NVAC NATIONAL VACCINE ADVISORY COMMITTEE

October 16, 2020, Virtual Meeting Minutes

Committee Members in Attendance

Robert H. Hopkins Jr., M.D., MACP, FAAP; Chair
Debra Blog, M.D.
Melody Anne Butler, B.S.N., RN, CIC (late arrival)
Timothy Cooke, Ph.D.
John Dunn, M.D., M.P.H. (late arrival)
Kristen R. Ehresmann, RN, M.P.H.
David Fleming, M.D.
Leonard Friedland, M.D.
Daniel F. Hoft, M.D., Ph.D.
Molly Howell, M.P.H.
Mary Anne Jackson, M.D., FAAP, FPIDS, FIDSA
Melissa Martinez, M.D., FAAFP
Cody Meissner, M.D., FAAP
Robert Schechter, M.D.
Geeta Swamy, M.D.
Robert Swanson, M.P.H.

NVAC Ex Officio Members

Troy Knighton, M.Ed., Ed.S., LPC, Department of Veterans Affairs (VA)
Linda Lambert, Ph.D., Biomedical Advanced Research and Development Authority (BARDA) (late arrival)
LTC Valerie Marshall, M.P.H. (for Marion Gruber, Ph.D.), Food and Drug Administration (FDA)
Jeffrey McCollum, D.V.M., M.P.H. Indian Health Service (IHS) (late arrival)
Mary Rubin, M.D., Division of Injury Compensation Programs, Health Resources and Services Administration (HRSA)
Geetha Srinivas, D.V.M., M.S., U.S. Department of Agriculture (USDA)

NVAC Liaison Representatives

Gina Charos, Public Health Agency of Canada (PHAC)
Hana El Sahly, M.D., Vaccine and Related Biological Products Advisory Committee (VRBPAC)
Claire Hannan, Association of Immunization Managers (AIM)
Jean-Venable "Kelly" Goode, Pharm.D., BCPS, FAPhA, FCCP, American Pharmacists Association (APhA)

Acting Designated Federal Officer

Ann Aikin, M.A., Communications Director, Office of Infectious Disease and HIV/AIDS Policy (OIDP), Department of Health and Human Services (HHS)

Proceedings

Call to Order and Rules of Engagement—Ann Aikin, M.A., Acting Designated Federal Officer, Communications Director, OIDP, HHS

Ms. Aikin called the meeting to order at 1 p.m.:

- Welcomed participants.
- Thanked NVAC members for their attendance and hard work in pulling together a draft report for discussion so soon after the September meeting.
- Thanked the OIDP staff for their support in organizing the meeting. Recognized Jordan Broderick, OIDP health communications specialist, on her last day of work and expressed appreciation for her contributions to NVAC.
- Explained that the meeting is in response to a charge from Admiral Brett Giroir, the Assistant Secretary for Health (ASH) and director of the National Vaccine Program.
- Briefly outlined the agenda and described key parts of the Federal Advisory Committee Act, its conflict-of-interest rules, and standards of ethical conduct for NVAC members.
- Noted that OIDP will post presentation files, meeting minutes, and meeting video links on the NVAC section of the HHS website.
- Concluded with the roll call.

Chair's Welcome—Robert H. Hopkins Jr., M.D., MACP, FAAP, NVAC Chair

- Welcomed participants and stated the purpose of the meeting—a discussion and vote on recommendations related to the charge given to NVAC by Admiral Giroir in September. Thanked the OADP vaccine team for bringing the meeting together in record time.
- Noted that the virtual meeting was accessible to the public via live webcast and telephone. Described technical logistics for committee discussion and public comments, noting that requests to comment would be accepted by email (nvac@hss.gov) until 2:30 p.m. The public can submit written comments to nvac@hhs.gov.
- Provided an overview of the meeting agenda, with three panels of experts discussing areas of focus on COVID-19 vaccines included in the charge from the ASH:

    1. Arguments for and against vaccinating children and potential approaches for doing so.
    2. How to harness lessons learned from the tremendous effort to promote innovation and shorten timelines for new and emerging vaccines.
    3. How to build confidence in the immunization system before, during, and after COVID-19 vaccine implementation, especially among underserved communities.

- Noted panels were to be followed by committee discussion and votes on Admiral Giroir's charge.
- Listed upcoming NVAC meeting dates: February 4-5, 2021; June 16-17, 2021; and September 15-16, 2021.
- Concluded by introducing the first panel.

Guidance on and Approach for COVID-19 Vaccination in Children

Dr. Barry Bloom, Ph.D., T.H. Chan School of Public Health, Harvard University

Dr. Bloom introduced himself as an immunologist and member of the Massachusetts Governor's Commission on COVID-19 Vaccines.

Dr. Bloom said he supported decisions by the government and companies not to include children in initial vaccine trials, citing public skepticism about vaccines, fear of new kinds of vaccines, distrust of government, and a low prevalence of serious disease in children. None of the vaccines has completed large Phase III trials, so little is known about their safety, efficacy, or duration of immunization.

The most appropriate time to begin studies of vaccinations of children will be after trials show the vaccines to be safe in adults and vulnerable populations and an emergency use authorization (EUA) is issued, said Dr. Bloom. Meanwhile, federal and state governments should plan how to disseminate vaccines to children.

Dr. Bloom's suggestions for a vaccine trial design included:

- A stepped non-wedge design in nationally representative districts with strong, consistently transparent reporting and strong registry systems to collect safety data as rapidly as possible.
- Age de-escalation that establishes safety with older adolescents before moving down to younger groups.
- A dose de-escalation required for the younger children, which could take time. Pfizer expanded its trial to age 12, but it is not known how many children are in the trial and how soon significant results will be available.
- A design that primarily looks for adverse effects in children at different ages and collects sufficiently compelling safety data to enhance parental confidence in having children vaccinated.

Dr. Bloom acknowledged that the medical and scientific communities are aware of and carefully considering potential concerns with such studies, including multi-system inflammatory syndrome (MIS-C) triggered by vaccination and later infection. He saw no urgency to push vaccines in children while the vaccines are in limited supply and needed for protecting the most at-risk populations.

