NVAC NATIONAL VACCINE ADVISORY COMMITTEE

June 15-16, 2022, Virtual Meeting Minutes

Committee Members in Attendance

Robert H. Hopkins Jr., M.D., MACP, FAAP; Chair
Melody Anne Butler, B.S.N., RN, CIC
Timothy Cooke, Ph.D.
John Dunn, M.D., M.P.H.
Jeffrey Duchin, M.D.
Kristen R. Ehresmann, R.N., M.P.H.
David Fleming, M.D.
Leonard Friedland, M.D.
Daniel F. Hoft, M.D., Ph.D.
Molly Howell, M.P.H.
Jewel Mullen, M.D., M.P.H.
Stephen Rinderknecht, D.O.
Robert Schechter, M.D., M.Sc.
Winona Stoltzfus, M.D.
Geeta Swamy, M.D.
Robert Swanson, M.P.H.

NVAC Ex Officio Members

Brooke Barry, Centers for Disease Control and Prevention (CDC)
Uzo Chukwuma, M.P.H., Indian Health Service (IHS)
Mary Beth Hance, Centers for Medicare & Medicaid Services (CMS)
Troy Knighton, M.Ed., Ed.S., LPC, Department of Veterans Affairs
Justin A Mills, M.D., M.P.H., FAAP, Agency for Healthcare Research and Quality (AHRQ)
Barbara L. Mulach, Ph.D., National Institutes of Health (NIH)
Christine Oshansky, Ph.D., Biomedical Advanced Research and Development Authority (BARDA)
Mary Rubin, M.D., Division of Injury Compensation Programs (DICP), Health Resources and Services Administration (HRSA)
Jay Slater, M.D., Food and Drug Administration (FDA)
Melinda Wharton, M.D., M.P.H., Centers for Disease Control and Prevention (CDC)
Bruce McClenathan, MD, FACP, FAAAAI, Defense Health Agency, Immunization Healthcare Division, Department of Defense (DOD)

NVAC Liaison Representatives

Meredith Allen, Dr.PH., M.S., Association of State and Territorial Health Officials (ASTHO)
Rebecca Coyle, M.S.Ed., American Immunization Registry Association (AIRA)
John Douglas, M.D., National Association of County and City Health Officials (NACCHO)
Jean-Venable "Kelly" Goode, Pharm.D., BCPS, FAPhA, FCCP, American Pharmacists Association
Claire Hannan, M.P.H., Association of Immunization Managers (AIM)
Chris Regal and Devin Plote, Ph.D., America's Health Insurance Plans (AHIP)
Kerry Robinson, Ph.D., Public Health Agency of Canada

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

Day One

Call to Order and Rules of Engagement—Ann Aikin, Acting Designated Federal Officer, NVAC

Ms. Aikin called the meeting to order at 9 a.m. ET and welcomed the participants. She 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. Ms. Aikin thanked the Office of Infectious Disease and HIV/AIDS Policy (OIDP) staff for its support in organizing the meeting and called the roll.

Opening Remarks—Admiral Rachel Levine, M.D., Assistant Secretary for Health (ASH), Department of Health and Human Services (HHS)

ADM Levine said that she works every day as the ASH to improve the health and well-being of all Americans. Building a strong foundation for immunization is an important part of that goal. The National Vaccine Advocacy Committee (NVAC) provides the U.S. government (USG) with recommendations for achieving optimal prevention of human infectious diseases through vaccine development and gives direction to prevent adverse reactions to vaccines.

ADM Levine discussed the relevance of mental health care, not only for members of the public, but also for health care workers. Surgeon General Vice ADM Vivek Murthy recently warned of the impacts of global health worker burnout and resignation following the COVID-19 public health crisis on the U.S. health care system.

ADM Levine expressed her commitment to addressing health disparities in access to care, social determinants of health, and COVID-19 vaccine uptake as key components of the national public health response to the COVID-19 pandemic and the health of the nation more broadly. Health equity is the foundation of all public health efforts advanced by HHS, including immunization equity, mental health, and public health response to COVID-19. The COVID-19 pandemic has revealed and exacerbated long-standing health inequities among historically marginalized and underserved populations. As HHS works to expand access to immunizations and remove systemic barriers to vaccination, actions and messaging must remain consistent to vaccinate all Americans against COVID-19 and catch-up on routine vaccinations across the lifespan. ADM Levine thanked public health workers for their continued effort and dedication in response to the COVID-19 health crisis. She also thanked the NVAC Vaccine Confidence Subcommittee for their work in dispelling increased misinformation surrounding vaccinations following the COVID-19 pandemic.

ADM Levine provided NVAC with two new charges. Firstly, ADM Levine charged NVAC to develop a new subcommittee on innovation to generate a report that includes (1) a review of both conventional and promising approaches to vaccine discovery and development; (2) recommendations for actionable, high-impact activities that HHS and federal partners can take to foster innovation; (3) an evidence-based approach for identifying and prioritizing vaccine candidates and immunization technologies, including their criteria for prioritization; (4) a list of vaccination innovation priorities including target antigens, molecular platforms, and immunization delivery technologies; (5) a forward-looking approach to introduce vaccines for special patient populations and neglected diseases to portray their value and importance; (6) a scientific agenda outlining a framework of research direction; and (7) a concise summary of findings ready for a vote by September 2023 during the next NVAC Meeting. In addition, after the report is generated, NVAC will publish an updated list of vaccination innovation priorities every two years to adjust for changes in immunization research and the development landscape.

Second, ADM Levine charged NVAC with reviewing previous vaccine safety efforts and provide recommendations on which strategies should be maintained for continuous improvement of the vaccine safety system as well as provide recommendations to build on new science, advancements in technology, and shifting public and partner expectations. To complete this assignment, ADM Levine charged NVAC to create a new subcommittee to (1) review related reports and outline opportunities for continual improvement of vaccine safety activities; (2) make recommendations to minimize preventable vaccine-related adverse events and improve all of the individual components needed for a strong safety system; (3) provide direction to improve coordination and stakeholder input into the timely detection and assessment of vaccine safety signals to better inform clinical decision making and public health policies; (4) describe science-based actions that HHS and federal partners can take to increase knowledge and use of the vaccine safety system; and (5) write a succinct report summarizing the findings before the June 2023 NVAC Meeting.

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

Dr. Hopkins welcomed the participants to the hybrid virtual and in-person public meeting, which was accessible to the public by live webcast and telephone. He outlined the agenda for this meeting. NVAC members unanimously approved the minutes of the February 10-11, 2022, meeting as written.

Dr. Hopkins described the procedure for delivering public comments during the meeting. Written comments can be sent to NVAC for consideration by e-mail (nvac@hhs.gov). The agenda, minutes, and recordings of past meetings are available online. NVAC is scheduled to meet next on September 22-23, 2022. (See the appendix for a list of abbreviations used in this report.)

The Vaccine Confidence Subcommittee Report Out

Vaccine Confidence Subcommittee—John Dunn, M.D., M.P.H., Chair

In response to a request from the ASH, the Vaccine Confidence Subcommittee has generated a report on the determinants of vaccine confidence across the lifespan, suggest actions that HHS might take to increase confidence in all recommended vaccines, and to provide guidance on the use of evidence-informed best practices to increase vaccine confidence through public, provider, and policy interventions. Dr. Dunn reviewed recent Subcommittee updates to that report.

The link between vaccine confidence and vaccine uptake is not clearly defined because increased confidence does not always lead to increased uptake. Vaccine uptake and confidence are highest among the 25 percent Americans who report trusting the government, highlighting the need for future vaccine uptake efforts to build trust in federal and state governments. Another way to increase vaccine confidence is to directly address public trust in the private vaccine enterprise. All efforts to increase vaccine confidence and uptake must be engaging and community-specific, and account for differences in the social dynamics of various communities. Within some communities, vaccination of an individual may lead to that individual's alienation and social exclusion from their community and social settings. HHS may develop outreach resources and messaging that provide challenging but non-combative responses to vaccine-negative comments within specific social networks.

New recommendations from the Subcommittee report were more explicit and specific than those shared during the prior NVAC meeting, recommending that future research be both focused on specific populations and responsive to local trends in vaccine uptake and confidence. HHS may be able to reach members of the public with lower vaccine confidence and uptake indirectly through their health care providers, some of whom also express lower confidence and uptake themselves, by offering providers more educational materials, messaging, and programs that contain accurate evidence from current research on the safety and efficacy of recommended vaccines.

Discussion

Rebecca Coyle, M.S.Ed., noted that the federal response to the COVID-19 pandemic involved several sectors of the government that have not traditionally played a role in public health (e.g., the military), highlighting the importance of approaching vaccination, and public health more broadly, from a whole-of-government approach (WGA) involving coordination of all government agencies.

John Douglas, M.D., discussed the relevance of misinformation and disinformation to undermining the vaccine enterprise. He also discussed the impact of public vaccine uptake on national security. Dr. Dunn recommended that federal agencies with a national security mandate should increase their focus on messaging and the flow of health-related information, both false and accurate.

Innovation and Prioritization for Vaccination

CEPI's Second Five Years: Disease X and the 100 Days Mission—Nicole Lurie, M.D., M.S.P.H., Coalition for Epidemic Preparedness Innovations (CEPI)

Disease X is an abstract concept representing a new disruptive and deadly pathogen that may emerge at some point in the future, for which there is no current vaccine. The goal of the 100 Days Mission is to develop and produce a vaccine, authorized for use, for Disease X within 100 days of scientists identifying a new, deadly outbreak. Four interrelated approaches facilitate a successful response to the next Disease X: (1) threat-level monitoring and benefit-risk assessment; (2) virus family targets and vaccine "banks" starting with mRNA; (3) day 100 response goal; and (4) prototypic vaccine approach.

Vaccine developers and manufacturers face difficulties in preparing for Disease X because no commercial market exists for a disease that has yet to emerge. The viral sequence necessary for SARS-CoV-2 vaccine development was completed 326 days after the emergency declaration. While this timeline is laudably shorter than that for any other global vaccine development effort, it does not meet the 100 Days Mission goal. Pre-crisis preparation and coordination between developers and manufacturers must drive the global development of future vaccines to meet the timeline goal. Had vaccine developers combined the best-in-class work from every stage of manufacturing, they could have developed the SARS-CoV-2 vaccine 75 days earlier.

Prior research on vaccines against Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), both members of the coronavirus family, enabled the National Institutes of Health (NIH) to support swift development of the SARS-CoV-2 vaccine. Vaccine developers can shorten the vaccine production timeline by developing shared libraries of "prototype vaccines" against the approximately 25-31 virus families that infect humans for swift access and adaptation to Disease X. Over the next 5 years, CEPI will prioritize the creation of libraries and clinical proof of concepts for vaccines against the 10 virus families that pose the greatest risk to public health. In addition, a globally distributed manufacturing network would enable rapid access to vaccine doses in low- and middle- income countries (LMICs) and allow for better, faster, and cheaper vaccine production closer to the source of an outbreak.

The Vaccine Innovation Prioritization Strategy (VIPS) for Low- and Middle- Income Countries (LMICs)—Tiziana Scarnà, Ph.D., Gavi, The Vaccine Alliance

VIPS is a global collaboration between Gavi, the World Health Organization (WHO), the Bill & Melinda Gates Foundation, PATH, and UNICEF that assessed vaccine-related innovations to prioritize and drive equitable vaccine coverage in LMICs. VIPS consulted with 61 countries to identify immunization barriers and desired vaccine attributes through an online survey. Survey results were used to identify the most important immunization challenges for 10 exemplar vaccines and to both understand the perceived programmatic challenges and benefits addressed by shortlisted innovations. These shortlisted vaccines were ranked through in-depth in-person interviews with health care workers and immunization decision-

makers. Collaborators analyzed nine shortlisted innovations with 17 priority vaccines and consulted with countries, manufacturers, and regulators to identify three technologies for vaccine developers to prioritize: (1) microarray patches (MAPs); (2) heat stable and controlled temperature chain (CTC) qualified vaccine formulation; and (3) barcodes on primary packaging during Phase II (2019-2020).

