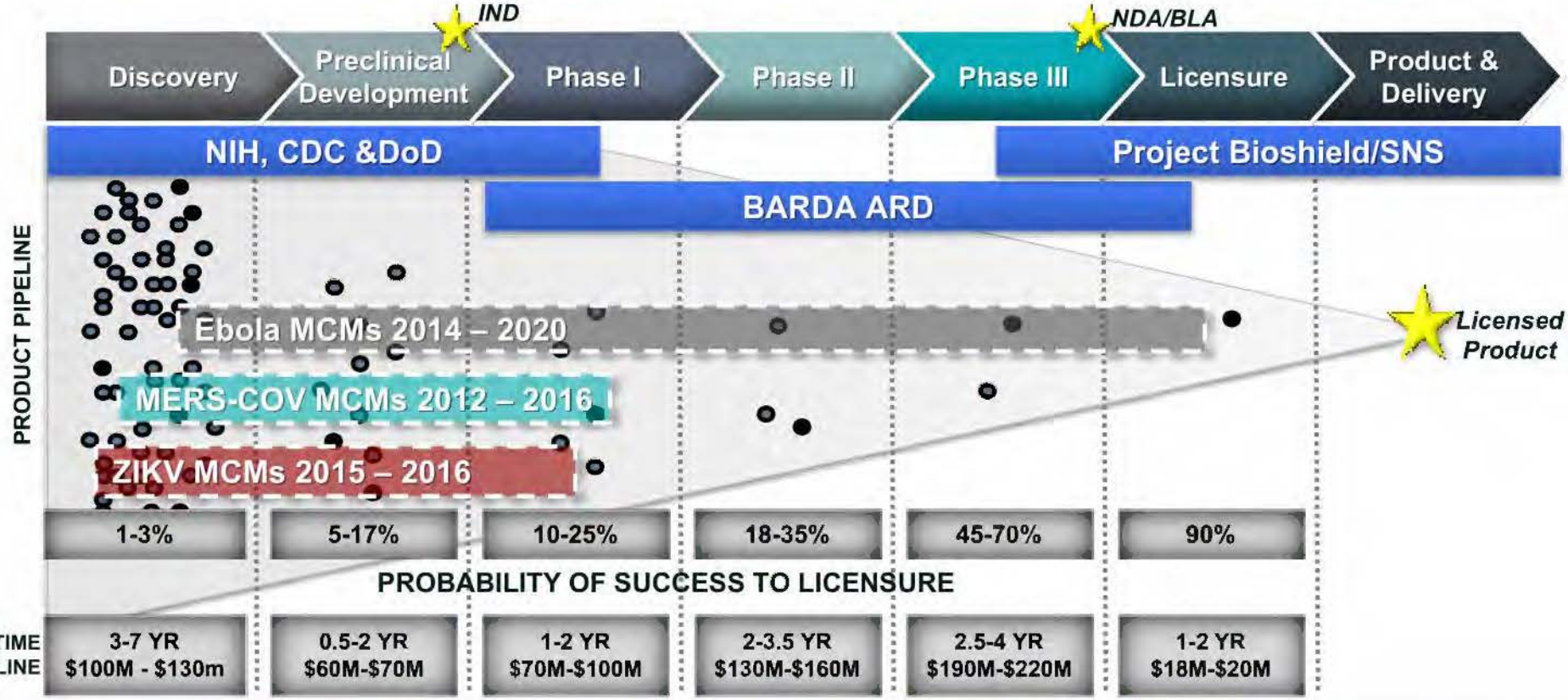

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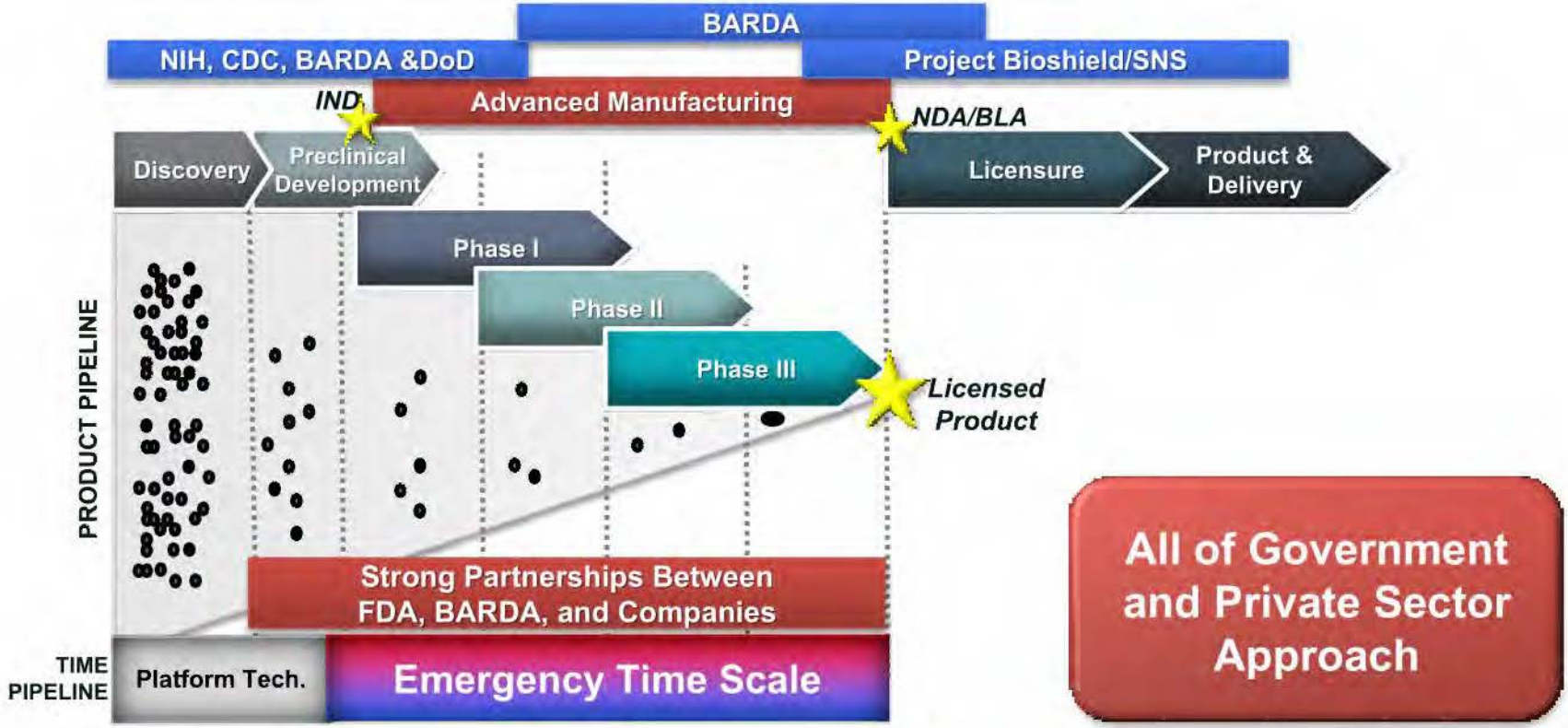

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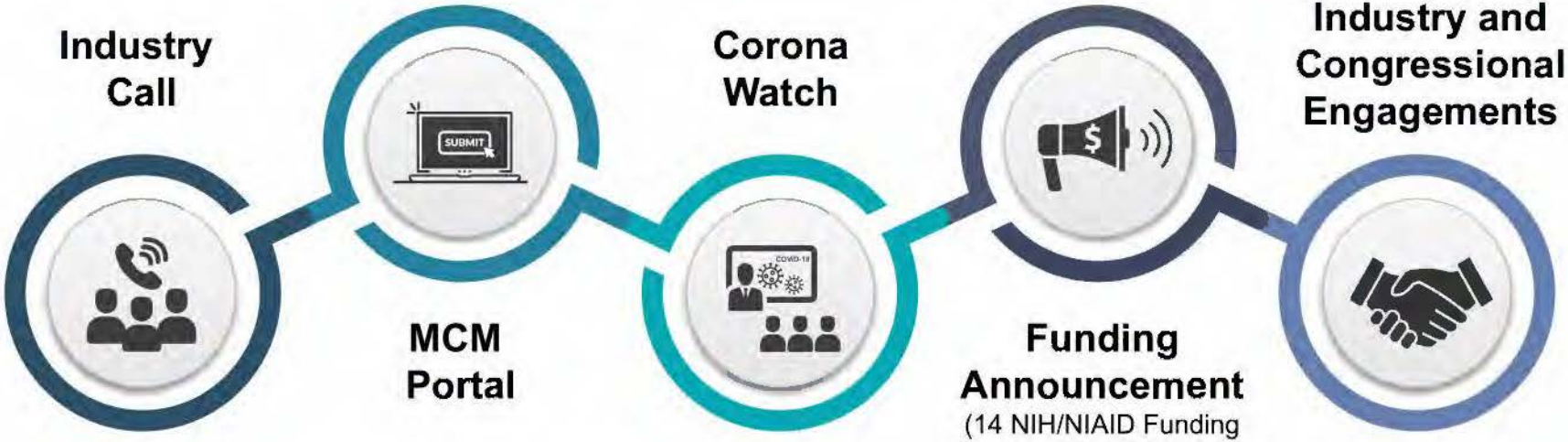

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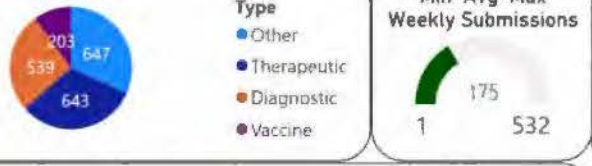

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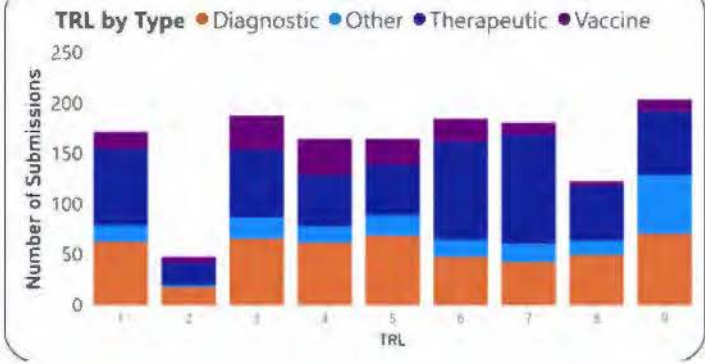

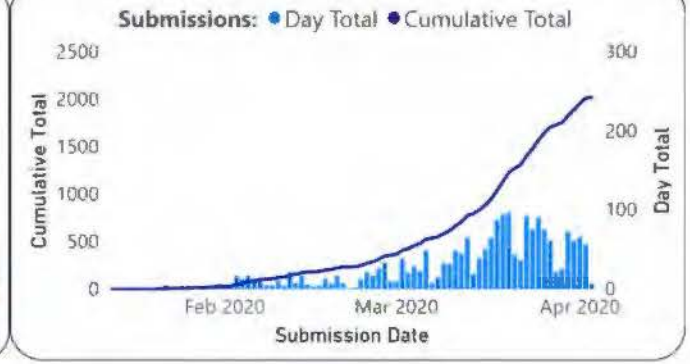

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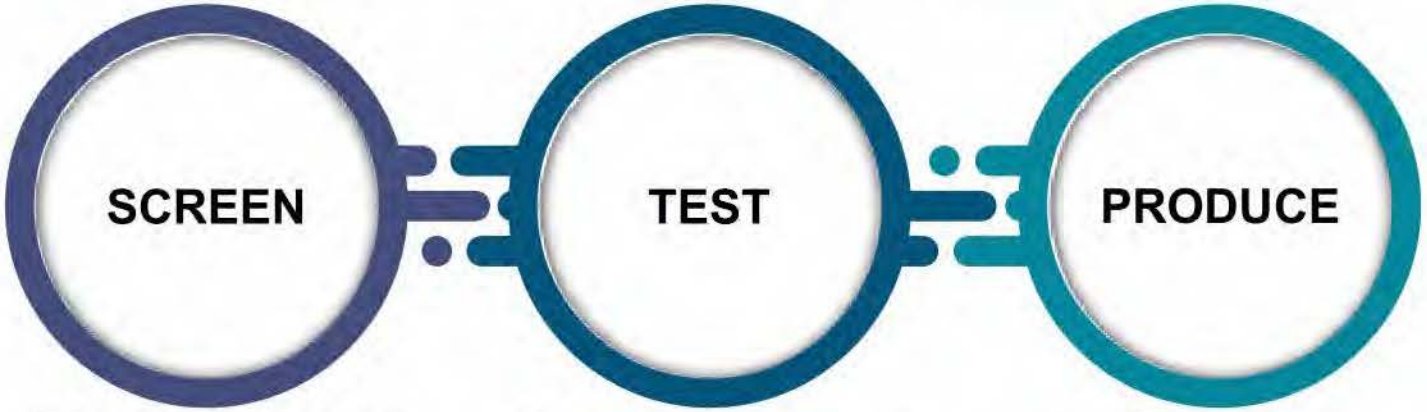
Repurposed Therapeutics



Thousands of compounds currently being screened-low cost/high impact
Many candidates identified and undergoing clinical evaluation

Allows rapid advancement to clinical trials (i.e. IL-6 monoclonal antibody trial started 2-weeks after identification)

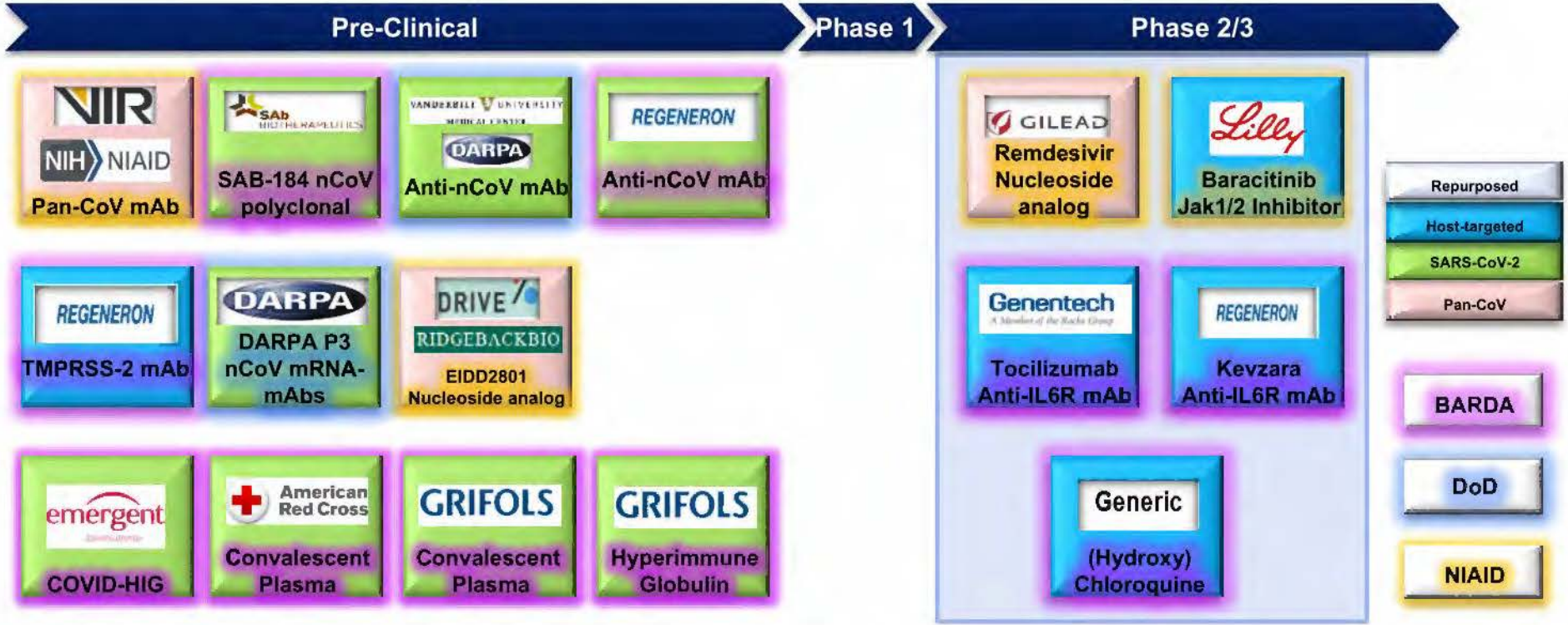
Utilize existing facilities for production;
Expand capacity through partnerships with large pharmaceutical partners

BARDA seeking to leverage existing infrastructure for rapid clinical trial initiation

Therapeutics Clinical Studies: US & ROW Summary

Product Type	US Trials	US + International Trials
All therapeutics	30	231
Remdesivir	4	12
HCQ/CQ	7	46
Sarilumab (Kevzara)	1	6
Tocilizumab (Actemra)	1	10

USG-Supported SARS-CoV-2 Therapeutics



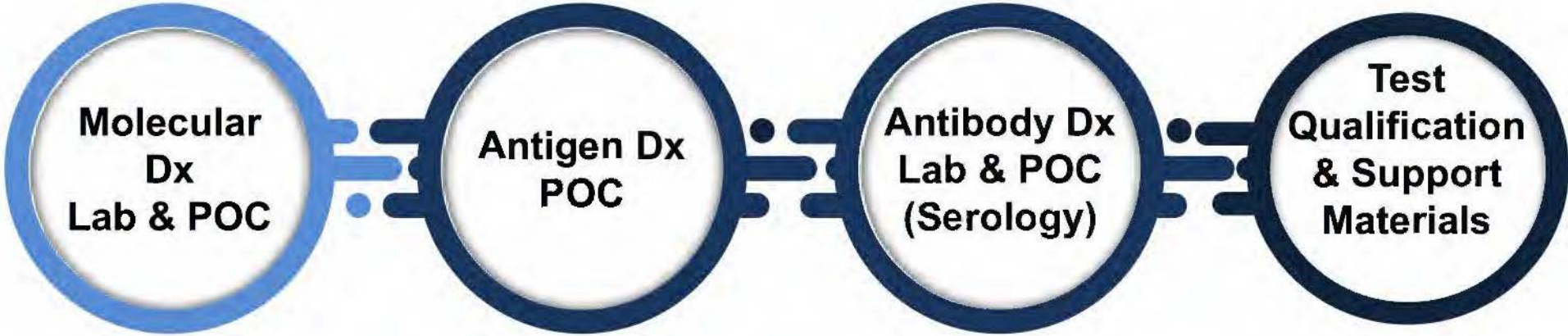
BARDA COVID-19 Therapeutic Investments

(b)(5)

BARDA / DoD / NIAID Supported Ongoing Studies

Product Type	Product (Developer)	ClinicalTrials Identifier	Primary Endpoint	Target Enrollment	Current Enrollment	Number of US Sites	Number of ex-US Sites	Notes
Therapeutic	Remdesivir (Gilead)	NCT04280705	Clinical status assessed at Day 15 using 8-point ordinal scale	440	390	41	8	Adaptive COVID-19 Treatment Trial; can add new candidates
Therapeutic	Sarilumab (Regeneron & Sanofi)	NCT04315298	Phase 2: Time to resolution of fever for 48h Phase 3: Time to improvement (2 points) using 7-point ordinal scale	400	617	50	0	Adaptive Phase 2/3 design; began enrolling March 19 and will enroll through 400th patient follow up and data analysis
Therapeutic	Tolilizumab (Genentech & Roche)	NCT04320615	Clinical status assessed at Day 28 using 7-point ordinal scale	330	0	TBD	TBD	Phase 3 study; Scheduled to begin enrollment during the week of April 3
Vaccine	mRNA-1273 (Moderna)	NCT04283461	Safety & Immunogenicity at 25µg, 100µg & 250µg	45	30	2	0	Second cohort (100µg) dosed and in monitoring phase; dosing of 250µg expected to begin Apr 8
Observational	n/a	n/a	Observational study to collect pathological data on COVID-19	n/a	8	4	0	Department of Defense's "EpICC" Study; complementary studies in planning phases

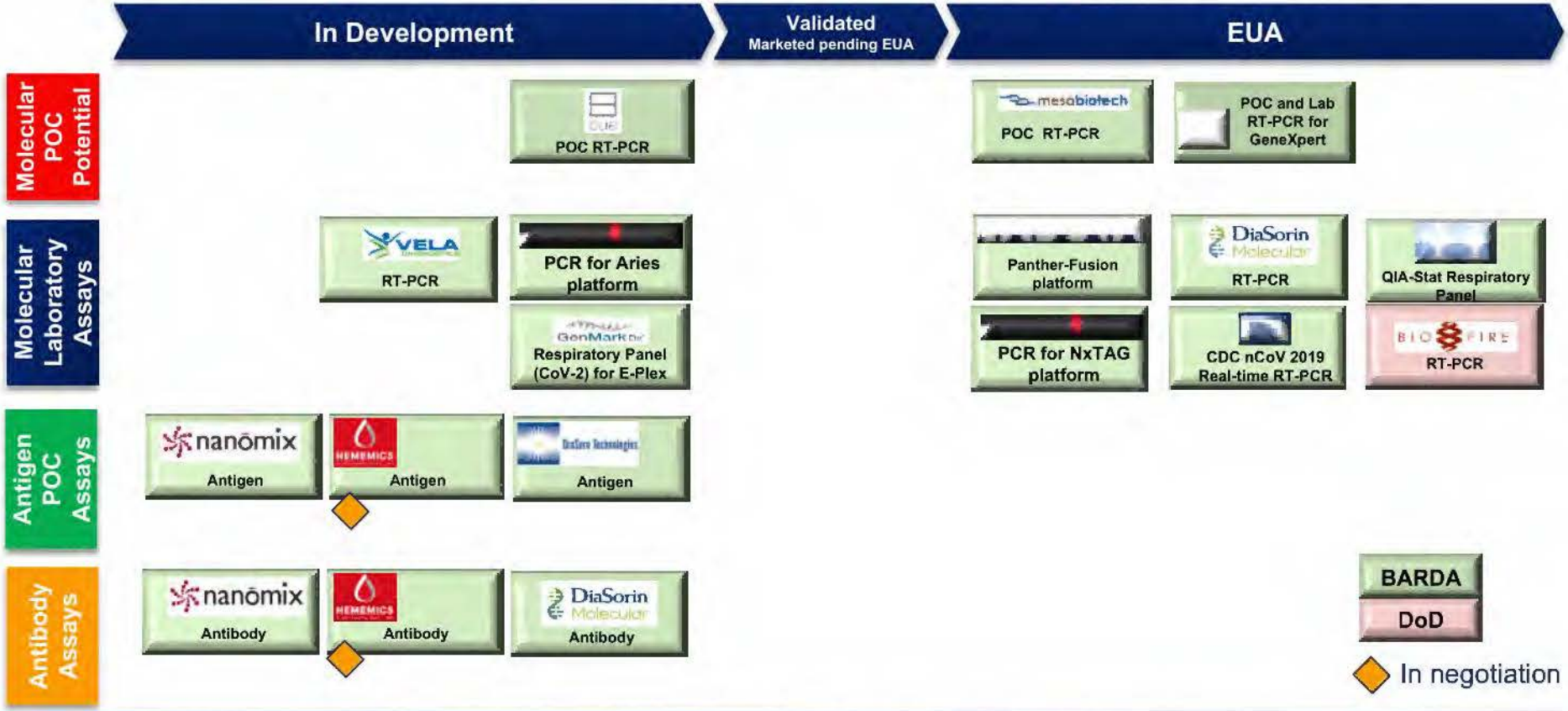
Diagnostics Development: Four-Pronged Approach