Any vaccination program will need an effective public information campaign, concluded Dr. Bloom. The campaign must emphasize safety data and the importance of protecting not only children, but the elderly and medically at-risk, which the Centers for Disease Control and Prevention (CDC) estimates make up about 47 percent of the U.S. population. The campaign must engage parents and community leaders, particularly in diverse communities, and planning must begin now.

Evan Anderson, M.D., Emory University School of Medicine

Dr. Anderson is a professor of both pediatrics and medicine at Emory University. After presenting disclosures of industry-funded grant activity and professional committee service, Dr. Anderson briefly reviewed the status of the six vaccines currently advancing to licensure under Operation Warp Speed. He said millions of doses may be available in early 2021 if the vaccines are shown to be safe and efficacious in Phase III studies.

The accelerated vaccine process is focused on adults, said Dr. Anderson, in part because of the initial impression that not many children get sick, become hospitalized, or die due to COVID-19. Data from COVID-NET indicates, however, that hospitalizations are now in the range of 19 per 100,000 for children ages 0-4 and 11 per 100,000 for ages 5-17, with many of these children from Black or Hispanic populations. In addition, thousands of children have been hospitalized with MIS-C). Little is known about the long-term consequences of this disease.

Dr. Anderson said there has been a lack of appreciation for the fact that COVID-19 is potentially life-threatening for children. The death rate is now greater than that observed for varicella, rubella, hepatitis A, and rotavirus in the pre-vaccine era. The COVID-19 death rate for children (119 for those 18 and under) is now in the range of annual influenza deaths (110-180). Dr. Anderson also noted the substantial nonmedical impacts of COVID-19 on children, including educational, economic, emotional, and psychological.

Although early data gave the impression that children do not transmit the virus, current knowledge shows that children are potential transmitters and sometimes do transmit, according to Dr. Anderson. He cited several cases where transmission occurred among children and from children to adults. The viral loads of children can be substantial, he said, citing a study in which the highest load was among children under 5.

Children are potential transmitters to their parents (including pregnant mothers for whom there are no U.S. vaccine trials currently planned), grandparents, other family members, school teachers and staff, administrators, and many others, continued Dr. Anderson. This makes community protection critical for preventing disease. Vaccinating children has had a substantial impact on adult burden of disease for hepatitis A and pneumococcal disease, among others.

Dr. Anderson told the committee that a COVID-19 vaccine for children is absolutely needed. Pediatric studies are needed to determine how an appropriate dose is affected by height, weight, body surface area, muscle mass, and fat distribution. Studies are also needed to understand the reactogenicity, safety, and immunogenicity in children to establish the correct dose. Dr. Anderson noted that only one Phase III study in the U.S. has expanded enrollment down to age 12. No manufacturer has fully committed to starting a U.S. pediatric study, although some have plans in Europe.

In the past, the Phase II and Phase III pediatric vaccine studies occurred without previous large studies of adult safety and efficacy, Dr. Anderson noted. Vaccines for rotavirus, mumps, polio, PCV7/13, hepatitis A, and rubella were licensed well before substantial adult data was available.

Dr. Anderson said he believes initial COVID-19 vaccine studies in children should occur in parallel with the adult Phase III studies. Substantial safety data now exists, he said, with up to 19,000 adults having received one dose of vaccine and between 11,000 and 15,000 adults having received at least two doses. Researchers already have far more data than typically would be needed to begin pediatric studies.

He acknowledged past vaccine safety issues, such as enhanced respiratory disease associated with the respiratory syncytial virus (RSV). No data to date supports occurrence of these issues in any adult studies. Data does show high neutralizing antibody titers and a Th1-biased response, the type of responses researchers like to see. Prevention of COVID-19 infection would also likely prevent MIS-C.

Dr. Anderson reiterated that initial vaccine studies should begin for children now and be

conducted carefully to evaluate safety and correct dosages. He concluded by acknowledging colleagues who have shaped the discussion about pediatric vaccines.

James Campbell, M.D., M.S., University of Maryland School of Medicine

Dr. Campbell is with the University of Maryland Center for Vaccine Development and Global Health. After presenting disclosures of industry-funded grant activity and professional committee service, Dr. Campbell presented his key points:

- The pediatric burden of disease is large and goes beyond infectious disease to include not being physically in school, not being able to participate in social activities, and other epiphenomena.

- COVID-19 imposes a disproportionate burden on children in minority communities. A vaccine could help level the playing field by reducing the burden across minorities and non-minorities.

- It is unethical to wait for natural "herd" effects, which would have to reach 60-80 percent to be significant. Currently, about 10 percent of America's children are infected. That means six to eight times as many children would need to be infected, which could result in six to eight times the hospitalizations and deaths.

- A COVID-19 vaccine would also bring major indirect benefits to the children and society, such as safely opening schools.

- A pediatric vaccine could prevent possible sequelae, both acute and long-term.

- The most successful immunization programs in the United States have been universal pediatric recommendations. Many U.S. programs started off by targeting high-risk populations, which bring individual benefit, but less public health benefit than universal vaccination.

- Children should benefit from the large taxpayer investment in jumpstarting the vaccine effort in the United States.

- There may be a conundrum for families and providers if multiple safe and effective vaccines are authorized for adults but there is no data available about the vaccines' effects in children. The best scenario would be to have data available for children in order to inform decisions about whether or not to vaccinate those under 18.

- Safety concerns about introducing vaccines to children—including enhanced respiratory disease or vaccine-induced MIS-C—are best addressed in careful, well-thought-out clinical trials.

- A Catch-22 has emerged where sponsors, funders, and manufacturers hesitate on pediatric vaccine testing because recommending bodies have not considered such tests due to lack of data. No movement on either side creates a Catch-22.

Dr. Campbell presented public documents that address issues surrounding pediatric COVID-19 vaccination:

- A letter from American Academy of Pediatrics President Sally Goza to HHS Secretary Alex Azar and FDA Commissioner Stephen Hahn encouraging them to ensure that COVID-19 vaccine trials are transparent, children are included, and the trials are conducted with rigorous oversight and review.

- A report from the Bioethics Consultation Service at NIH that considered whether or not it is ethically justifiable to conduct pediatric SARS-CoV-2 vaccine trials before adult trials are complete. The report concluded that such trials are ethically preferable to avoid substantially delaying access for children to the benefits of a safe and effective vaccine. The report urged stringent study design, age de-escalation, and geographic and demographic diversity.