VIPS reviewed MAPs business models and risk-sharing approaches. It also modeled the impact of various thermostability improvements and different CTC use cases for thermally stable vaccine formulations. Key insights from VIPS have been published in a *Vaccine* article that describes the evaluation and prioritization process, findings from consultations with three countries, and challenges to innovation experienced by LMICs. VIPS developed 5-year action plans to advance MAPs and heat-stable and CTC-qualified vaccine formulation. VIPS then established next steps for the widespread implementation of barcodes on both primary and secondary packaging.

Vaccines and Antimicrobial Resistance (AMR)—Timothy Jinks, Ph.D., Wellcome Trust

Tackling antimicrobial resistance (AMR) requires a multifaceted approach that prioritizes (1) prevention of infection through vaccines and the Centers for Disease Control and Prevention's (CDC's) Global Water, Sanitation, and Hygiene (WASH) program; (2) identification of antibiotic usage through innovative diagnostics and stewardship; and (3) treatment of antibiotic resistant pathogens with new antibiotics and alternative therapeutics. Vaccines combat AMR both directly by reducing infection carriage and the spread of resistant organisms and indirectly by reducing antibiotic use and therefore selective pressure that causes AMR to develop in response to excessive antibiotic use. As a result, the primary goal for controlling AMR is to encourage the use of existing vaccines and the development of new vaccines that can reduce drivers of AMR. CDC and WHO each produce lists of AMR pathogen priorities to direct development of new antimicrobials, although no equivalent list exists for AMR vaccine priorities.

Wellcome and the Boston Consulting Group (BCG) published a report that evaluates the research and development (R&D) of vaccines to combat drug-resistant infections and enable evidence-based decision-making for vaccine development. In producing the report, Wellcome and BCG researchers first consolidated available information from expert interviews and reviews of databases and scientific literature, taking an end-to-end view focused on research, development, and uptake factors for each vaccine. They then analyzed the data, developing a scorecard framework for assessing pathogens, with a focus on those with the greatest direct health impact on global mortality and morbidity and those with the greatest urgency of AMR threat. The researchers similarly prioritized pipeline robustness as a measure of the current state of R&D of vaccines that prevent infection by pathogens that were previously ranked by direct health impact. Finally, the researchers conducted a side-by-side comparison of pathogens, which enables prioritization by researchers, funders, and policymakers whose individual and institutional foci might vary.

The Wellcome and BCG report identified action items to encourage targeted attention and investment to fill knowledge gaps and promote vaccine development and uptake. The report also presents six recommendations to aid vaccination efforts against all diseases identified by the WHO as AMR priorities: (1) promote collection of robust epidemiological data and (2) model the evolution of AMR threat and potential health impact of interventions (Health Impact); (3) target investment to new R&D platforms relevant to AMR pathogens and (4) collaborating for regulatory innovation (vaccine R&D); and (5) utilize market shaping intervention and (6) develop the health economic case for vaccination programs (vaccine uptake).

Discussion

Timothy Cooke, Ph.D., inquired as to whether machine learning or artificial intelligence (AI) had been considered or used in any of the data aggregation or analysis processes described in the presentations.

Timothy Jinks, Ph.D., replied that while machine learning and AI are being investigated for use in the product development processes for individual vaccines, they were not used in the data aggregation or analysis processes. Nicole Lurie, M.D., M.S.P.H., assured the audience that machine learning is currently being used in the field of vaccine development and prioritization, although primarily for genome analysis focused on identifying genes related to pathogen transmissibility and disease severity as on predicting viral evolution relevant to SpillOver: Viral Risk Ranking— a collaborative effort that explores and directly compares hundreds of virus, host and environmental risk factors to identify viruses with the highest risk of zoonotic spillover from wildlife to humans. She further noted that DeepMind AI is another project that could be extremely powerful in the realm of vaccine development and pathogen analysis.

Kristen R. Ehresmann, R.N., M.P.H., drew connections between the *Vaccine Confidence Subcommittee Report Out* and *CEPI's Second Five Years: Disease X and the 100 Days Mission* presentation, commenting that public hesitancy about the SARS-CoV-2 vaccine was due in part to the speed at which the vaccine was developed and the relevance of that public hesitancy to the development of future vaccines with CEPI's 100 Days Mission. As the vaccine development process accelerates, public messaging and outreach must also increase in both scope and efficacy to ensure that members of the public not only trust vaccines that are developed more quickly, but also decide to get vaccinated.

Innovations for Immunity: Infants, Immunocompromised Persons, and the Elderly

Comments—James Mayne, Ph.D., Pharmaceutical Research and Manufacturers of America (PhRMA)

PhRMA maintains a tool that provides real-time tracking of various types of medicines in development, including both preventative and therapeutic vaccines. The company is currently tracking more than 300 SARS-CoV-2 vaccines at various stages of development representing a wide range of approaches across a rapid, global response. The vaccines being tracked use a variety of platforms, including the next-generation platforms (viral vector and nucleic acid) used by Pfizer, Moderna, and J&J, which helped to accelerate the process of developing an exploratory vaccine against a novel and threatening pathogen. However, the processes for clinical development, manufacturing, and the regulatory review process for new vaccines have not experienced similar acceleration. In fact, regulatory hurdles can impede swift vaccine development and deployment in an extremely time sensitive undertaking.

Collaborative approaches to vaccine development have proliferated since the start of the COVID-19 pandemic. These collaborations involve pre-competitive data sharing, sharing of manufacturing capabilities and resources, and open communication between a wide variety of private and public stakeholders, leading to creative and synergistic research programs. Similar improvements are needed for the manufacturing and supply chains, which require additional research and investment to keep pace with the accelerating vaccine development process.

Vaccinology 3.0 and Personalized Vaccinology in the 21st Century—Gregory A. Poland, M.D., M.A., F.I.D.S.A., M.A.C.P., F.R.C.P. (London), Mayo Clinic

Vaccinology, or the scientific study of vaccines, has already experienced one major historical transformation. The field began in the late 18th century by isolating, attenuating, and then injecting inactive pathogens (e.g., smallpox, diphtheria, tetanus, cholera) to stimulate the immune system. Post-WWII vaccinology (Vaccinology 2.0), which persists through the present day, instead uses recombinant technology, subunit vaccines, and undirected adjuvants (ingredients that strengthen the immune response) to design prophylactic vaccines for the general population, predominantly children. However, the Vaccinology 2.0 approach sometimes fails, due to pathogen variability, host immune system variability, and a lack of variability in vaccine delivery (i.e., a "one size fits all" approach).

In the future, *Vaccinology 3.0* will develop more personalized vaccines by drawing on vaccinomics, immune response network theory, immunogenomics, and immune profiling, as well as systems biology approaches to understanding and predicting immunity. The vaccines of the future will account for biological differences of the host (e.g., race and ethnicity, age, disease status, genetic polymorphisms). Future vaccines may also be delivered differently, possibly using oral, mucosal, and other delivery methods, and will likely use multiple highly specific adjuvants targeted at adult immune systems, as opposed to those of children, for both prophylactic and therapeutic indications.

To move from Vaccinology 2.0 to Vaccinology 3.0, researchers and vaccine developers must focus on two key areas: vaccination response assessment and bioinformatics. Vaccination response assessment includes advances in the fields of (1) genetics and genomics, (2) proteomics, (3) epigenomics, (4) metagenomics and the microbiome, (5) transcriptomics, (6) metabolomics, and (7) immune profiling. Bioinformatics can help researchers interpret the myriad data from vaccine response assessment and can help advance that assessment, as well. The entire process of vaccine development will benefit from data-directed statistical analysis and computational modeling in an iterative cycle of discovery, replication, validation, and application. Statistical and computational modeling improves predictive power, in particular, including prediction of significant adverse events following vaccination and the related field of adversomics, the genetic study of vaccine-related adverse events.

Adjuvanted Vaccines Targeted to Vulnerable Populations—David Dowling, Ph.D., Boston Children's Hospital

Immune responses to vaccines and resulting immunity vary, with distinct immune profiles at different ages and decreased strength of immune response at both ends of the lifespan. An understanding of immune ontogeny can lead to precision vaccinology, which tailors immunization for vulnerable populations with distinct levels of immunity. The Precision Vaccine Program (PVP) at Boston Children's Hospital achieves this goal by leveraging clinical trial and human in vitro samples to develop and test mechanistic hypotheses of immunogenicity and targeting adjuvant discovery through population-specific (i.e., age-specific) biosamples, appropriate animal models, and targeted clinical trials in specific vulnerable populations.

The PVP team collaborated with experts in vaccine technology and development to identify and acquire candidate small molecule adjuvants to produce novel SARS-CoV-2 vaccines optimized for older adults. The coalition evaluated these adjuvanted vaccines in aged animal models and then in Phase I clinical trials. PVP collaborators evaluated multiple adjuvant formulations to improve the immunogenicity of receptor-binding domain (RBD)-based vaccine, which is easy to produce at scale. Focusing on combinations of aluminum salts and pattern recognition receptor (PRR) agonists in a murine model, researchers found that RBD formulated with aluminum hydroxide-CpG (AH:CpG) induced robust production of anti-RBD neutralizing antibodies not only in young adult mice, but also in aged mice. Mechanistically, this formulation drives a classical immunological response in the lymph nodes but circumvents the suppression of helper cells seen in aged model organisms. Furthermore, AH and CpG synergistically enhance cytokine production from human peripheral blood mononuclear cells (PBMCs).

Individualized Influenza Vaccines—Nicholas Wohlgemuth, Ph.D., Kansas Health Science Center

Most medicines and medical therapies target an invading organism or diseased tissue, whereas traditional vaccines instead target healthy immune cells to stimulate protective, memory immune responses. However, human immune systems are significantly more diverse and complex than typical pathogens and diseased tissue, leading to frequent failures of the "one size fits all" vaccine model. For example, sex and gender influence influenza virus disease severity and vaccine efficacy. Males tend to have less adverse reactions at the injection site and greater tolerance of flu medications and treatments compared to females,

but females typically have greater protection and vaccine efficacy following influenza vaccination. Advanced age determines influenza disease severity and vaccine efficacy, with severity increasing and efficacy decreasing significantly after 65 years of age. Obesity, likewise, determines influenza severity and vaccine efficacy, with increased severity and decreased efficacy in obese and very obese individuals compared to non-obese controls.

Differential immune responses to vaccines require the use of different vaccines, as demonstrated by the higher dose influenza vaccine recommended for older adults. To rationally design future vaccines, vaccine developers must therefore (1) assess demographic differences in vaccine efficacy; (2) design demographic specific vaccines; (3) assess individual differences in vaccine efficacy; and (4) design new individual-specific vaccine formulations with new adjuvants.

An example of a personalized vaccine approach could be to use a standard dose of inactivated virus for normal, healthy individuals ages 6 months to 65 years and a high dose of inactivated virus for adults over 65 years of age. Alternatively, live-attenuated influenza vaccine (LAIV) have been shown in limited clinical settings to be useful in individuals with lower natural immunity. Therefore, LAIV may offer one solution for immunization for healthy children ages 2-8 years. LAIV effectiveness began decreasing with the inclusion of pH1N1 in routine seasonal vaccination in 2009 and suggests that the pH1N1 vaccine may be too attenuated to produce an effective immune response; LAIV virus with M2-S86A may replicate better and induce a more robust immune response, improving vaccine efficacy. Scientists have not yet found a solution to address immune inequities among obese, pregnant, or immunocompromised individuals. Personalized vaccines of the future must also be tailored to an individual's immune history and genetic predispositions, potentially through clinical immunoprofiling.

Discussion

Dr. Hopkins asked how health care providers would deliver personalized vaccines that may take months to develop and produce, compared to vaccinating a patient in a single clinic visit. Gregory A. Poland, M.D., M.A., FIDSA, MACP, FRCP, responded that developing the science of personalized vaccines is the first priority, and will be followed by strategies for implementation and uptake. He also suggested that widespread genotyping of the general population at birth may eliminate such clinical waits in the future.

