National Vaccine Advisory Committee meeting Sept 17-18, 2019

Agenda item: Vaccines for Uncommon Diseases and Small Patient Populations

Topic: Vaccines and Antimicrobial Resistance

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National Vaccine Advisory Committee Member

National Vaccine Advisory Committee. Sept 17, 2019
Disclosure

Employed by GSK where I am a vaccine research physician scientist

Presentation at the invitation of the Office of Infectious Disease Policy, National Vaccine Advisory Committee

Presentation is for educational purposes only; this is not a sales, marketing or promotional presentation

Content of presentation will not include unapproved or investigational uses of products or devices
Vaccines and Vaccination Programs

- Enable individuals to experience healthier lives
- Benefit global society:
  - increased economic health and strong healthcare systems
- Investment in vaccines and disease prevention:
  - proven, effective public health strategy
Driving the potential of new vaccines to transform human health

Scientific knowledge advances and modern vaccine technologies offer great potential for new vaccine development:

- uncommon and/or emerging diseases imparting significant morbidity & mortality
- patient populations small in number yet at risk of clinically important medical and healthcare-associated infections
- personalized vaccines based on subpopulation or individual genetic information
- AMR-relevant vaccines aimed at preventing target pathogens likely to drive antimicrobial use and resistance

New vaccines need to be discovered, developed through to commercialization, and implemented through evidence-based vaccination policy recommendations
Need for comprehensive approach to realize full potential and impact

Discovering innovative technologies and developing new vaccines: time, human and capital resource intensive, risky

Formulating vaccine policy decisions: consider broad view, beyond direct health and economic benefits

Evaluate:

- Moral, social, and ethical impact of vaccines, integrated alongside other societal health interventions and programmatic synergies beyond vaccines
- Impacts related to reduced antibiotic use and antibiotic resistance.
- Health equity and justice, community health gains and improved healthcare system function, and societal economic health
Evolution of the current paradigm is needed to optimize how we value new vaccines

Without considering full benefits and contribution to society of vaccines, stakeholders may not adequately value the next generation of vaccines, and policy recommendations may result in underutilization at the detriment of patients and public health.

Key considerations:

- Rapid development of new vaccine technologies enabling vaccines for vaccines targeted to less common diseases with significant impact
- Innovative clinical trial designs
- Role of real world evidence (i.e. post-licensure effectiveness) to adapt recommendations in real-time
- Improved collaboration and data-sharing
- Increased transparency throughout the development lifecycle
- High barriers to entry

Antibiotics

The discovery of antibiotics is one of the greatest medical advances of the 20th century.

Modern medicine is made possible by our ability to treat, and prevent, infection: transplantation, neonatal care, complex surgeries, joint replacement, caesarian sections, oncology treatment, sepsis …
Antibiotics

Unfortunately, their use has created an evolutionary response from microbes, and these gains in healthcare are under threat from AMR.
These events were predicted

Stanley Falkow (1934-2018) discovered the molecular mechanisms through which bacteria cause disease and predicted the rise of multidrug-resistant bacteria.

By the 1970s he predicted that overuse of antibiotics would soon lead to drug resistance and the loss of their utility.

Falkow already had plenty of evidence to base his predictions on.

His recommendation to stop the use of antibiotics in animals was not implemented by the US authorities.

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The Issue
Antibiotic-Microbial Resistance (AMR)

Multidrug resistant organisms increasingly common, extremely difficult to treat

Now encountering infections that are untreatable

Major contributor: over-prescription of current antibiotics in animals and humans
AMR
Why should we be worried?

Serious, growing threat to public health and economy

Deaths annually global, current:

- 60,000 tetanus
- 120,000 cholera
- 130,000 measles
- 1.2 M road accidents
- 1.4 M diarrheal dis
- 1.5 M diabetes
- 8.2 M cancer
- drug resistant infections: 50,000 US/EU; globally >700,000

If current trend holds: by 2050, ~10 million AMR deaths globally, world GDP reduced up to 2-3.5%
Worst case scenario: “post antimicrobial era”

Problem attracting global attention

Most proposed solutions focus on development of new technologies:

- Antibiotics
- Rapid diagnostic tests
- Vaccines
AMR is difficult for antibiotics alone

Bloom, Black Salisbury and Rappuoli. PNAS 2018:115;12869
Problem attracting global attention; most proposed solutions focus on development of new technologies: antibiotics, rapid diagnostic tests, and vaccines

Role of vaccination in controlling AMR frequently acknowledged, yet not led to concrete changes in policy or resourcing
Preventing infections to reduce society’s dependence on ABX

Bacterial infections are major drivers of antibiotic prescribing

Vaccines to prevent bacterial infections reduce antibiotic use
– vaccines for diphtheria, meningitis, pneumonia and pertussis have protected tens of millions of individuals from these bacterial infections

Non-bacterial infections can trigger inappropriate use of antibiotics
– vaccines for non-bacterial infections, such as influenza and rotavirus, avoid diseases that can trigger inappropriate use of antibiotics
Increase awareness of role of vaccines in addressing AMR

Requires collaborative global response from all stakeholders:
- scientific community
- pharmaceutical sector
- policy-makers
- healthcare funders
A Call for Greater Consideration for the Role of Vaccines in National Strategies to Combat Antibiotic-Resistant Bacteria: Recommendations from the National Vaccine Advisory Committee

Approved by the National Vaccine Advisory Committee on June 10, 2015

The emergence of a novel virus receives widespread attention in the news media and among the public. However, the greatest threat to public health in the United States is unlikely to be an exotic disease but, rather, the mounting threat of antibiotic resistance in commonly acquired bacterial infections. The human and economic costs of this growing crisis are unfathomable. In the 2015 report by the Centers for Disease Control and Prevention (CDCS), Antibiotic Resistance Threat in the United States, it is estimated that more than two million people contract an antibiotic-resistant infection each year in the United States, and approximately 23,000 die as a result of their infection. The escalating rate of resistance among bacterial pathogens is being facilitated by the abandonment (and often inappropriate) use of antibiotics, and concern is rising that the arsenal of effective products to treat bacterial infections will soon run out. For example, it is now estimated that 4,700 (13%) of the 34,100 health care-associated Pseudomonas aeruginosa infections that occur in the United States each year are resistant to at least three classes of antibiotics, and some strains show resistance to nearly all classes of antibiotics. The lack of effective antibiotic therapy will have a significant impact in nearly all areas of medicine, but especially in surgery, oncology, intensive care, and transplant medicine.