- A National Academies report, *Framework for Equitable Allocation of COVID-19 Vaccine*. that concludes if a vaccine is found to be safe and effective in adults, children should not be vaccinated unless data supports appropriate doses and frequency and studies side effects.

Dr. Campbell noted that for recently-licensed pediatric vaccines, sample sizes ranged from as low as 3,000 up to about 15,000. Rare events such as enhanced respiratory disease or MIS-C are unlikely to be discovered in trials within this size range. Such events are more likely to be discovered in the post licensure/post-authorization period. It would take a vaccine trial of immense size to rule out a problem that occurs in 1 in a million or 1 in 100,000 children.

Dr. Campbell offered the following conclusions:

- Carefully designed age de-escalation, immuno-bridging studies of COVID-19 vaccines for children should begin now.
- The number of children enrolled in these studies should allow for bridging to adult studies to capture uncommon but not rare adverse events.
- Transparency will foster trust. The more that information is open to all interested parties, the more it will lead to acceptance of a vaccine.
- Systems for post licensure/post authorization large scale safety surveillance are already available. It will be important to deploy them with SARS-CoV-2 vaccines.
- The paradigm of moving into carefully designed pediatric clinical trials without finalizing adult Phase III trials has been implemented successfully over many decades.

Dr. Campbell concluded by acknowledging the contributions of his colleagues.

Discussion

Dr. Jackson commented that since COVID-19 has impacted ethnic and racial minorities to a greater extent, it is critical to ensure that trials mirror the populations at risk and the U.S. population as a whole for both adult and pediatric trials. **Dr. Campbell** agreed that vaccines must be tested across all demographics within the U.S. childhood population, an important issue when designing trials and recruiting participants. Vaccines also must be deployed across all demographics.

Dr. Meissner offered a different viewpoint:

- He acknowledged that COVID-19 causes illness and death in children—about 120 deaths due to COVID-19. But about 185 or 187 children died of influenza this year during a shorter season than COVID-19.
- The analogy of coronavirus and varicella vaccines is not accurate. In the pre-vaccine era, there were 11,000 or 12,000 hospitalizations among children due to varicella. It was a very different setting when that vaccine was introduced.
- It is true that RotaShield vaccine was introduced for rotavirus after a small trial. But after an association with intussusception, subsequent rotavirus vaccine trials enrolled 60,000-70,00 children.
- The role of children in transmitting the coronavirus is not known. But COVID-19 is acquired between adults—not so much between children and transmission from children to adults. It is not like influenza.
- Pediatric vaccines pneumococcus cannot be compared to COVID-19. They are very different diseases. In addition, children are known to infect adults with pneumococcus.
- If a COVID-19 vaccine is introduced and causes an adverse event such as MIS-C, it will have a devastating impact on the whole immunization program.

Dr. Meissner concluded that he is not comfortable moving ahead with a COVID-19 vaccine in children.

Dr. Campbell said pediatric vaccine trials would probably not be large enough to show that MIS-C is less common among vaccinees than in the natural world. If that is a requirement, it would preclude a study of a safe and effective vaccine that could prevent deaths, hospitalizations, and infections and allow children to visit grandparents, play, and go to school.

Dr. Meissner said schools should be open now without a pediatric vaccine. He suggested collecting data on MIS-C in adult vaccinees first. He said that the burden of disease in children is so low that there is little tolerance for adverse events.

Dr. Campbell replied that he is worried about the harm of omission done by not studying COVID-19 vaccines in children. He said it could be a long time before sufficient data is available on MIS-C in the adult population. If the vaccine works, children will have been denied the benefits.

Dr. Meissner said that in a year's time after authorization, presumably millions of adults will have gotten the vaccine and the risk can be addressed. He recommended waiting for herd immunity, noting that if COVID-19 goes away in adults, it may also go away in children.

Dr. Hopkins read questions and comments from the chat line:

Dr. Fleming asked whether vaccination should be considered first for high-risk children, such as those with severe asthma or diabetes, with evidence gathered on safety. **Dr. Campbell** replied that such children would first need to be enrolled in a clinical trial to collect data before the vaccine is deployed to even a high-risk population.

Dr. Friedland commented that 185 deaths are 185 too many. Children have a burden of disease and some role in the transmission cycle.

Dr. Bloom said he does not challenge the importance of vaccination of children, but asked what kind of safety data is needed to give parents the confidence to allow their children to be

vaccinated? Right now, he said, there is not a lot of data to go on and three major trials have been paused for safety concerns. He maintained that if an EAU were granted unanimously by the FDA committee with the support of the NIH and CDC behind it, that would persuade people.

Dr. Anderson countered that there is a fair amount of CDC data for a number of vaccines in the Phase III trial. Some leading candidates have been given to more than 10,000 people, with a fair number of those having received a second dose. He noted that enrollment in a pediatric trial will take time.

Dr. Hopkins thanked the panel for presentations on both sides of a challenging issue.

Drs. Campbell and Anderson thanked NVAC members for their careful consideration, noting that everyone is thinking about what is best for families and children.

Dr. Hopkins called for a 10-minute break.

Break

Lessons Learned: COVID-19 Vaccine Development

Dr. Hopkins introduced the panel topic: What lessons can be learned from COVID-19 vaccine development more broadly, to promote innovation and shorten timelines to increase availability of new vaccines to the American public?

David Stephens, M.D., Emory University
Kathleen Neuzil, M.D., University of Maryland School of Medicine

After providing his disclosures, Dr. Stephens a gave brief background on the Vaccine Treatment and Evaluation Units. VTEUs were established by the National Institute for Allergy and Infectious Diseases (NIAID) in 1962 to conduct clinical trials of vaccines and treatments for infectious diseases, notably H1N1, influenza, avian influenza, Zika, and now COVID-19. The Infectious Disease Clinical Research Consortium (IDCRC)/VTEU Network formed in December 2019 and held its first meeting in January 2020.