Ms. Ehresmann speculated on the operationalization of personalized vaccines in the wider public health field, asking whether providers would likely genotype patients for routine immunizations. Dr. Poland responded that routine care would not include genotyping in most circumstances. Mayo Clinic is, however, developing large scale "biobanks" that support personalized medicine by correlating health outcomes and intervention efficacy with geno- and phenotypes. While 15 years ago physicians did not have the opportunity to provide targeted vaccines, the current availability of various vaccine types (e.g., LAIVs, recombinant vaccines, adjuvanted vaccines) enables a personalized medicine approach. However, additional research is still needed to identify how best to implement an individualized medicine approach (i.e., one unique to an individual based on geno- and phenotyping). For example, Mayo Clinic has genotyped several female patients to determine those for whom an HPV vaccine will prevent cervical cancer and those for whom it would prevent only genital warts.

Jewel Mullen, M.D., M.P.H., asked how public health workers and health care providers can communicate 21st-century medicine to patients, given the constraints of 20th-century communication technologies, the still uneven availability of tools such as genotyping, and the potential skepticism of vaccine hesitant patients. Dr. Poland shared his experience with the launch of genotyping at Mayo Clinic, where the greatest response and interest came from anti-vaccine or vaccine hesitant individuals who were interested in the use of genotyping to assess risk of severe adverse events. David Dowling, Ph.D., added that one goal of personalized vaccine development is to assess the minimum dose necessary to confer lifelong immunity, which may ultimately increase the rate of vaccine uptake among the most hesitant and

skeptical communities. James Mayne, Ph.D., continued the discussion, highlighting the importance of advancing the pace of vaccine research, regulation, development, manufacturing, and distribution to keep pace with new developments in medical technology. Along with the development of personalized vaccines comes new obstacles, such as the requirement for increased manufacturing and production capabilities.

Jay Slater, M.D., emphasized the need to transition safely and effectively from the generalized to the personalized vaccination model. As vaccinology progresses, many patients, especially vaccine hesitant patients, will not be completely satisfied with and accepting of a vaccine that relies on non-individualized, intermediary models, even those that provide efficacy and safety statistics. Vaccine hesitant patients will resist vaccination efforts until providers can honestly and empirically say that the individual patient is not at significant risk of developing a specific adverse event.

Unfinished Triumphs: Four Developmental Vaccines for Poverty-Associated Diseases

Chikungunya Virus (CHIKV) Vaccine Development—Emily Coates, Ph.D., National Institutes of Health (NIH)

NIH's National Institute of Allergy and Infectious Diseases (NIAID) classifies the Chikungunya Virus (CHIKV) as a category B pathogen on the Priority Pathogen National Defense List that is now endemic in Central and South America, the South Pacific, and India. CHIKV is a debilitating disease that presents with rash, stooped posture due to joint pain, and high fever lasting months to years. Long term symptoms, including arthralgia and arthritis, are estimated to occur in 30-40 percent of cases. The virus, which was first isolated in Tanzania in 1952, has evolved three geographically distinct genotypes in Asia, West Africa, and Eastern/Central/South Africa. The Asian lineage spread to the Americas in 2013, where it caused over 1.6 million reported cases between December 2013 and October 2015. Outbreaks continue worldwide with more than 130,000 cases globally as of 2021.

NIAID's Vaccine Research Center (VRC) worked to develop (CHIKV) virus-like particle (VLP) vaccine from conceptual design to Phase III clinical testing and product licensing. VLP vaccine platforms use a fraction of the viral genome that is recognized by the human immune system, is safe in humans, and does not replicate. Following successful non-human primate modeling in 2010, the VRC began Phase I clinical trials in 2011 and tested a two-dose administration in a Phase II randomized, placebo-controlled clinical trial in 400 healthy adult participants in 2015. The study demonstrated strong efficacy and safety. NIAID then licensed the vaccine to Emergent BioSolutions to conduct further Phase II trials using an aluminum adjuvant in 2018. The vaccine received an FDA Breakthrough Therapy designation in 2020 and entered Phase III clinical trials in September 2021, which are estimated to conclude in November 2022.

Advances in the Development of Lymphatic Filariasis Vaccine—Ramaswamy Kalyanasundaram, D.V.M, Ph.D., University of Illinois Chicago

The University of Illinois Chicago is currently the only organization developing a vaccine to prevent lymphatic filariasis (LF), also known as elephantiasis. LF is a tropical parasitic infectious disease transmitted by mosquitos that causes severe, often debilitating lymphatic swelling in one leg. According to WHO, LF is the world's second leading cause of disability, affecting approximately 51 million people and threatening 863 million people in 47 countries, primarily Brazil, India, and most countries in Africa. It exacerbates poverty among rural populations, who are rarely if ever able to afford plastic surgery to treat swelling.

WHO has spent more than $65 billion on the Global Program to Eliminate Lymphatic Filariasis (GPELF), which distributes medications to treat LF (e.g., ivermectin, albendazole). Although even partial removal of the LF parasite and larvae can significantly reduce pathology—because the parasite does not reproduce

inside the human host—many individuals still refuse to take these medications, because they do not eliminate adult parasites that cause lymphatic swelling and do not prevent future infection. Endemic LF infection regularly reemerges in villages and regions declared free from LF.

In 2020, the University of Illinois patented a tetravalent vaccine for pre-exposure prophylaxis of LF infection. The University of Illinois passed the prophylactic vaccine to the University of Nebraska Good Manufacturing Practices (GMP) Biological Process Development facility to prepare a master cell bank, and then to the University of Iowa Center for Biocatalysis and Bioprocessing facility for manufacturing. Several steps remain to ready the vaccine for deployment in impoverished rural communities, which are anticipated to be complete in 3-4 years. The University of Illinois has also partnered with the University of Washington's Fred Hutchinson Cancer Research Center to conduct in vitro studies to develop a monoclonal antibody (mAb) therapy to treat LF.

Updates of Developmental Vaccines for Poverty-Associated Diseases: Shigellosis—Lou Bourgeois, Ph.D., M.P.H., PATH

Shigellosis, caused by the *Shigella* bacterium, was the second leading global cause of diarrheal mortality in 2016, accounting for over 212,000 deaths. The greatest burden of *Shigella* infections falls on children under 5 years of age in LMICs with poor sanitation and hygiene. Childhood *Shigella* infection can lead to stunted growth, wasting, developmental cognitive deficits, and long-term intestinal issues later in life. No vaccines are currently licensed to prevent or treat *Shigella* infection, despite WHO prioritization. WHO published preferred product characteristics for a preventive vaccine for children between 6 and 36 months of age, including at least 60 percent efficacy at preventing moderate-to-severe diarrhea (MSD).

PATH has determined that inactivated whole cells have the greatest antigenic content of five available platforms for *Shigella* vaccines (OPS Conjugate, Invaplex, GMMA, Live Attenuated, and Inactivated Whole Cells), and would be the preferred platform for injectable *Shigella* vaccine development, although the subunit vaccine Invaplex, currently under development at Walter Reed Army Institute of Research (WRAIR), is also promising; it was selected as the medical invention of the year for 2022 by the U.S. Army Medical Research and Development Command (USAMRDC) Research and Development Command (USAMRDC).

The leading four *Shigella* candidate vaccines will likely succeed in development and are expected to complete Phase III clinical trials within the next 5-7 years. However, limited field trials indicate that both injectable and oral vaccine candidates may lack sufficient immunogenicity among infants and children under 3 years of age, suggesting that an adjuvant may be necessary. Furthermore, insufficient funding has slowed vaccine development and may delay licensure and deployment. A *Shigella* vaccine could be marketed to travelers in addition to LMICs to incentivize developers and commercial manufacturers to invest in promising candidates.

Schistosomiasis Vaccine—Afzal Siddiqui, Ph.D., Texas Tech University

Schistosomiasis has infected 250 million people and put 800 million at risk of infection in 79 countries, primarily in sub-Saharan Africa. Eggs of the parasitic schistosome worm causes granulomas to form in intestinal or liver-based Schistosomiasis, which is characterized by severe abdominal swelling. Adult worms can cause lesions on the female genital tract, resulting in a four-fold increase in HIV transmission. *Science* ranked the Schistosomiasis vaccine as one of the top 10 vaccines for urgent development, and WHO recommends vaccination against Schistosomiasis in addition to treatment using praziquantel as the optimal strategy to combat Schistosomiasis in high transmission settings.

Texas Tech University and partners have been developing SchistoShield® as a potential novel vaccine to prevent Schistosomiasis and reduce egg count by 90 percent. SchistoShield® interrupts the Schistosomiasis life cycle at four stages: (1) prophylactically killing infectious larvae, (2) therapeutically

killing existing adult worms, (3) blocking transmission by reducing egg viability and expulsion from the host, and (4) anti-pathologically reducing eggs and granulomas in host tissues. The other three candidate vaccines interrupt the Schistosomiasis life cycle prophylactically and anti-pathologically.

The SchistoShield® vaccine was in the pre-clinical development phase from 1991 to 2019. PAI Life Sciences, which held the vaccine license, initiated Phase I clinical trials in the United States from 2019 to 2022, and the University of Cambridge and the International Vaccine Institute initiated Phase Ib clinical trials in Africa estimated to conclude in 2024. Through 2031, PAI Life Sciences will scale the vaccine for Phase II, III, and IV clinical trials and deployment while applying for WHO prequalification and a Tropical Disease Priority Review Voucher from FDA.

Staying Focused: HIV Vaccine Pursuits

HIV Vaccines in 2022: Where to from Here?—Mitchell Warren, Ph.D., AIDS Vaccine Advocacy Coalition (AVAC)

Globally, 1.5 million people are infected with HIV every year. Although this infection rate is significantly lower than rates at the peak of the HIV epidemic, vaccine developers must continue to work on a safe and effective vaccine to end the epidemic entirely. HIV vaccine development faces several challenges. No human immune system has ever eliminated HIV, so researchers cannot study a successful immune response to the virus. Moreover, HIV targets and kills the immune cells the body uses to defend against disease.

To date, only two HIV candidate vaccines have shown promising results. The 2009 Thai Prime-Boost/RV 144 vaccine demonstrated modest efficacy (31.2 percent) and the 2021 Antibody Mediated Prevention (AMP) Studies found reduced risk of acquisition of a small subset of sensitive HIV strains. The AMP Studies demonstrated an important proof of concept for an antibody to prevent HIV, although the level of sustained serum neutralizing titers required for protection is higher than reasonably expected from current vaccination methods. Two ongoing trials show promise for future development of an HIV vaccine: the MOSAICO/HVTN706 trial and the PrEPVacc trial, which combines pre-exposure prophylaxis (PrEP) and a vaccine.

HIV vaccine researchers must determine whether it is possible to develop effective, long-lasting, broadly neutralizing antibodies for HIV prevention. Like most vaccine development efforts, successful development/implementation of an HIV vaccine require (1) sufficient and diversified research funding, (2) enhanced global coordination and collaboration, (3) support for research innovation and novel trial designs, (4) strengthened political commitment and urgency, (5) placement of affected communities at the center of vaccine research, and (6) early planning for success and equitable access to a vaccine.

HIV Vaccine Development: Challenges and Opportunities—Mary Marovich, M.D., National Institutes of Health (NIH)

HIV vaccine development faces numerous challenges, both scientific and social. In addition to the lack of an adequate human model, animal models are imperfect because they require researchers to work with viruses other than HIV (e.g., Simian Immunodeficiency Virus [SIV]). Socially, strong stigma against individuals with HIV/AIDS challenges public confidence in an HIV vaccine. Similarly, many members of the public are skeptical and distrustful of prophylactic and treatment efficacy.