In September 2014, the White House released the President’s National Strategy to Combat Antibiotic-Resistant Bacteria, which includes the President’s Council of Advisors on Science and Technology (PCAST) report and recommendations to the president on combating antibiotic resistance. Together, these reports identify priorities and guide coordination across U.S. government agencies to (1) better prevent and respond to the spread of antibiotic resistance through improved prevention and stewardship of antibiotic use; (2) increase surveillance of emerging antibiotic resistance in humans, animals, and the environment; (3) improve capabilities for detection and diagnostic; (4) accelerate development of new products, including new classes of antibiotics, therapeutics, and vaccines; and (5) enhance international collaboration.

The federal commitment to addressing this issue was further emphasized by Presidential Executive Order 13676, which calls for the development of a five-year National Action Plan that promotes concrete activities and milestones for achieving the goals outlined in the National Strategy and a presidential budget request to Congress for $1.2 billion.

PREVENTING INFECTIONS AND THE SPREAD OF ANTIBIOTIC RESISTANCE

Highlighting the role of vaccine and prevention in antibiotic stewardship.

The PCAST report, the National Strategy, and the National Action Plan strongly emphasize that practical and manageable actions can and should be accomplished toward the goals of improved antibiotic stewardship and the development of new products to treat antibiotic-resistant infections. We particularly welcome Objective 4.3 of the National Action Plan, which would incent research and development into new vaccines to prevent infections, thereby restraining the development of bacterial resistance and the general overuse of antibiotics.

However, although vaccines are mentioned as one component of the overall cadre of new products needed to combat emerging antibiotic resistance in humans medicine, their potential is significantly under-appreciated. Recent antibiotic misuse and thereby contribute to the ongoing threat of “increasing the longevity of current antibiotic resistance.”
RECOMMENDATIONS FOR INCENTIVIZING THE DEVELOPMENT OF VACCINES, DIAGNOSTICS, AND THERAPEUTICS TO COMBAT ANTIBIOTIC-RESISTANCE

SEPTEMBER 2017

PACCARB
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
Develop innovative AMR-relevant vaccines

Develop innovative AMR-relevant vaccines aimed at preventing infections where target pathogens are likely to drive antimicrobial use and resistance (e.g. Shigellosis, Tuberculosis, Malaria, Meningococcal Meningitides, Pneumococcus, COPD, RSV, Flu Universal, MRSA, Gonorrhea, HSV, candidiasis, C. difficile, Klebsiella, Pseudomonas)

New, global initiatives for R&D of new drugs and vaccines being deployed
1950-70 golden period for antibiotics
1980-today golden period for vaccines

Various advances in molecular biology have spurred vaccine development.

Bloom, Black Salisbury and Rappuoli. PNAS 2018:115;12870
Vaccine technology has been revolutionised in the past 30 years

Waves of new technologies have enabled the development of vaccines that were previously not possible and led to improvements in vaccine safety.

Potential vaccine game-changing technology

- Adjuvant Systems
- Synthetic vaccines (DNA/RNA)
- Adenoviral vectors
- Reverse vaccinology
- Structural vaccinology
- Platform Technologies
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https://vaccinesforamr.org/review-of-pathogens/vaccine-pipeline-information/ accessed May 5, 2019
Technologies to develop vaccines for AMR: Not the major challenge

Sustainability of vaccine development for AMR: The major challenge
Value of vaccines as tool for antimicrobial stewardship

– Collaborate across healthcare, research and policy community to:
  • Expand, strengthen evidence-base on vaccines and AMR
  • Present results via publications, scientific presentations
  • Produce, distribute educational materials
– Support expansion of AMR-sensitive economic models for vaccines accounting for the value of reduced antibiotic use, both in mass vaccination and targeted settings
– Include AMR value-add aspects of vaccines into larger attribution framework used by health authorities; explore potential for changes to vaccine labels to include how appropriate vaccines can impact AMR
Call to action:

- Prioritize vaccination, allocate funding, broaden points of access (e.g. pharmacy), encourage greater use of existing vaccines, and raise awareness amongst decision-makers of the role of vaccines in preventing AMR

- Incentivize development of AMR-relevant vaccines by:
  - Considering AMR-related benefits in regulatory submissions and HTA assessments
  - Developing new funding models such as public-private partnerships that share risk and costs of development where commercial viability is low

- Build body of data on vaccines and AMR through surveillance and research to facilitate decision-making by policy makers
A Call for Greater Consideration for the Role of Vaccines in National Strategies to Combat Antibiotic-Resistant Bacteria: Recommendations from the National Vaccine Advisory Committee

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Recommendation 1
NVAC recommends that the Assistant Secretary for Health (ASH), as the Director of the National Vaccine Program, work with agencies of the U.S. Department of Health and Human Services (HHS) and other federal and nonfederal partners to develop a stakeholder engagement plan to ensure that both vaccine and immunization stakeholders, as well as antibiotic stewardship stakeholders, include information on the role of existing vaccines in minimizing antibiotic use. These communication efforts should include information on vaccines against bacterial pathogens that may currently be or may potentially become antibiotic resistant, and viral vaccines that, by preventing viral illnesses, decrease the inappropriate use of antibiotics for viral infections as well as decrease bacterial superinfections leading to needs for antibiotics.

Recommendation 1.1
These efforts should include a comprehensive analysis modeling the reduction in disease burden due to antibiotic-resistant bacterial strains, the potential reduction in antibiotic prescribing and health-care encounters, and the anticipated cost savings to the health-care system expected from increased uptake of recommended vaccines in all age groups. Vaccines under development may also be included to support those vaccine development efforts.