Dr. Stephens presented the timeline for the mRNA-1273 COVID-19 vaccine trial, which involves IDCRC/VTEU and Moderna. The lessons learned from COVID-19 vaccine development—especially Phase I studies—include:

The importance of wide-ranging fundamental science in terms of the platforms necessary for vaccine development. These fundamentals include the critical background of viral pathogenesis (SARS-1, MERS, RSV); the importance of basic immunology and increasing understanding of basic immune mechanisms to antigens; a better understanding of what is really meant by vaccine heterogenicity; what is meant by vaccine-enhanced disease and how to define it; antigen delivery; and the correlates of protection.

The role of preclinical science, particularly data from non-human primate and other animal models.

Experience in humans with new vaccine platforms and adjuvants. Academic/public/private partnerships are enhancing this process.

- New platforms and adjuvants being applied to COVID-19 are helping the field move forward more quickly. These platforms have been based upon other emerging infections such as Ebola, Zika, and SARS. The spike stabilization of programs that were put in place for a number of these vaccines are making a significant difference in terms of immunogenicity.
- The vectors being used have also been used in previous human platforms (Ad26, ChAdOx).
- The experience of platforms being adapted for the spike proteins and adjuvants used in these vaccines are helping the field move forward quickly.

Human, financial and clinical trials infrastructure, including VTEUs as well as important and meaningful guidance documents from the FDA.

Public-private partnerships for rapid design and launch of Phase I clinical trials. This includes the issue of what is a neutralization assay in relationship to convalescent sera.

Dr. Stephens noted three published papers on vaccine development that resulted from the Moderna study and its academic/public/private partnerships—a preliminary report and two more papers looking at non-human primate data and the immunogenicity of older adults.

He discussed the mRNA-1273 (Moderna study) timeline under Operation Warp Speed, The VTEU Network has 10 major sites, 18 sub-sites, and a number of international sites. The COVID Prevention Network encompasses several hundred sites around the globe. Almost 30,000 individuals have been enrolled. Dr. Stephens credited the COVID Prevention Network with emphasizing diversity among enrollees. The Pfizer study has proceeded at similar speed, with 44,000 enrolled. Four other Phase III trials are underway.

Lessons learned from public-private partnerships for rapid design and launch of Phase III clinical trials include:

- Work in parallel to shorten the development timeline has been successful through the Warp Speed structure.
- The NIH Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) has been an important interface between the manufacturing community, government, and academia.
- There are issues with trial designs and endpoints.
- The COVID Prevention Network results on the validation of monoclonal antibodies and how that may relate to potential immune correlates of protection.

- **Safety and Immunogenicity**

    - Harmonization has been good as a COVID Prevention Network and Operation Warp Speed strategy.
    - A single data safety monitoring board has been important to look across trials.
    - The standardization of immune assays has been important in defining what is a neutralizing anitbody and what those titers really mean.
    - Adverse affects - Two trials have been put on hold, but this is a positive thing in terms of evaluating what could be serious adverse events.

- **Endpoints** – There has been much discussion about medically complicated illness vs. symptomatic illness vs. method of transmission. This includes when analyses are done and what the parameters are for looking at vaccine trial interim data.
- **Recruitment** – Diversity of population is important. So is looking at vaccine trials as they relate to the epidemiology of the outbreak.
- **Manufacturing** – There are manufacturing challenges, but those are being addressed.
- **Regulatory** – There is a debate about an EUA vs. a biologics license application and how that night influence other ongoing placebo-controlled trials.
- **Distribution** – The National Academy of Medicine and the Advisory Committee on Immunization Practices have recommended strategies for getting doses and populations in line for initial vaccine distribution.
- **Communications –** There is a right way and a wrong way to communicate about adverse events. Not enough attention has been paid to communication strategies for vaccines. Challenges need to be disucussed.
- **Global vaccines and vaccine nationalism** – Along with the focus on U.S. strategy, there must also be a continued focus on the global issues of COVID-19 and vaccines for the global population.

Dr. Neuzil commented that in addition to the science, vaccine development has been about partnership and the importance of established NIH-funded networks that could readily respond to the current critical need.

Richard Hatchett, M.D., Coalition for Epidemic Preparedness Innovations

Dr. Hatchett presented five factors that could speed vaccine development in the future. He added that managing public expectations is also an important topic that he could not address due to time constraints.

1. **Public sector investment.**

Public sector investment is critical to the speed and scale of vaccine development. Starting programs fast means that the programs get to clinical trials sooner. The first investments were made just 12 days after the viral sequences were released. Now eight of those nine candidates are in clinical trials, with three having reached Phase III. This represents about 30 percent of the global total. Public sector investment also has been critical to enabling manufacturing at risk. Companies would not have accumulated tens or even hundreds of millions of doses while the clinical trials are underway without such investment.

2. **Prepared platforms.**

Prepared platform technologies give a head start. Both the Moderna and the AstraZeneca Oxford vaccines are examples of prepared candidates. Both organizations spent years developing their respective platforms with public investment from the U.S. (Moderna) and the U.K. (Oxford) governments. Both were able to pivot quickly to adapt their platforms to respond to COVID-19. These experiences can inform the post-COVID R&D agenda to systematically reduce risk for future epidemics and pandemics.

3. **Managing risk across a portfolio of candidates.**

Risk in vaccine development comes in many dimensions. Producing hundreds of millions or billions of doses requires a large, diversified portfolio using multiple technologies to mitigate against the predictable kinds of failure—technical, safety, manufacturing, and quality. These risks are normal and can be hedged by investing in a broad array of approaches

4. **The potential to improve global financing and manufacturing arrangements.**

There has been an international scramble to secure both the necessary financing and manufacturing capacity to produce the vaccines, Dr. Hatchett noted. Governments were fairly quick to make financial commitments, but slow to provide cash. There also has been a scramble for contract manufacturing organization (CMO) slots. The current pandemic was not unanticipated. More can be done to create financial instruments and global manufacturing networks willing to work together when the next crisis emerges.

5. **The advantages of a collective response.**

Pandemics are transnational global threats and cannot be eliminated one country at a time, said Dr. Hatchett. The perpetuation of the pandemic anywhere means its perpetuation everywhere. COVAX now includes 182 countries representing more than 90 percent of the world's population. COVAX is an effort to pool risk and resources in vaccine development and distribution. If successful, this effort has the potential to end the pandemic's acute phase around the world by the end of 2021.Without such effort, the pandemic's human and economic devastation will persist into 2022 and beyond. Dr. Hatchett said that COVAX would welcome U.S. participation. COVAX represents a model for responding to future global threats.