The most effective vaccines against HIV provoke the body to create neutralizing antibodies (NAbs)—antibodies that neutralize the effects of infectious agents, like viruses, and are often protective. However, HIV NAbs were not identified until 2010 and researchers have only recently been able to apply their discovery to HIV vaccine development. Furthermore, the HIV virus constantly evolves, necessitating the

immune production of broadly neutralizing HIV antibodies (bNAbs)—NAbs that neutralize multiple generations of HIV. Researchers are not certain, however, if vaccines can provoke a protective level of bNAbs; multiple sequential vaccinations may be necessary to stimulate their production. HIV vaccine researchers are working to drive cells to produce bNAbs as part of the Scripps Consortium for HIV/AIDS Vaccine Development (CHAVD) immunogens.

HIV vaccine researchers could also accelerate development of vaccine designs that aim at new targets. The fusion peptide approach may use rapid mRNA platform production to perform small, targeted experimental medicine trials and high throughput analysis to guide development of the next generation of immunogens. The Collaborative HIV Immunogen Project (CHIP) will assemble several organizations to collaboratively define a set of immunogens that trigger neutralizing responses to one or more bNAb epitopes. CHIP will consider all sources of immunogens and prioritize and evaluate immunogens needed to elicit bNAbs.

Perspective: HIV Vaccines—COL Julia Ake, M.D., M.Sc., FACP, U.S. Military HIV Research Program

Globally, over 36 million people have died due to HIV/AIDS since 1981. Within the Department of Defense (DOD), approximately 300 new infections are reported annually, with an estimated $435,200 lifetime cost of therapy for each new infection leading to a total financial burden of more than $130 million annually to the DOD/VA. Furthermore, HIV infection threatens the national and military blood supplies needed for lifesaving transfusions and operations. Vaccines against HIV would be the most impactful tool in ending the HIV epidemic, potentially paired with broader male circumcision. In a 2016 publication, Thomas Harmon shared a model of the potential impact of an HIV vaccine, which showed that a 50 percent scale-up of the Investment Framework Enhanced (IFE) would significantly reduce annual new HIV infections by 2070 by 82.3 percent and cumulative HIV infections from 2013-2070 by 42.8 percent.

The Thai efficacy trial, also known as RV144, demonstrated that a preventative vaccine against HIV is possible. Vaccine efficacy on trial was 60 percent one year after immunization, compared to 31 percent in prior trials. The trial was discontinued before researchers were able to determine whether vaccine efficacy could be increased beyond 60 percent with sequential vaccination and boosting. An HIV vaccine with even 60 percent efficacy could significantly decrease the global incidence and transmission of the virus. Although a follow up clinical trial in sub-Saharan Africa did not demonstrate vaccine efficacy, researchers are not certain whether this was due to vaccine development limitations or the direct effect of the changes in setting, population, and prominence of infection among women in sub-Saharan Africa. The AMP Study evaluated two doses of a bNAb that failed to demonstrate overall prevention efficacy but did demonstrate 75.4 percent efficacy against isolated strains of HIV—providing a proof of concept for bNAb prevention.

The U.S. Army's RV217 Early Capture Cohort studies demonstrated that individuals infected with multiple strains of virus were more likely to subsequently develop bNAbs, suggesting that future HIV vaccine research efforts may successfully develop immunogens (the molecules that create an immune response) that are closely related to the original HIV strains for pre-clinical testing. Additionally, several emerging adjuvants provide promising potential for increasing immunity. advances including increased

HVTN 302/303: Protocol Overview—Jesse Clark, M.D., University of California, Los Angeles (UCLA)

The NIH launched a new Experimental Medicine (ExMed) pathway that takes a human immunology approach to support concept development and learn how to induce bNAbs. ExMed does not develop products, but instead iteratively designs immunogens—substances that produce an immune response.

Researchers utilizing the ExMed approach must continue to evaluate whether mRNA and lipid nanoparticle (LNP) delivery of soluble or membrane-bound HIV envelope (Env) trimers may provide a promising platform for rapid, iterative HIV vaccine development. Modified mRNA delivered within LNPs costs significantly less and can be GMP manufactured more rapidly than alternative delivery platforms. Most vaccine discovery efforts use soluble trimers due to difficulties associated with production and purification of membrane proteins. Trimer delivery by mRNA/LNPs allows for deployment of trimer immunogens that sit in the cell membrane, which may be advantageous for trimer conformational sampling and glycosylation. Most vaccine discovery efforts use soluble trimers due to difficulties associated with production and purification of membrane proteins., enzymatic attachment of a carbohydrate. Furthermore, membrane-bound trimer immunogens show a stronger anti-base response compared to traditional soluble trimers. The trimer may interact with CD4 and potentially alter the human antibody response. For this reason, HVTN 302 will also reveal whether vaccine developers should engineer HIV trimers for human immunization that lack CD4 affinity by evaluating the BG505 MD39.3 gp151 CD4KO HIV trimer mRNA vaccine.

The HIV Trials Network 302 Phase I clinical trial is evaluating the safety and immunogenicity of HIV trimer mRNA vaccines in healthy, HIV-uninfected adult participants. Subsets of participants will undergo fine-needle aspiration (FNA)—a diagnostic procedure using a small needle—to drain a lymph node after each vaccine dose or leukapheresis—separating white blood cells from a blood sample—after the second and third vaccine doses. FNA will allow researchers to study the magnitude (size of change) and kinetics (amount and speed of change) of B- and T-cell responses and how those differ between trimers. Investigators will not only assess and record safety and tolerability data using predetermined endpoints, but also enforce immunogenicity endpoints throughout the course of the clinical trial. Investigators will determine immunogenicity endpoints by measuring the occurrence and magnitude of serum antibody neutralization of pseudoviruses using the TZM-bl assay.

HVTN 303, a Phase I clinical trial, is evaluating safety, tolerability, and immunogenicity of the Adjuvanted HIV-1 Fusion Peptide Conjugate Vaccine alone or in Prime-Boost regimen with Adjuvanted HIV-1 Envelope Trimer 4571 vaccines in healthy, HIV-uninfected adult participants. The VRC identified a vulnerable region targeted by Nabs that shows promise for a vaccine approach that elicits reproducible, neutralizing immune responses in animal models according to pre-clinical studies. Investigators will first evaluate the safety, tolerability, and immunogenicity of single doses of the vaccines in a dose-escalation design prior to conducting a trial utilizing combinations of the three vaccine products.

Investigating Severe Hepatitis in Children

Overview of Nationwide Investigation of Pediatric Hepatitis of Unknown Etiology—David Sugerman, M.D., M.P.H., Centers for Disease Control and Prevention (CDC)

In November 2021, the Alabama Department of Public Health partnered with the CDC and treating physicians to investigate nine cases of acute hepatitis and adenovirus (AdV) viremia, for which a cause could not be identified. Testing confirmed that the children were negative for metabolic or autoimmune hepatitis. Two of the children, those with the highest AdV viral load, experienced acute liver failure and required liver transplants. Seven of the children were co-infected with other pathogens, although none were infected with nor vaccinated against SARS-CoV-2. Possible etiologies of hepatitis include (1) infections (i.e., Hepatitis viruses A-E, Herpes simplex virus, etc.); (2) medication toxicity; (3) immune dysregulation possibly from prior viral infection; or (4) metabolic disease. Even though AdV type 41 is known to cause hepatitis in immunocompromised children, AdV-linked hepatitis this has never been observed in immunocompetent children.

The UK Health Security Agency contacted the CDC in April 2022 to report an increase in local cases of acute pediatric hepatitis of unknown etiology. The U.K. Health Security Agency identified 197 such

cases, mostly among children under 5 years of age, between January and May 2022. UK clinicians detected AdV in 68 percent of cases tested and found that all AdV cases subtyped were type 41. U.K. clinicians also detected co-infection with SARS-CoV-2 in 15 percent of cases tested. Both U.S. and U.K. clinical investigators hypothesize that an unknown cofactor affecting young children renders normal AdV infections more severe or causes infections to trigger immunopathology.

Clinicians have detected 650 probable cases of pediatric hepatitis of unknown etiology from 33 countries. Nine deaths have been reported and 12 percent of cases required liver transplant. The U.S. and U.K. have reported most cases, with 61 percent of cases in the U.K. tested positive for AdV co-infection and approximately 46 percent of cases reported in the U.S. confirmed to have coinfection with AdV. U.S. clinicians define these cases in children under 10 years of age with elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 500 U/L who have unknown etiology for their hepatitis that have been identified after October 2021. The CDC has received preliminary reports of 274 patients under investigation that are distributed throughout the U.S. without clear geographic or temporal infection clusters. Over 90 percent of cases required hospitalization, 6 percent required a liver transplant, and nine children have died.

Help Eliminating the Silent Epidemic in America: New Adult Hepatitis B Immunization Recommendations

Expanding Adult Hepatitis B Vaccination: An opportunity to further hepatitis B elimination in the U.S.—Chari Cohen, Dr.P.H., M.P.H., Hepatitis B Foundation

Hepatitis B is a blood-borne viral infection of the liver. Over 2.4 million Americans live with chronic Hepatitis B and while there are effective treatments and five vaccines available in the U.S., there is currently no cure. Hepatitis B is primarily transmitted from mother-to-child at birth, through unprotected sex, and injection drug use that involves sharing equipment (e.g., needles). Acute Hepatitis B infections are increasing in the U.S. with 20,000-50,000 new infections annually. Only 25 percent of people infected with Hepatitis B are aware of their infection. Hepatitis B infection is the leading cause of liver cancer (e.g., hepatocellular carcinoma [HCC]) in the world. Vaccines against Hepatitis B are the first of their kind to prevent cancer. HCC has been the fastest growing cancer in incidence since 2013. In 2017, 41,000 new cases of HCC were diagnosed and 29,000 deaths were reported. Hepatitis B and HCC show the highest incidence among Asian American, Pacific Islander (AAPI), and African immigrant communities representing the primary health disparity for AAPIs.

Despite universal recommendation nationwide for vaccination against Hepatitis B for all adults ages 19-59 and adults over 60 years of age with risk factors, adult vaccine coverage against Hepatitis B has not kept pace with Hepatitis B Foundation and public health goals, in part due to stigma and low public awareness of Hepatitis B and associated negative health outcomes.

Looking ahead, the Hepatitis B Foundation and public health workers will overcome challenges through several key pathways: (1) improve awareness and expand access to the vaccine; (2) ensure that all stakeholders are part of the implementation; (3) create simple, widespread, and culturally competent messaging; (4) address hesitancy and stigma to increase vaccine demand; (5) provide training and resources for providers in various settings; (6) ensure state elimination plans include the Hepatitis B virus, specifically prevention, screening, and linkage to care; and finally (7) tell stories and engage with impacted persons.

Universal Hepatitis B Vaccination in Adults Aged 19-59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices—LCDR Mark K. Weng, M.D., M.Sc., Centers for Disease Control and Prevention (CDC)

Although the Advisory Committee on Immunization Practices (ACIP) only recommends vaccination against Hepatitis B for adults aged 19-59 years and adults aged 60 years and older with risk factors, the vaccine is also protective for adults over 60 years of age without known risk factors for Hepatitis B. ACIP recommends the routine three dose series of the PreHevbrio vaccine against Hepatitis B for adults over 18 years of age, although insufficient data exist for either the PreHevbrio or Heplisav-B vaccines to ensure safety and efficacy for individuals on hemodialysis, pregnant people, and breastfeeding people.

The CDC estimates that 20,700 Americans are infected with acute Hepatitis B annually, resulting in over $1 billion spent directly on Hepatitis- B-related hospitalization each year. The CDC further estimates that 1.89 million Americans live with chronic Hepatitis B infection with a 15 to 25 percent risk of premature death due to cirrhosis or liver cancer. The incidence of Hepatitis B in the U.S. has decreased significantly since the peak spread of infection in the mid-1980s primarily due to the increasing implementation of vaccination against Hepatitis B. In a 2018 paper, Peng-jun Lu showed that Hepatitis B vaccine coverage among adults is still relatively low (30 percent) despite wide availability of a vaccine. Hepatitis B infection rates are currently increasing among adults over 40 years of age. Approximately 67 percent of reported cases either report no identified risk or are missing risk data. Current infection rates have increased among Black American adults, up to three times the rate among AAPI and Hispanic groups. Public health workers and federal agencies could reduce these health disparities by universally recommending vaccination against Hepatitis B for all adults.