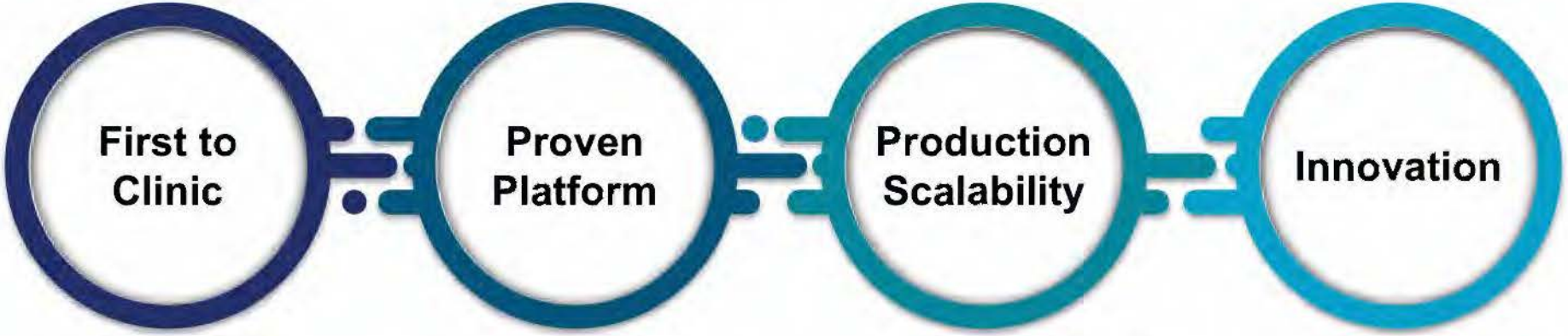
Leverage existing Laboratory Infrastructure & Equipment
Leverage Existing & Complete In-Development POC Equipment

04/02/20

USG-Sponsored SARS-CoV-2 Diagnostic Tests



Vaccine Development



e.g., mRNA based vaccines that allow rapid early development

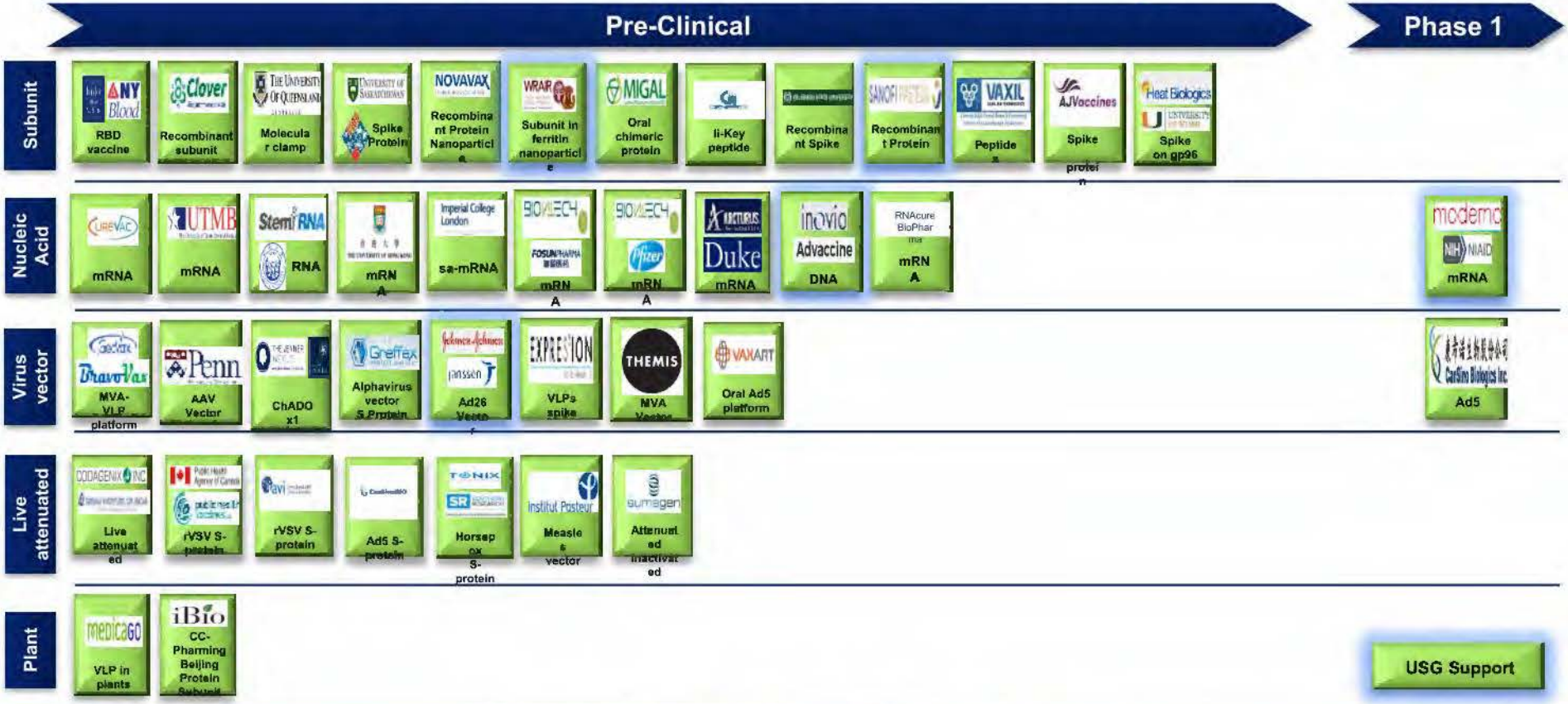
e.g., viral vectors with demonstrated safety and efficacy

e.g., Existing or readily amenable to large scale manufacturing, including experienced workforce

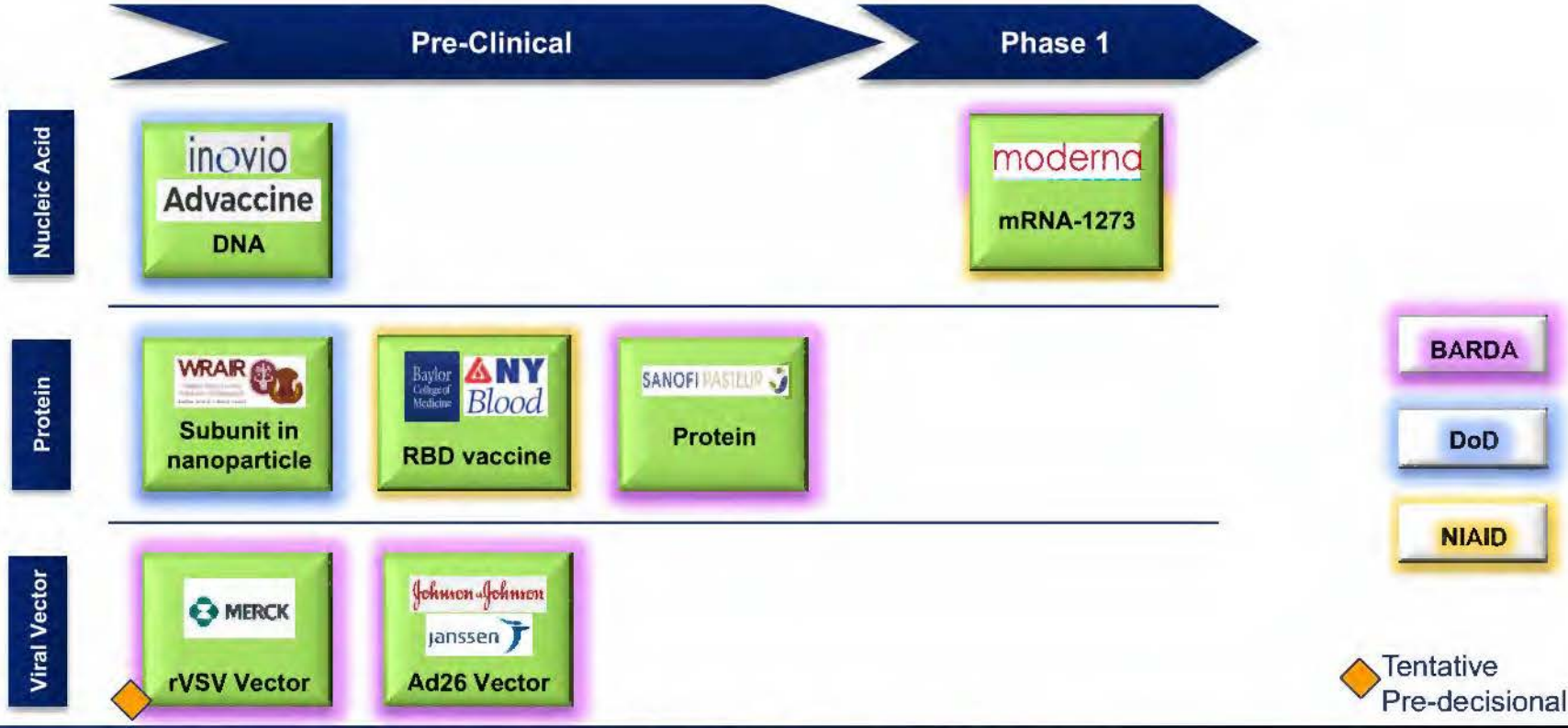
e.g., novel platforms, delivery approaches, or new thinking to transform the field

Leverage existing infrastructure for rapid MCM generation and production through partnerships (contracts and OTA) including other USG agencies

SARS-CoV-2 Vaccine Landscape



USG-Supported SARS-CoV-2 Vaccines



Vaccine Approach

Accelerate Development

Rapid Vaccine Platform Approaches
- Nucleic Acid
- Vectors
- Recombinant protein

Repurpose Licensed Products
- Viral Vector
- Recombinant Protein

Parallel Activities
- Overlapping clinical trials
- Scale up in parallel with clinical development

Mitigate Risk

Multiple Platforms
- Address potential yield risks
- Address potential dose risk

Multiple Presentations (recombinant, vector, etc.)
- Disease enhancement mitigation
- Alternative routes of delivery

Redundancy
- Take multiple products through large scale clinical trials
- Multiple manufacturing facilities for each product

Domestic Manufacturing

Scale Up & Scale Out
- Validate large scale process (i.e. larger tanks)
- Technology transfer to more facilities
- Increase fill/finish capacity

Raw Materials Supply Chains
- Remove bottlenecks
- Establish stockpiles

Leverage Existing Facilities
- Facilities of large pharma partners
- CMOs

Moderna

DEVELOPMENT

- First to clinic (1Q 2020)
- Phase 2 (2Q 2020)

(b)(5)

DOMESTIC MANUFACTURING

- Scale up (limited) and out
- Secure supply chain

Janssen

DEVELOPMENT

- Parallel Work Streams
- Robust preclinical screening
- Phase 1 by 3Q2020

(b)(5)

DOMESTIC MANUFACTURING

- Technology transfer to domestic facility
- Significant manufacturing experience mitigates risk

Sanofi Pasteur

DEVELOPMENT

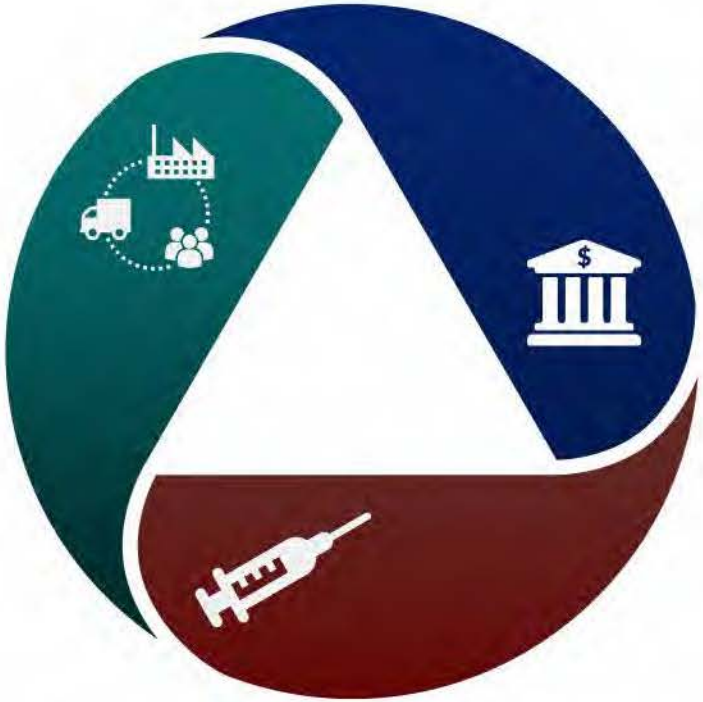
- FDA-licensed vaccine platform
- Parallel Work Streams
- Phase 1 by 3Q2020

(b)(5)

DOMESTIC MANUFACTURING

- Licensed manufacturing facility available
- Production levels likely to be robust
- Experienced manufacturing team

Innovation



AREAS OF INTEREST

- Product yield enhancement
- Faster time to protection
- Operational improvements

(b)(5)

TARGETED STRATEGY

- Initial 'seed' funding to assess feasibility
- Flexible funding approaches
- Cost Share

Estimated Vaccine Development Timelines

(b)(5)

From:	Houchens, Christopher (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7AC94A574BD04528B7C91BBD61893975-HOUCHENS, C <Christopher.Houchens@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>; Ventura, Christy (OS/ASPR/BARDA) (CTR) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9bb949caca464329823ca3cf77654a06-Ventura, Ch <Christy.Ventura@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>
CC:	MCM Task Force /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=49010f8ab3ab4aed868a72c707c08d08-MCM Task Fo <MCMTaskForce@hhs.gov>
Subject:	RE: MCM Task Force update for 4/8/2020
Date:	2020/04/07 18:18:34
Priority:	Normal
Type:	Note

Rick – Thank you for your comments. Regarding you direction to keep reporting out numbers on the Regeneron and Genentech mAb therapeutic studies, I mentioned yesterday that both of those companies have expressed concerns about reporting those numbers (please see attached and below). Please let me know if you have any thoughts regarding the below and how to proceed. Thanks, Chris

There continues to be concern from companies about reporting out any data that is not public even if it is non-attributional as the information could still identify the company (at which point it becomes a notifiable event if it is publicly-traded company). For example, it is publically known that we are supporting two IL-6R mAb therapy studies - one started over a month ago and one stated just last week and reporting higher enrollment numbers will identify the first while lower numbers will identify the second. If the numbers for either do not change for a period of time, and if this information gets released (I know that the Supply Chain Task Force numbers reported each day wind up in the WP the next day), then other stakeholders (investors, companies, regulators, etc) will ask why. However, there is a need to show progress on the MCM TF to our stakeholders and leadership during the daily VTC calls. So my recommendation is that the MCM report out on the following:

1. Total MCM awards and new awards, broken down by TX, VX, and DX
2. Total number of clinical studies and new initiated studies broken down by TX, VX, and DX AND Phase 1, 2, 3
3. Topline clinical study results when publically available.
4. EUAs and approvals by FDA
5. Total number of propasals submitted to portal and TechWatch meetings hosted
6. Any other data that BARDA and our partners feel would demonstrate progress
7. And we will continue to report out numbers for those companies that are OK with us doing so.

Christopher Houchens, PhD
Director (Acting) Division of CBRN Countermeasures
Biomedical Advanced Research and Development Authority (BARDA)
Office of Assistant Secretary for Preparedness and Response (ASPR)
Department of Health and Human Services (DHHS)
Office: 202-205-3633
BB:(b)(6)
Christopher.houchens@hhs.gov

From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Tuesday, April 7, 2020 6:03 PM
To: Ventura, Christy (OS/ASPR/BARDA) (CTR) <Christy.Ventura@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: MCM Task Force <MCMTaskForce@hhs.gov>
Subject: Re: MCM Task Force update for 4/8/2020

Great work, as always team. See some thoughts below. Rick

From: "Ventura, Christy (OS/ASPR/BARDA) (CTR)" <Christy.Ventura@hhs.gov>
Date: Tuesday, April 7, 2020 at 5:49 PM
To: "Bright, Rick (OS/ASPR/BARDA)" <Rick.Bright@hhs.gov>, Gary Disbrow <Gary.Disbrow@hhs.gov>, Linda Lambert <Linda.Lambert@hhs.gov>
Cc: MCM Task Force <MCMTaskForce@hhs.gov>
Subject: MCM Task Force update for 4/8/2020

Rick, Gary, Linda,

See below for tomorrow's updates for the MCM Task Force. Another item that we will not be reporting out tomorrow but that we are sharing for situational awareness is that NIAID is working with Eli Lilly and Gilead to add baracitinib to the ACTT. Arms are expected to be remdesivir, baricitinib, remdesivir + baricitinib, and placebo, all with SOC.

Here are the updates that we will report tomorrow.

Talking Points for 1200 and 1700 SLBs and 1230 VTC

Accomplishments

- USG funded clinical studies
- Therapeutics: 4 (+1) Phase 3 trials (2 BARDA, 1 NIAID) says 4, but lists 2 BARDA and 1 NIAID, where is the fourth?
- Vaccines: 2 Phase 1 trials (1 DoD, 1 NIAID)
- Observational Natural History Study: 1 DoD

- ACTT Clinical trial to test remdesivir for treatment of COVID-19: 526 (+29) new patients at 58 (+1) sites, including 5 military treatment facilities, in last 24 hrs (target = 700)
- ORCHID Clinical trial to test hydroxychloroquine in COVID-19 patients: 10 patients enrolled (target = 510)
- Two clinical trials to test antibody therapeutics continue Please do not stop reporting the enrollment of these, it is important to find some way to show progress being made on these.
- Emergency Use Authorizations granted by FDA: 28 (+1) molecular diagnostic tests, 5 (+1) laboratory-developed tests, 1 antibody test, and 2 repurposed treatments (chloroquine, hydroxychloroquine) Please include an update on the drugs pushed out from SNS for the CQ, HCQ EUA.
- 1964 (+42) market research submissions and 185 (+7) CoronaWatch meetings held

Please let us know if you have any concerns.

Thanks
Christy

FOUO/PROCUREMENT SENSITIVE

--
Christy L. Ventura, Ph.D.
Tunnell Government Services
Executive Secretary, SARS-CoV-2 Medical Countermeasures Task Force
Project Manager, CBRN/BARDA/ASPR/HHS
O'Neill 23L05
Office: 202-730-8643
Cell: (b)(6)

Sender:	Houchens, Christopher (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7AC94A574BD04528B7C91BBD61893975-HOUCHENS, C <Christopher.Houchens@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>; Ventura, Christy (OS/ASPR/BARDA) (CTR) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9bb949caca464329823ca3cf77654a06-Ventura, Ch <Christy.Ventura@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>; MCM Task Force /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=49010f8ab3ab4aed868a72c707c08d08-MCM Task Fo <MCMTaskForce@hhs.gov>
Sent Date:	2020/04/07 18:18:31
Delivered Date:	2020/04/07 18:18:34
From:	Houchens, Christopher (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7AC94A574BD04528B7C91BBD61893975-HOUCHENS, C <Christopher.Houchens@hhs.gov>

To:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>
CC:	Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>; Boucher, David (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=41293945651d475fa0413062a819aac5-Boucher, Da <David.Boucher@hhs.gov>; Ventura, Christy (OS/ASPR/BARDA) (CTR) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9bb949caca464329823ca3cf77654a06-Ventura, Ch <Christy.Ventura@hhs.gov>
Subject:	RE: Clinical Trial Status
Date:	2020/04/06 10:53:00
Priority:	Normal
Type:	Note

All - There continues to be concern from companies about reporting out any data that is not public even if it is non-attributional as the information could still identify the company (at which point it becomes a notifiable event if it is publicly-traded company). For example, it is publically known that we are supporting two IL-6R mAb therapy studies - one started over a month ago and one stated just last week and reporting higher enrollment numbers will identify the first while lower numbers will identify the second. If the numbers for either do not change for a period of time, and if this information gets released (I know that the Supply Chain Task Force numbers reported each day wind up in the WP the next day), then other stakeholders (investors, companies, regulators, etc) will ask why. However, there is a need to show progress on the MCM TF to our stakeholders and leadership during the daily VTC calls. So my recommendation is that the MCM report out on the following:

1. Total MCM awards and new awards, broken down by TX, VX, and DX
2. Total number of clinical studies and new initiated studies broken down by TX, VX, and DX AND Phase 1, 2, 3
3. Topline clinical study results when publically available
4. EUAs and approvals by FDA
5. Total number of proposals submitted to portal and TechWatch meetings hosted 6. Any other data that BARDA and our partners feel would demonstrate progress

In addition, I will work with NIH, FDA and DOD to obtain all information on al USG funded clinical studies (I will not collect information on preclinical studies). We have data on all on-going studies (please see attached) but the funding agency is not identified (I imagine most if not all are USG funded). This is information that will be shared on request to leadership. I will collect the following publically available information:

1. Product name
2. Product Type (VX or TX)
3. Company/Developer
4. USG Sponsor

5. Phase 1, 2 or 3
6. Target enrollment
7. Registration number
8. Trial Design
9. Last update
10. Location

Please let me know if you concur with this plan, if there is anything missing here and/or if you have any questions.

Thank you,

Chris

Christopher Houchens, PhD
Director (Acting) Division of CBRN Countermeasures
Biomedical Advanced Research and Development Authority (BARDA)
Office of Assistant Secretary for Preparedness and Response (ASPR)
Department of Health and Human Services (DHHS)
Office: 202-205-3633
BB: (b)(6)
Christopher.houchens@hhs.gov

-----Original Message-----
From: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Sent: Monday, April 6, 2020 7:42 AM
To: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Cc: Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>
Subject: RE: Clinical Trial Status

Chris,

The only caveat I would put on the second slide is an as of date. I do not believe the 730 for KevZara is accurate. That was the number as of Saturday. We need to make sure that even though the date on the cover slide is today's date, we need to have an AS OF DATE on the second slide. This will require the team working with NIAID to get the numbers each night by a certain time.