Karin Bok, Ph.D., NIH

Dr. Bok is a senior advisor at NIAID's Vaccine Research Center. She presented lessons learned from the NIH perspective. She noted that the Vaccine Research Center has worked on responding to pandemics and epidemics since almost its founding in 2000. She noted that the period from sequence selection to the first injection of COVID-19 vaccine in a human was only 65 days.

Prototype Pathogen Preparedness Plan – By the time SARS emerged, researchers had already been studying coronaviruses and which protein would be the best for a vaccine. Researchers knew in a matter of days which protein would be used and how to modify the sequence of that protein to have a better vaccine. This has been so important that five of the six COVID-19 vaccines supported by Operation Warp Speed use this protein design.

Collaboration within and between governments, industry, and academia – Dr. Bok highlighted key collaborators with NIAID to move in 65 days from vaccine design to use in humans. These collaborators include the NIH Division of Microbiology and Infectious Diseases, Moderna, the Coalition for Epidemic Preparedness, the Universities of Texas and North Carolina, the Department of Defense, and the Biomedical Advanced Research and Development Authority.

Advance development of strategically accelerated platforms – Dr. Bok emphasized the need to keep investing in platforms that have been extensively tested in the past. This reduces cost and allows production of hundreds of millions of doses. In the development of a COVID-19 vaccine, researchers have had access to nucleic acid platforms that by design are faster to produce and

easier to release and test. Those platforms are already in Phase III study. Also available are non-replication viral vectors and protein subunits.

Coordination of clinical trial sites – NIAID combined all its clinical sites to test vaccines. The agency was able to stagger the clinical trials and start them one after the other. This allowed NIAID to harmonize the efficacy trials to try to ensure that the endpoints of every Phase III protocol are comparable. A common safety and monitoring board tracks the safety data from all the different candidates, which advances the goal of finding a correlate of protection. This will be particularly important for future vaccines that may not be able to be tested in a normal Phase III trial because the virus is no longer circulating.

Dr. Bok concluded by thanking the meeting audience, the frontline workers, and the vaccine trial participants.

Florian Krammer, Ph.D., Icahn School of Medicine at Mount Sinai

Dr. Krammer, a professor in vaccinology at Mount Sinai, acknowledged that vaccine development often takes place at a glacial pace—up to 15 years. COVID-19 differs in two ways: The time from designing vaccines to getting them licensed hopefully will be crunched down to a range of months to very few years, and instead of banking on one platform, there are an unprecedented 11 platforms involved in Phase III.

Dr. Krammer discussed what can be learned from current vaccine development that can be applies "normal" vaccines—those not created in response to a pandemic:

Evaluation of a large number of vaccine platforms that are tested in clinical trials. A lot of these platforms use the same antigen—the stabilized form of the spike protein. Researchers have and will continue to learn a lot about these different platforms, all of which have different characteristics. Testing them in humans for the same target antigen/pathogen will likely be worth the high cost because it will help select the best candidates. In addition, some platforms might be better suited for some parts of the population than others.

Economic de-risking—giving money to companies so they do not have to worry about financing—can significantly speed up vaccine development. The sooner researchers know whether a vaccine does or does not work, the better for the population. Public-private partnerships are key to this process.

What can be learned for pandemic vaccines?

Ideally, the goal should be to have a vaccine ready for rollout three months after the virus emerges, Dr. Krammer suggested. He offered the following steps to do so:

- Select several viruses from the most dangerous families, e.g., paramyxoviruses, coronaviruses, and orthomyxoviruses.
- Advance them into Phase I and Phase II vaccine studies. This would allow study subjects to be followed for safety and immune response for years. It may also address the public's fears about unknown long-term effects.
- Establish correlates of protection for related viruses that circulate in humans. If researchers knew that neutralizing antibodies are a correlate of protection for human coronaviruses, there would be a lot more trust in the vaccine readouts.

- When a new virus hits, perform a strain change and start Phase III immediately. Plenty of safety and immunogenicity data would be available for a similar virus. Based on the correlate of protection, the vaccine may receive an EUA in a few months.

This process is applied now to influenza viruses. Vaccines get stockpiled. If one of the viruses hits, researchers can perform a strain change and roll out the vaccines knowing the correlate of protection. If the coronavirus had been the flu, millions of people would already be vaccinated.

Discussion

Noting the cycle of boom and bust funding for vaccine development as epidemics emerge and disappear, **Dr. Cook** asked whether the funding outlook would change again during inter-pandemic periods. **Dr. Hatchett** replied that he is seeing countries as diverse as India, Indonesia, Japan, Singapore, and Switzerland planning to invest in domestic manufacturing capacity to address risks of future epidemic and pandemic diseases. Coupled with a global research agenda built on the prototype pathogen approach, that investment creates an opportunity for global cooperation on effective risk reduction.

Dr. Bok expressed hope that those in the United States now understand that investing in R&D is a lot cheaper and less dramatic than responding to a pandemic in the way it has been done in 2020. **Dr. Stephens** noted his involvement in biodefense initiatives after 9/11. He said there is a clear need to maintain a presence not only for viruses, but for other infectious agents that create a need for vaccines.

Dr. Hopkins read a question from the chat line from **Mr. Swanson** asking panelists what they see as the biggest risks in compressing the time needed to license a vaccine. **Dr. Bok** replied that Operation Warp Speed is not taking any additional risks in compressing the timeline. She said the same rules and expectations apply from FDA as are being met with any other vaccine in any other timeline. **Dr. Hatchett** added that substantial financial risks are being taken to avoid risks with clinical efficacy and safety.

Dr. Hopkins read a chat question from **Dr. Schechter** asking what mechanisms best support basic research in microbiology, immunology and vaccinology of likely agents of future pandemics.