Recommendation 1.2
These efforts should also tie into surveillance efforts to determine the effects that vaccine uptake has produced on minimizing disease burden due to antibiotic-resistant strains in all age groups, and on the ecology of infections caused by both vaccine and non-vaccine strains. When possible, surveillance efforts also should inform on the effects that vaccine uptake, and the reduction in disease caused by vaccine, has had on the prevalence of antibiotic-resistant strains.

Recommendation 2
The NVAC strongly recommends that the ASH ensure NVAC remains regularly informed of efforts to address antibiotic resistance by revisiting the NVAC charter to include a liaison representative from the President’s Advisory Council on Combating Antibiotic Resistant Bacteria on the NVAC. The NVAC also encourages the ASH to support the further inclusion of an NVAC representative on the President’s Advisory Council on Combating Antibiotic Resistant Bacteria to provide knowledge of vaccines and the immunization system to those discussions. Cross-representation on committees maximizes the use of subject matter expertise and stakeholder input to better inform interdepartmental efforts.

Recommendation 3
The NVAC strongly encourages the ASH to communicate to the HHS Secretary and the CARB Economic Incentives Working Group that incentives proposed to stimulate antibiotic development must also be evaluated for their utility in accelerating the development of vaccines and other novel prevention strategies. Proposed incentives must be flexible enough to apply to a range of disease technologies to ensure that we continue to move toward long-term solutions to antibiotic resistance. Where incentives are not found to be cross-cutting, additional alternative incentives should be proposed and analyzed to promote a more robust and comprehensive pipeline that includes vaccines.

Recommendation 3.1
Once appropriate economic incentives are identified, the NVAC recommends that the ASH work with relevant federal and nonfederal stakeholders to prioritize promising vaccine candidates to ensure programmatic resources support for vaccine candidates with the greatest potential impact for combating antibiotic resistance and reducing the use of antibiotics in health-care and community settings.

Recommendation 4
The NVAC recommends that the ASH work with FDA and vaccine manufacturers (including pre-commercial-stage biotechnology companies) to encourage early discussion of appropriate regulatory pathways and clinical trial design requirements for the development of vaccines targeting antibiotic-resistant bacteria and vaccines that decrease the use of antibiotics.

Recommendation 5
The NVAC requests that the National Vaccine Program Office provide an annual update on the progress made in supporting the role of vaccines in strategies to combat antibiotic-resistant bacteria.
Evolution of the current paradigm is needed to optimize how we value new vaccines

Key considerations:

- Rapid development of new vaccine technologies enabling vaccines for vaccines targeted to less common diseases with significant impact
- Innovative clinical trial designs
- Role of real world evidence (i.e. post-licensure effectiveness) to adapt recommendations in real-time
- Improved collaboration and data-sharing
- Increased transparency throughout the development lifecycle
- High barriers to entry

Without considering full benefits and contribution to society of vaccines, stakeholders may not adequately value the next generation of vaccines, and policy recommendations may result in underutilization at the detriment of patients and public health.

Perspectives on Progress in Developing a Globally Effective HIV Vaccine

Larry Corey, MD
Principal Investigator, NIAID supported HIV Vaccine Trials Network (HVTN)
Past President and Director, Fred Hutchinson Cancer Research Center
Member, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center
Professor, Laboratory Medicine and Medicine, University of Washington
HIV is Unfortunately Alive and Well Throughout the World

- Globally there are 1.4 million new infections yearly
  - This is 5,000 acquisitions a day
- 180,000 infants a year still infected
- 37 million people living with HIV (76 million since the epidemic started)
- 770,000 HIV related deaths in 2018
- US has “tolerated” 35,000 - 40,000 new infections a year
ADULTS AND CHILDREN NEWLY INFECTED WITH HIV: 1990–2018

Source: UNAIDS 2019 estimates.
Relative Percentage of New Diagnoses in the United States by Geographic Region, 2016

Source: CDC and Office of the Assistant Secretary for Health
Indiana HIV Outbreak: Geographic Distribution
Scott County pop. 24,000; Austin, IN pop. 4,200

Adams, NEJM 2015;373:1379-1380
46 Counties Account for 50.3% of New HIV Diagnoses, 2016

Source: CDC and Office of the Assistant Secretary for Health
The Need for an HIV Vaccine

• With asymptomatic acquisition, prolonged subclinical infection, and sexual transmission, getting to an *AIDS Free Generation* will require a biologically based primary prevention modality with prolonged durability; preferably an effective HIV vaccine.

• Larry’s definition of an *AIDS Free Generation*: 95% reduction in incident cases annually:
  - USA < 2,500 cases yearly
  - Globally < 100,000 cases yearly
The Need for an HIV Vaccine

• Test and treat is an important strategy for individual health and can have an effect on transmission.

• U=U is correct.

• However, long term adherence and prompt identification of HIV infection is just not translatable and scalable on a large scale.
  • It has not eliminated mother to child transmission, which has a very definable exposure.
HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa


Effect of Universal Testing and Treatment on HIV Incidence — HPTN 071 (PopART)


Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana

The HIV prevention field needs something that is disruptive!

HIV Vaccine
Vaccines can bring infectious diseases under-control

Vaccines bring 7 diseases under control

Two hundred years after the discovery of vaccine by the English physician Edward Jenner, immunization can be credited with saving approximately 9 million lives a year worldwide. A further 16 million deaths a year could be prevented if effective vaccines were deployed against all potentially vaccine-preventable diseases.

So far only one disease, smallpox, has been eradicated by vaccines, saving approximately 5 million lives annually.
Why Has It Been So Hard to Develop an HIV Vaccine?

• Science issues:
  o Genetic diversity of the virus is greater than any other pathogen.
  o Envelope is less immunogenic than any other virus envelope protein; perhaps because of its’ glycan shield.
  o The gp160 envelope trimeric structure is unique, hard to simulate and there are fewer trimers on the surface than most viruses.
  o Animal models are expensive and non-predictive of vaccine efficacy.
  o There are no human cures of HIV and hence there are no models to mimic (0 of 72 million and counting).
An exciting time to be in vaccine discovery...