Please also reach out to Mary, Beryl and Brian (others if needed) to start tracking the collection of convalescent plasma and potential production of HIG. We need to start reporting on that as well.

Gary

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary
Director, Medical Countermeasure Programs Biomedical Advanced Research and Development Authority
BARDA Assistant Secretary for Preparedness and Response ASPR Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G Washington, D.C. 20201
Office: 202-260-0899
Mobile: (b)(6)
Fax: 202-205-0873
email: Gary.Disbrow@HHS.gov

-----Original Message-----
From: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>
Sent: Monday, April 6, 2020 7:36 AM
To: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Cc: Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>
Subject: FW: Clinical Trial Status

Rick and Gary - I meant to include you on this request from the WH via the NRCC for our table on MCM TF clinical studies. It's the same data we report out at the VTC with some additional detail wrt enrollment numbers, etc that they see each day.

Sorry for the lapse.

Chris

Christopher Houchens, PhD
Director (Acting) Division of CBRN Countermeasures Biomedical Advanced Research and Development Authority (BARDA) Office of Assistant Secretary for Preparedness and Response (ASPR) Department of Health and Human Services (DHHS)
Office: 202-205-3633
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Christopher.houchens@hhs.gov

-----Original Message-----
From: Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>
Sent: Monday, April 6, 2020 7:27 AM
To: Kozak, Marina (OS/ASPR/BARDA) <Marina.Kozak@hhs.gov>
Cc: MCM Task Force <MCMTaskForce@hhs.gov>; Donis, Ruben (OS/ASPR/BARDA) <Ruben.Donis@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Armstrong, Kimberly (OS/ASPR/BARDA) <Kimberly.Armstrong@hhs.gov>
Subject: FW: Clinical Trial Status

Marina,

Hi. we'll need to update the enrollment targets in the attached for the Regeneron trial based on the discussions yesterday. What should we put?

Thanks.

Robert

Robert Johnson, Ph.D.
Director, Influenza and Emerging Infectious Diseases Division Biomedical Advanced Research and Development Authority BARDA Assistant Secretary for Preparedness and Response ASPR Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G Washington, D.C. 20201
Office: 202-401-4680
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email: Robert.Johnson@HHS.gov

-----Original Message-----
From: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>
Sent: Monday, April 6, 2020 7:22 AM
To: FEMA-NRCC-NRCSD <fema-nrcc-nrcsd@fema.dhs.gov>; MCM Task Force <MCMTaskForce@hhs.gov>
Cc: FEMA-NRCC-CSXO <fema-nrcc-csxo@fema.dhs.gov>; FEMA-NRCC-sasc (DHS.GOV) <fema-nrcc-sasc@fema.dhs.gov>
Subject: RE: Clinical Trial Status

Good morning. Please see attached table with ongoing clinical trials supported by MCM TF members. Thank you, Chris

Christopher Houchens, PhD
Director (Acting) Division of CBRN Countermeasures Biomedical Advanced Research and Development Authority (BARDA) Office of Assistant Secretary for Preparedness and Response (ASPR) Department of Health and Human Services (DHHS)
Office: 202-205-3633
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Christopher.houchens@hhs.gov

-----Original Message-----
From: FEMA-NRCC-NRCSD <fema-nrcc-nrcsd@fema.dhs.gov>
Sent: Sunday, April 5, 2020 11:12 PM
To: MCM Task Force <MCMTaskForce@hhs.gov>
Cc: FEMA-NRCC-NRCSD <fema-nrcc-nrcsd@fema.dhs.gov>; FEMA-NRCC-CSXO <fema-nrcc-csxo@fema.dhs.gov>; FEMA-NRCC-sasc (DHS.GOV) <fema-nrcc-sasc@fema.dhs.gov>
Subject: FW: Clinical Trial Status

Can you please provide Gen. Roy with the updated status requested by the White House tomorrow morning... thanks, tom c.

Tom Criman
FEMA NRCS Deputy
fema-nrcc-nrcsd@fema.dhs.gov
202-212-5412 ... desk
(b)(6) ... cell

From: Williams, (b)(6)
Sent: Sunday, April 5, 2020 10:54:19 PM (UTC-05:00) Eastern Time (US & Canada)
To: FEMA-NRCC-NRCSC
Subject: Clinical Trial Status

Hello,

The Domestic Policy Council requests a status update (eg enrollment, timeline) on ongoing clinical trials sponsored by the US government (NIH/FDA). Thank you.

James Williams
Special Assistant to the President
The White House

Sender:	Houchens, Christopher (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7AC94A574BD04528B7C91BBD61893975-HOUCHENS, C <Christopher.Houchens@hhs.gov>
Recipient:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga

	<Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>; Boucher, David (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=41293945651d475fa0413062a819aac5-Boucher, Da <David.Boucher@hhs.gov>; Ventura, Christy (OS/ASPR/BARDA) (CTR) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9bb949caca464329823ca3cf77654a06-Ventura, Ch <Christy.Ventura@hhs.gov>
Sent Date:	2020/04/06 10:53:12
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Page 138

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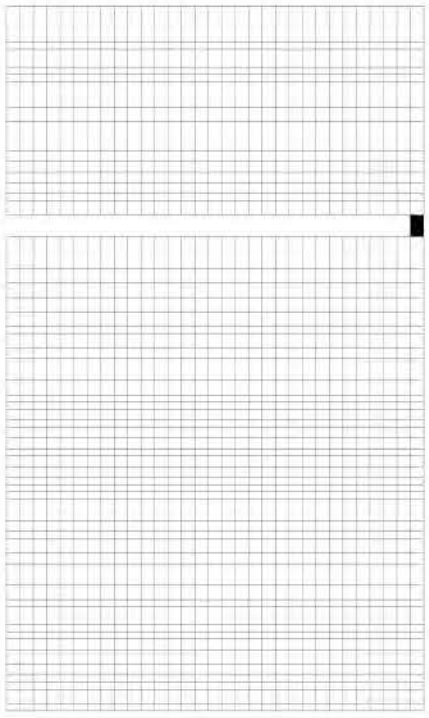

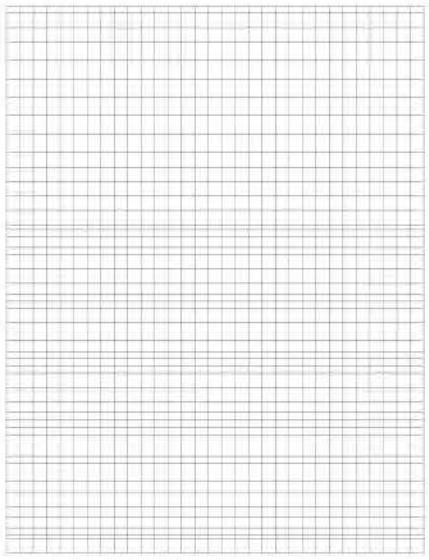

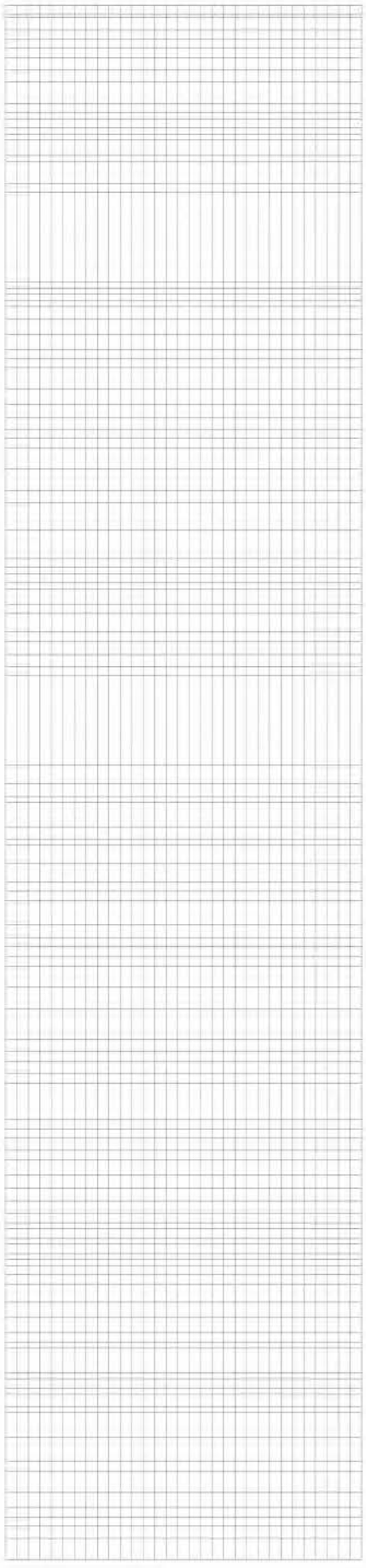

Page 148

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Country/Region	Name/Reference	Website	Comment	Number of Trials Found	Last Review Date
International	World Health Organization – International Clinical Trials Registry Platform https://www.who.int/ictrp/en/	http://apps.who.int/trialsearch/	Search: COVID	522; almost entirely chinese and backdated; seem to be doing updates by/when deprioritizing	4/1/2020
China	Chinese Clinical Trials Registry	http://www.chictr.org.cn/searchprojen.aspx	Search: COVID (Public Title) Interventional (Study Type)	288	4/5/2020
United States		https://www.clinicaltrials.gov/ct2/home	Search: COVID-19 (includes related terms)	306	4/5/2020
Canada	Health Canada Clinical Trial Database	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php	Search: COVID, sars cov 2 ncov	8	4/5/2020
European Union	EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/ctr-search/search	Search: COVID 19	31	4/5/2020
Germany	German Clinical Trials Register	https://www.drks.de/drks_web/	*Search: COVID, COVID 19, 2019 nCoV, SARS-CoV 2*	*5 (none relevant)*	*4/1/2020*
Switzerland	Swiss National Clinical Trials Portal	https://www.kofam.ch/en/snctp-portal/searching-for-a-clinical-trial/	*Search: COVID, COVID 19, 2019-nCoV, 2019 novel coronavirus, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2*	0	*3/24/2020*
United Kingdom	ISRCTN	http://www.isrctn.com/	*Search: COVID, COVID-19, 2019-nCoV, 2019 novel coronavirus, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2*	6	4/3/2020
Australia and New Zealand	Australia and New Zealand Clinical Trials Registry	https://www.anzctr.org.au/TrialSearch.aspx		2	4/5/2020
India	Clinical Trials Registry – India	http://ctri.nic.in/	Search: COVID	6	4/5/2020
Iran	Iranian Registry of Clinical Trials	http://www.irct.ir/	Search: COVID-19	52	4/5/2020
Japan	Japan Primary Registries Network	https://rctportal.niph.go.jp/en/	Search: COVID 19	10	4/5/2020
Korea	Clinical Research Information Service	https://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp	*Search: COVID, COVID 19, 2019-ncov, SARS-CoV-2*	8	*4/3/2020*
Philippines	Philippine Health Research Registry	http://registry.healthresearch.ph/	Search: COVID, COVID-19, 2019-nCoV, 2019 novel coronavirus, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2	0	4/3/2020
Singapore		https://www.hsa.gov.sg/clinical-trials/c	Search: Therapeutic area -> Infectious Diseases and search by pathogen; most covered on other registries	26; 3 relevant	4/3/2020
Sri Lanka	Sri Lanka Clinical Trials Registry	https://slctr.lk/		0	3/27/2020
Thailand	Thai Clinical Trials Registry	http://www.clinicaltrials.in.th/	Search: COVID, COVID-19, 2019-nCoV, 2019 novel coronavirus, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2	4	4/5/2020
Brazil	Brazilian Clinical Trials Registry	http://www.ensaiosclinicos.gov.br/	Search: COVID, COVID-19, 2019-nCoV, 2019 novel coronavirus, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2	3	4/5/2020
Cuba	Public Cuban Registry of Clinical Trials	http://registroclinico.sld.cu/en/home		0	4/3/2020
Peru	Peruvian Registry of Clinical Trials	https://www.ins.gob.pe/ensayosclinicos/	<Have to have an account to search> Search: COVID, COVID-19, 2019-nCoV, 2019 novel coronavirus, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2	0	4/3/2020
Africa	Pan-African Clinical Trials Registry	https://pactr.samrc.ac.za/		0	4/5/2020
South Africa	South African National Clinical Trials Registry	http://www.sanctr.gov.za/		0	3/30/2020
Tanzania	Tanzania Clinical Trials Registry	http://www.tctr.or.tz/			

Search Terms
COVID
COVID-19
nCoV
2019-nCoV
coronavirus
SARS CoV-2

Product Families

ART	CQ	anti-IL6/R	GM-CSF	*Janus kinase (JAK) and (MK2) inhibitor*	*ACE inhibitors*	*Chemotherapies* Bevacizumab	*Other anti-inflam*	*Vitamins / supplements* Vitamin D Ascorbic Acid	*NO* nitric oxide
Lopinavir/ritonavir	Plaquenil	Actemra	Leukine	Baricitinib			Afelimomab Adalimumab Mepolizumab		
Kaletra	Quensyl	Infliximab	Otu-GM-CSF	Otilimab					
		Kevzara Sarilumab Roflumilast	Sargramostim	Baricitinib Ruxolitinib					

From:	Elvander, Erika (OS/OGA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=AC87C0EC2D2741A69764E52F6CB4CA95-ELVANDER, E <Erika.Elvander@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:	Kerr, Lawrence (HHS/OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ce9de2e7497472bb758f8fd6e262c86-Kerr, Lawre <Lawrence.Kerr@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>
Subject:	Re: Gilead call notes - March 18
Date:	2020/03/20 15:46:46
Priority:	Normal
Type:	Note

Great!

Erika Elvander
Director, Asia and the Pacific
Office of Global Affairs, HHS
Sent from my iPhone

On Mar 20, 2020, at 3:41 PM, Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>wrote:

Thank you Erika, please keep us looped in on these items. Very helpful.

I'm looping in Gary and Robert Johnson for visibility. Rick

From: Elvander, Erika (OS/OGA) <Erika.Elvander@hhs.gov>
Sent: Friday, March 20, 2020 3:31 PM
To: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>; Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>
Subject: FW: Gilead call notes - March 18

Of interest.

From: Parrish Fuentes, Adrienne L (Beijing) <ParrishFuentesAL@state.gov>
Sent: Thursday, March 19, 2020 9:47 PM
To: Abdoo, Mark (FDA/OC) <Mark.Abdoo@fda.hhs.gov>; Ross, Bruce (FDA/ORA) <Bruce.Ross@fda.hhs.gov>; Christensen, Lane (FDA/OC) <Lane.Christensen@fda.hhs.gov>; Handley, Gray (NIH/NIAID) [E] <handleygr@niaid.nih.gov>; Elvander, Erika (OS/OGA) <Erika.Elvander@hhs.gov>; Sizemore, Christine (NIH/NIAID) [E] <csizemore@niaid.nih.gov>; Simonds, R. J. (CDC/DDPHSIS/CGH/OD)

<rxs5@cdc.gov>
Cc: Koo, Han (OS/OGA) (CTR) <Han.Koo@hhs.gov>; Kopolow, Aimee (OS/OGA) <Aimee.Kopolow@hhs.gov>
Subject: Gilead call notes - March 18

Colleagues,

Please see below my notes from a call Ambassador Branstad had with the CEO of Gilead this week. We are doing some follow up here on the protocol amendment details. Please let me know if other questions.

Best,
Adrienne

Amb. Branstad call with Gilead CEO Daniel O'Day – Wed March 18

Remdesivir clinical trials – progress update

Relationship with China absolutely fundamental – tremendous cooperation thus far
Hopeful about therapeutic use but still don't know if it works clinically – lab environment positive responses
2 trials in China – one for severe cases and one for moderate cases – sever enrollment is further along – enrollment goal is 400 participants – but enrollment was slowing down.
Trial enrollment was slowing down but now (this week) the protocol was amended to allow patients to enroll if also taking other medication such as TCM.(following up with Gilead to understand these amendments better)
Primary engagement with Chinese gov. has been with Wang Chen (lead of research task force), VC of NMPA and MOST.

Supply and manufacturing

Gilead is repurposing facilities so can scale up production as needed
Reliant on China for API – single sourced for now
Relationship with Chines company Fosun pharma is critical - they provide some material so Gilead can complete the product (so that end March should have 30,000 treatment courses)
Important to keep Fosun involved so that we can ensure the Remdesivir value chain
Working on supply chain to be "China free" by the end of this year – to source API 60-70% in the US and 30-40% in Europe (Italy, France, Germany)
Mid-April should receive next API shipment out of China

Distribution and Access

Need to understand the Remdesivir demand in China better – engaged with VP Sun on this
Planning 10,000 treatments for China
IP protection – early issues and rumors – but public Chinese statements have been supporting of ensuring IP protection

Adrienne Parrish Fuentes
Health Attaché
U.S. Department of Health and Human Services
U.S. Mission to China

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Mobile: +(b)(6)
ParrishFuentesAL@state.gov

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Recipient:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Kerr, Lawrence (HHS/OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ce9de2e7497472bb758f8fd6e262c86-Kerr, Lawre <Lawrence.Kerr@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>
Sent Date:	2020/03/20 15:46:45
Delivered Date:	2020/03/20 15:46:46

Phase II/III two dose mRNA COVID-19 Vaccine Trial

2 April 2020

Dean Follmann

John Beigel

NIH

Basic design

- mRNA-1273 vaccine
  - lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine
  - SARS-CoV-2 full-length, prefusion stabilized spike (S) protein
- Two dose day 0, day 28
- Double blind placebo controlled
- Phase 2/3
  - Phase 2 to select dose
  - Phase 3 to assess efficacy
  - Use all data

Population

- Enroll higher risk groups in sites with higher expected attack rates & lower seroprevalence
  - Health Care/Hospital workers
  - Teachers?, College Students?
  - Communities
- Choices to be informed by modeling from expert coalition
- More sites/fewer enrollees per site to increase chance some sites have high attack rate

Phase 2

Cohort	Sample Size	Stratum (Years of Age)	First and Second Dose
1	100	18-55	100 mcg mRNA-1273
2	100	18-55	250 mcg mRNA-1273
3	50	18-55	Placebo
4	100	≥56	100 mcg mRNA-1273
5	100	≥56	250 mcg mRNA-1273
6	50	≥56	Placebo

Phase 2

- Will stage enrollment based on data
  - Safety and immunogenicity data from phase 1
  - Preclinical safety (vaccine enhanced disease).
    - Mouse
    - NHP
  - Balance risk and data available

Endpoints

- Primary:
  - Clinical Disease & PCR+ from symptom driven visits
  - Safety
- Key Secondary:
  - Immunogenicity
  - Case-control immune correlates, from serial antibodies
  - Antibody positive to non-vaccine SARS-CoV-2 antigens
  - Death/Severe disease
  - Sieve analysis-differential efficacy by infecting substrain
- Exploratory
  - Viral Shedding

Analysis Populations

- mITT -- all randomized who are SARS-COV-2 negative at baseline*
  - Primary Efficacy analysis population
  - Answers real world question
  - Properly incorporates potential early enhancement/inefficacy
- Safety Population---all randomized with 1+ dose
  - Assess safety
- Per Protocol – all randomized who receive both doses
  - Assess efficacy for full dose vaccine

*or have as exclusion criterion

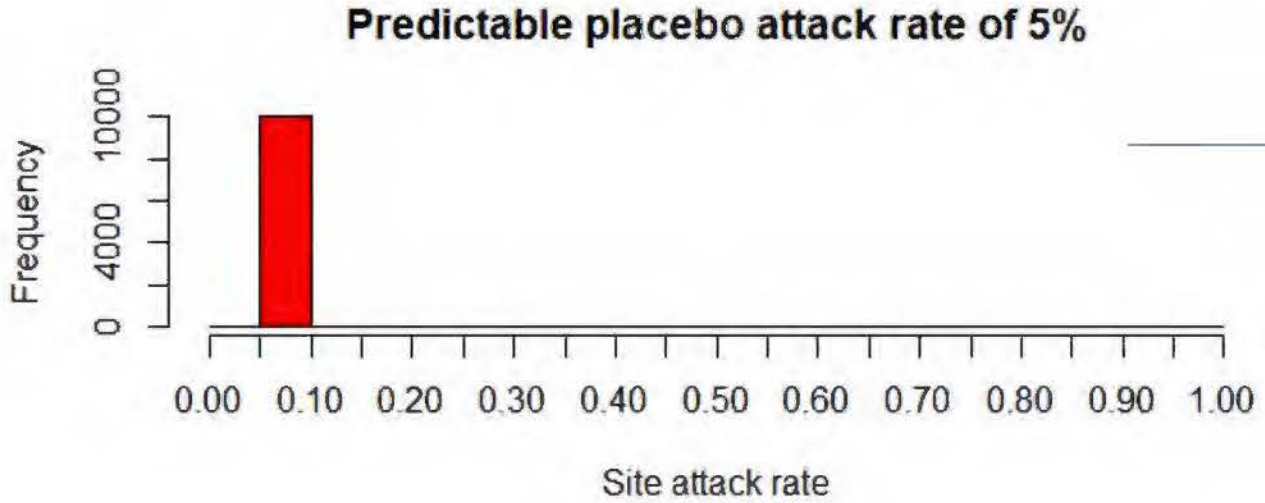
Cases needed to rule out VE<30% with 90% power

Vaccine Efficacy	# Cases	# Cases*
60%	**134**	177
65%	**87**	**115**
70%	58	**77**
75%	40	53

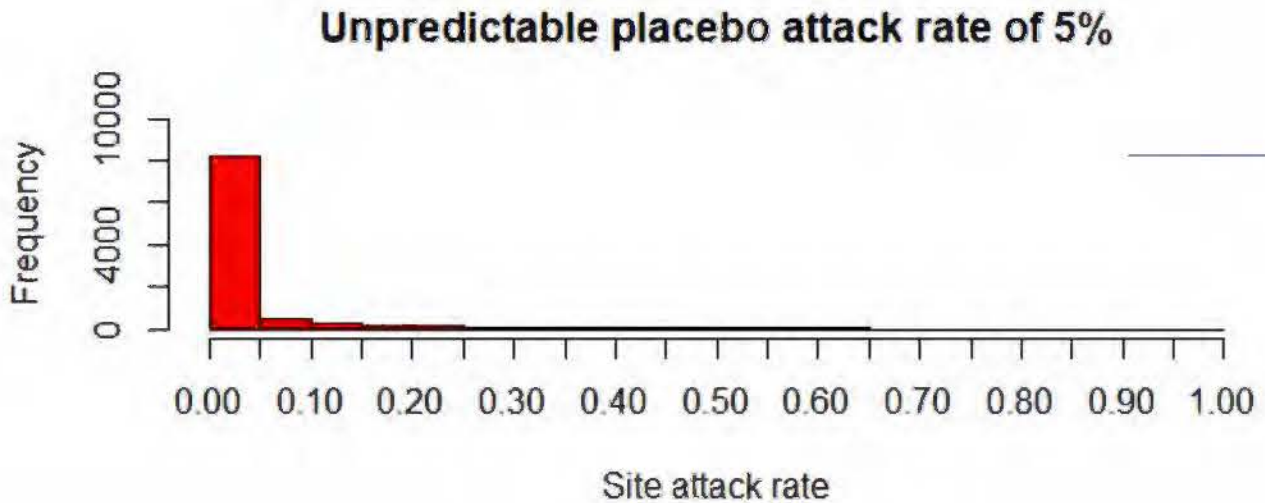
*Reduces VE by 5% to allow for early weak efficacy in first two months

Two-sided type I error rate = 0.05
Sample size for log-rank test adapted from Freedman (1981)

Site attack rate is highly unpredictable with substantial consequences for sample size



Each site has a .05 attack rate
Each placebo flips a .05 coin for infection



Site attack rate is highly variable
Each placebo flips a site-specific coin for infection
Median coin 0.0004
90th % coin 0.17

Time to 100 cases depends on multiple factors

	Theoretical Yearly Attack Rate	Variable Site Attack rate* Median	90th %	# sites	Total N	100 cases in 9^ months?	100 cases in 15^ months?
1	0.050	0.00	0.17	10	5000	33%	63%
2	0.050	0.00	0.17	25	5000	36%	79%
3	0.050	0.00	0.17	25	10000	67%	95%
4	0.050	***0.014***	***0.15***	25	5000	34%	91%
5	***0.100***	0.014	0.34	25	5000	79%	99%
6	***0.010***	0.00	0.002	***100***	***50000***	62%	92%

*Attack rate will vary from site to site---Illustrative beta-binomial with E(p)=YAR and $\alpha+\beta=2$, except 5th row
^3 months added to reflect not all vaccinees are vaccinated on day 1.
Above calculations assume 60% VE

Enrollment Considerations

- Enroll a large number of subjects across many sites
  - Faster answer
  - 'hedges' against possibility many sites may have very low attack rates
- Differential roll-out of sites, if any, should be based on current epidemiology and high risk groups
  - Activate sites in August with anticipated November crest
  - Enroll teachers at least a month before school starts
- Plan to expand beyond original sample size if chosen sites have low attack rates

Portfolio Management: Clockwork world

- How to evaluate two vaccines?
  - Sequential 2 arm trials: V1 vs Pla, then V2 vs Pla. Each takes 1 year N=5000 x 2*
  - 3 arm trial: V1 & V2 vs Pla. Trial takes 1.5 years N=7500
- Vaccines have uncertain efficacy
  - Both work: Sequential 2 arm trials get a winner in 1 year
  - Neither work: 3 arm trial gets both answers in 1.5 years
  - One vaccine works
    - 3 arm trial gets answer in 1.5 years for sure
    - Sequential 2 arm trials is either 1 year or 2 years.