Strategies to Implement Universal Hepatitis B Vaccination for Adults 19-59—Rita Kuwahara, M.D., M.I.H., Georgetown University

A National Family Physician Survey from 2022 found that, of the 265 physicians that responded, only 55 percent were aware of the new ACIP Universal Hepatitis B Vaccine Guidelines and only 8 percent were implementing those ACIP Guidelines in their daily practices. These findings reveal a dire need to raise clinician awareness and familiarity with vaccine options and dosing schedules, possibly through partnership with the Medical Societies for Clinician Education. Federal, state, and local governments must increase available infrastructure and funding for Hepatitis B vaccination to improve access to vaccines for all Americans, including the uninsured and under-insured. One way to increase infrastructure is by expanding the existing COVID-19 vaccine infrastructure. The federal government should establish a Federal Immunization Information System that may enable use of Section 317 funding from the Public Health Service Act and the Vaccines for Adults Program as part of the President's Budget for the Fiscal Year of 2023.

Clinical protocols must stay up to date with most recent ACIP Guidelines and take proactive measures to increase the rate of vaccination against Hepatitis B among adult patients. Clinics should stock Hepatitis B vaccines and have standing orders to increase or maintain those stocks. Clinicians may also program alerts in electronic health records to show notifications for unvaccinated patients and coordinate patient reminders to encourage initial and follow-up vaccination for multi-dose Hepatitis B vaccines. All members of a clinic's health care team should discuss and encourage vaccination with patients and be prepared to provide educational materials in multiple languages to increase accessibility of vaccine information. These efforts should include partnerships between clinics and pharmacies to coordinate care and reminders, as well as to ensure that vaccination costs are covered to reduce barriers to vaccine accessibility.

Future vaccination efforts must emphasize outreach to and vaccination of high-risk communities—particularly AAPI and African immigrant communities and persons who inject drugs—preferably through

local community outreach programs. Vaccine information should also be available in multiple languages in non-clinical settings. Syringe service and exchange programs would further reduce the risk of Hepatitis B transmission among persons who inject drugs. Vaccine information should also be available in multiple languages in non-clinical settings. Clinics, pharmacies, and insurance providers must collaborate to reduce the out-of-pocket costs associated with vaccination against Hepatitis B and provide reimbursement for associated costs where possible. Clinics, pharmacies, and public agencies should streamline messaging and harmonize protocols to minimize confusion and promote clarity for patients. Furthermore, clinicians must direct patients that do screen positive for Hepatitis B to appropriate care. The CDC is currently updating their Hepatitis B Screening Recommendations to align with the U.S. Preventive Services Task force recommendation from 2020.

Hepatitis B Vaccination of High-Risk Adults and Dose-Series Completion—Carolyn B. Bridges, M.D., FACP, Immunization Action Coalition (Immunize.org)

In a 2019 paper, Carolyn Bridges published findings from a CDC pilot program conducted from 2012-2015 with Affordable Care Act (ACA) Prevention and Public Health Funding aimed at reducing Hepatitis B infection among high-risk adults through vaccination. The CDC funded 14 health department awardees, prioritizing locations with an acute incidence of Hepatitis B (greater than or equal to 1.2 cases per 100,000 total population). The CDC required that all department awardees use evidence-based strategies to improve vaccination rates. Awardees distributed 161,171 vaccine doses%, although only 91 percent were administered due to vaccine waste or lack of demand. Most of the doses were administered to health departments, corrections facilities, and sexually transmitted disease (STD) clinics.

Only an average of 40.4 percent of participants received a second vaccine dose and only 22.3 percent of participants received a third dose. Vaccinated individuals may not have returned for subsequent doses of the Hepatitis B vaccine due to stigma associated with visiting some of the vaccine sites (HIV clinics, STD clinics, and drug treatment facilities).

Awardees reported several challenges in administering Hepatitis B vaccines, including staff hiring and turnover, staff workload, limited experience with immunization information systems (IIS) data entry, and inherently mobile populations of incarcerated and homeless persons. Awardees recommended several strategies to improve vaccination such as infrastructure funding to facilitate staff training and vaccine storage as well as reminders and recalls for patients who received their first dose. Clinics must implement NVAC's Standards for Immunization Practice to improve not only Hepatitis B vaccination, but also vaccination against other diseases for which vaccines exist and are recommended.

Moving the Needle: Injection-Free Inoculations

Innovative Needle-Free Vaccine Delivery technologies—Myron M. Levine, M.D., D.T.P.H., University of Maryland (UMD)

All nations would benefit from advancements through facilitation of mass vaccination capacity during epidemics, pandemics, and potentially weaponized pathogens. LMICs stand to benefit from needle-free vaccine delivery technologies due to the increased risk of HIV transmission from sharps injuries, although this benefit extends to high-income countries (HICs) as well. In the U.S. the primary benefits are in decreasing discomfort in pediatric populations and among individuals who avoid needles due to intense fear. All nations would benefit from needle-free vaccine advancements through facilitation of mass vaccination capacity during epidemics, pandemics, and potentially weaponized pathogens. Researchers are developing promising needle-free alternatives such as trans- or percutaneous (through the skin) vaccination including jet injectors, hydration patches, and microneedle array patches (MAPs) as well as mucosal vaccination including oral, sublingual (under the tongue), and nasal delivery technologies.

Several jet injectors are already approved for clinical use in vaccine administration, such as the Bioject 2000 and the Pharmajet. Clinical trials in humans have shown jet injectors to be safe and effective.

Health workers may prefer mucosal vaccination due to its practicality, alignment with parental preference, and handling safety. Mucosal vaccines can also elicit rapid and long-lasting immunity by stimulating all areas of the immune system. Similarly, clinicians prefer mucosal vaccination against mucosal pathogens. For example, patients show tolerance to the Ty21a oral typhoid vaccine that delivers effective, long-term protection for at least 7 years. Powerful mucosal adjuvants enhance immune response to co-administered mucosal vaccines such as Cholera toxin (CT) and *E. coli*, though clinicians found that intranasal administration with non-toxic mutant adjuvants was most effective and well tolerated. However, researchers described cases of transient Bell's palsy reported following intranasal vaccination in Switzerland during the 2000-2001 flu season due to interactions between the *E. coli* adjuvant used and the facial nerve.

Small Volume Superficial Injections: No Needles, Less Pain and Trash—David Fernandez Rivas, Ph.D., M.Sc., Massachusetts Institute of Technology (MIT)

Superficial skin administration of needle-free vaccines would significantly reducing medical waste, sharps accidents, and the volumes of vaccine product necessary to confer immunity. Alternatives to traditional needle vaccine administration include jet injectors, microjet injectors, microneedles, and tattoo vaccination.

The University of Twente's jet injector heats liquid medicine or vaccine product with a continuous-wave (CW) laser beam, rapidly creating a bubble that forces the liquid product out of the cartridge with enough force to penetrate the skin or mucosa. This approach to vaccination and medicine delivery portable, less expensive, and safer than traditional injections. Superficial, needle-free injection also requires smaller volumes of vaccine product than traditional, deep-penetrating vaccine injections.

Jet injections may have applications to other medical procedures such as medical pigmenting, injections into the eye, diagnostics such as allergy testing, as well as cosmetic procedures such as Botox injection. For example, Twente's CW jet injector had higher vertical dispersion velocity compared to topical application and traditional needle injection without causing significant trauma to the skin. The University of Twente created a spinoff company, FlowBeams, to increase investment in the technology and secure buy-in from governments, private companies, and regulatory agencies.

Vaccine Delivery by 3D-Printed Microarray Patches—Shaomin Tian, Ph.D., University of North Carolina at Chapel Hill and Jillian Perry, Ph.D., University of North Carolina at Chapel Hill

MAPs carry arrays of microneedles for precise delivery of drugs to the thin layers of the skin. MAPs application is painless and can be completed by the individual receiving the vaccination. Dry formulations can potentially enhance thermostability and eliminate the need for cold chain storage and shipping, facilitating widespread distribution. The epidermis layer of the skin lacks sensory nerves that register pain, unlike in intramuscular and subcutaneous injection. Furthermore, the epidermis level of the skin contains a higher number of immune cells than deeper layers, enabling smaller doses.

The first generation of MAPs were created in the 1990s and early 2000s through microfabrication with uniform geometries (the 3D shape of the microneedle). Second generation MAPs of the mid 2000s were created through molding lithography and had limited geometries. Dissolvable MAPs were also developed during this second generation. The third and current generation of MAPs were first developed in 2016 using several manufacturing techniques (e.g., additive manufacturing, 3D printing) with direct fabrication of complex geometries, increasing microneedle surface area and vaccine volume capacity. Third

generation MAPs can be produced rapidly in either solid-coated or liquid-containing form. Patch level integration allows for delivery of an antigen and an adjuvant. Dynamic design elements enhance skin retention and vaccine product delivery using retractable hinges that deploy upon application.

Current MAP development efforts are focused on delivery of purified proteins from viruses for use in subunit vaccines, as well as lipid and polymeric nanoparticles for RNA vaccines. Future efforts will incorporate live attenuated vaccines, like those used for the measles vaccine. MAP vaccine production is developing capacity to manufacture large quantities of MAPs for mass vaccination needs with the MAP vaccine "gigafactory" producing 100 million doses in three months.

"Albumin Hitchhiking" Vaccines as a Strategy for Needle-free Mucosal Immunization—Darrell Irvine, Ph.D., Massachusetts Institute of Technology (MIT)

Mucosal immunization can elicit a strong immune response at the mucosa against respiratory pathogens, particularly SARS-CoV-2 and influenza, but the body's natural defenses can make this difficult. The mucosal lining and epithelial barrier are adapted to remove material and prevent penetration to the nasal-associated lymphoid tissue (NALT)—the layer that is the main site for immune responses in both natural infection and vaccination. To get past this barrier, scientists identified albumin as a potential chaperone. Researchers have designed amphiphile or "amph" vaccines that are made that of molecules that bind to albumin that attach to a target protein antigen.

Vaccine developers are testing albumin hitchhiking in animal models to deliver antigens both in new SARS-CoV-2 and HIV amph vaccines. Amph-proteins exhibit enhanced uptake and accumulation in nasal mucosa compared to other models. Investigators confirmed that the amph vaccine uptake was actively transported across the nasal mucosal epithelium to underlying NALT in a mouse model. Investigators found stronger systemic immunity to SARS-CoV-2, including in mucosal tissues distant from the nasal mucosa, among experimental mice that were given mucosal amph vaccines compared to control mice that were given free antigen in the mucosa alone. Investigators repeated this study in non-human primates with comparable results, showing strong immunogenicity using nasal mucosa amph-protein immunization against HIV.

Public Comment

No public comments were offered.

Adjourn

Dr. Hopkins thanked the participants and OIDP staff and recessed the meeting for the day at 5:44 p.m.

Day Two

Call to Order and Rules of Engagement—Ann Aikin, Acting Designated Federal Officer, NVAC

Ms. Aikin called the meeting to order at 9 a.m. ET on June 16, 2022 and welcomed the participants. She 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. Ms. Aikin thanked the Office of Infectious Disease and HIV/AIDS Policy (OIDP) staff for their support in organizing the meeting and called the roll.

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

Dr. Hopkins summarized the proceedings of day one and reviewed the agenda for day 2.