<table>
<thead>
<tr>
<th><strong>THE SCIENCE ISADVANCING THROUGH CLINICAL TRIALS</strong></th>
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<tbody>
<tr>
<td>• Four pivotal HIV vaccine related efficacy trials are underway. (AMP/Uhambo/Imbokodo)/Mosaico)</td>
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<tr>
<td>• These trials will define if either or both neutralizing and/or non-neutralizing antibodies can be tweaked to provide reasonable vaccine efficacy in high risk regions of the world.</td>
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<table>
<thead>
<tr>
<th><strong>SCIENTIFIC ADVANCES ARE FUELING VACCINE DISCOVERY</strong></th>
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<tbody>
<tr>
<td>• Antibody isolation and characterization has revolutionized our understanding of the immune response.</td>
</tr>
<tr>
<td>• Technologic advances allow researchers to understand where antibodies target the virus in unprecedented detail.</td>
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<tr>
<td>• Stabilization of the HIV Env trimer allows for engineering of trimeric mimics.</td>
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<tr>
<td>• Have shifted from empiric approaches to hypothesis-driven approaches.</td>
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<th><strong>NEXT GENERATION VACCINES ARE ENTERING THE CLINIC</strong></th>
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<tbody>
<tr>
<td>• Native-like trimers meant to resemble HIV’s Env spike.</td>
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<tr>
<td>• Germline-targeting approaches generated using structure-based vaccine design.</td>
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Questions remain:

Do bnAbs protect? 
Potency and durability? 
HIV variability? 
bnAab maturation?
RV144: ALVAC prime, gp120 boost Vaccine Efficacy (31%)

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand
S Rerks-Ngarm, JH Kim et al. for the MOPH–TAVEG Investigators
Correlation Between Antibodies to the V1V2 Loop and Vaccine Efficacy in RV144

- Antibodies to the conserved region of V2, previously almost completely ignored by the HIV vaccine field, were highly correlated with efficacy.
1. Active Immunization to induce binding antibodies

Vaccination to stimulate binding antibodies previously shown to correlate with reduced risk of HIV infection in RV144 or in NHP challenge models. This is being tested in the large efficacy trials: HVTN 702, HVTN 705, HVTN 706

2. Passive Immunization (POC)

Pre-formed broadly neutralizing antibody e.g. VRC 01, a neutralizing antibody targeting the CD4 binding site. This is being tested in the HVTN POC 703 (AMP trial). Other NABs targeting other sites on the env are being evaluated in phase 1.

3. Active Immunization to induce neutralizing antibodies (POC)

Coaxing the immune system to develop broadly neutralizing antibodies with immunogens e.g. lineage based vaccine design, germline targeting or epitope based vaccine design.
Current Phase 2B/3 HIV Vaccine Efficacy Trials

- AMP (POC) HVTN 703/704
- Uhambo (Phase 2B/3) HVTN 702
- Imbokodo (Phase 2B POC) HVTN 705
- MOSAICO (Phase 3) HVTN 706
# Ongoing HVTN Vaccine Efficacy Studies

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<td>ALVAC/gp120</td>
<td>5400</td>
<td>14</td>
<td>70:30 split women &amp; men</td>
<td>South Africa</td>
<td>P5</td>
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<td>Janssen/J&amp;J and NIAID/HVTN</td>
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<td>MSM, TG</td>
<td>Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain, US</td>
<td>Janssen/J&amp;J and NIAID/HVTN</td>
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2010 Formation of the P5 Partnership

Purpose:
To build on RV144 data and ultimately license a pox-protein based HIV vaccine with the potential for broad and timely public health impact.

Strategy:
- Developed a partnership to extend the RV144 concept to Clade C regions of the world.
- Use expert committees to select the strains and then use company expertise to manufacture these vaccines for immunogenicity, safety and efficacy.
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<tr>
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<td>Oct. 2016</td>
<td>ALVAC prime, gp120 boost</td>
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<tr>
<td>HVTN 705</td>
<td>Nov. 2017</td>
<td>rAd26 prime, gp140 boost</td>
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**HIV Vaccine Efficacy Studies**

- **HVTN 702**: Modified RV144 prime-boost regimen
  - HIV Clade C: ALVAC-HIV + gp120 protein subunit vaccine with MF59 adjuvant
  - Target: n = 5,400 men and women aged 18-35 years

- **Imbokodo trial (HVTN 705/HPX2008)**
  - Phase 2b; target n= 2,600 HIV-negative women in sub-Saharan Africa
  - Quadrivalent, Ad26-vectored mosaic vaccine + recombinant clade C HIV gp140
### HVTN 702 Schema:
5400 South Africans (18-35 yrs)

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APPROACH (Ph 2):
Mixture of 4 mosaic Ad26 constructs + gp140 Clade C boost
Study Schema: HVTN 705/Imbokodo

Chairs: Glenda Gray,
Co-chairs: Susan Buchbinder, Kathy Mngadi and Frank Tomaka
HVTN efficacy trial locations in sub-Saharan Africa
Durability of ELISA responses in HVTN 117, the Ad26/gp140 phase 2 qualifying trial. Top line is HVTN 705 regimen Ad26/gp140 (HD = high dose)
Antenatal care and the Imbokodo Study

Most vaccines cause the body to make antibodies, HIV vaccines currently being tested in studies, are no different. If someone takes part in an HIV vaccine study, their body may make antibodies to HIV, which just means they are responding to the vaccine, not that they are HIV infected, or that they are protected by these antibodies. However, the most common tests for HIV infection, used at all public sector clinics, also look for these antibodies. These tests are quick, reliable and affordable. Therefore, someone who has gotten an HIV vaccine may have a positive HIV test, even if they are not infected with HIV. This is called VISIP (Vaccine-Induced Seropositivity), and is the reason that all vaccine trial volunteers should get HIV tests only at the vaccine trial site.

At the study site tests that look for the virus (PCR based) are used. These tests are expensive and not commonly available at public clinics. They can also tell the difference between true HIV infection and no HIV infection, by looking for the virus itself, not the antibody. This is why all participants should only get tests through the study site throughout the vaccine trial. Those who continue to need testing for the virus after the study is over can continue to come to the study site for this testing.
HVTN 706 Schema

Total dose of Ad26.Mos4.HIV is 5x10^10 viral particles (vp)/0.5 mL injection. Clade C gp140, Mosaic gp140, adjuvanted: adjuvanted protein formulation with a dosage strength of 80 mcg Clade C protein, 75 mcg Mosaic protein and 425 mcg aluminum (as aluminum phosphate adjuvant). Note: previously the dose of Clade C gp140 and/or Mosaic gp140 was reported as mcg of glycoprotein: 125 mcg Clade C gp140 and 125 mcg Mosaic gp140 glycoprotein correspond with 80 mcg and 75 mcg of protein, respectively.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Month 0</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1,900</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo +</td>
<td>Placebo +</td>
</tr>
</tbody>
</table>
Proposed 2020 configuration of HVTN CRSs in the US and Latin America
Two non-neutralizing strategies are being undertaken:
  o 1 based upon RV144 correlates data and the other based upon correlates in NHP challenge experiments.
  o Both approaches suggest correlates relate to both binding/functional antibodies (ADCP and ADCC), as well as some T cell response (CD4 envelope and the other ELISPOT data).
  o We shall see whether these presumed correlates are shown to be consistent in human efficacy trials.
  o We shall see if any NHP challenge studies are predictive of vaccine efficacy.
  o In the end it may take both neutralizing and non-neutralizing antibodies to achieve success.
1. Active Immunization to induce binding antibodies

Vaccination to stimulate binding antibodies previously shown to correlate with reduced risk of HIV infection in RV144 or in NHP challenge models. This is being tested in the large efficacy trials: **HVTN 702, HVTN 705, HVTN 706**

2. Passive Immunization (POC)

Pre-formed broadly neutralizing antibody e.g. VRC 01, a neutralizing antibody targeting the CD4 binding site. This is being tested in the **HVTN POC 703 (AMP trial)**. Other NABs targeting other sites on the env are being evaluated in phase 1.

3. Active Immunization to induce neutralizing antibodies (POC)

Coaxing the immune system to develop broadly neutralizing antibodies with immunogens e.g. lineage based vaccine design, germline targeting or epitope based vaccine design.
Broadly Reactive Neutralizing Antibodies Discovered since 2009

- Isolated from HIV-infected individuals
- Penetrate glycan shield
- Potently neutralize most strains of HIV-1

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014
Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults: MSM in Americas & heterosexual women in sub-Saharan Africa

- Placebo controlled trial of VRC01 mAb (IV), given on 8 weekly schedule
- Two cohorts:
  - 2,400 MSM + TG in North & South America (HVTN 704/HPTN 085)
  - 1,900 Women in sub-Saharan Africa (HVTN 703/HPTN 081)

- Both trials opened in April/May 2016
- 703/081 Accrued September 20, 2018 (End Jan 2021)
- 704/085 Accrued October 5, 2018 (End Oct 2020)

Chairs: Lawrence Corey, HVTN
Mike Cohen, HPTN
Co-chairs: Srilatha Edupuganti
Nyaradzo Mgodi
## Cohorts for the AMP Studies

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Antibody (VRC01) 10mg/kg</th>
<th>Antibody (VRC01) 30mg/kg</th>
<th>Placebo Saline</th>
<th>Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVTN704/HPTN085: MSM &amp; TG persons (Clade B) United States, Peru, Brazil &amp; Switzerland</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>2,700</td>
</tr>
<tr>
<td>HVTN703/HPTN081: Heterosexual women (Clade C) Sub-Saharan Africa – 7 countries</td>
<td>634*</td>
<td>634*</td>
<td>634*</td>
<td>1,900</td>
</tr>
<tr>
<td>Total</td>
<td>1,534</td>
<td>1,534</td>
<td>1,534</td>
<td>4,600</td>
</tr>
</tbody>
</table>

* Due to the randomization scheme, the numbers of vaccine and control recipients may differ slightly.
### Study Schema for the AMP studies

**INFUSION SCHEDULE (WEEKS)**  
[A = VRC01 infusion; C = Control infusion]

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>0</th>
<th>8</th>
<th>16</th>
<th>24</th>
<th>32</th>
<th>40</th>
<th>48</th>
<th>56</th>
<th>64</th>
<th>72</th>
<th>80*</th>
<th>92**</th>
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<tr>
<td>Group 1</td>
<td>10 mg/kg</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<tr>
<td>Group 2</td>
<td>30 mg/kg</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
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</tr>
<tr>
<td>Group 3</td>
<td>Control</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<td>C</td>
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</tbody>
</table>

2700 (1900) for the MSM + TG (WSM) group; (1/3 VRC01 30 mg/kg; 1/3 VRC01 10 mg/kg; 1/3 control

---

**Week 80:** last study visit to evaluate efficacy – primary end point  
**Week 92:** final study visit to evaluate safety and tolerability; co-primary end point
Enrollment and Retention Updates

- **703/081**
  - African Women
  - 1924 enrolled
  - 96% retention
  - 98% adherence

- **704/085**
  - MSM + TG
  - 2701 enrolled
  - 95% retention
  - 100% adherence
Moving to Self Administered Subcutaneous Injections

Extended Half Life preparations
Safety will be discussed next presentation
Enhanced half-life and augmented antibody levels in cervical biopsies of VRC01-LS vs. VRC01 in HVTN 116

Relative concentrations of antibody extracted from cervical biopsy tissue.
Note the much higher and more stable mAb levels with the LS mutation (purple lines) vs. parental (pink lines).
Summary

• If any of the HIV vaccines or antibodies in efficacy trial testing are effective, it will unleash an enormous explosion in scientific inquiry to improve, adapt and most importantly - bring to the world a new form of HIV prevention.

• An HIV vaccine will be the most complex vaccine ever designed:
  • Yes, the regimens will be an implementation challenge.
  • Vaccination may disrupt the way we diagnose HIV.
  • Vaccines will, however, overcome the current barriers to population based control of HIV and provide a tool that could get us to an HIV free generation; a reality that is not present with the current tools.

• And yes, the science behind such a vaccine will have additional spin offs.
Acknowledgements

All the study staff, the community engagement teams, and most of all, the participants who join the journey!
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**Janssen**
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Study Volunteers

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Bart Haynes, Larry Liao and colleagues

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- Cheryl Louw
- Kathy Mngadi
- Graeme Meintjes
- Craig Innes
- Nicole Hunt
- Phillip Kotze
- Francis Martinson

- Jani Ilesh
- Stewart Reid
- Leonard Maboko
- Maphoshane Nchabeleng
- Lungiswa Mtingi
- Dumezweni Ntshangase
- William Brumskine
- Zvavahera Chirenje
- Mookho Malahlela
- Modulakgotla Sebe
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- Lindsey Baden
- Ken Mayer
- Richard Novak
- Benigno Rodriguez
- Spyros Kalams
- Scott Hammer
- Beryl Koblin
- Ian Frank
- Michael Keefer
- Susan Buchbinder
- Julie McElrath
- Gepi Pantaleo
- Jorge Sanchez
- Martin Casapia
- Robinson Cabello
Need for and Challenges with Hepatitis C Vaccine Development

Andrea L. Cox, MD, PhD

Professor of Medicine and Oncology
Viral Hepatitis Center
No Conflicts of Interest
HCV is a serious blood born infection

• ~70 million infected world-wide
HCV is a serious blood born infection

- ~70 million infected world-wide
- Leading cause of end stage liver disease (ESLD) and hepatocellular carcinoma (HCC) in US and many other countries
HCV is a serious blood born infection

- ~70 million infected world-wide
- Leading cause of ESLD, HCC in US and many other countries
- HCV kills ~20,000 Americans annually
HCV Deaths Now Exceed Deaths from the Other Nationally Notifiable Infectious Diseases* combined

* HIV, TB, Hepatitis B and 56 other infectious conditions reported to CDC

Worldwide Deaths from HBV and HCV High and Rising

WHO Called for Viral Hepatitis Elimination by 2030

- Vaccines against HAV, HBV, and HEV
- Antiviral medications suppress HBV
WHO Called for Viral Hepatitis Elimination by 2030

- Vaccines against HAV, HBV, and HEV
- Antiviral medications suppress HBV
- Direct acting antivirals (DAAs) cure HCV- termed sustained virologic response (SVR)
WHO 2030 Targets for Viral Hepatitis Global Control

Achieve a:

• 90% reduction in new infections
• 90% of infected patients diagnosed
• 80% of infected eligible patients treated
• 65% reduction in liver-related deaths
WHO 2030 Targets for Viral Hepatitis Global control-on target?

- 2019 Study assessed the progress made in 45 high-income countries (HIC) in meeting WHO 2030 HCV elimination targets.

Razavi H., et. al. 2019. J Hepatol 70, 1, Supplement, page e748
Results

80% not on track for 2030
67% off by >20 years

Razavi H., et. al. 2019. J Hepatol 70, 1, Supplement, page e748
Progress report on 45 HIC with data

Slide Courtesy of Homie Razavi of the Center for Disease Analysis
Progress report on 45 HIC with data

4 WHO targets for HCV elimination:
- 34 countries failed to meet incidence target by 2030
- 30 countries failed to meet mortality target by 2030
- 29 countries failed to meet treatment target by 2030
- 22 countries failed to meet diagnosis target by 2030
2015 HCV incidence: 1.75 million and highly variable

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Estimated incidence</th>
<th>Uncertainty (X1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>309,000</td>
<td>222-544</td>
</tr>
<tr>
<td>Americas</td>
<td>63,000</td>
<td>59-69</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>409,000</td>
<td>363-426</td>
</tr>
<tr>
<td>European Region</td>
<td>565,000</td>
<td>460-603</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>287,000</td>
<td>243-524</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>111,000</td>
<td>104-124</td>
</tr>
<tr>
<td>Global</td>
<td>1,751,000</td>
<td>1,572-2,210</td>
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</table>

WHO Global Hepatitis Report 2017
Epidemiological data for 2016 were extracted from national reports, publications and the Polaris Observatory. There were 91/210 countries with data on SVR, HCV-related deaths and new infections available for analysis; 109 countries had net change in epidemic size projected from the regional prevalence of HCV, extrapolated to their population size. ‘Net cure’ was defined as the number of people with SVR, minus new HCV infections, plus HCV-related deaths in 2016. Results: For the 91 countries analysed, there were 57.3 million people with chronic HCV infection in 2016. In the remaining 109 countries, the projected epidemic size was 12.2 million, giving a global epidemic size of 69.6 million. Across the 91 countries, there was a fall from 57.3 to 56.9 million people in 2017, a 0.7% reduction. The projected global net change was from 69.6 to 69.3 million, a 0.4% reduction. Ten countries had at least five times more people reaching SVR than new HCV infections, including Egypt and USA. In 47/91 countries, there were more HCV infections than SVR in 2016. Conclusion: Very few countries are on target to achieve elimination of HCV as a public health problem by 2030. While the North American, North African/Middle East and Western European regions have shown small declines in prevalence, the epidemic is growing in sub-Saharan Africa and Eastern Europe. Far higher rates of DAA treatment are required for worldwide elimination of HCV.
An epidemic of opioid use and overdose in the US
Increasing incidence of acute HCV infection, US 2005-2016
• 2x more in nonurban than urban

• Strongly correlated with IDU

• From 2000-2002, incidence rates for acute hepatitis C decreased among all age groups, except for persons aged 0–19 years; rates remained fairly constant among all age groups from 2002-2010.

• In 2013, the rate of acute hepatitis C increased among all age groups, except for persons aged ≥60 years, compared with rates in 2010. The largest increases were among persons aged 20–29 years (from 0.75 cases per 100,000 population in 2010 to 2.01 cases per 100,000 population in 2013) and persons aged 30-39 years (from 0.60 cases per 100,000 population in 2010 to 1.36 cases per 100,000 population in 2013).

• In 2013, among all age groups, persons aged 20–29 years had the highest rate (2.01 cases per 100,000 population) and persons aged ≥60 years had the lowest rate (0.10 cases per 100,000 population) of acute hepatitis C.
Changes in Rates of New HCV Cases Reported by State 2010-2014
Focus has been more on diagnosis/cure than prevention
Challenges to cure

• Treatment remains expensive
Challenges to cure

- Treatment remains expensive
- We have already treated many of those easiest to treat—~$60 billion on DAAs 2014-2017, but numbers of new patients initiating DAAs declining
Challenges to cure

- Treatment remains expensive
- We have already treated many of those easiest to treat
- Finding the people who need treatment remains challenging
Identification of HCV Infected people is challenging

- Infection usually silent until ESLD present
- Highest risk groups are marginalized
- Knowledge of infection status limited
Percent of HCV Diagnosed Globally 2016

WHO Target: 90% diagnosed

High Income Countries: 44%
Upper-Middle Countries: 17%
Lower-middle Countries: 15%
Low income Countries: 9%

Data from Polaris database, Andrew Hill
Challenges to cure

- Treatment remains expensive
- We have already treated many of those easiest to treat
- Finding the people who need treatment remains challenging
- Drugs do not provide protection against reinfection
Challenges to cure

- Treatment remains expensive
- We have already treated many of those easiest to treat
- Finding the people who need treatment remains challenging
- Drugs do not provide protection against reinfection
- Treatment in the later stages doesn’t reverse all disease
Incidence of HCC after SVR is high in cirrhotics.

Consider some additional focus on prevention…
Is protective immunity possible?
Baltimore Before and After Acute Study of Hepatitis (BBAASH)

Enrolled: 18-35yo People Actively Injecting HCV Ab & RNA negative

Anti-HCV Ab = black bar

HCV RNA = red bar

Persistent Infection (73%)

Spontaneous Clearance (27%)
We are able to study the natural history of HCV infection using the BBAASH cohort, a group of young injection drug users in Baltimore who are followed prospectively beginning while they are HCV negative. Despite counselling, some of these individuals continue to inject and some of them become infected with HCV. These donors are then followed longitudinally with regular blood sampling during acute infection and then during HCV clearance or chronic infection.
Baltimore Before and After Acute Study of Hepatitis (BBAASH)

Enrolled: 18-35yo People Actively Injecting HCV Ab & RNA negative

Anti-HCV Ab = black bar  HCV RNA = red bar

Persistent Infection (73%)

Spontaneous Clearance (27%)

Spontaneous clearance of reinfection in 83%

Osburn et. al. Gastroenterology 2010;138:315–324
We are able to study the natural history of HCV infection using the BBAASH cohort, a group of young injection drug users in Baltimore who are followed prospectively beginning while they are HCV negative. Despite counselling, some of these individuals continue to inject and some of them become infected with HCV. These donors are then followed longitudinally with regular blood sampling during acute infection and then during HCV clearance or chronic infection.
HCV- Can we make an effective vaccine?
HCV- considerations for creating a vaccine

- Limited culture systems make production of a live-attenuated or inactivated whole HCV vaccine challenging
HCV - considerations for creating a vaccine

- Limited culture systems make production of a live-attenuated or inactivated whole HCV vaccine challenging
- Virulence factors unknown
HCV- considerations for creating a vaccine

- Limited culture systems make production of a live-attenuated or inactivated whole HCV vaccine challenging
- Virulence factors unknown
- Correlates of protective immunity not completely known
HCV- considerations for creating a vaccine

- Limited culture systems make production of a live-attenuated or inactivated whole HCV vaccine challenging
- Virulence factors unknown
- Correlates of protective immunity not completely known
- Viral diversity
Genetic Diversity of HCV is a challenge
The issue
HCV- considerations for testing a candidate vaccine

• No animal model
HCV- considerations for testing a candidate vaccine

- No animal model
- Only predictably high incidence group without high HIV rates is people who inject drugs (PWID)
Efforts to develop a prophylactic HCV vaccine

Proteins in adjuvants, peptides, DNA, VLP, replicating & non replicating viral vectors

Proteins, VLP, DNA, Viral vectors

Macaques, Chimps

Protein, viral vectors

Low-risk Humans

Viral vectors

High-risk Humans

HCV- Can we make an effective vaccine?

- Use vectors to deliver HCV antigens in a system that induces robust innate and adaptive immune responses.
Prophylactic vaccine based on viral vectors to generate T cell immunity

• Prime: Low seroprevalence chimpanzee derived Adenovirus – ChAd3

• Boost: attenuated strain of modified vaccinia Ankara (MVA)
Prophylactic vaccine based on viral vectors to generate T cell immunity

- Vectored HCV antigen: Nonstructural proteins of HCV, not envelope (targets of neutralizing Ab)
VIP: Vaccine is Prevention

- **Design:** Double blind, randomized, placebo controlled at JHU, UCSF, UNM
VIP: Vaccine is Prevention

- **Design**: Double blind, randomized, placebo controlled at JHU, UCSF, UNM

- **Population**: 18-45 yo PWID actively injecting at high risk for but not infected with HCV at screening
VIP: Vaccine is Prevention

- **Design:** Double blind, randomized, placebo controlled at JHU, UCSF, UNM

- **Population:** 18-45 yo PWID actively injecting at high risk for but not infected with HCV at screening

- **Enrollment completed in 2016:** 545
VIP: Vaccine is Prevention

- **Design:** Double blind, randomized, placebo controlled at JHU, UCSF, UNM

- **Population:** 18-45 yo PWID actively injecting at high risk for but not infected with HCV at screening

- **Enrollment completed in 2016:** 545

- **Goal:** assessment of safety, induction of HCV specific immune responses, and efficacy in preventing chronic HCV infection
VIP Design

- Two injections administered at 0 and 8 weeks: AdCh3NS & MVA-NS
- Immune responses assessed
VIP Design

• Two injections administered at 0 and 8 weeks:
  AdCh3NS & MVA-NS
• Immune responses assessed
• HCV RNA tested monthly
VIP Results

• Vaccine induced robust T cell responses and was safe, but did not reduce progression to chronic infection.
Conclusions

- A prophylactic HCV vaccine is needed.
Conclusions

- A prophylactic HCV vaccine is needed.
  - Comprehensive strategy
Conclusions

• A prophylactic HCV vaccine is needed.
  – Comprehensive strategy
    • Prevention, harm reduction
    • Diagnosis
    • Treatment
Conclusions

• A prophylactic HCV vaccine is needed.
• Protective immunity likely exists in vivo.
Conclusions

- A prophylactic HCV vaccine is needed.
- Protective immunity likely exists *in vivo*.
- New prophylactic vaccine development efforts needed.
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Our Study
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Alfredo Nicosia
Elisa Scarselli
Questions

• Thank you for your attention!
Vaccines for Uncommon Diseases: The Issue of Cost

H. Cody Meissner, M.D.
Professor of Pediatrics
Tufts University School of Medicine

NVAC
September 17-18, 2019
Washington DC
Disclaimers/Disclosure

• I have no financial relationship with the manufacturer(s) of any commercial product(s) discussed in this presentation

• I may discuss the use of vaccines in a manner not consistent with the Package Insert, but all recommendations are in accordance with recommendations from the ACIP & AAP
Opening & Closing Questions

• Can a safe & effective vaccine ever be too expensive?
  – What does “too expensive” mean?
  – A vaccine for a limited population will have similar development costs as a routine vaccine
  – Are quality adjusted life years saved the most appropriate measure of cost?
    • Is this equitable?
    • Is this sustainable?
  – Is the responsibility of pharmaceutical industry only to stockholders or to both community & stockholders?
### 2018 Figures for United States

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gross Domestic Product (GDP)</strong></td>
<td>$20.9 trillion</td>
</tr>
<tr>
<td><strong>Health Care Spending (HCS)</strong></td>
<td>$3.7 trillion (17.7% GDP)</td>
</tr>
<tr>
<td><strong>Total $ spent/year on vaccines</strong></td>
<td>$11.4 billion (0.3% HCS)</td>
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<tr>
<td>(birth to &lt;19 yrs)</td>
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<tr>
<td><strong>Total $ spent/person on vaccines</strong></td>
<td>$2,850</td>
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<tr>
<td>(birth to &lt;19 yrs)</td>
<td></td>
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</tbody>
</table>
Purchase Costs of Recommended Vaccines, Ages 0 - <19 years, 1996-2014

Chen W, Messonnier M, Zhou F. Vaccine 2016;34(39):4706
<table>
<thead>
<tr>
<th>Vaccines For Selected Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Development</strong></td>
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<td>1. C. difficile</td>
</tr>
<tr>
<td>2. Dengue</td>
</tr>
<tr>
<td>3. HIV</td>
</tr>
<tr>
<td>4. GAS</td>
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<tr>
<td>5. Lyme</td>
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<tr>
<td>6. Norovirus</td>
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<td>7. S. aureus</td>
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<td>8. West Nile virus</td>
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<td>9. Zoonotic influenza viruses</td>
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<tr>
<td><strong>WHO Priority</strong></td>
</tr>
<tr>
<td>1. Crimean-Congo hemorrhagic fever</td>
</tr>
<tr>
<td>2. Ebola &amp; Marburg virus disease</td>
</tr>
<tr>
<td>3. Lassa fever</td>
</tr>
<tr>
<td>4. MERS-CoV, SARS</td>
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<tr>
<td>5. Nipah virus (henipavirus)</td>
</tr>
<tr>
<td>6. Rift Valley Fever</td>
</tr>
<tr>
<td>7. Zika</td>
</tr>
<tr>
<td>8. Disease X</td>
</tr>
</tbody>
</table>
Questions

The value of a vaccine should be based on reduction in illness, pain, disability, mortality & reduction in (direct & indirect) health care costs

But how should a vaccine’s value be balanced against pharmaceutical profit?

Are QALYS the best assessment of society’s willingness to for a specific intervention (vaccine)?
Reported Cases of Lyme Disease -- United States, 2017

1 dot placed randomly within county of residence for each confirmed case
Opening & Closing Questions

• Can a safe & effective vaccine ever be too expensive?
  – What does “too expensive” mean?
  – A vaccine for a limited population will have similar
development costs as a routine vaccine
  – Are quality adjusted life years saved the most
appropriate measure of cost?
    • Is this equitable?
    • Is this sustainable?
  – Is the responsibility of pharmaceutical industry
only to stockholders or to both community &
stockholders?
First International Conference on Measles Immunization, Nov 1961

Courtesy of Sam Katz, M.D.
In 1941 in the United States, 894,134 people were reported to contract measles.

In 2018, more people reached the summit of Mount Everest (807) than contracted measles in a whole year in United States (372).
Thank You
Albert Sabin, Jonas Salk & Basil O’Connor, 1961

Courtesy of March of Dimes
## Modeled Costs of 2 Programs for Polio Vaccination & Prevention of VAPP, 1994

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Total Program Cost (millions)</th>
<th>Cases of VAPP Prevented</th>
<th>Total Benefits (millions)</th>
<th>Net Incremental Cost (millions)</th>
<th>Cost per Case of VAPP Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 OPV</td>
<td>$375</td>
<td>0</td>
<td>$0</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>4 IPV</td>
<td>$416 (+$41)</td>
<td>9.5</td>
<td>$11.4</td>
<td>$28.1</td>
<td>$3.0 M ($1.7 to $11.2)</td>
</tr>
</tbody>
</table>

Miller MA, Sutter RW, Strebel PM, Hadler SC
JAMA 1996;276(12):967