**numbers and duration are for illustration*

Portfolio Management: uncertain world—

- Vaccines have uncertain efficacy
  - Both work: Sequential faster to identify winner
  - Neither work: 3 arm faster to both answers
  - One vaccine works (*drought or deluge* e.g.)
    - Get 100 infections in 4 years
      - Both strategies slow.
    - Get 400 infections in 6 months
      - 3 arm: Identify the winner quickly
      - Sequential: Half the time pick the loser and waste 300 infections.

Evaluating multiple vaccines hedges your bets and might get two quick answers
If you're quite confident the vaccine will work, sequential trial should be somewhat faster

Questions

Outbreak considerations

- mITT analysis counts day(0,35) cases, if not rare, dilutes power, thus
  - Blinded review of data to adjust case target
    - Modest number of early cases (i.e. day 0,35) moderate increase in case target
    - Large number of early cases, *possibly* form two primary analyses.
      - VE over Day(0,35) focused on early enhancement/early benefit
      - VE over Day(35+) focused on ideal world efficacy
- Monitor baseline seroprevalence (lowers attack rate in study *& community*)
  - Pivot to sites with lower current & anticipated seroprevalence
  - Increase sample size

Time to 100 cases depends on multiple factors

Theoretical Yearly Attack Rate	Variable Site Attack rate* Median	90th %	# sites	Total N	100 cases in 9^ months?	100 cases in 15^ months?
0.050	0.00	0.17	10	5000	33%	63%
0.050	0.00	0.17	40	5000	35%	86%
0.050	0.00	0.17	10	10000	50%	80%
0.050	0.00	0.17	40	10000	75%	99%
0.200	0.10	0.57	10	5000	93%	100%
0.025	0.00	0.05	40	10000	36%	74%
0.010	***0.00***	***0.002***	***100***	***50000***	62%	92%
0.050	***0.05***	***0.05***	10	5000	8%	100%

*Attack rate will vary from site to site---Illustrative beta-binomial with E(p)=YAR and $\alpha+\beta=2$, except last row

^3 months added to reflect not all vaccinees are vaccinated on day 1.

Above calculations assume 60% VE

Other elements

- Frequent monitoring for safety/potential enhancement
- Monitoring for efficacy with 3 or 4 equally spaced looks using traditional O'Brien-Fleming spending function.
- Stratify randomization by site
- Stratify analysis
  - SARS-CoV-2 serology positive at baseline

After the trial

- Vaccine not efficacious
  - Wait for next vaccine/prevention drug
- Vaccine efficacious—impact on trial
  - Vaccine offered to all
  - Continue serial immunogenicity if feasible
- Vaccine efficacious— opportunities in roll-out
  - Observational studies of efficacy/disinhibition
  - Any role for step-wedge-type rollout?
  - Vaccine durability can be assessed with test negative in vaccinees e.g.
    - 'control' = day(0,35)
    - 'vaccine' = day(35+)
    - stratify by site/calendar time

Surveillance (sub)studies can help plan for PEP-type vaccine or mAb

- Enroll family members of mild index case
  - Estimate secondary attack rate over time
- Enroll PCR negative subjects who sought testing
  - Estimate subsequent attack rate in them & family members over time
- If enough cases happen 7-14 days after sentinel subject presents, do vaccine ring-family trial (individual or cluster randomization).
- Could do a mAb ring-family trial in index case and family members to answer two questions (cluster randomization)
  - 1) Early treatment for index case
  - 2) PEP for family members with index treatment

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 three million doses of chloroquine phosphate donated by Bayer Pharmaceuticals for possible use in treating patients hospitalized with COVID-19. The companies ramped up production to provide the medication.

"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."

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HHS' Office of the Assistant Secretary for Preparedness and Response (ASPR) with colleagues within HHS, the companies, the Department of State, and the Department of Homeland Security 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 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 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.

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 or case series suggest that these drugs may offer some benefit in the treatment of COVID-19 patients.

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.

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 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.

The FDA has issued emergency use authorization for multiple diagnostics and personal protective equipment for the COVID-19 response.

Sandoz and Bayer are the latest companies stepping up to strengthen the U.S. response to COVID-19, and ASPR's Biomedical Advanced Research and Development Authority (BARDA) is working with additional companies willing to donating additional 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.

In addition to accepting and distributing the donated medicines, HHS is funding clinical trials of two drugs, Kevzara 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.

# # #

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

From:	Ventura, Christy (OS/ASPR/BARDA) (CTR) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=9BB949CACA464329823CA3CF77654A06-VENTURA, CH <Christy.Ventura@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:	Houchens, Christopher (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ac94a574bd04528b7c91bbd61893975-Houchens, C <Christopher.Houchens@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>; MCM Task Force /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=49010f8ab3ab4aed868a72c707c08d08-MCM Task Fo <MCMTaskForce@hhs.gov>
Subject:	RE: MCM Task Force update for 4/8/2020
Date:	2020/04/08 08:48:53
Priority:	Normal
Type:	Note

Rick,

Thanks for the clarification. I've removed the Regeneron and Genentech numbers. Today's updates are attached. Note that only the information on the first page is reported to FEMA. The rest is for BARDA internal use/situational awareness only.

Christy

FOUO/PROCUREMENT SENSITIVE

--
Christy L. Ventura, Ph.D.
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Executive Secretary, SARS-CoV-2 Medical Countermeasures Task Force
Project Manager, CBRN/BARDA/ASPR/HHS
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From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Tuesday, April 7, 2020 10:27 PM
To: Ventura, Christy (OS/ASPR/BARDA) (CTR) <Christy.Ventura@hhs.gov>
Cc: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; MCM Task Force <MCMTaskForce@hhs.gov>
Subject: Re: MCM Task Force update for 4/8/2020

Christy. I caused confusion and Chris corrected me. Please do not report the regen antibody numbers. My mistake. Sorry. Thanks. Rick.

On Apr 7, 2020, at 9:44 PM, Ventura, Christy (OS/ASPR/BARDA) (CTR) <Christy.Ventura@hhs.gov>wrote:

All,

Updated talking points are below. I'm awaiting confirmation from Tremel on the number of actual requests vs shipments from the SNS.

Accomplishments

- • USG funded clinical studies
  - • Therapeutics: 4 (+1) Phase 3 trials (2 BARDA, 1 NIAID, 1 NHLBI)
  - • Vaccines: 2 Phase 1 trials (1 DoD, 1 NIAID)
  - • Observational Natural History Study: 1 DoD

- ACTT Clinical trial to test remdesivir for treatment of COVID-19: 526 (+29) new patients at 58 (+1) sites, including 5 military treatment facilities, in last 24 hrs (target = 700)
- ORCHID Clinical trial to test hydroxychloroquine in COVID-19 patients: 10 patients enrolled (target = 510)
- First antibody therapeutic trial: 916 (+86) new patients dosed at 53 (+2) sites
- Second antibody therapeutic trial initiated: 9 (+7) new patients dosed, 11 (+9) sites activated
- Requests for chloroquine/hydroxychloroquine from the SNS
  - 2 clinical trial requests received, 1 fulfilled
  - 11 EUA requests received and 2 shipped
- Emergency Use Authorizations granted by FDA: 28 (+1) molecular diagnostic tests, 5 (+1) laboratory-developed tests, 1 antibody test, and 2 repurposed treatments (chloroquine, hydroxychloroquine)
- • 1964 (+42) market research submissions and 185 (+7) CoronaWatch meetings held

Christy

FOUO

--
Christy L. Ventura, Ph.D.
Tunnell Government Services
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From: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>
Sent: Tuesday, April 7, 2020 6:19 PM

To: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>; Ventura, Christy (OS/ASPR/BARDA) (CTR) <Christy.Ventura@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: MCM Task Force <MCMTaskForce@hhs.gov>
Subject: RE: MCM Task Force update for 4/8/2020

Rick – Thank you for your comments. Regarding you direction to keep reporting out numbers on the Regeneron and Genentech mAb therapeutic studies, I mentioned yesterday that both of those companies have expressed concerns about reporting those numbers (please see attached and below). Please let me know if you have any thoughts regarding the below and how to proceed. Thanks, Chris

There continues to be concern from companies about reporting out any data that is not public even if it is non-attributional as the information could still identify the company (at which point it becomes a notifiable event if it is publicly-traded company). For example, it is publically known that we are supporting two IL-6R mAb therapy studies - one started over a month ago and one stated just last week and reporting higher enrollment numbers will identify the first while lower numbers will identify the second. If the numbers for either do not change for a period of time, and if this information gets released (I know that the Supply Chain Task Force numbers reported each day wind up in the WP the next day), then other stakeholders (investors, companies, regulators, etc) will ask why. However, there is a need to show progress on the MCM TF to our stakeholders and leadership during the daily VTC calls. So my recommendation is that the MCM report out on the following:

1. Total MCM awards and new awards, broken down by TX, VX, and DX
2. Total number of clinical studies and new initiated studies broken down by TX, VX, and DX AND Phase 1, 2, 3
3. Topline clinical study results when publicolly available.
4. EUAs and approvals by FDA
5. Total number of proposals submitted to portal and TechWatch meetings hosted
6. Any other data that BARDA and our partners feel would demonstrate progress
7. And we will continue to report out numbers for those companies that are OK with us doing so.

Christopher Houchens, PhD
Director (Acting) Division of CBRN Countermeasures
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Office of Assistant Secretary for Preparedness and Response (ASPR)
Department of Health and Human Services (DHHS)
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Christopher.houchens@hhs.gov

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Sent: Tuesday, April 7, 2020 6:03 PM

To: Ventura, Christy (OS/ASPR/BARDA) (CTR) <Christy.Ventura@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: MCM Task Force <MCMTaskForce@hhs.gov>
Subject: Re: MCM Task Force update for 4/8/2020

Great work, as always team. See some thoughts below. Rick

From: "Ventura, Christy (OS/ASPR/BARDA) (CTR)" <Christy.Ventura@hhs.gov>
Date: Tuesday, April 7, 2020 at 5:49 PM
To: "Bright, Rick (OS/ASPR/BARDA)" <Rick.Bright@hhs.gov>, Gary Disbrow <Gary.Disbrow@hhs.gov>, Linda Lambert <Linda.Lambert@hhs.gov>
Cc: MCM Task Force <MCMTaskForce@hhs.gov>
Subject: MCM Task Force update for 4/8/2020

Rick, Gary, Linda,

See below for tomorrow's updates for the MCM Task Force. Another item that we will not be reporting out tomorrow but that we are sharing for situational awareness is that NIAID is working with Eli Lilly and Gilead to add baracitinib to the ACTT. Arms are expected to be remdesivir, baricitinib, remdesivir + baricitinib, and placebo, all with SOC.

Here are the updates that we will report tomorrow.

Talking Points for 1200 and 1700 SLBs and 1230 VTC

Accomplishments

- USG funded clinical studies
- Therapeutics: 4 (+1) Phase 3 trials (2 BARDA, 1 NIAID) says 4, but lists 2 BARDA and 1 NIAID, where is the fourth?
- Vaccines: 2 Phase 1 trials (1 DoD, 1 NIAID)
- Observational Natural History Study: 1 DoD

- ACTT Clinical trial to test remdesivir for treatment of COVID-19: 526 (+29) new patients at 58 (+1) sites, including 5 military treatment facilities, in last 24 hrs (target = 700)
- ORCHID Clinical trial to test hydroxychloroquine in COVID-19 patients: 10 patients enrolled (target = 510)
- Two clinical trials to test antibody therapeutics continue Please do not stop reporting the enrollment of these, it is important to find some way to show progress being made on these.
- Emergency Use Authorizations granted by FDA: 28 (+1) molecular diagnostic tests, 5 (+1) laboratory-developed tests, 1 antibody test, and 2 repurposed treatments (chloroquine, hydroxychloroquine) Please include an update on the drugs pushed out from SNS for the CQ, HCQ EUA.
- 1964 (+42) market research submissions and 185 (+7) CoronaWatch meetings held

Please let us know if you have any concerns.

Thanks
Christy

FOUO/PROCUREMENT SENSITIVE

--
Christy L. Ventura, Ph.D.
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Project Manager, CBRN/BARDA/ASPR/HHS
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Sent Date:	2020/04/08 08:48:50
Delivered Date:	2020/04/08 08:48:53

SARS-CoV-2 Medical Countermeasures Task Force
Date: April 8, 2020
FOR OFFICIAL USE ONLY

Agencies reporting: BARDA, NIAID, DoD, FDA, USDA
Agencies not reporting: CDC, DHS

Talking Points for 1200 and 1700 SLBs and 1230 VTC

Accomplishments

- USG funded clinical studies
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- 1964 (+42) market research submissions and 185 (+7) CoronaWatch meetings held

(b)(5)

- Adaptive COVID-19 Treatment Trial - NIAID
  - Currently remdesivir vs. placebo control (with options to add additional arms as needed)
  - Target enrollment = 440
  - Inclusion criteria – Confirmed SARS-CoV-2 infection (efficacy, but a little gray area PEP too)
  - Primary endpoint:
    - 8pt ordinal scale scored at Day 15, ranging from death to discharged with no limitation on activities and no requirement for home oxygen

- Sarilumab (Anti IL-6R mAb, aka Kevzara), Regeneron/Sanofi
  - Sarilumab high dose vs. Sariluman low dose vs. placebo control

  - Target enrollment = 400
  - Inclusion criteria – Confirmed SARS-CoV-2 infection AND evidence of pneumonia and severe disease (a true efficacy study)
  - Primary endpoints:
    - Time to resolution of fever for at least 48 hours
    - 6pt ordinal scale scored on Day 15, ranging from death to discharged

- mRNA-1273, Moderna
  - Phase I safety/immunogenicity
  - Target enrollment = 45
  - NHV study
  - Cohorts (all n=15, including 4 sentinels):
    - Low dose = 25ug
    - Medium dose = 100ug
    - High dose = 250ug

- EpICC Study, IDCRP
  - Observational natural history study
  - Clinical parameters being evaluated: risk factors, outcomes, virology, immunology

Proposed Clinical Trials

Vaccine / Therapeutic Product	Date / Range for Entry into Clinic
Convalescent plasma	Approx. late April/early May
IVIg	Late Spring 2020
Regeneron SARS-CoV-2 specific mAbs	June-July 2020 for treatment study in COVID-19 patients
Janssen screening leads	Early Summer 2020 or later; highly dependent on leads identified
SAb	June to mid-Summer 2020
Janssen Ad26 Vaccine	Phase 1: Q3-2020
Moderna mRNA Vaccine	Phase 1 enrollment: March 16, 2020 Phase 2: Q2-2020 (likely about June 2020)
Sanofi-Pasteur Vaccine	Phase 1: Q1-2021 (September/October 2020 provided to CBER)

NIAID is planning:

- *ACTG HCQ+Azithro vs SOC treatment in COVD outpatients*
- *INSIGHT Network remdesivir vs. hyperimmuneglobulin vs. SOC in COVID outpatients at risk of severe dz*
- *BET – Big Effect Trial in haspitalized pts with COVID and pulmanary involvement*
- *Eventually a Phase 2/2b for Moderna (and ideally linked to trials for other candidates)*

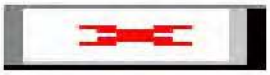
NHLBI is planning:

- *Convalescent plasma treatment inpts*
- *HCQ treatment inpatients: began enrolling 4/6/2020*
- *Possibly ARDS adaptive*

NCATS is still deciding

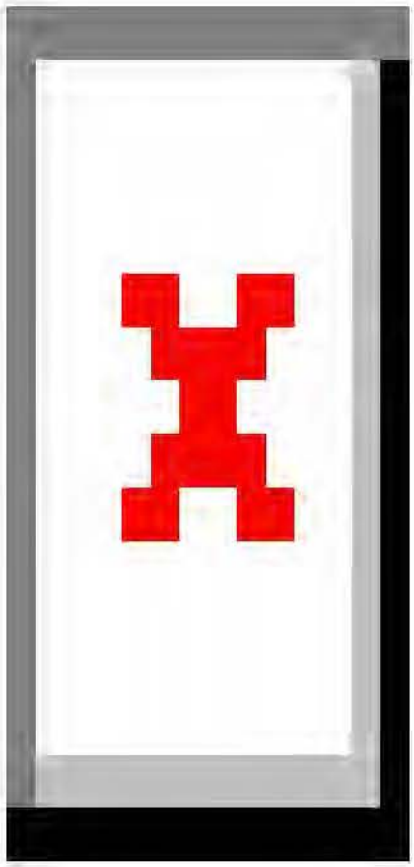
NINDS has a proposal to do an HCQ ppx trial in first responders at the Temple Siren site"

From:	Jeanna <reply@selleckchemical.com>
SentVia:	Jeanna <reply=selleckchemical.com@pmta259.dedicated.bmsend.com>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	[SUSPECTED SPAM] Science: Race to Find COVID-19 Treatments Accelerates
Date:	2020/03/31 08:44:22
Priority:	Normal
Type:	Note



Inhibitor Expert (Inhibitors,Compound Libraries)

Race to Find COVID-19 Treatments Accelerates



Experimental treatment strategies attempt to inferfere with different steps (numbered) in the coronavirus replication clycle

Science. 2020 Mar 27;367(6485):1412-1413.
doi: 10.1126/science.367.6485.1412.

- At least **12 potential COVID-19 treatments** are being tested, including drugs already in use for HIV and malaria, experimental compounds that work against an array of viruses in animal experiments, and antibody-rich plasma from people who have recovered from COVID-19;

- **WHO** chose an experimental antiviral called **remdesivir**; the malaria medication **chloroquine** (or its chemical cousin hydroxychloroquine); a combination of the HIV drugs **lopinavir** and **ritonavir**; and that combination plus **interferon-beta**, an immune system messenger that can help cripple viruses.

Mechanism and Drawback for Treatments

Treatments	Mechanism	drawback

Remdesivir >>	Remdesivir shuts down viral replication by inhibiting a key viral enzyme, the RNA polymerase. "It has the best potential," says Shibo Jiang of Fudan University.	It's an [intravenous] drug, it's expensive, and 85 out of 100 people don't need it.
Hydroxychloroquine >> &Chloroquine >>	hydroxychloroquine and chloroquine decrease acidity in endosomes, compartments that cells use to ingest outside material and that some viruses co-opt during infection. They have received intense attention because of positive results from small studies.	Studies in cell culture have suggested chloroquine can cripple the virus, but the doses needed are usually high and could cause severe toxicity; Hydroxychloroquine has many side effects and can, in rare cases, harm the heart—and people with heart conditions are at higher risk of severe COVID-19.
Lopinavir >> &Ritonavir >>	Lopinavir and ritonavir were developed to inhibit the protease of HIV, an enzyme that cleaves a long protein chain during assembly of new viruses. The combination has worked in marmosets infected with the MERS virus, and has also been tested in patients with SARS and MERS, though those results are ambiguous.	The first trial with COVID-19 was not encouraging. When doctors in Wuhan, China, gave 199 patients standard care with or without lopinavir-ritonavir, the outcomes did not differ significantly.
Lopinavir &Ritonavir &Interferon-beta	Interferon-beta involved in regulating inflammation that has lessened disease severity in marmosets infected with MERS. But it might be risky for patients with severe COVID-19.	"If it is given late in the disease it could easily lead to worse tissue damage, instead of helping patients", Herold, an expert on

		pulmonary infections at the University of Giessen, says.
Baricitinib >> &Corticosteroids	The drugs can reduce inflammation, a treatment for rheumatoid arthritis.	
Camostat mesylate >>	Camostat mesylate inhibits a human protein involved with infection, a drug licensed in Japan for pancreatitis	
Favipiravir >>	Favipiravir is an influenza drug.	