Easing Cold Chain Considerations

Cold-Chain Vaccine Distribution: Innovations for Efficiency, Effectiveness, Equity—Julie Swann, Ph.D., North Carolina State University

Dr. Swann began by providing an overview of supply chains, which are guided by systems that manage product flow, information flow, and movement of money and people. Supply chains aim for timely and cost-effective supply of the correct product to the right customer. While trade-offs between efficiency, effectiveness, and equity often occur within public health supply chain systems, addressing equity is imperative, particularly due to the differences in exposure and risk across the population. *Efficient* supply chains operate economically, *effective* supply chains help deliver meaningful outcomes, and *equitable* supply chains address disparities by providing resources that meet differing needs within the population.

In early 2021, supply chains dealt with a variety of challenges, many of which reflect general supply chain difficulties, such as demand uncertainty, supply variability, and difficulty forecasting. Various phases of the supply chain experienced challenges differently during the pandemic. Exacerbating these varying challenges is the fact that capacity limitations at different points along the supply chain are not well-understood. For example, the upstream sections of the supply chain (i.e., raw materials and supply steps) had difficulty managing the sudden increased demand for vaccines that were previously produced in labs at small quantities. Public health supply chains can be bolstered by improving the stability of supply, data and information sharing systems, information centralization, incentives and performance measurement, pooling (i.e., gathering information on demand to aid resource allocation), and providing a portfolio of products.

While challenges remain, improvements have been made since the H1N1 pandemic. The NASEM prioritization strategy (July 2020), increased speed and standardization, and improved partnerships, infrastructure, and data systems. Opportunities remain to improve (1) data systems and data sharing; (2) ultra-low cold chain requirements for safe vaccine distribution; (3) shifting roles and responsibilities; (4) allocation plans for resources with limited supply; (5) understanding of equity; (6) public-private-academic partnerships; and (7) public trust in the system, including identifying methods for combatting misinformation. Research can inform the strategies that address various gaps and opportunities that exist in current public health supply chains. Research examining previous pandemics' vaccine distribution provides insight into how supply chain factors impact vaccine coverage. For example, H1N1 vaccine coverage was higher when (1) a shorter lead time occurred between vaccine allotment and shipment; (2) vaccines were sent by states to broad access locations (e.g., pharmacies and clinics); and (3) new groups' eligibility was delayed. Research has also shown that inventory visibility can benefit supply chain systems. While industrial and commercial supply chain systems often have high inventory visibility, achieving this visibility is more difficult in public health systems.

Prioritization of front-line workers can reduce inequities while producing good mortality and morbidity outcomes. Additionally, combining targeted distribution while ensuring physical access—particularly for those without transportation or mobility—can help enforce prioritization for who receives vaccines. Lastly, practices that increase efficacy and efficiency—such as producing data visualizations that can facilitate effective decision support—can help reduce inequities. Ongoing challenges to be addressed by future research include supply chain vulnerability, trust and misinformation issues, limited resource availability, challenges during the last mile, poor prioritization that ensures equitable access, and ongoing problems related to data systems and data sharing. Including neutral supply chain experts on advisory committees could help address these ongoing challenges.

Supply Chain Networks, Labor, and Resilience—Anna Nagurney, M.D., University of Massachusetts Amherst

Dr. Nagurney emphasized that we live in a supply chain network economy and bolstering the resilience of supply chains is critical. This resilience can be fostered through multidisciplinary approaches, operations research, network theory, game theory and data science and algorithm development. Together, network theory and predictive and prescriptive analytics can help build resilience in supply chains, save lives, and preserve the economy by helping supply chains prepare for challenges *before* they occur.

While preserving quality across the supply chain is imperative for preserving trust with the public, quality failure occurred many times during the COVID-19 pandemic, including failures during vaccine manufacturing. Dr. Nagurney's work identifies the most important areas to target and guides investment by displaying network interactions between various supply chains, products, and pharmaceutical companies. These networks can help visually organize the many components that make up vaccine manufacturing, and globally map where necessary resources come from—an important feature given how global emergencies can impact resource availability.

Supply chain models derived from network and game theory—two different mathematical models—must recognize labor as a critical resource for supply chains, because people and their labor are at the heart of supply chains and manufacturing. Game theory can display how labor competition and demand markets interact. Dr. Nagurney's recent work constructed supply chain game theory network models to better understand how disruptions in labor relate to supply and productivity. Network models can identify areas for supply chain optimization and display how various nodes in the network model relate to labor constraints. Dr. Nagurney's research identified three key findings: (1) free movement of labor across the supply chain network results in improved efficiency and resilience; (2) reduction in labor productivity can impact efficiency and resilience; and (3) the presence of electronic commerce escalates efficiency but reduces resilience.

A lack of labor in a single supply chain can have major negative impacts on supply chain network product flows and prices. Preserving worker health and wellbeing and having appropriate healthcare pandemic mitigation processes and procedures in place are essential for continuing operations.

Innovations that Improve Vaccine Cold Chain Distribution—Joanie Robertson, Ph.D., PATH

PATH uses a multidisciplinary approach and private-public partnerships to improve global equity and access to health, primarily through technology development in LMICs. To support cold chain distribution, PATH has contributed to the development of vaccine vial monitors (VVM) and freeze-preventive vaccine carriers.

VVMs are small stickers that adhere to vaccine vials and change color as the vaccine is exposed to heat, informing health workers of whether to use or discard a vaccine. VVMs' ability to quickly display vaccine potency serves many functions, including providing reassurance to healthcare workers administering the vaccine, facilitating vaccine management policies, supporting the assessment of potency after cold chain breaks occur, and providing a visible vial-level tool for managing vaccines. VVM development was a lengthy process, beginning in the 1980s and leading to FDA approval in the 2000s. Because VVM is still a sole-source technology under Temptime, PATH is working to get new VVM technologies approved by WHO to improve VVM sourcing diversity. Different VVM types can be used to address variance in vaccine thermostability, and new VVM types can be developed as needed when new vaccines are created.

Out of UNICEF's $1.7 billion annual procurement for vaccines, $1.2 billion worth are freeze-sensitive vaccines, which can lose potency when exposed to freezing temperatures during transport and outreach. PATH has developed freeze-preventive vaccine carriers, which have an engineered barrier that prevents

accidental freezing of vaccines. These carriers can hold ice packs without risk of vaccine exposure to freezing temperatures. By separating the ice and the vaccine with a uniquely engineered material, temperatures above freezing can be maintained. These carriers also simplify logistics, save health worker time, and reduce long-term training burden. This technology was transferred to multiple manufacturing partners to bring the product to market, and devices are now globally available.

Discussion

Dr. Dunn inquired as to the feasibility of implementing VVMs and freeze-preventive vaccine carriers in HICs such as the U.S. as both technologies have potential uses beyond their intended application in LMICs. Dr. Robertson responded that yes, both technologies can be readily implemented in HICs. However, vaccine manufacturers must purchase VVMs for specific vaccines and they are unlikely to take on additional costs without consumer or vaccine purchaser demand. For example. the Canadian government has taken steps to require VVM labeling. To address this, manufacturers may prefer the freeze-preventive vaccine carriers from China and India, which may be less expensive than carriers currently in use in the U.S.

Dr. Cooke asked whether coverage rates would have been different in the U.S. had the SARS-CoV-2 vaccines from Pfizer and Moderna not required specialized cold storage. Dr. Swann conjectured that while the vaccine may have been more accessible to communities without cold storage earlier in the pandemic, many Americans still would have expressed concern and hesitancy about the SARS-CoV-2 vaccine regardless of cold-chain storage and distribution due to the novelty of the pathogen and vaccine. Dr. Robertson added that the temperature requirements of the vaccines were unknown until later in vaccine development adding a time constraint that stressed the existing vaccine distribution system.

COVID-19 Vaccine Safety Review

COVID-19 Vaccine Safety Technical (VaST) Work Group: Safety Assessment—Robert Hopkins, Ph.D., National Vaccine Advisory Committee (NVAC)

VaST serves as the central hub for technical subject matter expertise from federal agencies conducting post-authorization/approval safety monitoring by reviewing, evaluating, and interpreting COVID-19 vaccination safety data. VaST continues to review COVID-19 vaccination safety data from passive and active surveillance systems, including the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), the FDA Biologics Effectiveness and Safety (BEST) System, the Department of Veterans Affairs (VA), Indian Health Service (IHS), and the DoD. International partners include the Public Health Agency of Canada and the Global Advisory Committee on Vaccine Safety. VaST conducts special evaluations, including on myocarditis case follow-up studies.

From December 21, 2020, through February 11, 2022, VaST held 55 independent meetings to review vaccine safety data, 15 joint meetings with ACIP COVID-19 Vaccines Work Group, and 16 ACIP meeting presentations or reports with VaST assessments. On April 20, 2022, VaST used data from their VaST Assessment of Safety of COVID Vaccine Booster Vaccination in a meeting with ACIP to discuss the second booster dose of SARS-CoV-2 vaccines in adults. On May 19, 2022, VaST met with ACIP to consider the second booster dose of SARS-CoV-2 vaccines in children aged 5-11 years. VaST found that systemic reactions following booster vaccination were less frequent in adults over 18 years old and slightly more frequent in adolescents ages 12 to 17 compared to the primary series second dose. VAERS found that myocarditis rates were highest among males ages 12 to 29 years old. VAERS also found that pericarditis was reported similarly by sex and age group, although low case counts complicated estimation of actual rates.

VSD Rapid Cycle Analysis (RCA) revealed that the only safety signal for SARS-CoV-2 first booster dose was myocarditis or pericarditis. In individuals ages 12 to 39 myocarditis or myopericarditis were most

common vaccine adverse events with onset less than 7 days after vaccination. The event rate per million first booster doses was not higher than after primary series second dose. In individuals over 40 years old, pericarditis was the most common vaccine adverse event, with onset up to three weeks after vaccination. RCA revealed no safety signals for mRNA booster dose within 21-days post-dose. Chart review confirmed 15 myocarditis or pericarditis reports after booster dose: 10 cases of pericarditis and 5 of myocarditis. They also found 14 of the 15 reported incidents occurred in individuals over 40 years of age.

VaST provided assessments on booster dose safety at four ACIP meetings. Reactogenicity was similar to or lower than rates seen after the primary vaccine series and the myocarditis risk appears lower than after the primary series second dose. Further analyses are needed to understand the risk of pericarditis. While available data do not suggest safety concerns beyond those previously identified, VaST will carefully monitor data on myocarditis and pericarditis after booster doses.

Providers administered 18.1 million doses of the Pfizer vaccine to children ages 5 to 11 years in the U.S. VaST reviewed the most recent available data from VAERS, V-Safe, and VSD to assess safety after the primary vaccination series in children ages 5 to 11 years and after booster doses in adolescents ages 12 to 15 years. Safety data do not suggest potential safety concerns regarding a Pfizer COVID-19 vaccine booster dose for children ages 5 to 11 years beyond those concerns identified in older age groups.

The CDC Immunization Safety Office and FDA have standard and systematic methods for following up on all reported deaths following vaccination. Population-based studies conducted to date have not identified increased risk of death following vaccination against COVID-19.

Monitoring COVID-19 Vaccine Safety in Real-Time Within the Vaccine Safety Datalink—Nicola Klein, M.D., Ph. D., Kaiser Permanente Vaccine Study Center

The VSD was established in 1990 as a collaborative project between CDC and nine integrated health care organizations for over 12 million people in the U.S. VSD uses a distributed data model to integrate health information from electronic medical records (EMR) to update CDC on a weekly and annual basis. Every week, VSD updates data and analyses through RCAs for 11 vaccines as well as the available, approved vaccines against SARS-CoV-2. RCAs are best suited for serious, clinically well-defined, and coded outcomes with acute onset within days or weeks of vaccination. RCA surveillance began in December 2020 and aims to monitor the safety of COVID-19 vaccines on a weekly basis using 23 pre-specified outcomes of interest and describe the uptake of COVID-19 vaccines over time by age, site, race, and ethnicity.