Dr. Krammer answered that there are good surveillance systems in place for avian and mammalian influenza viruses and such systems are needed for coronaviruses and many other types of viruses. Basic pathogenicity studies are also needed. Most surveillance is done by sequencing. This needs to be supported so researchers can predict what is going to be dangerous. Non-human primate studies are important to find out what pathogenicity mechanism are there. He said even preclinical studies with experimental vaccines would be helpful to look at risks. This type of research is done extensively for influenza, but not other viruses.

Dr. Stephens emphasized that studies in basic human immunology could reveal a lot about the potential adverse events of vaccines.

Dr. Hopkins expressed hope that when the next challenge arises, the United States will be better prepared to respond more rapidly in vaccine development. He concluded by calling for a 15-minute break.

Break

Building Confidence in the Immunization System Before, During, and After COVID-19 Vaccine Implementation

Dr. Hopkins introduced the question to be discussed by the panel: What should HHS do before, during, and after the COVID-19 vaccination campaign to improve the confidence in these vaccines and the nation's immunization system, especially within underserved communities, including racial and ethnic minorities?

Jason Schwartz, Ph.D., Yale School of Public Health

Dr. Schwartz said that broad public confidence is a prerequisite for any vaccination program that is capable of changing the trajectory of the current public health crisis. Communication and educational efforts must be rooted in evidence, thoughtfully developed, and collaboratively disseminated by federal, state, and local health officials and partner organizations.

Relying on nonpartisan government scientists at FDA and CDC and transparent science-based processes provide the best chance for promoting public confidence in COVID-19 vaccines, according to Dr. Schwartz. Strategies to promote public confidence should be integrated into all stages of policy development and implementation.

Dr. Schwartz highlighted the Medicaid program as essential to promoting public confidence in a COVID-19 vaccination program. Right now, the word Medicaid appears only once in the 57-page CDC COVID-19 vaccination program interim playbook. Dr. Schwartz pointed out, however, that Medicaid is how the healthcare system is accessed by a significant portion of the high-risk adult population, including racial and ethnic minorities and senior citizens.

There is concern about these groups' willingness to receive a vaccine. Issues include the challenges of adult vaccination, persistent disparities in vaccination among Medicaid beneficiaries, and the expectation that vaccines will be administered in a variety of locations other than traditional Medicaid providers. But Medicaid providers are often rooted in their communities and can work with federal and state public health agencies and immunization programs to deliver evidence-based messages that build confidence in vaccines, said Dr. Schwartz.

HHS should ensure that state Medicaid programs have the additional financial resources and the emergency authorities needed to support COVID-19 vaccination, he continued, including adequate reimbursement to Medicaid providers. Without this additional investment, greater racial and ethnic disparities are more likely in COVID-19 vaccination coverage. Dr. Schwartz concluded.

Efthimios Parasidis, J.D., M.Bioethics, Ohio State University

Mr. Parasidis discussed the legal and ethical tools that can help build confidence in the immunization system.

Although vaccine hesitancy based on fear of injury is as old as vaccination, in recent years it has been fueled by internet misinformation and growing mistrust towards government and the biopharmaceutical industry, Mr. Parasidis told committee members. Vaccine hesitancy has become even more mainstream during the coronavirus pandemic. Lawmakers, candidates, and

scientists have raised alarm bells. A majority of Americans believe that politics drive FDA decision making. and several states indicate they will set up their own review boards to reassess FDA decisions.

The public's fears are not unreasonable, he continued. The White House exerts political pressure on FDA, HHS, and the CDC, agency leaders have buckled to the pressure and altering science-based decisions.

Public mistrust is likely to have a long-term impact beyond the pandemic, predicted Mr. Parasidis. Government mistrust is particularly high among the poor and people of color. It will take meaningful efforts beyond traditional public health outreach to instill trust. He said it will take concrete, legally enforceable measures such as:

- Create a robust social safety net in the form of a Coronavirus Healthcare & Compensation Fund. The fund would provide free access to healthcare during the pandemic for people who contract coronavirus or suffer a vaccine injury. This may make people more comfortable about accepting a vaccine. The compensation fund should be specifically for COVID-19, with a lenient standard of proof of injury.

- Recalibrate liability shields. Lawsuits should be available if a manufacturer is negligent in the development, production, or distribution of a vaccine. With more than 150 vaccines in development, competition is fierce to be the first to market, which may incentivize companies to cut corners. Manufacturers would be on the hook only if they engage in unreasonable practices.

- Given that vaccine hesitancy is likely to continue beyond COVID-19, expand access to healthcare and expand the 1980's-era Childhood Vaccine Injury Compensation Program to provide a stronger safety net for those who suffer vaccine injuries.

Dr. Parasidis also discussed principles of public health ethics that could encourage vaccine uptake:

- Transparency by public officials in explaining the scientific knowns and unknowns, especially concerning the endpoints used during clinical trials. For example, to what extent does the vaccine reduce the severity and transmission of COVID-19 and how long does immunity last? This may require more exacting clinical trial endpoints prior to marketing a vaccine and robust post-market surveillance.

- Equitable distribution of benefits and burdens. COVID has disproportionally impacted poorer people of color, which may call for early access to a vaccine, but early access is likely to be riskier than later access. The first group of vaccinated individuals may be the first to reveal adverse effects. Addressing disparities will require a multifaceted approach.

Linda Fu, M.D., M.S., George Washington University School of Medicine & Health Sciences

Dr. Fu introduced herself as a pediatrician, professor of pediatrics, and researcher on vaccine acceptance and health disparities. She focused her remarks on the three most important factors in encouraging public confidence about a coronavirus vaccine: communication, vaccine distribution that meets recipients' needs, and equity in all communication and implementation plans.

Based on prior vaccine campaigns, public enthusiasm for the coronavirus vaccine should be high right now because the disease is prevalent, said Dr. Fu. Instead, coronavirus vaccination intent has dropped from 72 percent in May 2020 to 51 percent in September 2020. Although 1 in 920 Black Americans has died of coronavirus, fewer than one-third intend to be vaccinated.

Dr. Fu told NVAC that the key components of an effective health communication strategy are:

Transparency, especially given the unprecedented speed of coronavirus vaccine development. Anxiety over side effects is high among those who do and do not intend to be vaccinated. Peer-reviewed trial data must be published so that independent reviewers can endorse the vaccine and share their support on social media. That creates a diversity of voices promoting the vaccine, not just the federal government. It is also important to manage expectations by clearly explaining the public benefit of herd immunity in decreasing the circulating amount of coronavirus with a vaccine that has 50-60 percent effectiveness.

Individual education. The public almost universally trusts doctors and hospitals to handle the coronavirus outbreak, but so far there has not been enough effort to make sure that medical professionals are able to make a strong recommendation for the vaccine once it comes out. An organized method is needed to train providers on the vaccine's safety and efficacy and how to make a strong recommendation to patients.

Social norms. Someone who receives frequent social cues to vaccinate and sees others like them accept vaccines develops a strong favorable attitude. The individual accepts the coronavirus vaccine because it is consistent with existing beliefs. In order to establish pro-vaccine social norms among racial and ethnic groups that have historically been marginalized, the medical establishment must engage cultural leaders and organizations as equal partners in vaccination campaigns. Extras funds will be needed to tailor communication and distribution of the vaccine among historically disenfranchised and underserved populations. They need help not only with vaccination, but with other issues causing them economic and social hardships during the pandemic. If vaccination mandates are put in place, they must come after a robust educational campaign or they will backfire. Mandates should not impose an undue financial or effort burden on any particular subpopulation.

Glen Nowak, Ph.D., Grady College of Journalism and Mass Communication, University of Georgia

Dr. Nowak is the director of the Grady Center for Health and Risk Communications. He recommended the following actions to improve confidence in the U.S. vaccination system:

- Develop a unified, proactive, highly visible communication structure about COVID-19 vaccine development, safety processes, approvals, and recommendation criteria.
- Create realistic expectations about vaccine safety, effectiveness, and availability among the general pubic as well as healthcare providers, policymakers, and the media
- Conduct proactive, extensive, and ongoing community engagement, particularly within racial and ethnic minorities and underserved communities.
- Craft messages based on how people make preventative health decisions and what their health priorities are. Identify the social, behavioral, and cultural factors that either foster acceptance or impede acceptance of vaccination recommendations.
- Find the influential, trusted health information sources and educate these healthcare

providers about the vaccine. This includes educating them about the best responses to the public's questions.

Dr. Nowak urged committee members to expect a more complex, challenging, and dynamic communications environment than with previous vaccine campaigns. This is due to the uncertainties regarding COVID-19 vaccines, including safety, effectiveness, duration of protection, availability, and the likelihood of multiple, non-interchangeable vaccines.

Discussion

Dr. Douglas asked panelists to reflect on the value of expensive mass market campaigns such as those launched for other biologic products, perhaps featuring celebrities. **Dr. Nowak** acknowledged the need for visibility and credible spokespeople, but added that not one message or influential person speaks to all audiences. Money may be better spent on targeted, community-based efforts. **Dr. Fu** commented that social media has not been harnessed sufficiently. She said it is difficult to underestimate the importance of local people with wide social influence being able to normalize vaccine acceptance. **Mr. Parasidis** encouraged the committee to think more about the message and less about the messenger. He said people are sophisticated enough to digest scientific information if it is presented in a clear way.

Public Comment

Dr. Hopkins said NVAC received two written public comments prior to the start of the meeting. Bayli Larson from the American Society of Health-System Pharmacists was scheduled to give oral public comment but could not be reached due to technical difficulties. NVAC members began their charge discussion while waiting for Dr. Larson's testimony.

Charge Discussion and Potential Vote

Dr. Hopkins read the ASH's charge questions:

To Support Communications to Enhance Informed Vaccine Decision Making:
What should HHS do before, during, and after the COVID-19 vaccination campaign to improve the confidence in these vaccines and our nation's immunization system, especially within underserved communities, including racial and ethnic minorities?

To Enhance Vaccination of Diverse Populations:
The FDA standards for approval and licensure of vaccines for COVID-19 address safety and effectiveness and encourage inclusion of minorities, the elderly, pregnant women, and people with medical comorbidities in clinical trials. In particular, for the COVID 19 vaccine, I am interested in the approach the nation should take in regard to vaccination of children, given that there will be relatively little data on children from some of the early clinical trials. As context, the case fatality rate for children under age 18 is .02%. What is the appropriate approach and timing of generating the needed data and proceeding to potential childhood vaccination as we move forward?

To Develop New and Improved Vaccines:
What lessons can we learn from COVID-19 vaccine development more broadly to promote innovation and shorten timelines to increase availability of new vaccines to the American public?

Dr. Cooke observed that the third charge question can be interpreted different ways. "Availability" could mean that there is an ample supply of vaccine at administration sites or that the vaccines actually get into the target population. He also wondered whether the term "new vaccines" applies to vaccines for pandemic preparedness or infectious disease vaccines in general. **Dr. Hopkins** commented that beyond the urgency of addressing COVID-19, a lot of the issues—investment, collaboration, platforms—are similar. **Dr. Friedland** pointed out that language in NVAC's draft recommendations go back and forth between COVID-19 and a broader focus. He and Dr, Cooke agreed the recommendations should be edited to clarity the focus.

Dr. Cooke also pointed to the wording on the availability of new vaccines to "the American public." That wording limits the scope of NVAC's answer, he said, asserting that without global vaccine distribution, the pandemic will not go away. Dr. Cooke added that NVAC's 2020 national plan promotes global immunization. **Dr. Hopkins** agreed that responding to a pandemic must be done with a worldwide view.

Dr. Meissner said he is uncomfortable putting minorities, the elderly, pregnant women, people with comorbidities, and children in the same group under Question 2. Pregnant women need to be included in clinical trials, but it is unclear whether they have more severe disease and whether the virus is transmitted from mother to baby. He suggested separate categories for pregnant women and perhaps people with medical comorbidities. He also expressed concern about including children until solid data is available about what happens in adults.

Dr. Meissner said he is comfortable with NVAC Recommendation 2.1, which supports vaccine evaluation in children after data is available on safety and efficacy in other groups and post marketing surveillance is in effect. Dr. Meissner also supported Recommendation 2.3 warning against an EUA for COVID-19 vaccines in children.