View this in web browser version.

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<Katherine.thyer@hhs.gov>;
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Fisher, Robert (FDA/OC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=28923afbf58b4b03a9f624448be88039-robert.fish <Robert.Fisher@fda.hhs.gov>;
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Post, Diane (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ec55458ad48f484daad641dc9ec4d7f0-diane.post. <postd@niaid.nih.gov>;

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<tmu0@cdc.gov>;
Gin, Julia (OS/ASPR/SPPR) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=e4b899460dab4897b83dfd838c376bf9-Gin, Julia
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Spiro, David (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a7c5a1fe05314a58ae927cdbba519660-david.spiro <david.spiro@nih.gov>;
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'Sangeeta Underwood' </h\/G\ >;
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Subject:	2019 nCoV Meeting/Naturitious, Diagnostic
Date:	2020/03/22 18:39:11
Start Date:	2020/03/26 14:00:00
End Date:	2020/03/26 14:30:00
Priority:	Normal
Type:	Schedule.Meeting.Request
Location:	WebEx
Attendees:	OS - ASPR - BARDA - ALL; OS - ASPR - VTC Support; Williams, Deitra (OS/ASPR/BARDA); (b)(6); Katherine.thyer@hhs.gov; Sam.lee@fda.hhs.gov; Tom.winters@nih.gov; (b)(6); Hrdina, Chad (OS/ASPR/SPPR); Jones, Juanita (OS/ASPR/BARDA); Harris, James (OS/ASPR/BARDA); Siddiqui, Abid (OS/ASPR/BARDA) (CTR); Fisher, Robert (FDA/OC); (b)(6); (b)(6); Wong, Diana (OS/ASPR/SIIM); Butts, Keane (OS/ASPR/BARDA); (b)(6); Gorman, Susan (ASPR/SNS); (b)(6); Coleman, Norman (NIH/NCI) [E]; Woodson, Sara (NIH/NIAID) [F]; jerome.cordts@associates.hq.dhs.gov; Caneva, Duane (DHS.GOV); Koerner, John (OS/ASPR/SPPR); Cliffer, Kenneth (OS/ASPR/SPPR); Post, Diane (NIH/NIAID) [E]; Shabman, Reed (NIH/NIAID) [E]; Uyeki, Timothy M. (CDC/DDID/NCIRD/ID); Gin, Julia (OS/ASPR/SPPR); Delaney, Lisa (CDC/NIOSH/OD); Peterson, Jeff (CDC/NIOSH/NPPTL/CVSDB); Dowell, Chad (CDC/NIOSH/OD); D'Alessandro, Maryann M. (CDC/NIOSH/NPPTL); Miller, Colleen S. (CDC/NIOSH/NPPTL/CVSDB); Pallansch, Mark A. (CDC/DDID/NCIRD/DVD); Gerber, Susan I. (CDC/DDID/NCIRD/DVD); (b)(6); Biggins, Julia (MIL); (b)(6); (b)(6); (b)(6); Marston, Hilary (NIH/NIAID) [E]; Bozick, Brooke (NIH/OD) [E]; kimberly.taylor3@nih.gov; Sciotti, Rick (NIH/NIAID) [E]; Beanan, Maureen (NIH/NIAID) [E]; Patel, Anita (CDC/DDID/NCIRD/OD); Mair, Michael (FDA/OC); Measer, Gregory (FDA/OC) (CTR); Carroll, Darin (CDC/DDID/NCEZID/OD); Kuhnert-Tallman, Wendi (CDC/DDID/OD); Osorio, Manuel (FDA/CBER); Florence, Clint (NIH/NIAID) [E]; (b)(6); Honey, Kristen (OS/IOS); Eloff,

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Early diagnosis of COVID-19 is crucial for disease treatment and control. Compared to RT-PCR, our testing kit may be a more reliable, practical and rapid method to diagnose and assess COVID-19, especially in the epidemic area. Our Viralert testing kit is extremely easy, simple, requiring very little skill or effort. Two testing method, either Nasal or Throat swab-based test that does not require blood. Result in 15 minutes, and easy to read: two lines mean positive and one line means negative. Currently, our testing kit was used in Chinese hospitals, aiding the PCR test to get more accurate results. Some patients show negative in PCR, but positive in our testing kit, together with CT imaging to get positive COVID-19 results. Aiding to detect possible COVID-19 when the person has no symptoms so that a person can get early treatment and prevent further spread. Tests for SARS-CoV-2, the virus that causes COVID-19, look for the genetic material of the virus, for instance in saliva or nasal, oral, or anal swabs, using the polymerase chain reaction (PCR). They have one huge drawback: They only give a positive result when the virus is still present. The tests can't identify people who went through an infection, recovered, and cleared the virus from their bodies. Our antibody test kit can help to find the source of a cluster of COVID-19 cases in community infection. In summary, we developed highly specific and sensitive colloidal gold immunochromatographic strips for detecting COVID-19. The test strip could be a practical tool for screening large numbers of samples during outbreaks. Its advantages are its rapid, simple, cost-effective and sensitive characteristics.

Hi Ralph Balsamo,
Ralph Balsamo updated this WebEx meeting for which you are an alternate host:
Naturitious LLC
Host: Ralph Balsamo
When it's time, start your meeting from here:

Start the meeting

When: Thursday, March 26, 2020, 2:00 pm (30 mins), Eastern Daylight Time (New York, GMT-04:00).

Access Information

Meeting Number:

(b)(6)

Password:

(This meeting does not require a password.)

Host Key:

(b)(6) Use this key during the meeting if you ever need to reclaim the host role.)

Audio Connection

(b)(6) (Meeting Server Main Number)

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<mark.williams4@nih.gov>;
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Dunsmore, Sarah (NIH/NIGMS) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=95b386cb524443e7810d6e373f3932df-sarah.dunsm <dunsmores@nigms.nih.gov>;
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FEMA

Medical Countermeasures Task Force

15 April 2020

SARS-CoV-2 Medical Countermeasures Task Force

Align MCM development across interagency partners to avoid duplication of effort, identify opportunities for synergy, and fill potential gaps

NIH NIAID

BARDA Biomedical Advanced Research and Development Authority

ASPR Assistant Secretary for Preparedness and Response

CDC Centers for Disease Control and Prevention

FDA

Department of Defense United States of America

VA U.S. Department of Veterans Affairs

USDA

Homeland Security

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MCM Task Force Objectives

- Collaborate across the USG to share data and information critical to accelerate the development, manufacture, and availability of COVID-19 MCMs
- Provide real-time information to leadership for decision-making
- Identify approaches and opportunities to coordinate with interagency partners to accelerate MCM research & development
- Address questions regarding use of currently available MCMs

FEMA

SARS-CoV-2 Medical Countermeasures Task Force

Task Force Lead
Rick Bright, BARDA

Task Force Chair: Chris Houchens, BARDA
Executive Secretary: Christy Ventura, BARDA

ASPR Lead
(David) Chris Hassell

BARDA Lead
Robert Johnson
David Boucher

CDC Lead
Amanda Cohn

DoD Lead
Jennifer Kishimori
Julia Biggins

DHS Lead
Duane Caneva
Herb Wolfe

FDA Lead
Michael Mair
Robert Fisher

NIAID Lead
Hilary Marston
Alan Embry

USDA Lead
Cyril Gay

Sample Sharing Sub-Working Group
Lead: Ruvani Chandrasekera, ASPR

Therapeutic Prioritization Sub-Working Group
Lead: TBD

NIAID RCT Sub-Working Group
Lead: John Beigel, NIAID

Diagnostics Working Group
Lead:
Rosemary Humes, BARDA

Vaccines Working Group
Leads:
Erik Stemmy, NIAID
Dan Wolfe, BARDA

Therapeutics Working Group
Leads:
Ann Eakin, NIAID
Tina Guina, BARDA

Clinical Trials Working Group
Leads:
Robert Walker, BARDA
Matt Hepburn, DoD

FEMA ESF-6 LNO
Joseph Zaydel, FEMA

FEMA Legal LNOs
Linda Davis, FEMA
Jennifer Steinberg, FEMA

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Elleen Kane, ASPR

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Chris Fall, DOE

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Ian Watson, OSTP
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CMS LNO
Jeffrey Kelman, CMS

National Guard LNOs
Maj Kingsley Okoli, USAF
LTC Luis Rodriguez, USA
LTC John Syprunowicz, USA
LTC Alisa Englert, USA

As of 4/7/2020

Assistant Secretary for Preparedness & Response

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Biomedical Advanced Research & Development Authority

- Activities (3 bullets)
  - Established and expanding diverse MCM portfolio
  - Working with product development and USG partners to shorten development timelines
  - Implementing blood products strategy for convalescent and hyperimmune products.

- Major Accomplishments/Contributions
  - Improving diagnostics: Diagnostic funding resulted in XXX EUAs
  - Improving therapeutic options: Multiple treatment trials ongoing
  - Over twenty products under development, as well as multiple support efforts (model development, sample collection, etc.)

- Challenges
  - Compressing therapeutic and vaccine development timelines
  - MCM manufacturing scale up/out

Centers for Disease Control and Prevention

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Department of Defense

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Department of Homeland Security

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Food and Drug Administration

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

National Institute of Allergy and Infectious Diseases

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

NIH NIAID

United States Department of Agriculture

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

USDA

Partnering to Improve Preparedness

VACCINES
- Proven platforms
- Large scale manufacturability
- Speed
- Multiple approaches

DIAGNOSTICS

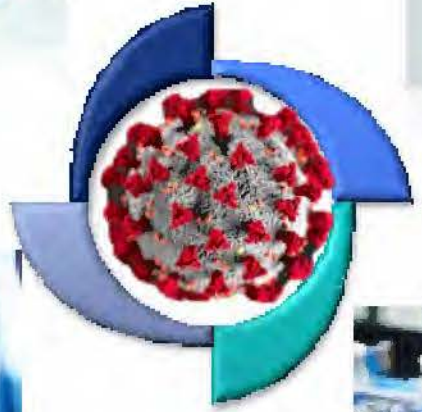
Faster and easier to use
More accurate

⬇

Earlier Identification

⬇

Earlier Treatment



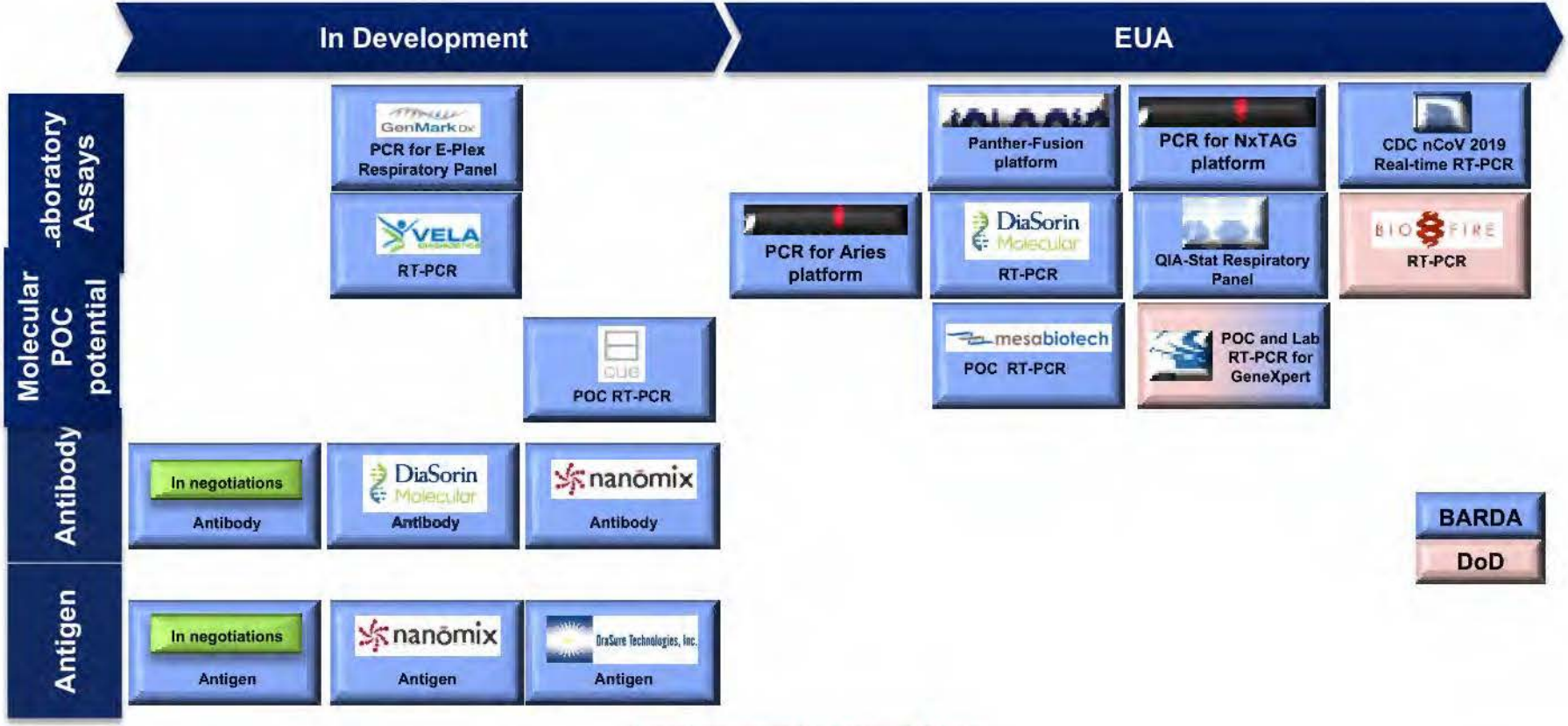
THERAPEUTICS
- Platform-based monoclonal antibodies
- Repurposed therapeutics
- Host targeted therapeutics

DOMESTIC MANUFACTURING
- Expand production
- Increase fill/ finish capacity

Diagnostics Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

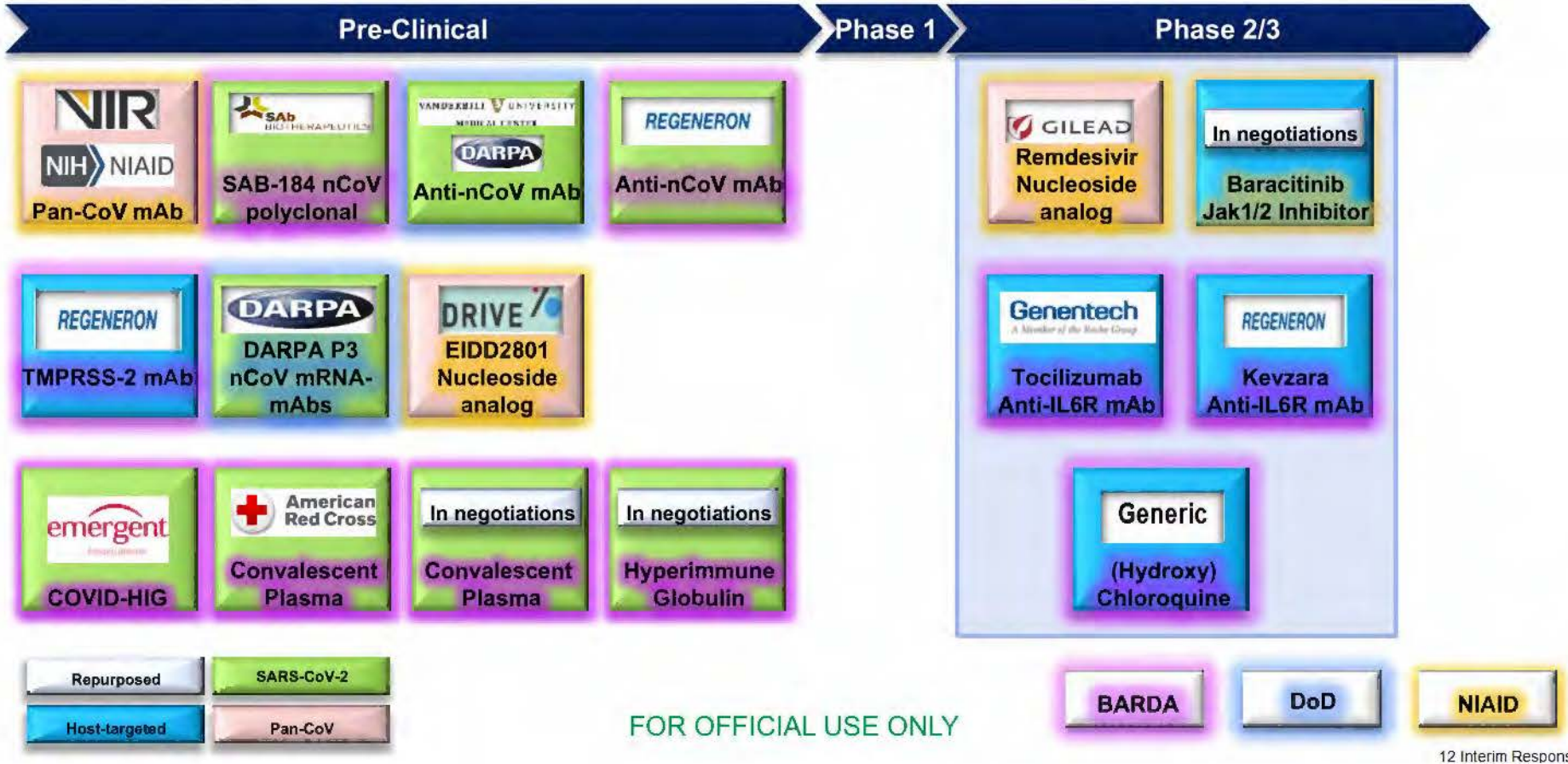
USG-Sponsored SARS-CoV-2 Diagnostic Tests



Therapeutics Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

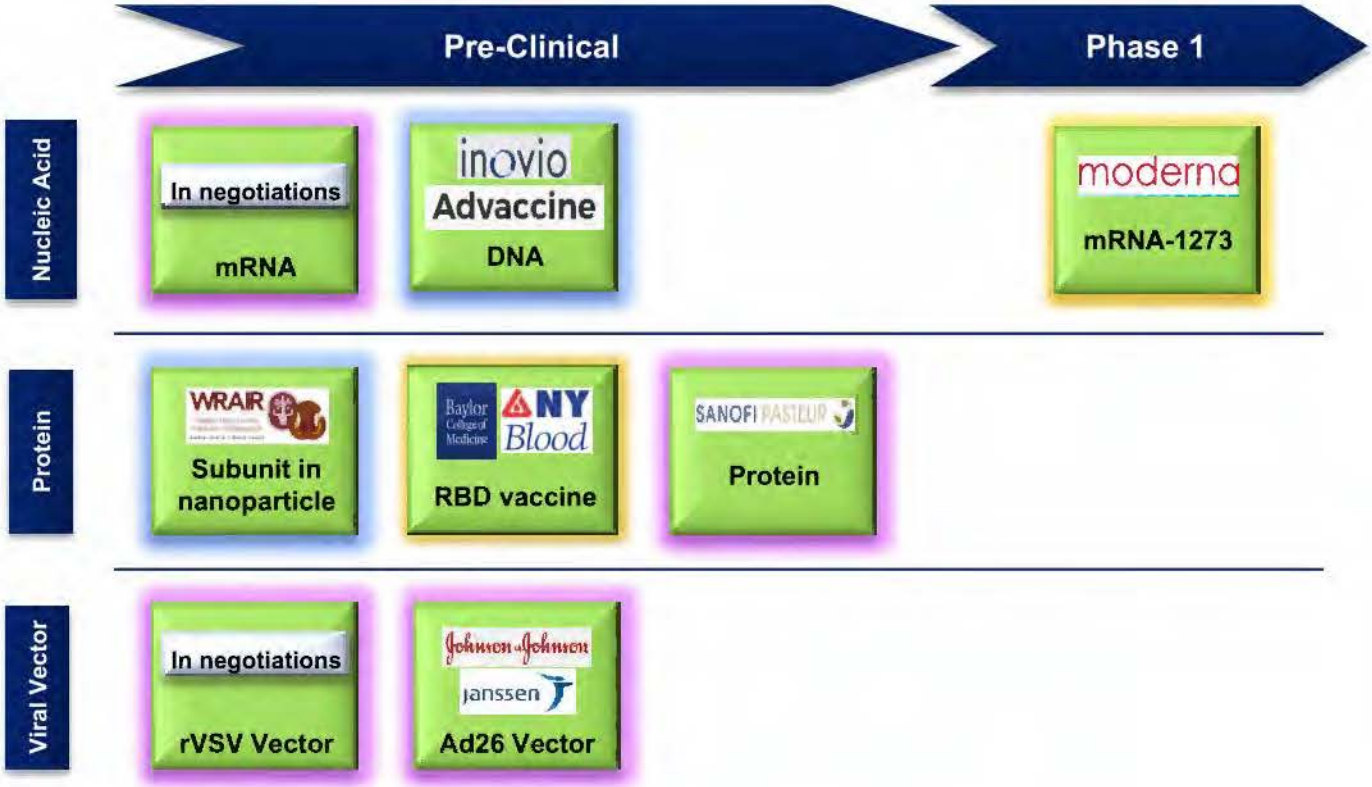
USG-Supported SARS-CoV-2 Therapeutics



Vaccines Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

USG-Supported SARS-CoV-2 Vaccines



Clinical Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Clinical Trials Table

Product Type	Product (Developer)	Primary Endpoint	Target Enrollment	Current Enrollment	Number of Sites	Notes
Therapeutic	Remdesivir (Gilead)	Clinical status assessed at Day 15 using 8-point ordinal scale	700	604	64	Adaptive COVID-19 Treatment Trial; can add new candidates
	Sarilumab (Regeneron & Sanofi)	Phase 2: Time to resolution of fever for 48h Phase 3: Time to improvement (2 points) using 7-point ordinal scale	400	991	53	Adaptive Phase 2/3 design; continuing enrollment beyond initial target
	Tolilizumab (Genentech & Roche)	Clinical status assessed at Day 28 using 7-point ordinal scale	330	9	11	Phase 3 study for COVID-19
	Hydroxy-chloroquine	Clinical status assessed at Day 15 using 7-point ordinal scale	510	44	12	Phase 3 study for COVID-19
Vaccine	mRNA-1273 (Moderna)	Safety & Immunogenicity at 25µg, 100µg & 250µg	45	34	2	Third cohort (250µg) sentinels dosed and in monitoring phase
	INO-4800 (Inovio)	Safety & Immunogenicity at 1 mg and 2 mg, administered days 0, 28	40	Enrolling	2	First cohort
Observational	n/a	Observational study to collect pathological data on COVID-19	N/A	41	5	Department of Defense's "EPiCC" Study; complementary studies in planning phases

Sample Sharing Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Serology Project Team

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Supply Chain Task Force

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

- providing information about PPE and supply shortages for MCM development, manufacturing, and clinical studies

Manufacturing Scale-up and Procurement

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From:	Clark Tibbs PhageVax-VHO <PhageVax@roadrunner.com>
To:	Clark Tibbs PhageVax-VHO <PhageVax@roadrunner.com>
Subject:	Compassionate Use of ^Remdesivir^ (Antiviral) for Patients with Severe Covid-19 ... from NEJM 4-11-20 tech team
Date:	2020/04/11 15:06:35
Priority:	Normal
Type:	Note

Let's hope that the mutating CoVs don't become resistant to this Antiviral from Gilead.