New cases of serious outcomes following vaccination are identified within EMR systems during an appropriate interval following vaccination against COVID-19, followed by a quick chart review within one week to confirm if the case is meets the VSD definition of an incident. Cases that meet VSD definition continue on to full chart abstraction and adjudication and feed into the weekly RCA. Statistical analysis revealed that rate of myocarditis following vaccination is statistically significant in the first seven days following vaccination. VSD further identified similar risk of myocarditis and pericarditis in the first seven days following booster vaccination among individuals over 12 years old. Myocarditis and pericarditis risk was elevated after mRNA vaccination after both the primary series and the first booster for individuals aged 12 to 39 years.

Safety of Heterologous COVID-19 Booster Vaccines—John Beigel, M.D., National Institutes of Health (NIH)

The Heterologous Platform Boost Study set out to determine the immune response following booster vaccination against SARS-CoV-2 as well as the safety profile of booster vaccination using a vaccine developed by a different company than that used for the primary vaccination series (e.g., the safety of boosting with the Pfizer vaccine after first receiving Moderna or Janssen). NIH designed the study to

generate immunity data to inform public health decisions with approximately 50 participants per group and a total of 458 participants.

Researchers reported that every combination of vaccine and booster provided immunity using the three vaccines available in early 2021. While immunogenicity was stronger in both the Moderna and Pfizer vaccines and boosters, the Janssen vaccine was still protective, and boosting was still effective. Heterologous boosts (boosts from different manufacturers) had similar rates of solicited adverse events (AEs) as homologous boosts (boosts from the same manufacturer). Most related AEs were not serious, and included vomiting, fatigue, and insomnia. Two serious AEs were reported but determined to be unrelated to vaccination. Investigators concluded that heterologous boosts elicited similar or better responses compared and similar rates of reported AEs, suggesting that the safety of heterologous boosts are not significantly different than homologous boosts.

The Potential Influence of a COVID-19 Vaccine's Effectiveness and Safety Profile of Vaccination Acceptance: Results from a National Survey—Robert Kaplan, Ph.D., Stanford University

Vaccination against SARS-CoV-2 holds the greatest promise for resolving the COVID-19 pandemic and refusal to take the vaccine diminishes the likelihood of achieving herd immunity. The Stanford Clinical Excellence Research Center (CERC) collaborated with YouGov to conduct a national survey of 1,000 people from all states in August 2020 and again in December 2020. CERC designed the survey using a 3-by-3-by-3 experimental design estimating the impact of three factors: vaccine efficacy, minor side effects, and serious adverse effects. The survey asked participants how likely they would be to take a free, hypothetical vaccine against COVID-19 given a range of vaccine efficacy and minor side effects at rates of 50, 70, or 90 percent each, as well as a range of serious adverse effects at rates from 1 in 100,000 people, 1 in 1 million people, or 1 in 100 million people.

The survey sample was matched to the demographics of the U.S. population by sex, race, and age using weighting methodologies. Efficacy was systematically and linearly related to likelihood of taking the vaccine. Overall, most respondents reported that they would be unlikely to take the vaccine (27.2 percent "very likely", 13.1 percent "somewhat likely", 36.1 percent "somewhat unlikely", and 23.6 percent "very unlikely"). Respondents reported being less likely to take the vaccine if serious adverse events were more common, although minor side effects were unrelated to likelihood of taking the vaccine. Further analysis revealed that information on safety and efficacy has much lower impact than political ideology and educational attainment with conservative respondents and those with lower levels of education expressing greater hesitancy to get vaccinated.

Discussion

Dr. Dunn asked whether experiencing a vaccine adverse event with any one dose correlated to a higher likelihood of adverse events from subsequent doses. For example, people that experience an adverse event following vaccination may be less likely to get vaccinated again, potentially skewing booster safety data. Dr. Klein responded that the data required to perform such an analysis are not actively being collected and unavailable to run analyses. However, the existing data come from large populations suggest that attrition is unlikely to skew booster safety data.

Kristen R. Ehresmann, R.N., M.P.H., drew the connection between rates of myocarditis and pericarditis following vaccination compared to rates following COVID-19 infection. Dr. Klein responded that the VSD so far only looked at data from vaccinated individuals. Assessing the rate of myocarditis and pericarditis following COVID-19 infection is an important consideration but would involve a significant undertaking collecting data from a large population beyond the scope of VSD. Dr. Hopkins added that cases of myocarditis and pericarditis following vaccination tend not to last as long or be as severe compared to cases following COVID-19 infection.

Dr. Mullen suggested that future communications about the safety and efficacy of vaccination against SARS-CoV-2 should include information about the reduction in symptom severity of infection following vaccination to educate hesitant communities about the overall benefits of vaccination. While vaccination does not completely prevent new infections, infections following vaccination are significantly less severe. This finding would be useful for individuals that may be hesitant about vaccination.

Dr. Duchin inquired as to what, if any, information may cause vaccine hesitant individuals to reconsider their hesitancy. Dr. Kaplan responded that people are influenced by efficacy information more than safety. Survey results showed that vaccine hesitancy did not drop between August and December, calling into question the effectiveness of information campaigns and efforts. By December, both Pfizer and Moderna had already released safety and efficacy results that were much better than those given for the hypothetical vaccine in the survey.

Dr. Schechter inquired if Dr. Kaplan had any insights into initial and persistent disinterest extending from time before availability regarding risk benefit perception. Dr. Kaplan emphasized again that CERC did not see the decrease in vaccine hesitancy that they had initially expected following the publication of vaccine safety and efficacy data as well as the ongoing information campaigns. Dr. Kaplan noted that the survey did ask questions about participant suspicion of dishonest or deceitful government practices and a hasty rush for vaccine EUA. Survey investigators found that education and political ideology, rather than safety and efficacy concerns, were dominant factors in vaccine hesitancy.

Monkeypox 2022: U.S. Situation Summary

Monkeypox Update—CPT Brett Peterson, M.D., M.P.H., Centers for Disease Control and Prevention (CDC)

Monkeypox is caused by the monkeypox virus of the *othopoxvirus* genus and presents clinically as a disseminated pustular rash associated with fever, lymphadenopathy (swelling of the lymph nodes), and malaise. Human-to-human transmission occurs with direct contact with body fluid or lesions, respiratory secretions, and possibly through bodily fluids. As of June 13, 2022, 65 total cases of monkeypox have been reported in the United States, primarily in California, New York, and Illinois. Globally, 35 countries reported a combined 1,678 confirmed cases.

Two vaccines are currently available to prevent spread of monkeypox: JYNNEOS and ACAM2000. FDA licensed JYNNEOS in September 2019 and ACAM2000 in August 2007. JYNNEOS is currently approved for use in adults aged 18 and older determined to be at high risk for monkeypox infection. CDC is currently developing an expanded access Investigational New Drug protocol to allow the use of JYNNEOS in pediatric populations. CDC-held Emergency Access Investigational New Drug protocol allows for ACAM2000 use during monkeypox outbreaks. The two-dose series JYNNEOS vaccine appears to have a lower risk of serious adverse events compared to the single dose ACAM2000 vaccine. The risk of myopericarditis following ACAM2000 is believed to be higher compared to the JYNNEOS vaccine.

ACIP voted to recommend JYNNEOS vaccination for select persons at risk for occupational exposure to *orthopoxviruses*. PrEP vaccination is recommended for clinical and research laboratory personnel who handle *orthopoxvirus* samples as well as certain health care and public health response team members designated by public health authorities for preparedness purposes. ACIP contraindications for monkeypox PrEP vaccination include serious allergy of vaccine components for JYNNEOS vaccination. For the ACAM2000 vaccine, ACIP contraindications include (1) history or presence of atopic dermatitis, (2) other active exfoliative skin conditions, (3) conditions associated with immunosuppression, (4) pregnancy, (5) age under 1 year, (6) breastfeeding, (7) serious vaccine component allergy, (8) known underlying heart disease, (9) three or more known major cardiac risk factors. Brief interactions and those

conducted using appropriate personal protective equipment (PPE) in accordance with Standard Precautions do not pose a high risk and generally do not warrant post-exposure prophylaxis (PEP).

Many individuals infected with monkeypox have a mild disease course without treatment. The prognosis for monkeypox depends on multiple factors, such as previous vaccination status, initial health status, and concurrent illnesses or comorbidities. Providers can treat monkeypox with tecovirimat, cidofovir, and Vaccinia Immune Globulin Intravenous (VIGIV). Tecovirimat is an antiviral medication, available from the Strategic National Stockpile, that is FDA-approved for the treatment of human smallpox disease in adults and pediatric patients weighing at least 13 kg (about 29 lbs.) administered either orally or intravenously. Cidofovir is an antiviral medication approved by FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. VIGIV is licensed by FDA for the treatment of complications due from a vaccinia virus.

Discussion

Dr. Hoft inquired whether JYNNEOS had been studied for PEP indication. Dr. Petersen responded that clinical research on JYNNEOS for PrEP or PEP indication is limited. Data from the smallpox era suggest that vaccination provided an 85 percent protection. CDC believes that approved smallpox vaccines can be effective at preventing monkeypox. No new cases of monkeypox were reported during the two-year monitoring period in an ongoing study of monkeypox vaccination among health workers in the Democratic Republic of the Congo, although one participant was diagnosed with monkeypox after the monitoring period.

Dr. Douglas asked about the timeframe for PEP vaccination following exposure. CAPT Petersen responded that limited data make it difficult to determine the exact window of PEP protection following exposure. CDC recommends PEP vaccination immediately after exposure, if possible, but estimates that PEP may still provide protective effects up to four days after exposure and symptom reduction up to 14 days after exposure. Dr. Douglas asked CAPT Petersen to predict the potential severity of this most recent outbreak of monkeypox. CAPT Petersen responded that CDC is genuinely concerned by the current outbreak, because it is the largest recorded outbreak outside of endemic countries. The rate of monkeypox infection is disproportionately high among men who have sex with men, whose network is often private, making the disease difficult to track.

Dr. Mullen inquired about CDC's approach to communicating to the public and providers about the risks, transmission, and stigma associated with monkeypox. Dr. Petersen responded that CDC is collaborating with STI and HIV experts to address the evolving epidemiology of monkeypox in the United States and to produce non-stigmatizing public communication.

Dr. Schechter inquired whether the incubation periods of the current outbreak of monkeypox have varied compared to previous outbreaks. The clinical presentation has changed slightly compared to previous outbreaks. Previous monkeypox outbreaks have been characterized by a prodrome of early fever, fatigue, and flu-like symptoms preceding rash-like symptoms. Recent findings suggest that skin lesions may appear before this prodrome. CDC is also reporting shorter incubation periods in this current outbreak, potentially related to the route of sexual transmission. Dr. Petersen responded that CDC recently released a Health Alert Network communication describing the clinical and epidemiological details of the most recent outbreak.

A Paradigm Shift: Improving Representation in Clinical Trials

Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups—Carlos del Rio, M.D., Emory University

Improving representation in clinical research is urgently needed to address disparities in chronic diseases and requires sustained investment, transparency, and accountability by researchers to increase trust among underrepresented communities. Representation in clinical research is the responsibility of all stakeholders including participants, communities, investigators, institutional review boards (IRBs), industry sponsors, institutions, funders, regulators, journals, and policymakers. Improving representation also requires a paradigm shift that transfers the balance of power from the institutions, placing it at the center of the community, with a focus on community priorities, interests, and voices.