Dr. Hoft agreed with Recommendations 2.1, 2.2, and 2.3 that more information is needed about the role of children in transmission, long-term effects, and connection. He asked NVAC members to consider being more specific about timing, such as delayed bridging down to initial trials in pediatric populations until a vaccine has an EUA for delivery in adults. **Dr. Fleming** suggested wording to recommend a cautious, deliberative development of a vaccination strategy for children that is staged with what researchers learn from adult vaccination.

Dr. Swamy noted that no industry sponsor has a plan to include pregnant women in a vaccine trial. She urged that NVAC's recommendations for the second charge question address inclusion of pregnant women in trials.

Dr. Hopkins agreed that NVAC should provide some guidance on the process for groups that are not in trials—pregnant women and children—so that once a vaccine is available, researchers can relatively quickly pivot and study those groups.

Ms. Aikin noted that regulations require that the NVAC conduct a public meeting to address any recommendations that are not finalized by the end of the current meeting.

Dr. Hopkins summarized NVAC draft recommendations in answer to the ASH's first question:

- Recommendation 1.1 - Coordination of a comprehensive communication plan in accord with vaccine communication information in previous NVAC reports.
- Recommendation 1.2 – Collaboration with the CDC, FDA, and others to spearhead education and training programs for healthcare professionals and public stakeholders.

- Recommendation 1.3 – Advising HHS to work with a variety of partners in developing occupational training programs.
- Recommendation 1.4 – Using an immunization information system (IIS) to identify sites that need to adopt an IIS for tracking COVID vaccines.
- Recommendation 1.5 – Convening a meeting to address the need for broad demographic data, identify privacy concerns, and outline technical and operational capabilities of an IIS to gather needed data.
- Recommendation 1.6 – Encouraging participation by underrepresented groups in Phase III trials.

Dr. Dunn and **Dr. Fleming** said they were comfortable with the recommendations, with **Dr Hopkins** recognizing the vetting done by the Vaccine Confidence Subcommittee.

Dr. Hopkins asked for comment on Recommendation 2.1 – Due to relatively low disease burden in children, NVAC recommends evaluating vaccines in children after data have been gathered on safety and efficacy in other groups and post-marketing surveillance is in effect.

Dr. Fleming suggested modifying the recommendation to say that studies done in children be timed according to when available safety data suggests those trials would be safe. Several committee members agreed that more specific language is needed on vaccine trials in children. **Dr. Swamy** said specific language is also needed to address the issue of pregnant women in vaccine trials.

Dr. Hopkins suggested the following modification: "We need to proceed with a cautious but deliberate development of a strategy to vaccinate children. The bridging study should be designed now and potentially begin based on Phase III adult trial results which demonstrate no significant safety concerns. Phase III trials in children should be designed and initiated based on well-defined post-usage surveillance in adults."

Committee members discussed whether it is too restrictive to require an EUA for adults before proceeding with a trial in children; if so, what safety language needs to be included; and whether specific age categories need to be added.

Dr. Hopkins moved on to Recommendation 2.2 in which NVAC suggests further epidemiology and pathogenesis studies be developed to better assess risk mechanisms, rates of rare disease in children, and transmission by children of SARS-COVID before launching an active vaccination strategy. Dr, Hopkins suggested that the wording be changed from "developed" to "implemented," since development should be under way now.

Committee members made no objection to Recommendation 2,3, which warns against an EUA for COVID-19 vaccines in children considering the typically mild disease burden, except for MIS-C.

Dr. Hopkins noted that the committee's greatest concern seems to be with Recommendation 2.1. He added that a recommendation 2.4 needs to be added to address pregnant women. Committee members agreed that language should also be added to clarify that pregnant women should not be part of an EUA because surveillance and safety data is needed.

The committee agreed that items under Recommendation 2 need edits and additions that need to be addressed at a later meeting. NVAC members also agreed that Recommendation 3 needs

editing for clarification.

With previous technical difficulties resolved, the committee paused in its discussion to hear a public comment.

Public Comment

Dr. Bayli Larson, ASHP

Dr. Larson presented principles that ASHP released recently related to COVID-19 vaccine development, distribution, allocation, administration, and monitoring and surveillance. The principles bridge lessons learned from previous mass vaccination efforts, current experience with the COVID-19 pandemic, and best practices in effective pandemic preparedness, supply chain management, and clinical practice. The principles also emphasize pharmacy staff expertise in optimizing vaccine supply and use.

Specific items include enforcing a transparent and rigorous process for vaccine development, approval, and post-marketing surveillance; and vigilance with continued research and comprehensive surveillance. Dr. Larson requested that information on storage and handling vaccines be available as early as possible. She explained that ASHP members are already preparing to receive the vaccine and want to avoid making critical decisions based on hypothetical scenarios.

Dr. Meissner asked if pharmacists have the capacity to store vaccines at the required minus 50 or 70 degrees. Dr. Larson replied that hospitals' current storage and handling capabilities likely will not meet vaccine requirements. That is why timely storage and handling information is crucial.

Discussion

Dr. Hopkins then continued the committee's discussion of its recommendations by reading proposed language for Recommendation 2.1:

"Due to the relatively low burden of disease in children, [citing the AAP state-level data report] NVAC recommends evaluating vaccines in children after data have been gathered on safety and efficacy in other groups and post-marketing surveillance is in effect [citing CDC vaccine safety monitoring].

NVAC encourages a cautious but deliberate development of a strategy to vaccinate children and phased trials based in part on what we're learning from the adult vaccine trials and use.

A safe and effective vaccine for children would have to value protecting them as well as communities and would enable safer schools and daycares and the myriad of other settings where children congregate with adults. Bridging studies should be designed now and potentially begin based on Phase III adult trial results demonstrating no significant safety concerns. And Phase III trials in children should be designed and initiated based on well-defined post-usage surveillance in adults, that seemingly could begin relatively quickly, absent safety signals, as millions of adult doses will likely be administered within the next few months or begin the first few months of beginning use."

Committee members decided to delay approval of all three recommendations pending edits and

clarifications and include then together with the panel's report. Drs. Swamy, Meissner, Fleming, Friedland, and Jackson volunteered to work on Recommendation 2. Drs. Hopkins, Cooke, and Friedland volunteered to work on Recommendation 3.

Ms. Aikin and Dr, Hopkins planned to contact groups to set up a meeting date and time.

Dr. Hopkins adjourned the meeting.