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See:

Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease ... https://mbio.asm.org/content/9/2/e00221-18

No. of Patients in Oxygen-Support Group after Treatment (%)		No. of Patients in Oxygen-Support Group at Baseline (%)			
		Invasive (N=34)	Noninvasive (N=7)	Low-flow oxygen (N=10)	Ambient air (N=2)
Category on ordinal scale →		5	4	3	2
Death	6	6 (18)	1 (14)	0	0
Invasive	5	9 (26)	1 (14)	0	0
Noninvasive	4	3 (9)	0	0	0
Low-flow oxygen	3	0	0	0	0
Ambient air	2	8 (24)	0	0	0
Discharged	1	8 (24)	5 (71)	10 (100)	2 (100)
Improvement		**19 (56)**	**5 (71)**	**10 (100)**	**2 (100)**

Category on ordinal scale

Compassionate Use of Remdesivir for Patients with Severe Covid-19

ORIGINAL ARTICLE FROM NEJM

Compassionate Use of Remdesivir for Patients with Severe Covid-19

Jonathan Grein and Others

A cohort of patients with severe Covid-19 received treatment with remdesivir under a compassionate-use protocol. Improvement in oxygen-support status was observed in **68%** of patients, and overall mortality was **13%** over a median follow-up of 18 days.

Read the article.

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https://www.nejm.org/doi/full/10.1056/NEJMoa2007016?query=C19&cid=DM89880_NEJM_COVID-19_Newsletter&bid=181538478

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ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

ABSTRACT

BACKGROUND

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

METHODS

We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

RESULTS

Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

CONCLUSIONS

In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

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Since the first cases were reported in December 2019, infection with the severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic.[1,2] Covid-19 — the illness caused by SARS-CoV-2 — is overwhelming health care systems globally.[3,4] The symptoms of SARS-CoV-2 infection vary widely, from asymptomatic disease to pneumonia and life-threatening complications, including acute respiratory distress syndrome, multisystem organ failure, and ultimately, death.[5-7] Older patients and those with preexisting respiratory or cardiovascular conditions appear to be at the greatest risk for severe complications.[6,7] In the absence of a proven effective therapy, current management consists of supportive care, including invasive and noninvasive oxygen support and treatment with antibiotics.[8,9] In addition, many patients have received off-label or compassionate-use therapies, including antiretrovirals, antiparasitic agents, antiinflammatory compounds, and convalescent plasma.[10-13]

Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses.[14-17] In vitro testing has also shown that remdesivir has activity against SARS-CoV-2. Remdesivir appears to have a favorable clinical safety profile, as reported on the basis of experience in approximately 500 persons, including healthy volunteers and patients treated for acute Ebola virus infection,[18,19] and supported by our data (on file and shared with the World Health Organization [WHO]). In this report, we describe outcomes in a cohort of patients hospitalized for severe Covid-19 who were treated with remdesivir on a compassionate-use basis.

METHODS

PATIENTS

Gilead Sciences began accepting requests from clinicians for compassionate use of remdesivir on January 25, 2020. To submit a request, clinicians completed an assessment form with demographic and disease-status information about their patient (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Approval of requests was reserved for hospitalized patients who had SARS-CoV-2 infection confirmed by reverse-transcriptase–polymerase-chain-reaction assay and either an oxygen saturation of 94% or less while the patient was breathing ambient air or a need for oxygen support. In addition, patients were required to have a creatinine clearance above 30 ml per minute and serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than five times the upper limit of the normal range, and they had to agree not to use other investigational agents for Covid-19.

In approved cases, the planned treatment was a 10-day course of remdesivir, consisting of a loading dose of 200 mg intravenously on day 1, plus 100 mg daily for the following 9 days. Supportive therapy was to be provided at the discretion of the clinicians. Follow-up was to continue through at least 28 days after the beginning of treatment with remdesivir or until discharge or death. Data that were collected through March 30, 2020, are reported here. This open-label program did not have a predetermined number of patients, number of sites, or duration. Data for some patients included in this analysis have been reported previously.[20-22] Details of the study design and conduct can be seen in the protocol (available at NEJM.org).

STUDY ASSESSMENTS

Data on patients' oxygen-support requirements, adverse events, and laboratory values, including serum creatinine, ALT, and AST, were to be reported daily, from day 1 through day 10, and additional follow-up information was solicited through day 28. Although there were no prespecified end points for this program, we quantified the incidence of key clinical events, including changes in oxygen-support requirements (ambient air, low-flow oxygen, nasal high-flow oxygen, noninvasive positive pressure ventilation [NIPPV], invasive mechanical ventilation, and extracorporeal membrane oxygenation [ECMO]), hospital discharge, and reported adverse events, including those leading to discontinuation of treatment, serious adverse events, and death. In addition, we evaluated the proportion of patients with clinical improvement, as defined by live discharge from

the hospital, a decrease of at least 2 points from baseline on a modified ordinal scale (as recommended by the WHO R&D Blueprint Group), or both. The six-point scale consists of the following categories: 1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5, hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 6, death.

PROGRAM OVERSIGHT

Regulatory and institutional review board or independent ethics committee approval was obtained for each patient treated with remdesivir, and consent was obtained for all patients in accordance with local regulations. The program was designed and conducted by the sponsor (Gilead Sciences), in accordance with the protocol. The sponsor collected the data, monitored conduct of the program, and performed the statistical analyses. All authors had access to the data and assume responsibility for the integrity and completeness of the reported data. The initial draft of the manuscript was prepared by a writer employed by Gilead Sciences along with one of the authors, with input from all the authors.

STATISTICAL METHODS

No sample-size calculations were performed. The analysis population included all patients who received their first dose of remdesivir on or before March 7, 2020, and for whom clinical data for at least 1 subsequent day were available. Clinical improvement and mortality in the remdesivir compassionate-use cohort were described with the use of Kaplan–Meier analysis. Associations between pretreatment characteristics and these outcomes were evaluated with Cox proportional hazards regression. Because the analysis did not include a provision for correcting for multiple comparisons in tests for association between baseline variables and outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive associations with outcomes. All analyses were conducted with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT RANDOMIZATION

In total, 61 patients received at least one dose of remdesivir on or before March 7, 2020; 8 of these patients were excluded because of missing post-baseline information (7 patients) and an erroneous remdesivir start date (1 patient) (Fig. S1 in the Supplementary Appendix). Of the 53 remaining patients included in this analysis, 40 (75%) received the full 10-day course of remdesivir, 10 (19%) received 5 to 9 days of treatment, and 3 (6%) fewer than 5 days of treatment.

BASELINE CHARACTERISTICS OF THE PATIENTS

Table 1 shows baseline demographic and clinical characteristics of the 53 patients in the compassionate-use cohort. Patients were enrolled in the United States (22 patients), Japan (9), Italy (12), Austria (1), France (4), Germany (2), Netherlands (1), Spain (1), and Canada (1). A total of 40 patients (75%) were men, the age range was 23 to 82 years, and the median age was 64 years (interquartile range, 48 to 71). At baseline, the majority of patients (34 [64%]) were receiving invasive ventilation, including 30 (57%) receiving mechanical ventilation and 4 (8%) receiving ECMO. The median duration of invasive mechanical ventilation before the initiation of remdesivir treatment was 2 days (interquartile range, 1 to 8). As compared with patients who were receiving noninvasive oxygen support at baseline, those receiving invasive ventilation tended to be older (median age, 67 years, vs. 53 years), were more likely to be male (79%, vs. 68%), had higher median serum ALT (48 U per liter, vs. 27) and creatinine (0.90 mg per deciliter, vs. 0.79 [79.6 μmol per liter, vs. 69.8]), and a higher prevalence of coexisting conditions, including hypertension (26%, vs. 21%), diabetes (24%, vs. 5%), hyperlipidemia (18%, vs. 0%), and asthma (15%, vs. 5%). The median duration of symptoms before the initiation of remdesivir treatment was 12 days (interquartile range, 9 to 15) and did not differ substantially between patients receiving invasive ventilation and those receiving noninvasive ventilation (Table 1).

CLINICAL IMPROVEMENT DURING REMDESIVIR TREATMENT

Over a median follow-up of 18 days (interquartile range, 13 to 23) after receiving the first dose

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
Median age (IQR) — yr	67 (56–72)	53 (41–68)	64 (48–71)
Age category — no. (%)			
<50 yr	6 (18)	8 (42)	14 (26)
50 to <70 yr	14 (41)	7 (37)	21 (40)
≥70 yr	14 (41)	4 (21)	18 (34)
Male sex — no. (%)	27 (79)	13 (68)	40 (75)
Region — no. (%)			
United States	14 (41)	8 (42)	22 (42)
Japan	8 (24)	1 (5)	9 (17)
Europe or Canada	12 (35)	10 (53)	22 (42)
Oxygen-support category — no. (%)			
Invasive ventilation	34 (100)	—	34 (64)
Invasive mechanical ventilation	30 (88)	—	30 (57)
Extracorporeal membrane oxygenation	4 (12)	—	4 (8)
Noninvasive oxygen support	—	19 (100)	19 (36)
Noninvasive positive-pressure ventilation	—	2 (11)	2 (4)
High-flow oxygen	—	5 (26)	5 (9)
Low-flow oxygen	—	10 (53)	10 (19)
Ambient air	—	2 (11)	2 (4)
Median duration of symptoms before remdesivir therapy (IQR) — days	11 (8–15)	13 (10–14)	12 (9–15)
Coexisting conditions — no. (%)			
Any condition	25 (74)	11 (58)	36 (68)
Hypertension	9 (26)	4 (21)	13 (25)
Diabetes	8 (24)	1 (5)	9 (17)
Hyperlipidemia	6 (18)	0	6 (11)
Asthma	5 (15)	1 (5)	6 (11)
Median laboratory values (IQR)			
ALT — IU per liter	48 (31–79)	27 (20–45)	37 (25–61)
AST — IU per liter	39 (30–76)	35 (28–46)	36 (29–67)
Creatinine — mg per deciliter	0.90 (0.66–1.17)	0.79 (0.63–1.00)	0.89 (0.64–1.08)

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and IQR interquartile range. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

of remdesivir, 36 of 53 patients (68%) showed an improvement in the category of oxygen support, whereas 8 of 53 patients (15%) showed worsening (Fig. 1). Improvement was observed in all 12 patients who were breathing ambient air or receiving low-flow supplemental oxygen and in 5 of 7 patients (71%) who were receiving noninvasive oxygen support (NIPPV or high-flow supplemental oxygen). It is notable that 17 of 30 patients (57%) who were receiving invasive mechanical ventilation were extubated, and 3 of 4 patients (75%) receiving ECMO stopped receiving it; all were alive at last follow-up. Individual patients' changes in the category of oxygen support are shown in Figure 2. By the date of the most recent follow-up, 25 of 53 patients (47%) had been

discharged (24% receiving invasive ventilation [8 of 34 patients] and 89% [17 of 19 patients] receiving noninvasive oxygen support).

By 28 days of follow-up, the cumulative incidence of clinical improvement, as defined by either a decrease of 2 points or more on the six-point ordinal scale or live discharge, was 84% (95% confidence interval [CI], 70 to 99) by Kaplan–Meier analysis (Fig. 3A). Clinical improvement was less frequent among patients receiving invasive ventilation than among those receiving noninvasive ventilation (hazard ratio for improvement, 0.33; 95% CI, 0.16 to 0.68) (Fig. 3B) and among patients 70 years of age or older (hazard ratio as compared with patients younger than 50 years, 0.29; 95% CI, 0.11 to 0.74) (Fig. 3C). Sex, region of enrollment, coexisting conditions, and duration of symptoms before remdesivir treatment was initiated were not significantly associated with clinical improvement (Table S1).

MORTALITY

Seven of the 53 patients (13%) died after the completion of remdesivir treatment, including 6 of 34 patients (18%) who were receiving invasive ventilation and 1 of 19 (5%) who were receiving noninvasive oxygen support (see the Supplementary Appendix for case narratives). The median interval between remdesivir initiation and death was 15 days (interquartile range, 9 to 17). Overall mortality from the date of admission was 0.56 per 100 hospitalization days (95% CI, 0.14 to 0.97) and did not differ substantially among patients receiving invasive ventilation (0.57 per 100 hospitalization days; 95% CI, 0 to 1.2]) as compared with those receiving noninvasive ventilation (0.51 per 100 hospitalization days; 95% CI, 0.07 to 1.1]). Risk of death was greater among patients who were 70 years of age or older (hazard ratio as compared with patients younger than 70 years, 11.34; 95% CI, 1.36 to 94.17) and among those with higher serum creatinine at baseline (hazard ratio per milligram per deciliter, 1.91; 95% CI, 1.22 to 2.99). The hazard ratio for patients receiving invasive ventilation as compared with those receiving noninvasive oxygen support was 2.78 (95% CI, 0.33 to 23.19) (Table S2).

SAFETY

A total of 32 patients (60%) reported adverse events during follow-up (Table 2). The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. In general, adverse events were more common in patients receiving invasive ventilation. A total of 12 patients (23%) had serious adverse events. The

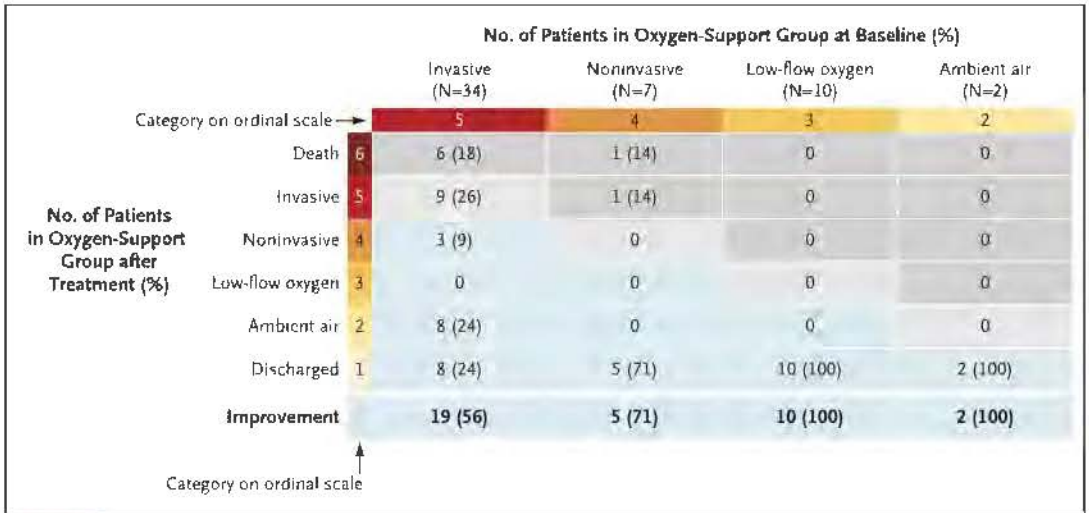

Figure 1. Oxygen-Support Status at Baseline and after Treatment.

For each oxygen-support category, percentages were calculated with the number of patients at baseline as the denominator. Improvement (blue cells), no change (beige) and worsening (gray) in oxygen-support status are shown. Invasive ventilation includes invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or both. Noninvasive ventilation includes nasal high-flow oxygen therapy, noninvasive positive pressure ventilation (NIPPV), or both.

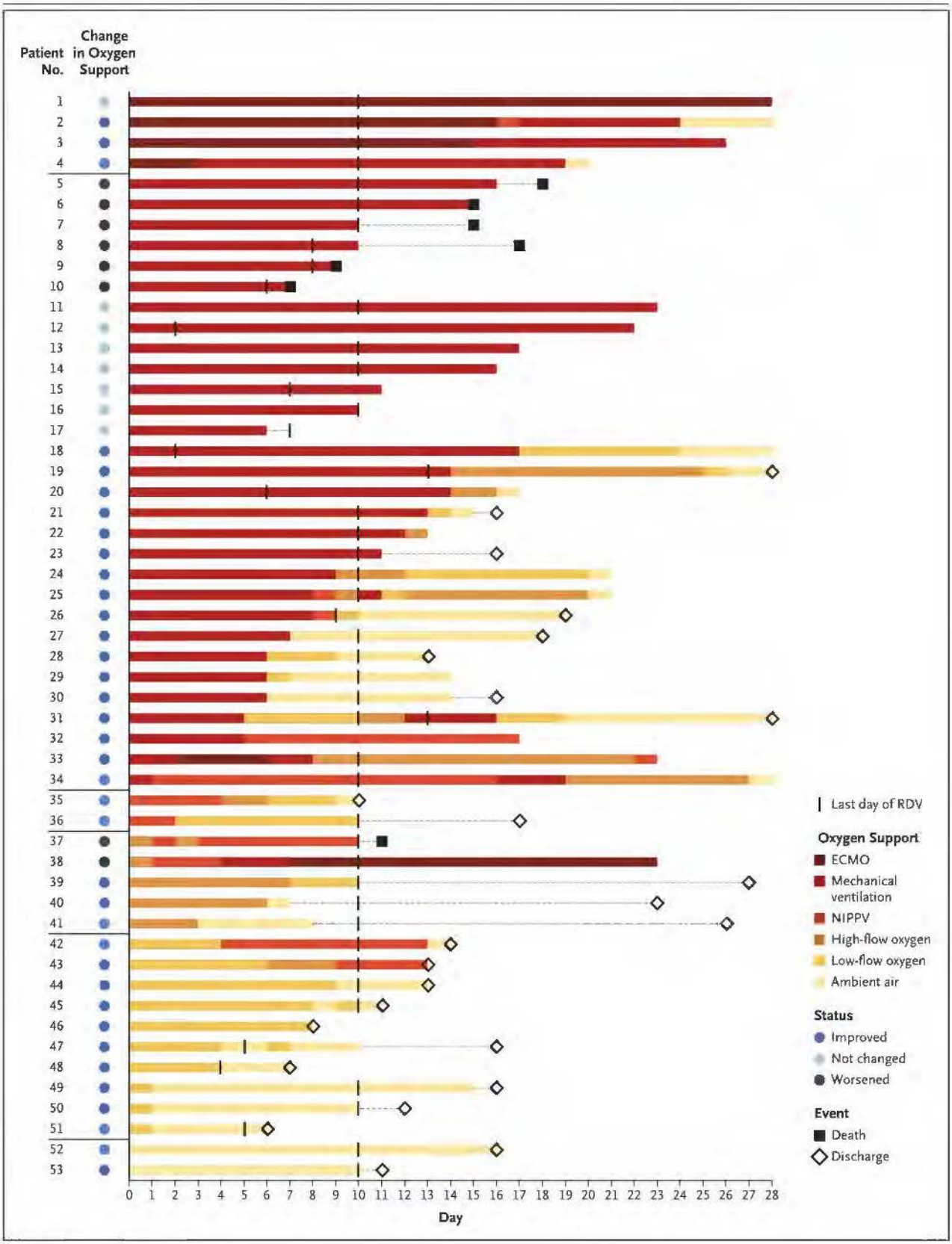

Figure 2 (facing page). Changes in Oxygen-Support Status from Baseline in Individual Patients.

Baseline (day 0) was the day on which treatment with remdesivir (RDV) was initiated. Final oxygen support statuses shown are based on the most recent reported data. For each patient, the colors in the line represent the oxygen-support status of the patient over time. The colored circles to the left of each line indicate the patient's overall change in status from baseline. A patient's status "improved" if the oxygen-support status improved before the last follow-up or the patient was discharged. The vertical black marks show the last day of treatment with RDV. The gray dashed lines represent missing data between the patient's most recent reported oxygen status and an event (death or discharge) or the last dose of RDV. A solid square at the end of a line indicates that the patient died; an open diamond indicates that the patient was discharged from the hospital. If there is neither a square nor a diamond at the end of a line, neither death nor discharge had occurred. Patient 2 was breathing ambient air through day 36. Patients 19 and 31 were discharged on day 44.

most common serious adverse events — multiple-organ-dysfunction syndrome, septic shock, acute kidney injury, and hypotension — were reported in patients who were receiving invasive ventilation at baseline.

Four patients (8%) discontinued remdesivir treatment prematurely: one because of worsening of preexisting renal failure, one because of multiple organ failure, and two because of elevated aminotransferases, including one patient with a maculopapular rash.

LABORATORY DATA

Given the nature of this compassionate-use program, data on a limited number of laboratory measures were collected. Median serum ALT, AST, and creatinine fluctuated during follow-up (Fig. S2).

DISCUSSION

To date, no therapy has demonstrated efficacy for patients with Covid-19. This preliminary report describes the clinical outcomes in a small cohort of patients who were severely ill with Covid-19 and were treated with remdesivir. Although data from several ongoing randomized, controlled trials will soon provide more informative evidence

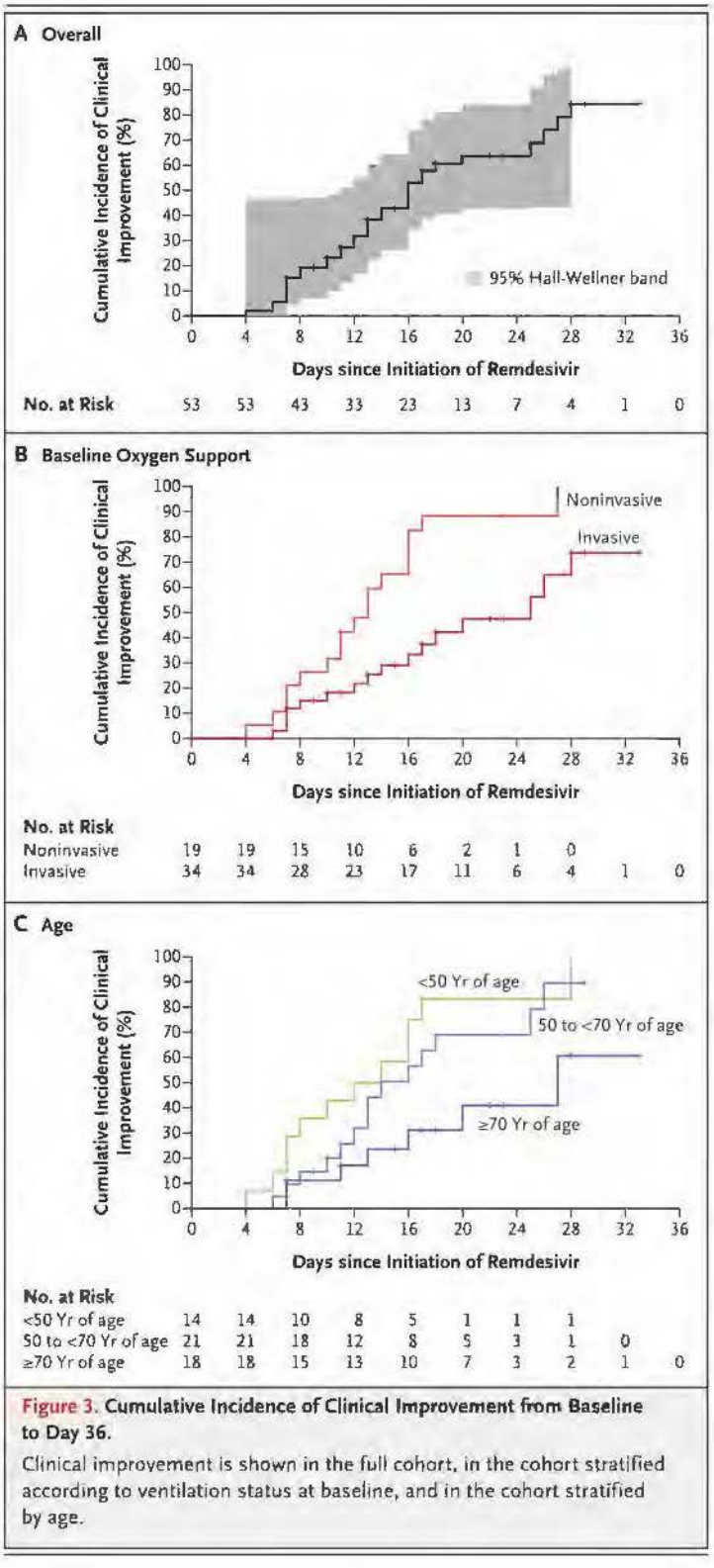

Figure 3. Cumulative Incidence of Clinical Improvement from Baseline to Day 36.

Clinical improvement is shown in the full cohort, in the cohort stratified according to ventilation status at baseline, and in the cohort stratified by age.

Table 2. Summary of Adverse Events.

Event	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
	number of patients (percent)		
Any adverse event	22 (65)	10 (53)	32 (60)
Adverse events occurring in 2 or more patients			
Hepatic enzyme increased*	8 (24)	4 (21)	12 (23)
Diarrhea	1 (3)	4 (21)	5 (9)
Rash	3 (9)	1 (5)	4 (8)
Renal impairment	4 (12)	0	4 (8)
Hypotension	3 (9)	1 (5)	4 (8)
Acute kidney injury	2 (6)	1 (5)	3 (6)
Atrial fibrillation	2 (6)	1 (5)	3 (6)
Multiple-organ-dysfunction syndrome	3 (9)	0	3 (6)
Hypernatremia	3 (9)	0	3 (6)
Deep-vein thrombosis	3 (9)	0	3 (6)
Acute respiratory distress syndrome	1 (3)	1 (5)	2 (4)
Pneumothorax	2 (6)	0	2 (4)
Hematuria	2 (6)	0	2 (4)
Delirium	1 (3)	1 (5)	2 (4)
Septic shock	2 (6)	0	2 (4)
Pyrexia	1 (3)	1 (5)	2 (4)
Any serious adverse event	9 (26)	3 (16)	12 (23)
Serious events occurring in 2 or more patients			
Multiple-organ-dysfunction syndrome	2 (6)	0	2 (4)
Septic shock	2 (6)	0	2 (4)
Acute kidney injury	2 (6)	0	2 (4)
Hypotension	2 (6)	0	2 (4)

* Adverse-event terms are based on the *Medical Dictionary for Regulatory Activities*, version 22.1. Hepatic enzyme increased includes the following terms: hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased. Elevated hepatic enzymes resulted in discontinuation of remdesivir therapy in 2 patients.

regarding the safety and efficacy of remdesivir for Covid-19, the outcomes observed in this compassionate-use program are the best currently available data. Specifically, improvement in oxygen-support status was observed in 68% of patients, and overall mortality was 13% over a median follow-up of 18 days. In a recent randomized, controlled trial of lopinavir–ritonavir in patients hospitalized for Covid-19, the 28-day mortality was 22%.[10] It is important to note that only 1 of 199 patients in that trial were receiving invasive ventilation at baseline. In case series and cohort studies, largely from China, mortality rates of 17 to 78% have been reported in severe cases, defined by the need for admission to an intensive care unit, invasive ventilation, or both.[23-28] For example, among 201 patients hospitalized in Wuhan, China, mortality was 22% overall and 66% (44 of 67) among patients receiving invasive mechanical ventilation.[7] By way of comparison, the 13% mortality observed in this remdesivir compassionate-use cohort is noteworthy, considering the severity of disease in this patient population; however, the patients enrolled in this compassionate-treatment program are not directly comparable to those studied in these other re-

ports. For example, 64% of remdesivir-treated patients were receiving invasive ventilation at baseline, including 8% who were receiving ECMO, and mortality in this subgroup was 18% (as compared with 5.3% in patients receiving noninvasive oxygen support), and the majority (75%) of patients were male, were over 60 years of age, and had coexisting conditions.

Unfortunately, our compassionate-use program did not collect viral load data to confirm the antiviral effects of remdesivir or any association between baseline viral load and viral suppression, if any, and clinical response. Moreover, the duration of remdesivir therapy was not entirely uniform in our study, largely because clinical improvement enabled discharge from the hospital. The effectiveness of a shorter duration of therapy (e.g., 5 days, as compared with 10 days), which would allow the treatment of more patients during the pandemic, is being assessed in ongoing randomized trials of this therapy.

No new safety signals were detected during short-term remdesivir therapy in this compassionate-use cohort. Nonclinical toxicology studies have shown renal abnormalities, but no clear evidence of nephrotoxicity due to remdesivir therapy was observed. As reported in studies in healthy volunteers and patients infected with Ebola virus, mild-to-moderate elevations in ALT, AST, or both were observed in this cohort of patients with severe Covid-19.[18,19] However, considering the frequency of liver dysfunction in patients with Covid-19, attribution of hepatotoxicity to either remdesivir or the underlying disease is challenging.[20] Nevertheless, the safety and side-effect profile of remdesivir in patients with Covid-19 require proper assessment in placebo-controlled trials.

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 8 of the patients initially treated, and the lack of a randomized control group. Although the latter precludes definitive conclusions, comparisons with contemporaneous cohorts from the literature, in whom general care is expected to be consistent with that of our cohort, suggest that remdesivir may have clinical benefit in patients with severe Covid-19. Nevertheless, other factors may have contributed to differences in outcomes, including the type of supportive care (e.g., concomitant medications or variations in ventilatory practices) and differences in institutional treatment protocols and thresholds for hospitalization. Moreover, the use of invasive ventilation as a proxy for disease severity may be influenced by the availability of ventilators in a given location. The findings from these uncontrolled data will be informed by the ongoing randomized, placebo-controlled trials of remdesivir therapy for Covid-19.

Supported by Gilead Sciences.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Sarah Tse, Deborah Ajayi, and Gretchen Schmelz of BioScience Communications for creating earlier versions of the figures. Writing and editorial assistance with earlier versions of the manuscript were provided by David McNeel and Sandra Chen, both of Gilead Sciences. The names of those who assisted in the care of the patients in this program are listed in the Supplementary Appendix. We express our solidarity with those who are or have been ill with Covid-19, their families, and the health care workers on the front lines of this pandemic.

APPENDIX

The authors' full names and academic degrees are as follows: Jonathan Grein, M.D., Norio Ohmagari, M.D., Ph.D., Daniel Shin, M.D., George Diaz, M.D., Erika Asperges, M.D., Antonella Castagna, M.D., Torsten Feldt, M.D., Gary Green, M.D., Margaret L. Green, M.D., M.P.H., François-Xavier Lescure, M.D., Ph.D., Emanuele Nicastri, M.D., Rentaro Oda, M.D., Kikuo Yo, M.D., D.M.Sc., Eugenia Quiros-Roldan, M.D., Alex Studemeister, M.D., John Redinski, D.O., Seema Ahmed, M.D., Jorge Bernett, M.D., Daniel Chelliah, M.D., Danny Chen, M.D., Shingo Chihara, M.D., Stuart H. Cohen, M.D., Jennifer Cunningham, M.D., Antonella D'Arminio Monforte, M.D., Saad Ismail, M.D., Hideaki Kato, M.D., Giuseppe Lapadula, M.D., Erwan L'Her, M.D., Ph.D., Toshitaka Maeno, M.D., Sumit Majumder, M.D., Marco Massari, M.D., Marta Mora-Rillo, M.D., Yoshikazu Mutoh, M.D., Duc Nguyen, M.D., Pharm.D., Ewa Verweij, M.D., Alexander Zoufaly, M.D., Anu O. Osinusi, M.D., Adam DeZure, M.D., Yang Zhao, Ph.D., Lijie Zhong, Ph.D., Anand Chokkalingam, Ph.D., Emon Elboudwarej, Ph.D., Laura Telep, M.P.H., Leighann Timbs, B.A., Ilana Henne, M.S., Scott Sellers, Ph.D., Huyen Cao, M.D., Susanna K. Tan, M.D., Lucinda Winterbourne, B.A., Polly Desai, M.P.H., Robertino Mera, M.D., Ph.D., Anuj Gaggar, M.D., Ph.D., Robert P. Myers, M.D., Diana M. Brainard, M.D., Richard Childs, M.D., and Timothy Flanigan, M.D.

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Medical Center (S. Chihara), Seattle — all in Washington; Fondazione IRCCS Policlinico San Matteo, Pavia (E.A.), IRCCS, San Raffaele Scientific Institute (A. Castagna) and Azienda Socio Sanitaria Territoriale Spedali (ASST) Santi Paolo e Carlo, Department of Health Services, University of Milan (A.D.M.), Milan, National Institute for Infectious Diseases, IRCCS, L. Spallanzani, Rome (E.N.), Università degli Study of Brescia, ASST Civili di Brescia, Brescia (E.Q.-R.), San Gerardo Hospital, ASST Monza, University of Milan–Bicocca, Monza (G.L.), and Azienda Unite Sanitarie Locali–IRCCS, Reggio Emilia (M.M.) — all in Italy; Universitätsklinikum Düsseldorf, Düsseldorf, Germany (T. Feldt); Université de Paris, Infection, Antimicrobiens, Modélisation, Evolution (IAME), INSERM, and Assistance Publique–Hôpitaux de Paris, Department of Infectious Diseases, Bichat Hospital, Paris (F.-X.L.), Centre Hospitalier Régional et Universitaire de Brest–La Cavale Blanche, Brest (E.L.), and Division of Infectious Diseases and Tropical Medicine, University Hospital of Bordeaux, Bordeaux (D.N.) — all in France; St. Alexius Medical Center, Hoffman Estates, IL (S.A.); Mackenzie Health, Richmond Hill, ON, Canada (D. Chen); Columbia University Irving Medical Center, New York (J.C.); Hospital Universitario La Paz–Carlos III, Instituto de Investigación Hospital Universitario La Paz, Madrid (M.M.-R.); Bernhoven Hospital, Uden, the Netherlands (E.V.); Kaiser Franz Josef Hospital, Vienna (A.Z.); the U.S. Public Health Service Commissioned Corps, Washington, DC (R.C.); and Miriam Hospital, Providence, RI (T. Planigan).

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020; 91:157-60.
2. Spinelli A, Pellino G. COVID-19 pandemic: perspectives on an unfolding crisis. Br J Surg 2020 March 19 (Epub ahead of print).
3. Fauci AS, Lane HC, Redfield RR. Covid-19 — navigating the uncharted. N Engl J Med 2020;382:1268-9.
4. Mahase E, Kmietowicz Z. Covid-19: doctors are told not to perform CPR on patients in cardiac arrest. BMJ 2020;368: m1282.
5. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 2020 March 13 (Epub ahead of print).
6. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet 2020;395:1014-5.
7. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020 March 13 (Epub ahead of print).
8. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020 March 23 (Epub ahead of print).
9. Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. JAMA 2020 March 26 (Epub ahead of print).
10. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2001282.
11. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020 March 27 (Epub ahead of print).
12. Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res 2020 March 5 (Epub ahead of print).
13. Baden LR, Rubin EJ. Covid-19 — the search for effective therapy. N Engl J Med. DOI: 10.1056/NEJMe2005477.
14. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A 2020;117:6771-6.
15. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9(396):eaal3653.
16. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222.
17. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269-71.
18. Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381:2293-303.
19. European Medicines Agency. Summary on compassionate use: Remdesivir Gilead. April 3, 2020 (https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf).
20. Kujawski SA, Wong KK, Collins JP, et al. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. medRxiv, March 12, 2020 (https://www.medrxiv.org/content/10.1101/2020.03.09.20032896v1).
21. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382: 929-36.
22. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis 2020 March 27 (Epub ahead of print).
23. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020 March 19 (Epub ahead of print).
24. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020 February 7 (Epub ahead of print).
25. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 February 24 (Epub ahead of print).
26. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
27. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region — case series. N Engl J Med. DOI: 10.1056/NEJMoa2004500.
28. ICNARC report on COVID-19 in critical care. London: Intensive Care National Audit & Research Centre, March 27, 2020 (https://www.icnarc.org/DataServices/Attachments/Download/b5f59585-5870-ea11-9124-00505601089b).
29. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020 March 4 (Epub ahead of print).

Operational Task Forces	
Community Based Testing Sites (CBTS)	Accomplishments in last 24 hours 1. Please be succinct, but use plain language and ensure appropriate contextualization 2. Currently Working 1. Describe actions currently underway. Be sure to include any barriers or limiting factors. 2.
Community Mitigation	Accomplishments in last 24 hours 1. Please be succinct, but use plain language and ensure appropriate contextualization 2. Currently Working 1. Describe actions currently underway. Be sure to include any barriers or limiting factors. 2.
Continuity of Operations and	Accomplishments in last 24 hours 1. Please be succinct, but use plain language and ensure appropriate contextualization 2. Currently Working 1. Describe actions currently underway. Be sure to include any barriers or limiting factors. 2.
Data and Analysis	Accomplishments in last 24 hours 1. Please be succinct, but use plain language and ensure appropriate contextualization 2. Currently Working 1. Describe actions currently underway. Be sure to include any barriers or limiting factors. 2.
Healthcare Resilience	Accomplishments in last 24 hours 1. Please be succinct, but use plain language and ensure appropriate contextualization 2. Currently Working 1. Describe actions currently underway. Be sure to include any barriers or limiting factors. 2.
Laboratory Diagnostics	
Medical Countermeasure (MCM)	**Accomplishments:** • Clinical trial to test remdesivir for treatment of COVID-19: 480 (+11) new patients in last 24 hrs (target = 700) • Clinical trial requests for SNS chloroquine/hydroxychloroquine: 2 received, 1 fulfilled and 1 pending review **Currently Working** • Continuing to enroll patients in clinical trials to evaluate vaccines and therapeutics for COVID-19

Supply Chain

BARDA COVID-19 Response
March 31, 2020

Rick Bright, PhD
Deputy Assistant Secretary for Preparedness and Response,
Director, Biomedical Advanced Research and Development Authority (BARDA)

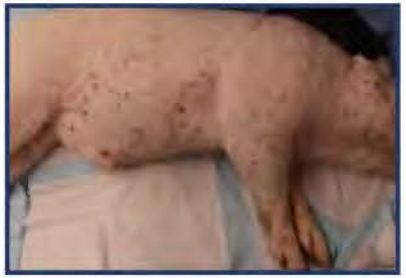
America's Response to the COVID-19 Outbreak

UNCLASSIFIED

ASPR Mission

Save Lives and Protect Americans from 21st Century Health Security Threats

21st Century: An Increasingly Complex & Dangerous World

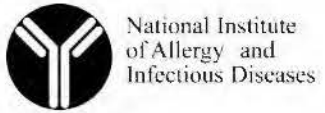


The BARDA Model

BARDA develops and makes available medical countermeasures **(MCMs)** by forming unique public-private partnerships to drive innovation off the bench to the patient to save lives.

Our Industry Partners

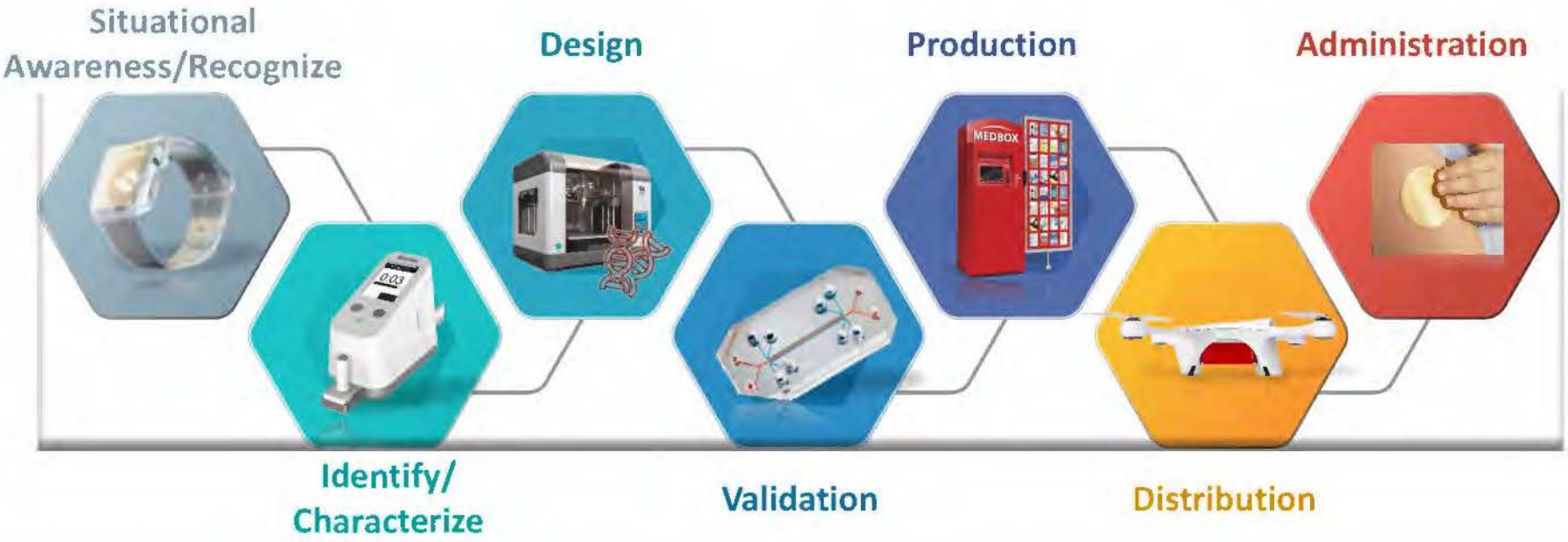
Our Government Partners



54 FDA Approvals, Licensures, and Clearances


Speed is the critical component of response.
Even the most advanced countermeasures fail unless
present in sufficient quantities with minimal delay
at the location of need.

Addressing End to End Solutions



BARDA COVID-19 Medical Countermeasure Response Strategy

Acceleration:
Leverage existing partners and platforms with a track record of rapidly responding to protect Americans and save lives

Risk Mitigation:
Prioritize investments based on greatest public health impact and probability of success

Manufacturing Capacity & Supply Chains:
Mobilize the industrial base and expand domestic-based manufacturing capabilities for MCMs

Acceleration

Parallel Work Streams
- USG and Industry sharing risk

Flexible Contracting
- OTA
- EZ-BAA

Emergency Regulatory Framework
- EUA
- FDA guidance

Access to Core Services
- Samples
- Animal models

Risk Mitigation

Multiple Vaccine Platforms

- Nucleic Acid
- Vectors
- Recombinant

Multiple Diagnostic Platforms

- Central Labs
- Hospital
- POC

Evaluate Currently Approved Drugs

- Remdesivir
- Immunotherapy
- Anti-IL-6R, CQ, HCQ

Raw Materials Supply Chains

- Remove bottlenecks
- Establish stockpiles

Domestic Manufacturing Capacity

Scale Up & Scale Out
- Expand
- Partnering
- Redundancy

CIADM/CMO
- Tech transfer
- Assay Development

Raw Materials Supply Chains
- Expand
- Secure Domestic

Fill-Finish
- CMO
- Partnering

COVID-19 Medical Countermeasures Task Force

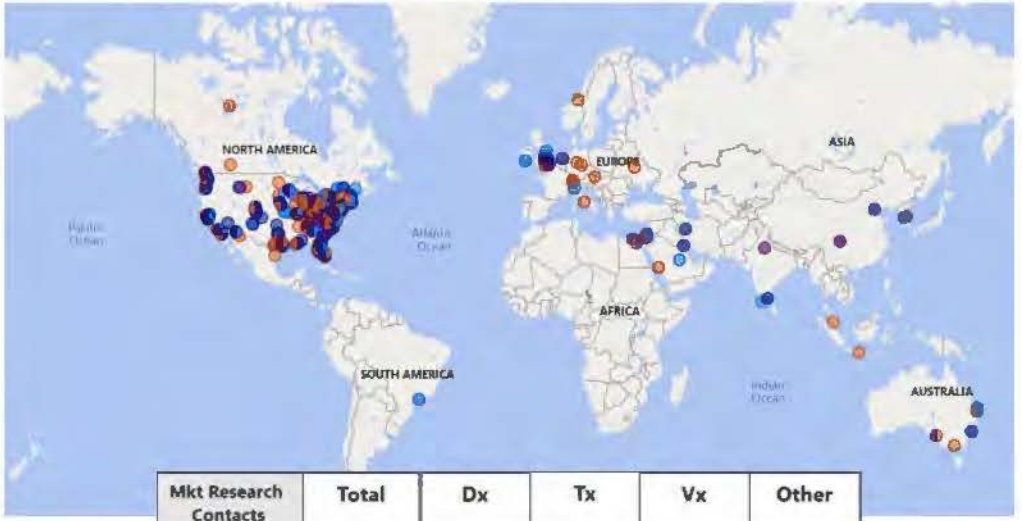
Align MCM development across interagency partners to avoid duplication of effort, identify opportunities for synergy, and fill potential gaps

medicalcountermeasures.gov

Industry Engagement & Partnership Opportunity

Active Partnership Opportunities	
EZ-BAA / BAA	Diagnostic assays (SARS-CoV-2 & pan-coronavirus)
EZ-BAA / BAA	Vaccine (including adjuvants & alternative administration)
BAA	Therapeutics (including immunomodulators or therapeutics targeting lung repair; pre-exposure & post-exposure prophylaxis)
BAA	Respiratory protective devices
BAA	Ventilators
EZ-BAA / BAA	Advanced manufacturing technologies

Market Research & EZ-BAA / BAA Submission Locations



Mkt Research Contacts	Total	Dx	Tx	Vx	Other
All Contacts	1621	377	554	173	517
TWs Held	163	63	40	31	29

BARDA is Pandemic Tested!...and rapidly responding to today's novel threat.

BARDA Medical Countermeasures Response

Portfolio

Therapeutics

- Anti-viral Library Screening (Johnson & Johnson / Janssen)
- Anti-nCoV mAb (Regeneron)
- Anti-IL6R mAb (Kevzara®) (Regeneron)
- Anti-IL6R mAb (Actemra®) (Roche / Genentech)
- Convalescent Plasma Collection (American Red Cross)

Vaccines

- Ad26 Vector (Johnson & Johnson / Janssen)
- Recombinant Protein (Sanofi Pasteur)
- mRNA-1273 (Moderna)

Diagnostics

- Panther Platform EUA
- RT-PCR EUA (DiaSorin Molecular)
- POC & Lab RT-PCR for GeneExpert EUA
- POC RT-PCR EUA
- NxTAG EUA (Luminex)
- ePlex EUA (GenMark Dx)
- ARIES (Luminex)
- QIA-Stat NeuMoDx
- RT-PCR (VELA Diagnostics)
- Portable Molecular Diagnostic (cue)

Supporting Efforts

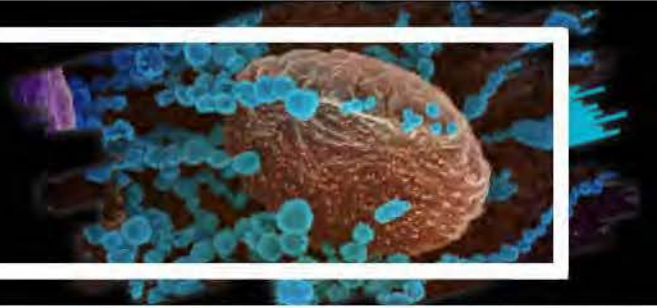
- Animal Model Development (Battelle)
- Animal Model Development (Lovelace Biomedical)
- U.S.-Manufacturing (Phlow)
- Clinical Sample Collection (NYU)
- Animal Model Development (MRIGlobal Dx)
- Reagent prep to support diagnostic development

Some awards made in as little as 14 days with the EZ BAA


BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY
BARDA


SAVING LIVES
50TH
APPROVAL
AND PROTECTING AMERICANS

CORONAVIRUS (COVID-19)
HOW TO CONTACT BARDA



ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

phe.gov/BARDA
Program description, information, news, announcements, connect to CoronaWatch

Medical Countermeasures.gov

medicalcountermeasures.gov
Portal to BARDA:
Register to request a CoronaWatch meeting!

BARDA's Easy Broad Agency Announcement EZ-BAA)

BAA-20-100-SOL-0002
https://beta.sam.gov/opp/b4f7923443a448218d369209723141c5/view

BARDA's Broad Agency Announcement (BAA)

BAA-18-100-SOL-00003
https://beta.sam.gov/opp/1b46a4169fcb4902b9c4fcbb5bf981f7/view

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From:	Kerr, Lawrence (HHS/OS/OGA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=8CE9DE2E7497472BB758F8FD6E262C86-KERR, LAWRE <Lawrence.Kerr@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>
Subject:	Automatic reply: AMR re: Remdesivir
Date:	2020/03/02 06:56:26
Priority:	Normal
Type:	Note.Rules.OofTemplate.Microsoft

I am out of the office on TDY Monday 2 March through Friday 6 March with some access to my emails during that time (+6 hrs EST).

If you need to reach me in an emergency, please email or call Arnela.Lopez@HHS.gov at 202-691-2033.

Jose Fernandez is Deputy Director for PET; he can be reached at Jose.Fernandez@HHS.gov. For all issues related to the novel coronavirus please contact Jose and OGA-Wuhan-nCoV@HHS.gov

If the issue relates to Ebola: Tiffany.Locus@HHS.gov

If the issues relates to Influenza, Ebola, other EIDs, please adress correspondence to Collin.Weinberger@HHS.gov, Tiffany.Locus@HHS.gov, Seth.Ferrey@HHS.gov, and Adam.Aasen@HHS.gov

If the issue relates to GHSA, please address correspondence to Jose.Fernandez@HHS.gov, Shuen.Chai@HHS.gov, and Julia.Kibunja@HHS.gov

If the issue relates to AMR , please address correspondence to Lynn.Filpi@HHS.gov and Natalie.LaHood@HHS.gov

I will reply to emails at the earliest time possible.

Thank you.

Larry

Sender:	Kerr, Lawrence (HHS/OS/OGA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=8CE9DE2E7497472BB758F8FD6E262C86-KERR, LAWRE <Lawrence.Kerr@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>
Sent Date:	2020/03/02 06:56:26

From:	<Rick.Bright@hhs.gov>
To:	Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@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>; Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>
Subject:	Re: Request for BARDA help with DLG | International MCM Access and population prioritization for MCM
Date:	2020/04/14 11:49:54
Priority:	Normal
Type:	Note

Linda. That is not even something we can contribute to, let alone lead. SPPR is the policy shop and should lead policy topics such as suggested. Ian Watson is leading SPPR now and they have a full staff for policy and dlg issues.

On Apr 14, 2020, at 11:43 AM, Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>wrote:

Rick and Gary
SPPR is asking for a BARDA rep to help work up a DLG on population prioritization for CQ/HCQ and possibly broader.

I'll let them know that we can't staff this because of our response mode today. **Holler if otherwise.**

Linda

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Tuesday, April 14, 2020 11:26 AM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>; DLGDESK (HHS/ASPR/OPP) <DLGDESK@hhs.gov>
Subject: RE: DLG | International MCM Access

Thanks, Linda. We'd be interested to have whoever at BARDA would be appropriate to discuss how to frame the DLG discussion on population prioritization decisions that would include international access to MCMs, especially when they are limited. Who would be the right person?

From: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Sent: Tuesday, April 14, 2020 11:17 AM
To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>; DLGDESK (HHS/ASPR/OPP) <DLGDESK@hhs.gov>
Subject: RE: DLG | International MCM Access

Hi All,
Thank you for the invite. I do not think I can contribute to population prioritization. My expertise is micro and product development with a minor in human resources/HR since joining ASPR.
L

From: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Sent: Tuesday, April 14, 2020 11:09 AM
To: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>; DLGDESK (HHS/ASPR/OPP) <DLGDESK@hhs.gov>
Subject: RE: DLG | International MCM Access

I could meet between 11:00 and 12:00 tomorrow. We'll need a rep from the DLG team also. Dan

---

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Tuesday, April 14, 2020 11:05 AM
To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Thank you, Dan. Could we please schedule a time with you and Linda (and whoever else needs to be on the call) to discuss bringing the issue of population prioritization that includes the international piece to the DLG? Dan and Linda, what is your availability tomorrow between 11-2? Thank you both!

From: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Sent: Tuesday, April 14, 2020 9:33 AM
To: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA)

<Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Thanks all. Let us know if/when you want to consider a DLG on this topic. As noted, it might be similar to other DLGs we've had on related topics. I'm happy to discuss. Dan

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From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Tuesday, April 14, 2020 8:31 AM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Hi Linda,

Thank you very much for the quick turnaround on this. This is helpful!

All the best,

Ana

From: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Sent: Monday, April 13, 2020 7:46 PM
To: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Cc: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Hi Ana,

We aren't aware of any ongoing discussions in BARDA on this as it's a policy issue. However, a suggestion came back. Should Remdesivir demonstrate efficacy it was suggested that a policy position on Remdesivir could be considered for COVID-19 the same way that it was during the 2 Ebola outbreaks.

Thank you all again. We appreciate SPPR checking in with us on this.

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Monday, April 13, 2020 4:21 PM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Kerr, Lawrence (HHS/OS/OGA)

<Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

+ Rachel Wood

From: Ayala, Ana (OS/ASPR/SPPR)
Sent: Monday, April 13, 2020 4:20 PM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Subject: FW: DLG | International MCM Access

Hi Linda,

Dan Dodgen (copied here) suggested that we reach out to you as one of the starting points as we look into the possibility of having an HHS-internal discussion within the DLG on how international access to COVID-19 MCMs should be handled and balancing that with domestic needs. Some of us have started considering the various complications that could arise as MCMs like Remdesivir become available but in limited numbers, at which point we expect that international stakeholders like WHO and other foreign governments will reach out. Has BARDA started to have conversations internally (or externally with stakeholders) on this issue? We would be interested to hear what BARDA is thinking on the issue.

Many thanks in advance,

Ana

Ana S. Ayala, J.D., LL.M.
Senior Global Health Officer
Office of Global Affairs
U.S. Department of Health and Human Services (HHS)
o: (202) 205-5894 | **m:** (b)(6)
ana.ayala@hhs.gov

From: Ayala, Ana (OS/ASPR/SPPR)
Sent: Monday, April 13, 2020 3:04 PM
To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>

Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>
Subject: RE: DLG | International MCM Access

Thank you, Dan. We haven't had discussions with BARDA on international access to Remdesivir yet. We'll reach out to Linda Lambert to see whether they've begun considering the issue. Regardless, it would be good to have the HHS-internal discussion within DLG to start addressing international access to MCMs in general (does not need to be limited to Remdisivir). Of course, it would make sense to have it as part of a discussion on how various populations will be prioritized when amounts are limited—don't think the DLG could consider the international piece without addressing this first.

If you could please share with us the DLG paper, that would be great. Since Robin and Ruvani helped draft the paper at the early stages, we did not hear on further developments. We'd be particularly interested in how ASPR plans to move forward. Thanks in advance!

Ana

From: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Sent: Monday, April 13, 2020 2:26 PM
To: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Hi Ana, Thanks for your message. As you know, we are currently finalizing a DLG paper regarding the use of HHS-held chloroquine and hydroxychloroquine in international clinical trials. There may be content relevant to your question in the paper, which we hope to finalize today or tomorrow.

Have you spoken with BARDA about the Remdesivir question yet? They have been so engaged in the Remdesivir trials that they may have already given some thought to this issue. I would start with Linda Lambert.

That said, this could be a potential DLG topic if we need broader HHS input and/or consensus. Let's see how BARDA responds. Dan

---

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Monday, April 13, 2020 2:06 PM
To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: DLG | International MCM Access

Hi Dan,

Hope you are doing well. We are reaching out with respect to an issue that has begun to come up and which we expect will continue to grow in significance. With advocacy for Remdesivir increasing as a hopeful COVID-19 MCM and considering that the DLG is the coordinating body for high-level policy decisions, we would like to inquire about the possibility of starting an internal HHS conversation about the issue of international access to Remdesivir and our approach with respect to WHO inquiries about accessing it. Has the DLG started discussions on prioritizing populations with respect to Remdesivir or other hopeful MCM candidates? This may be the starting point to consider the potential international aspects of what may be soon coming down the pike.

Many thanks!

Ana

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Sender:	<Rick.Bright@hhs.gov>
Recipient:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>
Sent Date:	2020/04/14 11:49:53
Delivered Date:	2020/04/14 11:49:54
Message Flags:	Unsent

From:	The Well News <sftw@thewellnews.com>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	Governors Do It Better, the New Normal, Building Bipartisan Task Force
Date:	2020/04/18 07:11:48
Priority:	Normal
Type:	Note

View in browser

TheWell NEWS

Straight from The Well

Saturday, April 18, 2020

2020 ELECTIONS

Kasich, McAuliffe on COVID-19's Impacts on Campaigns, Elections, and Voter Security

Despite continued uncertainty over how the Coronavirus pandemic will end, its economic impact will surely cast a shadow over the November election, according to a pair of former governors.

Govs. John Kasich, a Republican of Ohio, and Terry McAuliffe, a Democrat of Virginia, spoke about COVID-19's potential impact on the upcoming presidential campaign, election, and voter security at a virtual forum from the Meridian International this week.

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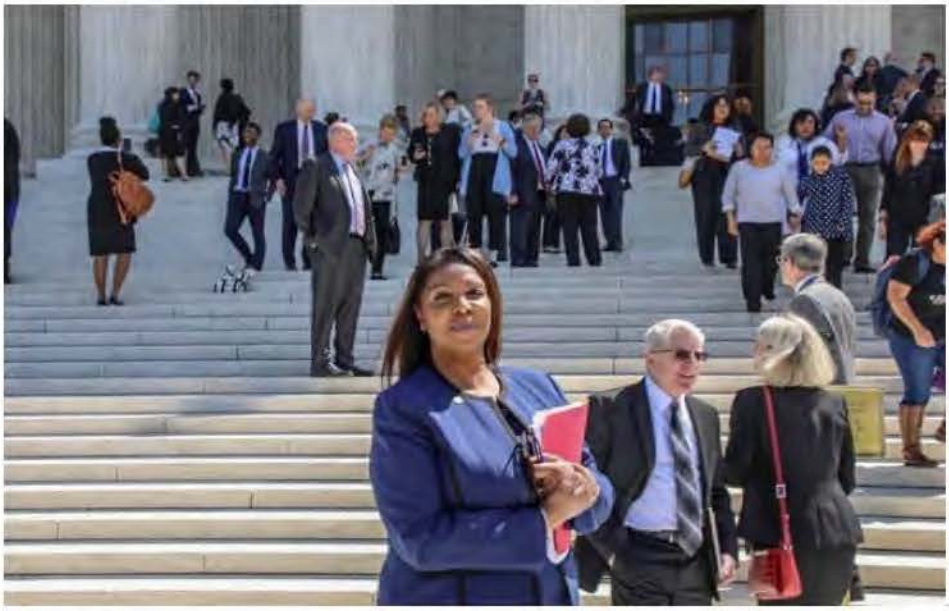
HEALTH

New York AG Orders Four Companies to Stop Selling COVID-19 Tests, Cures



New York Attorney General Letitia James ordered four companies to immediately stop selling unauthorized coronavirus home test kits and purported cures. "This isn't a game," James said in a post on Twitter. "Giving people a false sense of security is not only illegal, but it also puts communities at risk."

The attorney general said Hong Kong Royal Resource Technology Company and a second firm, Rightangled, have been misleading consumers into believing their products can detect if an individual has contracted the virus.

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CONGRESS

Rules Chairman Devises Path Forward for Remote Voting by Congress

After weeks of calls for some kind of tech-based system to allow members of Congress to work from their districts during the COVID-19 pandemic, the chairman of the powerful House Rules Committee proposed a decidedly low-tech alternative -- having another member vote for you.

Under this plan, any member unable to travel to Washington due to the pandemic could provide specific instructions for each vote to a fellow member who is able to be physically present in the House chamber and authorized to cast those votes on their behalf," Rules Committee Chair James McGovern, D-Mass., said in a written statement.

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IN THE NEWS

- • Hospital Hackers Seize Upon Coronavirus Pandemic
  By Jenni Bergal
- • The 'Veepstakes' Are Usually Top Secret. Why Biden's Search Is Spilling Into Public View
  By David Catanese
- • Trump Faces Ugly Electoral College Map as Coronavirus Jolts Reelection Push
  By Dave Goldiner
- • Chicago Goatherds, Shepherds and Duck Owners Wary of New Push to Regulate Livestock After Death of Horse
  By Jessica Villagomez
- • States Go Their Own Ways on Environmental Enforcement During Crisis
  By Caroline Tanner

VETERANS

President Signs Cunningham/Katko Bill Establishing Virtual VA Claims Hearings

President Donald Trump has signed into law bipartisan legislation that enables veterans to virtually attend Department of Veteran Affairs claims hearings from home. The legislation was introduced by Reps. Joe Cunningham, D-S.C, and John Katko, R-N.Y. in October.

Prior to the bill becoming law, the Board of Veterans' Appeals, which is based in Washington, D.C., only conducted tele-hearings from certain VA locations, meaning veterans had to travel sometimes great distances to testify in support of their claims for benefits and other services.

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MORE FROM THE WELL

GOP Moving Forward With Convention Plans Despite Pandemic Uncertainty

The Republican party is moving forward with plans to hold its National nominating convention in Charlotte, N.C. this summer, despite continued uncertainty over when the coronavirus outbreak will finally crest and go away. "Truthfully, there really isn't a contingency plan, at least in terms of not having a convention," convention CEO Marcia Lee Kelly told reporters on a conference call Wednesday. "Public safety is paramount," Kelly said, emphasizing the RNC and all those working on the convention are in constant contact with public health officials regarding the viral pandemic.

IAVA Expands Effort to Provide Timely Help to Vets During Pandemic

Newly rebranded as the IAVA's "Quick Reaction Force," the initiative provides confidential peer-to-peer support, comprehensive care management and resource connections for any assistance a veteran requires, 24 hours a day, seven days a week. The newly expanded program ensures that all veterans, regardless of their service era, discharge status, and geographic location are getting the care and have access to the resources they need, said Jeremy Butler, the organization's CEO.

COMMENTARY | "Trust Us" - Exposing Huawei's Influence Playbook in the COVID Era

As phrases like "deep fakes" and "bot farms" have recently become mainstays of our lexicon, it is easy to overlook the less sophisticated ways foreign adversaries are attempting to influence our way of life. There are simple and effective ways that foreign countries, particularly China, are seeking to influence American public opinion. One need look no further than the ongoing battle with Huawei and the future of 5G to truly understand how far China is willing to go to win the battle of ideas.

Kilmer, Murphy Among Those Named to White House Task Force on Rebuilding American Economy

Reps Derek Kilmer, D-Wash., and Stephanie Murphy, D-Fla., are among the bipartisan group of congressional lawmakers named to a White House panel tasked with counseling the White House on when and how to get the economy moving again in the wake of the coronavirus outbreak. The details of how the restart will work are far from worked out.

Unemployment Claims Surge By Another 5.2 Million As White House Eyes Restarting Economy

Initial unemployment claims, a proxy for layoffs, jumped by another 5.2 million last week, bringing the four-week total to about 22 million, the Labor Department reported Thursday. That number wipes out the total number of jobs created during the nine-and-a-half years that have elapsed since the global economic meltdown of 2007 and the recession that followed. All told, nearly 12 million people are now receiving unemployment checks, roughly matching the peak reached in January 2010, shortly after the Great Recession officially ended.

CARTOONS OF THE WEEK


STUCK-AT-HOME WAR MOVIES
THE GREAT ESCAPE
GIMME THAT!
MOM!?
LET GO!
CRASH!
DAAAD?
A FRIDGE TOO FAR
THE LONGEST MONTH
APRIL
WORK
ALL QUIET ON THE WESTERN LAWN
APOCALYPSE NOW
SOMEWHERE OVER THE RAINBOW...
SING IT LOUDER, KID...
CUOMO
ECONOMY
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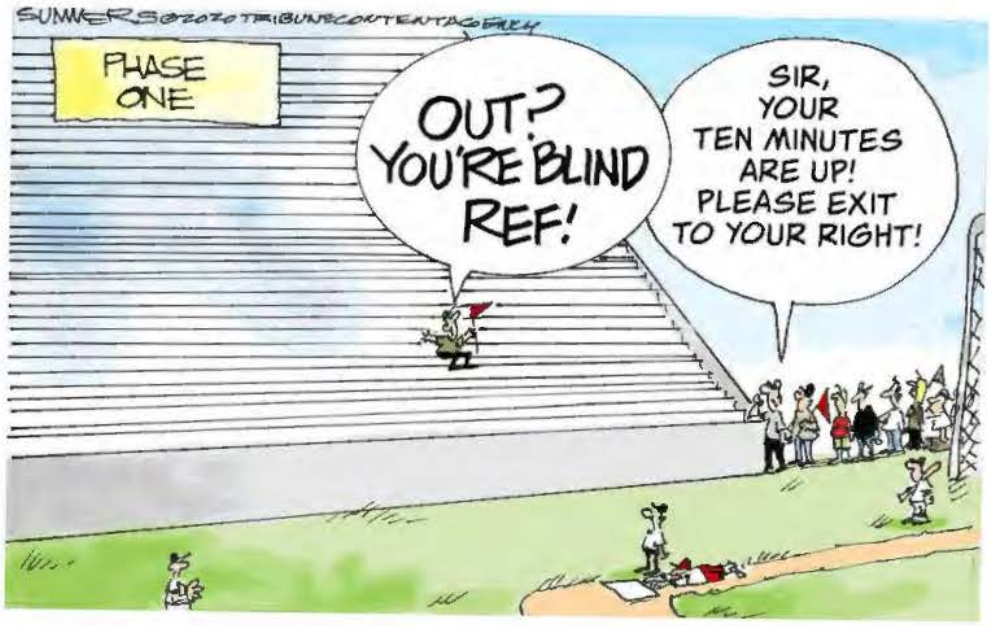
I JUST WANT TO SAY THAT YOU MEDICAL PEOPLE ARE HEROES.
I'M NOT A DOCTOR, I'M JUST GOING TO THE GROCERY STORE.


CAN'T BE NEAR ANYONE!!
DEBATE RAGES OVER WHEN TO OPEN UP
COVID 19
ZERO GROWTH OPPORTUNITIES!!
DEBATE RAGES OVER WHEN TO OPEN UP
COVID 19
I GOTTA GET BACK TO WORK!!
DEBATE RAGES OVER WHEN TO OPEN UP
THIS SHUTDOWN IS KILLING ME!!!
DEBATE RAGES OVER WHEN TO OPEN UP
COVID 19


PHASE ONE
OUT? YOU'RE BLIND REF!
SIR, YOUR TEN MINUTES ARE UP! PLEASE EXIT TO YOUR RIGHT!


BE SAFE- BACK UP A STEP
CUOMO
de BLASIO


MASKS PLEASE!
"SOME PEOPLE JUST CAN'T TAKE ANYTHING SERIOUSLY"


TAKE ME TO YOUR SCAPEGOATS

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