Insufficient representation may compromise generalizability of clinical research and undermine trust in the findings, recommendations, and products of clinical research in the United States. The persistent lack of representation of key populations (i.e., male, Black, American Indian, and Hispanic populations) in clinical research prompted Congress to commission a report by NASEM. This report assessed 230 U.S.-based trials with a combined total of 219,555 participants. While each trial reported participant sex and age, only 58.3 percent of trials reported race and only 34.3 percent of trials reported ethnicity. In those trials that reported race and ethnicity, white individuals were overrepresented compared to Black, American Indian, and Hispanic individuals and females were overrepresented compared to males. The NASEM report made several recommendations to Congress:

1. HHS should establish an intradepartmental task force on research equity charged with coordinating data collection and developing better accrual tracking systems across federal agencies.
2. NIH should standardize the submission of demographic characteristics for trials beyond existing guidelines so that trial characteristics are labeled uniformly across the database and can be easily disaggregated, exported, and analyzed by the public.
3. FDA should require study sponsors to submit a detailed recruitment plan no later than at the time of Investigational New Drug and Investigational Device Exemption application submission that explains how they will ensure that the trial population appropriately reflects the demographics of the disease or condition under study.
4. The Office of Human Research Protections (OHRP) and FDA should direct local IRBs to assess and report the representativeness of clinical trials as one measure of sound research design that it requires for the protection of human subjects.
5. Congress should direct FDA to enforce existing accountability measures, as well as establish a taskforce to study new incentives for new drug and device for trials that achieve representative enrollment.
6. The Centers for Medicare and Medicaid (CMS) should expedite coverage decisions for drugs and devices that have been approved based on clinical development programs that are representative of the populations most affected by the treatable condition.
7. CMS should incentivize community providers to enroll and retain participants in clinical trials by reimbursing for the time and infrastructure that is required.
8. Federal regulatory agencies, including OHRP, NIH, and FDA, should develop explicit guidance to direct local IRBs on equitable compensation to research participants and their caregivers.
9. All entities involved in the conduct of clinical trials and clinical research should ensure a diverse and inclusive workforce, especially in leadership positions.
10. HHS should substantially invest in community research infrastructure that will improve representation in clinical trials and clinical research.

Improving Representation in Clinical Trials—Zeke McKinney, M.D., M.H.I., M.P.H., FACOEM, HealthPartners

The COVID-19 pandemic has disproportionately affected Black, Indigenous, and people of color (BIPOC) communities—in part due to the legacy of slavery in the United States, which includes racial and ethnic segregation, disproportionate levels of poverty, and lack of access to health care. This legacy is known as systemic racism, the effects of which were apparent throughout the COVID-19 pandemic response. During the pandemic, infection rates have been highest among marginalized populations who are least likely to have access to testing, such as undocumented residents, incarcerated people, people of color, and members of the LGBTQ community. Furthermore, the most marginalized workers have been disproportionately burdened by infection and disease, as has been the case historically for all diseases for which the workplace environment is a root cause. In addition, disproportionately affected groups are most likely to be missed in tracked cohorts of cases and therefore underrepresented in pandemic monitoring data collection.

In addition to decreasing access to testing and increasing workplace risk, systemic racism influences treatment in the clinic. Clinicians are not immune to systemic racism, demonstrating implicit bias against BIPOC patients. This bias not only impacts medical decision-making, but also communication between clinicians and patients. Perceived clinician bias combined with peripheral traumas (i.e., poor clinical and social experiences resulting from systemic racism) and a history of harmful medical research and law enforcement violence have culminated in deep seated mistrust and distrust of health care and medical research among BIPOC communities. Peripheral trauma is one of the strongest factors of distrust and mistrust and can include elements of clinical experiences such as clinicians labeling patients of color as drug seeking or difficult and elements of social experiences such as immigration laws and associated stigma. Historical examples of racist medical research contribute to peripheral trauma such as the Tuskegee Syphilis trials and Marion Sims' experimentation on enslaved people in the 19th century. Stigmatization of infectious diseases further contributes to peripheral trauma and mistrust in health care and clinical research. For example, stigma arose surrounding HIV/AIDS as an alleged disease of the LGBTQ community or COVID-19 as the "China Virus."

Communities of color would likely express strong skepticism if medical research were conducted using exclusively White or Black participants. Clinical research must strive for demographic equity in investigations to not only improve external validity of studies, but also build trust among communities of color. To this end, health information must be made accessible, and clinicians must actively acknowledge the concerns of patients. Concerned individuals may have competing interests, requiring them to weigh vaccination against childcare, transportation, and employment.

Federal Agency and Liaison Representative Updates

Biomedical Advanced Research and Development Authority—Christine Oshansky, Ph.D.

BARDA continues to coordinate and collaborate with industry and inter-agency partners to support the federal COVID-19 response through advanced development and procurement of vaccines. In addition, BARDA continues supporting Merck's development of ERVEBO®, a vaccine against Ebola that may soon be approved for use in pediatric and HIV-positive populations. BARDA is also supporting efforts to vaccinate populations against monkeypox through licensure of Bavarian Nordic's JYNNEOS vaccine. Lastly, BARDA continues to work on projects for anthrax, Zika, and pandemic influenza vaccines and needle-free vaccine delivery.

Centers for Disease Control and Prevention—Melinda Wharton, M.D., M.P.H., CDC

José R. Romero, M.D., was recently appointed Director of the National Center for Immunization and Respiratory Diseases (NCIRD) and Georgina Peacock became Acting Director of NCIRD's Immunization Services Division (ISD). ACIP will hold a meeting on June 17, 2022, to discuss the use of

Pfizer's and Moderna's SARS-CoV-2 vaccines in infants and children aged 6 months to 4 years or 5 years, respectively. ACIP will also hold a regularly scheduled meeting on June 22-23, 2022, to discuss the use of the Moderna SARS-CoV-2 vaccine in older children ages 6-17 years.

Department of Defense Health Agency, Immunization Healthcare Division— Bruce McClenathan, M.D., FACP, FAAAAI

As of May 16, 2022, DOD had administered 8.2 million doses of FDA-approved or -authorized COVID-19 vaccinations globally. During the pandemic, DOD has connected VAERS reports to its own health care record system to enable investigation of reported adverse events and has operated an all-hours immunization-related Support Center for questions related to adverse events. DOD continues its annual southern hemisphere influenza vaccine program and is following several reports of monkeypox in multiple global location.

Food and Drug Administration— Jay Slater, M.D.

One June 3, 2022, FDA approved the PRIORIX vaccine against measles, mumps, and rubella (MMR) for individuals aged 12 months or older. Over the past six months, FDA updated the EUAs for three SARS-CoV-2 vaccines from Janssen, Moderna, and Pfizer and on January 31, 2022 approved Moderna's mRNA vaccine for use in adults 18 years of age and older. FDA convened three meetings of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss the SARS-CoV-2 vaccine manufactured by Novavax and potential EUA approval for pediatric and infant use of Moderna's and Pfizer's SARS-CoV-2 vaccines. VRBPAC will meet again on June 28, 2022 to discuss whether the SARS-CoV-2 strain composition of vaccines should be modified and, if so, what strains should be selected for Fall of 2022.

Indian Health Service—Uzo Chukwuma, M.P.H.

IHS maintains its COVID vaccine task force, initiated in September 2020 to facilitate the agency-wide allocation, distribution, and administration of COVID-19 vaccines within the IHS or graded facilities, the Tribal Health programs, and urban Indian organizations. IHS is currently preparing for tribal community distribution of SARS-CoV-2 vaccines to children under 5 years of age following EUA. IHS maintains its commitment to providing up-to-date messaging on vaccine safety and efficacy, including information on SARS-CoV-2 vaccine boosting for children between 5 and 11 years of age and information for vaccine hesitant communities. IHS has leveraged its COVID-19 vaccine strategies to implement recommendations for the new 20-valent pneumococcal vaccine, the Zoster vaccine in immunocompromised individuals 19 years and older, and the expanded use of the hepatitis B vaccine.

America's Health Insurance Plans —Devin Plote, Ph.D.

AHIP helped vaccinate over 2 million senior citizens against SARS-CoV-2 in 100 days through the Vaccine Community Connectors program. During the pandemic, AHIP has also encouraged providers to maintain routine vaccination regimens among all age groups and has used data from insurance claims to identify individuals who have not yet received routine or SARS-CoV-2 vaccination to encourage them to schedule vaccination appointments. AHIP further collaborates with providers to deliver accurate and culturally competent education materials to promote the safety and efficacy of the SARS-CoV-2 vaccine among vaccine hesitant individuals.

Association of Immunization Managers—Claire Hannan, M.P.H.

AIM is hosting its Leadership in Action Conference to provide leadership training for immunization program managers August 30 to September 1, 2022. In August 2022, AIM partnered with CDC on the Immunization Champion Award, which recognizes individuals who have made major contributions to promote vaccination nationwide. AIM recently participated in a virtual roundtable with HHS Secretary

Xavier Becerra on increasing routine vaccination and is partnering with local jurisdictions in six states to send reminder postcards to families of children and adolescents who are due for routine vaccines.

American Pharmacists Association—Jean-Venable "Kelly" Goode, Pharm.D., BCPS, FAPhA, FCCP

APhA is the largest pharmacist organization in the United States, representing more than 60,000 members. Pharmacists continue to play a critical role in vaccinating communities against SARS-CoV-2 and are prepared to begin vaccinating children under 5 years of age. APhA supports pharmacists through provision of immunization awards, trainings, information, and resources.

Association of State and Territorial Health Officials— Meredith Allen, Dr.PH., M.S.

ASTHO has collaborated with partners to prepare for the upcoming approval of SARS-CoV-2 vaccines for younger pediatric populations by funding vaccine purchases and providing communication materials on the safety and efficacy of vaccination. ASTHO also recently held a national COVID-19 summit. ASTHO is currently developing "technical packages" for health officials, including one package focused on increasing immunization in adult populations, and with the Office of the National Coordinator for Health Information Technology (ONC) is helping cross-sector teams implement immunization data sharing plans and action steps.

National Association of County and City Health Officials— John Douglas, M.D.

NACCHO maintains an incident management structure to help local health departments respond to COVID-19, largely through vaccinations. NACCHO's recently updated its policy statement on influenza vaccination for health care personnel, is equipping local health departments to address vaccine hesitancy and increase vaccine uptake, and—through its Partnering for Vaccine Equity program—is addressing racial and ethnic disparities in vaccination rates. Local health agencies nationwide have been preparing for monkeypox, by raising awareness, performing contact tracing, and offering post-exposure prophylactics recommendations.

Written updates only were provided by the U.S. Department of Agriculture, Department of Veterans Affairs, and Public Health Agency of Canada.

Public Comment

No public comments were offered.

Adjourn Meeting

Dr. Hopkins thanked the participants and NVAC members and adjourned the meeting at 1:49 p.m.

Appendix: Abbreviations List

ACCV	Advisory Commission on Childhood Vaccines
ACIP	Advisory Committee on Immunization Practices
AHA	American Hospital Association
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
APhA	American Pharmacists Association
ASPE	Office of the Assistant Secretary for Planning and Evaluation
ASH	Assistant Secretary for Health
ASTHO	Association of State and Territorial Health Officials
BARDA	Biomedical Advanced Research and Development Authority
CDC	Center for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CHIP	Children's Health Insurance Program
CMS	Centers for Medicare & Medicaid Services
CoP	correlate of protection
COVID-19	Coronavirus disease 2019
CRISP	Chesapeake Regional Information System for Our Patients
DTP	Diphtheria, Tetanus, and Pertussis vaccine
DTP3	third dose of DTP or DTaP
EHR	electronic health record
EO	Executive Order
EUA	emergency use authorization
FDA	Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources
H-CORE	HHS Coordination Operations and Response Element
HHS	Health and Human Services
HIMSS	Healthcare Information and Management Systems Society
HL7	Health Level Seven
IHS	Indian Health Service
IIS	Immunization Information System
LMICs	low- and middle-income countries
MMR	measles/mumps/rubella vaccine
NACCHO	National Association of County and City Health Officials
NCI	National Cancer Institute
NHP	non-human primate
NIH	National Institutes of Health
NSC	National Safety Council
NTDs	Neglected tropical diseases
NVAC	National Vaccine Advocacy Committee
NVIC	National Vaccine Information Center
NVPO	National Vaccine Program Office
OCR	Office of Civil Rights
OIDP	Office of Infectious Disease and HIV/AIDS Policy
ONC	Office of the National Coordinator for Health Information Technology
OSHA	Occupational Safety and Health Administration
PPP	Public-private partnerships
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus disease 2019
USG	U.S. Government
WHO	World Health Organization

VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST	Vaccine Safety Technical Work Group
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink