NVAC NATIONAL VACCINE ADVISORY COMMITTEE

September 22-23, 2022, 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.
Jeffrey Duchin, M.D.
John Dunn, M.D., M.P.H.
Kristen R. Ehresmann, R.N., M.P.H.
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.
Geeta Swamy, M.D.
Robert Swanson, M.P.H.

NVAC Ex Officio Members

Uzo Chukwuma, M.P.H., Indian Health Service (IHS)
Robert Johnson, Ph.D., Biomedical Advanced Research and Development Authority (BARDA)
Mary Beth Hance, Centers for Medicare and Medicaid Services (CMS)
Troy Knighton, M.Ed., Ed.S., LPC, Department of Veterans Affairs
Sheena Harris, M.D., Agency for Healthcare Research and Quality (AHRQ)
Barbara L. Mulach, Ph.D., National Institutes of Health (NIH)
Ram Koppaka, M.D., Centers for Disease Control and Prevention (CDC)
Roxanna Diba, M.D., M.S., Division of Injury Compensation Programs (DICP), Health Resources and Services Administration (HRSA)
Jay Slater, M.D., Food and Drug Administration (FDA)
Limone Collins, M.D., 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)
Roxanna Diba, M.D., M.S., Advisory Commission on Childhood Vaccines (ACCV)
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)
Christopher Regal, M.S., 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. She also noted that statements made during the meeting do not necessarily reflect those of the Department of Health and Human Services (HHS) or NVAC. Ms. Aikin called the roll.

Opening Remarks—Admiral Rachel Levine, M.D., Assistant Secretary for Health (ASH), HHS

Welcome

ADM Levine welcomed NVAC members, speakers, and meeting attendees. She thanked NVAC members for their efforts in promoting and advancing immunizations, which are critical for addressing major public health concerns such as COVID-19 and monkeypox and for preventing the resurgence of childhood infectious diseases such as measles and polio. She encouraged NVAC members to identify gaps and potential innovations in current COVID-19 immunization programs.

COVID-19 Vaccine Updates

In autumn of 2022, HHS is focused on ensuring equitable access to COVID-19 vaccines and boosters, including the recently-authorized bivalent boosters, which contain antigens for both the wildtype (WT) SARS-CoV-2 (i.e., the original strain of SARS-CoV-2 identified in humans) and Omicron SARS-CoV-2 variants. Greater than 90 percent of Americans can find vaccine locations (e.g., pharmacies, community vaccination centers) on vaccines.gov within five miles of their homes. HHS is collaborating with vaccine providers to offer additional walk-in appointments and times outside of normal business hours (i.e., evenings and weekends).

HHS remains focused on protecting people at greater risk of serious COVID-19 complications than the general population, including older and immunocompromised people. HHS is ensuring that older Americans can find information on COVID-19 vaccines and access transportation and mobility assistance through the Eldercare Locator. HHS recently issued guidance that expands access to supplemental pre-exposure prophylaxis (PrEP) treatments for adults that are moderately or severely immunocompromised.

Encouraging Innovations in Vaccines and Biotechnology

HHS remains focused on encouraging innovations in vaccine development and biotechnology. The Biden-Harris administration issued an executive order to launch a National Biotechnology and Biomanufacturing Initiative. This initiative includes:

- Expanding domestic biomanufacturing
- Fostering biotechnology innovations to improve patient care and health outcomes
- Investing in biotechnology for strengthening supply chains (e.g., pharmaceuticals, antibiotics)
- Training the next generation of biotechnologists

HHS is also assisting with fostering innovations as part of the Cancer Moonshot initiative, which aims to reduce cancer death rates by 50 percent by 2047 and improve the lives of people with cancer and cancer

survivors. NVAC can play a key role in this initiative by leveraging previous experience developing vaccines that prevent cancer (e.g., human papillomavirus [HPV], hepatitis B).

HHS is leveraging innovations to address the current monkeypox outbreak, including efforts to expand the availability of tests and vaccines, particularly in at-risk communities. HHS recently announced $11 million in additional funding for monkeypox vaccine production, and the Administration for Strategic Preparedness and Response (ASPR) is expanding vaccine and therapeutic distribution.

Influenza Vaccines

HHS is collaborating with influenza vaccine manufacturers to ensure that Americans have access to multiple vaccine options, including vaccine types (e.g., inactivated virus, recombinant protein) and vaccination centers (e.g., pharmacies, primary care providers). Vaccine manufacturers predict that they will produce between 175 million and 183 million influenza vaccine doses for the 2022-2023 influenza season. HHS is supporting influenza vaccination outreach efforts, particularly among people at higher risk of serious complications from influenza than the general population. CDC also conducts viral surveillance, including infections and hospitalizations, and monitors avian influenza outbreaks for potential transmission to humans.

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 June 15-16, 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 February 2-3, 2023. (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

Since 2015, the Vaccine Confidence Subcommittee Working Group has synthesized and summarized existing evidence and research to address vaccine confidence–defined as a person's belief in the efficacy and safety of vaccines as part of a trustworthy medical system. Vaccine confidence is closely intertwined with attitudes, intentions, and behaviors toward vaccination, including vaccine providers (e.g., clinics), manufacturers, and safety oversight organizations.

Since the last meeting, the Vaccine Confidence Subcommittee worked to finalize the recommendations, strategies, and approaches for increasing and sustaining vaccine confidence. The goals of the report are to: a) describe the factors that determine which vaccines individuals receive, along with the lifespans of individuals; b) suggest ways for HHS to improve confidence in all recommended vaccines; c) provide guidance on the utilization of evidence and how to form effective practices for a wide range of research fields.

The Vaccine Confidence Subcommittee's five main recommendations are as follows:

1. Invest further in vaccine confidence, research, and data.
2. Build trust in government and vaccine enterprise; trust in the health system and the government is correlated with vaccination behavior.
3. Educate and empower healthcare providers.
4. Foster community engagement and education.

5. Advance communication strategies to increase vaccine confidence.

Additional, more detailed sub-recommendations are included in the report. The report was unanimously approved by the meeting members.

Discussion

Inclusion and Acknowledgement of Systemic Racism

Jeffrey Duchin, M.D., highlighted the need to address systemic racism and implicit bias in healthcare and medicine, especially in the realm of vaccine confidence. He expressed concern about the level of community distrust in the medical system and government, as highlighted by the COVID-19 pandemic, and asked about the Vaccine Confidence Subcommittee's approach to building sustainable relationships with communities to bolster vaccine confidence and educate communities about vaccines and broader health concerns. Dr. Dunn answered that furthering community awareness was included in recommendation 3.2. He added that mistrust of the healthcare system is a broad issue that extends well beyond vaccinations.

Empowering Community Leaders and Childhood Education

Kerry Robinson, Ph.D. lauded the Vaccine Confidence Subcommittee report for its comprehensive and multi-faceted actions and recommendations. Empowering leaders in diverse groups and sectors, such as faith-based and cultural leaders, has improved vaccine confidence in Canada. She urged that the recommendation emphasizing vaccine literacy in middle school students should be broadened to include elementary school students and those in early childhood. The Public Health Agency of Canada will draw on HHS's report for their vaccine literacy efforts in Canada.

Erosion of Vaccine Confidence and Hope for the Future

Stephen Rinderknecht, D.O., also complimented the committee on the breadth and scope of the recommendations in the report. He shared that, as a clinician, he has frequently observed decreased vaccine confidence among his patients, especially during the COVID-19 pandemic, which he attributed to decreased confidence in established government institutions and health care providers. He expressed hope that, in time, vaccine confidence will improve.

Progress and Emerging Threats in Polio Eradication

Polio Vaccines and Eradication: A Personal Perspective—Peter L. Salk, M.D., Jonas Salk Legacy Foundation/University of Pittsburgh School of Public Health

Two types of polio vaccines are currently in use:

1) Inactivated (i.e., killed) poliovirus vaccines (IPVs), the first to be introduced, were developed by Dr. Jonas Salk and administered by intramuscular injection.
2) Oral polio vaccines, which use attenuated (i.e., weakened) live poliovirus, were developed by Dr. Albert Sabin.

Oral vaccines have become the main vaccine used for global polio eradication efforts rather than inactivated vaccines because they (1) produce more potent and longer-lasting immune responses and (2) induce mucosal and intestinal immunity, further protecting recipients. While the introduction of both polio vaccines significantly reduced WT poliovirus (i.e., naturally-occurring strains of polio) infections and paralytic poliomyelitis, the use of oral attenuated vaccines created new health challenges. In the late 1960s and early 1970s, cases of vaccine-associated paralytic poliomyelitis (VAPP) began to appear, in which the vaccine virus itself caused paralysis. During this period, many parents were unaware of the two options and so their children were simply given oral vaccines. Many scientists claimed that VAPP was

rare enough to justify continued administration of the oral vaccines. However, additional research demonstrated that oral poliovirus strains can revert attenuating (i.e., weakened) mutations by recombination (i.e., sharing of genetic code among viruses), which can restore the viruses' ability to replicate and spread to other hosts. This reversion to contagious polio viruses is termed circulating vaccine-derived poliovirus (cVDPV). Over the past 20 years, multiple cVDPV outbreaks have occurred in Africa, South Asia, Southeast Asia, and Hispaniola. Because most cases of cVDPV were linked to Type II poliovirus, this type was removed from oral vaccines. However, cVDPV outbreaks continue to occur, particularly in sub-Saharan Africa, Afghanistan, and Pakistan.

Efforts are underway to reduce the risk of oral polio vaccine, including developing new methods for attenuating (i.e., weakening for use in vaccination) viral strains to reduce the likelihood of these viruses regaining their ability to spread. Researchers are also examining methods to strengthen inactivated polio vaccines through techniques such as microneedle patches and the addition of adjuvants (i.e., compounds that stimulate immune responses). Full eradication of polio may require multiple simultaneous approaches such as combining optimized oral vaccines with IPV and booster shots in areas that no longer have regular polio outbreaks.

Status of Global Polio Eradication Initiative and the Effect of the COVID-19 Global Pandemic—Steven Wassilak, M.D., Centers for Disease Control and Prevention (CDC)

Eradication of polio by the Global Polio Eradication Initiative (GPEI) has led to a reduction from more than 125 countries impacted by polio in 1988 to four polio-endemic countries in 2006. However, spread of WT poliovirus from these countries and cases of cVDPV have caused many countries to experience imported cases of WT poliovirus and cVDPV. GPEI continues to provide planning, logistics, and outreach support efforts to many impacted areas, including sub-Saharan Africa, Afghanistan, and countries with declining rates of routine childhood immunizations due to the COVID-19 pandemic.

The majority of cVDPV cases between 2006 and 2016 were caused by Type 2 poliovirus, the second of three serotypes (i.e., distinguishable strains, for polioviruses Types 1-3), which along with Type 3 causes complications such as cVDPV and VAPP. Therefore, in 2016 the CDC and Strategic Group of Experts on Immunization recommended that oral vaccines switch from trivalent vaccines (i.e., containing all three serotypes) to bivalent vaccines (i.e., containing Types 1 and 3) to reduce cases of cVDPV. However, the switch to bivalent oral vaccines led to *increased* cases of cVDPV due to limited poliovirus surveillance and reduced immunity resulting from bivalent vaccines. As a result, cVDPV now accounts for the majority of paralytic polio cases. To prevent additional cVDPV cases, a consortium led by the Bill and Melinda Gates Foundation recently developed the Novel Oral Poliovirus Type II vaccine, which is designed to be more genetically stable than previous vaccine strains and thus less likely to lead to cVDPV.

Rockland County, NY Paralytic Polio Case, July 2022—Patricia Schnabel Ruppert, D.O., M.P.H., D.A.B.F.M., F.A.A.F.P., Rockland County Commissioner of Health

On July 18, 2022, the New York State Department of Health (NYSDOH) notified the Rockland County Department of Health and CDC of an unvaccinated, immunocompetent young adult in Rockland County who was hospitalized with paralytic Type II cVDPV. Based on this report, the Rockland County Department of Health, NYSDOH, and CDC launched a joint investigation and response. Contact tracing indicated that the patient could have been exposed to polio during a period between 4 to 17 days prior to symptom onset. Less than one percent of polio infections cause paralysis, so wastewater samples from Rockland and Orange County, NY were retrospectively analyzed to track all infections, including those that did not cause paralysis. Analyses identified 43 positive samples containing Type II cVDPV genetically linked to samples from the patient's stool. These results suggest many more people within these counties may have contracted or transmitted polio.

This case was the first U.S. case of cVDPV since 2005. Since 2000, routine immunizations have used only inactivated polio vaccines rather than oral vaccines, so this case was likely imported from other countries still using oral polio vaccines. Analyses of polio vaccination rates in Rockland County show two ZIP codes—10977 and 10952—with significantly lower polio vaccination rates compared to other ZIP codes. These ZIP codes have larger vaccine-hesitant communities, which may have enabled the polio outbreak to occur.

In response to the paralytic polio case, NYSDOH released a public advisory to educate residents and health care providers. NYSDOH also increased public health and clinical surveillance of polio cases, including wastewater surveillance and monitoring of symptoms consistent with milder polio symptoms (e.g., flu-like symptoms). NYSDOH, in cooperation with the Rockland County Department of Health, also launched polio vaccination clinics in Rockland County and supplied additional inactivated polio vaccine doses to Rockland County providers. This case illustrates the crucial importance of polio vaccinations; two doses provide at least 90 percent protection from infection, and three doses provide at least 99 percent protection.

Recent Increases in Vaccine Hesitancy—David Oshinsky, Ph.D., New York University

When polio vaccines were first introduced in the 1950s, public faith in vaccines was high and interest was widespread. Dr. Jonas Salk was personally thanked by President Dwight D. Eisenhower, and many medical textbooks published in the late 1950s and early 1960s predicted that vaccines would eventually eliminate infectious diseases. Over the next several decades, several incidents created doubt in vaccine efficacy:

- In April 1955, 200,000 children received polio vaccines that mistakenly contained virulent polio virus, resulting in major polio outbreaks. These batches were later linked to Cutter Laboratories, leading to this incident being labeled the "Cutter incident."
- In 1998, Dr. Andrew Wakefield and his colleagues published studies purporting to show a link between the measles, mumps, and rubella (MMR) vaccine and autism. Although these studies were later retracted in 2010 and the *British Medical Journal* showed how Dr. Wakefield falsified their results, concerns about vaccine-induced autism remain prevalent among some members of the public, and this concern has spread to other routine childhood vaccines (e.g., polio).
- When the Trump-Pence administration took office in 2017, many vaccinologists initially expressed concern about Trump's public statements implying a linkage between childhood vaccines and autism. However, early in the COVID-19 pandemic the Trump-Pence administration launched Operation Warp Speed and used the Defense Production Act to accelerate development and testing of COVID-19 vaccines.

At the beginning of 2021, the change of presidential administration and beginning of COVID-19 vaccine mandates coincided with a significant reduction in vaccine confidence among many segments of the U.S. population, resulting in resistance to vaccination efforts and increased numbers of religious exemptions. By July 2022, a study by the Kaiser Family Foundation showed that only 7 percent of parents with children under 5 already had their children vaccinated against COVID-19 and 10 percent stated they will vaccine their children as soon as possible; 27 percent stated they would "wait and see," and 43 percent stated they would "definitely not" get their children vaccinated. Top concerns about COVID-19 vaccines included insufficient research or testing (19 percent), side effects (14 percent), and safety concerns (13 percent).

This increase in COVID-19 vaccine hesitation could reduce rates of routine childhood vaccinations (e.g., MMR, polio). As of September 2022, 20 states had banned COVID-19 vaccine mandates, which may lead many states to ban other vaccine mandates and introduce permissive exemption policies.

Mississippi is a bellwether of the effect of COVID-19 vaccine skepticism on rates of other vaccinations. Mississippi has one of the highest routine vaccination rates but also one of the lowest COVID-19 vaccination rates of all U.S. states. The high percentage of routine childhood vaccinations is due to Mississippi state courts overwhelmingly ruling that childhood vaccine mandates are legal and allowing only *medical* exemptions (i.e., not allowing religious exemptions). Mississippi state legislators are currently introducing bills to expand potential religious exemptions and weaken vaccine mandates, which may lead to reduced routine childhood vaccination rates.

Discussion

Dr. Ruppert noted that Rockland County, NY has encountered increased vaccine skepticism over the past several years, and this skepticism persisted even after the paralytic polio case was publicly announced. Although this vaccine skepticism preceded the COVID-19 pandemic, the public debate over COVID-19 vaccines and mandates exacerbated skepticism, particularly among demographics already hesitant to receive routine vaccinations. Following the announcement of the paralytic polio case, many Rockland County residents received automated phone messages spreading vaccine disinformation and urging residents to avoid receiving the polio vaccine. Furthermore, the Defender, an anti-vaccine website led by Robert F. Kennedy Jr., mistakenly stated that only one case of polio occurred; one *paralytic* polio case was observed, but wastewater surveillance detected 43 samples containing cVDPV, suggesting many more cases of polio.

The Rockland County Health Department identified community liaisons for previous vaccinations efforts (e.g., measles), but many of these liaisons are no longer active after receiving death threats. Rockland County continues to reach out to new community liaisons, particularly among communities with religious concerns regarding vaccinations. However, these populations are heterogenous with many different leaders and influencers, which presents difficulties for encouraging vaccinations.

Dr. Oshinsky concurred with many of the challenges encountered by Dr. Ruppert. He noted that many California school districts initially attempted to mandate COVID-19 vaccinations for school students before withdrawing these mandates due to intense controversy.

Boosting Supply During the Monkeypox Emergency

U.S. National Monkeypox Vaccine Strategy—Rosalind J. Carter, Ph.D., CDC

As of September 20, 2022, CDC has reported 63,117 monkeypox cases globally, including 24,203 in the United States. Monkeypox vaccines are a keystone of efforts to mitigate the spread of monkeypox. In the U.S., two vaccines are approved by the FDA:

- ACAM2000™ is a replication-capable Vaccinia (i.e., poxvirus) vaccine initially developed for smallpox. ACAM2000 is administered as a single dose by pricking the skin surface. Following a successful inoculation, a lesion containing the replicating virus develops at the site of the vaccination (i.e., a "take") and Vaccinia virus in this lesion can be spread to other parts of the body or to other people.
- JYNNEOS™ is a replication-incapable Vaccinia vaccine administered as two subcutaneous (i.e., just under the skin) injections four weeks apart; for individuals over 18, the FDA has also approved an alternative intradermal (i.e., within skin layers) administration. Unlike ACAM2000, the virus in JYNNEOS cannot replicate; thus, JYNNEOS does not create a viral lesion or pose risks of the virus spreading to other body parts or other people.

JYNNEOS is the preferred monkeypox vaccine, particularly among people who are immunocompromised or have other medical contraindications, because it has fewer medical contraindications (e.g., immune

deficiency disorders, atopic dermatitis/eczema) and lower risks of serious adverse events (SAEs) (e.g., myopericarditis) and side effects relative to ACAM2000.

On June 28, 2022, the Biden-Harris Administration announced the U.S. National Monkeypox Vaccine Strategy, which focuses on (1) vaccinating and protecting people at risk for monkeypox, (2) prioritizing vaccines for areas with the highest numbers of cases, and (3) providing guidance to state, tribal, local, and territorial health officials to aid their planning and response efforts. This program includes three vaccination strategies:

1) Post-exposure prophylaxis (PEP): vaccination after known exposure (i.e., confirmed through case investigation, contract tracing, or risk exposure assessment) to monkeypox.
2) Expanded post-exposure prophylaxis (PEP++): Vaccination after known *or presumed* exposure to monkeypox.
3) PrEP: Vaccination *before* exposure to monkeypox.

In June 2022, CDC initially began administering JYNNEOS using a PEP strategy to high-risk populations (those at higher risk of contracting monkeypox, e.g., men who have sex with men [MSM] compared to the general population). However, many people diagnosed with monkeypox reported sexual contact with partners who were either anonymous or could not be identified for contact tracing, so CDC and partner agencies (e.g., FDA, state and local health agencies) expanded the strategy to PEP++ and PrEP in high-risk populations in July 2022.

Because JYNNEOS supplies are currently limited, the CDC is not encouraging mass vaccination for the general public or all sexually active people; instead, high-risk groups, including MSM, transgender and gender nonbinary people, sex workers, and people living with human immunodeficiency virus (HIV), are prioritized for monkeypox vaccinations. Furthermore, because published studies have demonstrated that single doses of JYNNEOS elicit neutralizing antibodies (nAbs) for up to two years, many public health departments have prioritized administering first doses and have only recently begun administering second doses.

CDC encourages communicating with high-risk populations using non-stigmatizing language, emphasizing data privacy, and partnering with stakeholders and community-based organizations (CBOs). On August 30, 2022, the Biden-Harris administration announced a new pilot program to target high-risk populations who may face barriers to vaccine access, including stigma associated with attending public vaccine events that require disclosure of sexual identity, gender identity, or level of sexual activity. As supplies of JYNNEOS increase, the CDC and partner agencies will increasingly encourage additional PrEP vaccinations among higher-risk groups as well as increase the number of second doses provided.

Strategic National Stockpile (SNS) Response Operations, 2022 U.S. Monkeypox Outbreak— Steven Adams, M.P.H., Administration for Strategic Preparedness and Response (ASPR)

ASPR focuses on meeting U.S. medical and health needs by preparing and responding to both natural and anthropogenic (i.e., caused by human activity) emergencies. To prepare for future emergencies, ASPR manages the SNS, the U.S. federal government's largest repository of emergency medical countermeasures (MCMs), including antibiotics, antitoxins, chemical antidotes, antiviral drugs, vaccines, personal protective equipment (PPE), medical supplies and other equipment (e.g., ventilators).

In May 2022, the SNS Operations Center began supporting the U.S. National Monkeypox Vaccine Strategy and public health responses. The SNS Operations Center has shipped more than 819,000 vials of the JYNNEOS vaccine, eight vials (i.e., 800 doses) of the ACAM2000 vaccine, and 38,700 courses of TPOXX® (tecovirimat) for treating monkeypox infections. The large amounts of vaccines and tecovirimat in SNS were initially accumulated to prepare for potential smallpox outbreaks.

To further expand MCM availability, ASPR awarded a contract to AmerisourceBergen to increase the number of shipments and direct delivery locations for state, local, and tribal public health agencies. Under this contract, AmerisourceBergen is currently distributing up to 2,500 shipments of JYNNEOS vaccine and 2,500 tecovirimat shipments per week. ASPR is also acquiring additional JYNNEOS vaccines for both the current outbreak as well as future poxvirus outbreaks. By summer of 2023, ASPR projects that the U.S. federal government will have 7 million doses of monkeypox vaccines available.

Monkeypox Vaccination in New York City—Ashwin Vasan, M.D., Ph.D., New York City Department of Health and Mental Hygiene

New York City (NYC) experienced a significant outbreak of monkeypox cases in July and August of 2022. To address this outbreak, heavily-impacted communities (e.g., LGBTQ CBOs) partnered with NYC public health officials, resulting in a reduction of new monkeypox cases by late September.

PEP++ vaccinations played a key role in NYC's response with 106,985 vaccine doses administered by September 21, 2022. NYC currently limits vaccine eligibility to people who had at least two sexual partners within the past 14 days and who identify as MSM, transgender, gender non-conforming or nonbinary, or sex workers. Based on the limited supplies of the JYNNEOS vaccine, NYC initially adopted a strategy of inoculating eligible residents with the first dose only. As the supply of JYNNEOS has increased, NYC Department of Health and Mental Hygiene began offering second doses in early September.

Distribution of monkeypox vaccines has varied among NYC boroughs and demographic groups. Dr. Vasan noted these patterns are similar to differences in vaccination for COVID-19 and may reflect differences in public health infrastructure in these areas.

Dr. Vasan highlighted the necessity for larger discussions on the need to balance speed versus equity during public health emergencies—particularly in communities that are often distrustful of government agencies after being historically underserved and stigmatized by public health agencies. Based on data collected by the Department and affiliated CBOs, encouraging vaccine-hesitant African Americans in high-risk neighborhoods to receive the monkeypox vaccine often requires 5-10 conversations per vaccine-reluctant person, with one CBO reporting up to 16 conversations per reluctant person. Over time, continued positive engagement with underserved communities can reduce stigmatization, distrust, and reluctance. Some techniques for reaching these communities include vaccine appointments outside of normal business hours (i.e., evenings and weekends); reserved vaccine appointments for priority groups (ZIP codes at high risk of monkeypox transmission, referrals through CBOs and trusted health partners); and event-based outreach (e.g., Pride events, LGBTQ bars) for both vaccinations and educational materials on monkeypox.

Discussion

Measuring Outreach Efforts to Vaccine-Hesitant Residents

The NYC Department of Health and Mental Hygiene tracks conversations encouraging eligible, vaccine-hesitant residents to get the monkeypox vaccine using an engagement tracking approach first developed during the COVID-19 pandemic. Under the COVID-19 program, CBO volunteers initially tracked interest in COVID-19 vaccines before they received Emergency Use Authorizations (EUAs); these metrics shifted to tracking the number of conversations required to encourage vaccine-hesitant residents to receive COVID-19 vaccines. The Department continues to use this tracking approach for monkeypox vaccines.

Differences in Vaccine Distribution Systems

John Douglas, M.D., noted that COVID-19 vaccines are ordered and tracked through the Health Partner Ordering Portal (HPOP) system, whereas many other vaccines (e.g., monkeypox vaccines) are ordered and tracked through CDC Vaccine Tracking System (VTrckS). He asked whether these two approaches can be combined for future public health responses. Dr. Adams responded that ASPR continues to focus on bulk distribution to respond to outbreaks and other public health emergencies and is currently collaborating with different jurisdictional partners to identify improvements to this system. Monkeypox vaccine distribution by SNS was built upon the federal infrastructure for smallpox vaccination distribution, which assumed a government-wide mobilization in response to a smallpox outbreak and bulk distribution of vaccines by federal agencies to states and municipalities. In contrast, the distribution of COVID-19 vaccines through HPOP was sometimes slowed by bureaucratic and appropriations issues among different states and municipalities.

Differential Declines in Monkeypox Cases Among Demographic Groups and Boroughs

Dr. Douglas asked whether the speed of decline in new monkeypox cases has varied among demographic groups and boroughs of NYC. Dr. Vasan replied that outer boroughs (e.g., Staten Island) have slower rates of decline compared to other boroughs (e.g., Manhattan), which often reflects demographic differences. Access to monkeypox testing has also varied among boroughs with reduced testing in outer boroughs. The NYC Department of Health and Mental Hygiene will soon publish data on differences in access to monkeypox treatments.

Experiences in the Field: Avian Flu Monitoring

Avian Influenza Control Strategies— Matthew J. Sylte. D.V.M., Ph.D., D.A.C.V.M., United States Department of Agriculture (USDA)

New strains of Avian influenza, which belongs to the same family as human influenza, can occur quickly by reassortment of different segments of the viral genome. Avian influenza strains are classified into two types based on virulence in poultry: low pathogenic avian influenza (LPAI) and highly pathogenic avian influenza (HPAI). Because most poultry are immunologically naïve (i.e., not previously exposed) to avian influenza, HPAI can create massive outbreaks and high mortality in poultry farms.

Four avian influenza strategies are currently used: 1) poultry quarantine to limit potential HPAI introductions; 2) avian influenza surveillance, including analyzing viral strains from both wild birds and commercial poultry; 3) vaccination, which is useful for 5 of 36 HPAI strains; and 4) depopulation, which involves mass euthanasia of birds in high-density poultry houses.

Depopulation remains the main strategy used in the U.S. because vaccination alone can lead to avian influenza strains with vaccine-resistant mutations. However, vaccination paired with depopulation offers an opportunity to better control HPAI strains. The USDA Animal and Plant Health Inspection Service (APHIS) Center for Veterinary Biologics regulates the development and licensing of avian influenza vaccines for commercial poultry, including detailed requirements for vaccine type, efficacy studies, and field safety studies. Although avian influenza offers opportunities to reduce avian influenza susceptibility and viral shedding, multiple challenges prevent widespread usage, including trade restrictions, potential masking of clinical symptoms, and vaccination program costs.

Unfinished Triumph: Universal Flu Vaccine Update

Influenza Vaccines Research and Development (R&D) Roadmap and Universal Influenza Vaccine Technology Landscape— Michael T. Osterholm, Ph.D., M.P.H., Center for Infectious Disease Research & Policy (CIDRAP), University of Minnesota

The Influenza Vaccines R&D Roadmap (IVR) Initiative aims to accelerate the development of improved, more durable influenza vaccines, including universal flu vaccines by providing a ten-year roadmap for prioritizing and coordinating global influenza vaccine R&D efforts. The Global Funders Consortium for Universal Influenza Vaccine Development began developing the IVR in 2019 and launched the roadmap in 2021. The IVR includes six key R&D areas: 1) universal influenza vaccines; 2) seasonal influenza vaccines; 3) virology; 4) immunology; 5) animal and human models; and 6) policy, financing, and regulation.

The IVR Initiative also developed the Universal Influenza Vaccine Technology Landscape, which is a database of novel universal influenza vaccine candidates in late preclinical (e.g., in vivo toxicology studies) or clinical (e.g., Phase I clinical trials) stages of vaccine development. This landscape is continuously updated and provides a dashboard for viewing progress of different universal influenza vaccine candidates, which informs strategies and funding decisions for future R&D efforts.

As of October 5, 2022, the landscape included 150 universal influenza vaccine candidates, which can be sorted by both vaccine type (i.e., platform) and development stage. Of these 150 candidates, 122 (81 percent) are in preclinical development, 16 (11 percent) are in Phase I clinical trials, 7 (5 percent) are in Phase II trials, and 5 (3 percent) are in Phase III trials. Researchers and policymakers can view more details for each candidate to monitor its progress.

A New Approach to Universal Influenza Vaccines: BPL-1357 Phase I Trial— Matthew J. Memoli, M.D., M.S., National Institutes of Health (NIH)

Universal influenza vaccines are novel vaccine candidates designed to provide more durable and broader protection than most current seasonal influenza vaccines. The latter target humoral immune responses based on hemagglutinin (HA) subtypes of influenza strains that are dominant in a given season; they do not capture cell-based immune responses (e.g., B-cell and T-cell responses) or mucosal immunity, which can play key roles in protection against influenza. Thus, universal or broadly protective vaccines should provide the following:

- Breadth of protection across influenza strains, including genetic variation in seasonal strains.
- Breadth of people protected by this vaccine, including elderly people, children, and people with comorbidities (e.g., compromised immune system) that create higher risk for serious complications.
- Breadth of immune mechanisms affected by the vaccine, including enhanced mucosal, B-cell, and T-cell immune responses as well as responses to different neuraminidase (NA) subtypes.

Based on these requirements, Dr. Memoli's research team is examining the ability of BPL-1357, an inactivated whole virus vaccine containing four LPAI strains, to protect against multiple strains of influenza. These four strains were selected based on phylogenetic analyses of HA and NA subtypes of avian influenza strains that have been transmitted (i.e., "jumped") to humans. Efficacy studies in mice showed that this vaccine provided significant protection against many different influenza strains. Compared to mice treated with a placebo, vaccinated mice had significantly lower viral load, signs of lung damage (e.g., alveolar damage), and fewer cases of pneumonia. These results were replicated in similar studies in ferrets.

Dr. Memoli's team is currently enrolling for a Phase I randomized, placebo-controlled trial in which 45 participants are being assigned to one of three treatments: 1) intramuscular (IM) BPL-1357 and intranasal

(IN) placebo; 2) IM placebo and IN BPL-1357; and 3) IM and IN placebo. The study has enrolled and treated 36 participants thus far and plans to complete enrollment and initial inoculations by November 2022. Participants receive both doses at two timepoints 28 days apart, and researchers follow participants regularly for 210 days following the first inoculation. Researchers frequently collect blood and nasal mucosal samples to examine immune responses over this period. Results from this study will not only inform future development of BPL-1357 but can also inform future universal flu vaccine R&D efforts, including identifying new techniques for developing more broadly protective influenza vaccines.

Discussion

Timothy Cooke, Ph.D., asked whether mRNA vaccines are currently being researched as universal influenza vaccine candidates and whether mRNA vaccines could be modified for IN administration to enhance mucosal immunity. Dr. Memoli noted that numerous studies on universal influenza vaccines have highlighted the importance of selecting appropriate antigen(s) rather than different vaccine types (e.g., mRNA, recombinant proteins). Many vaccines are developed around one antigen that is often strain-specific and then clinical trial individuals are examined for antibodies that bind to that specific antigen. However, this approach can pose challenges for broadening immune responses beyond a specific strain, particularly in viruses like influenza with significant variation in antigens.

Vaccines and Reduced Risk of Dementia

Protective Effects of Immunization on Alzheimer's Disease (AD)—Paul Schulz, M.D., University of Texas Health Science Center at Houston

Our understanding of the nuances of immune system functioning is continually evolving in light of new research. Current research indicates that vaccines may display protective qualities against AD and declining cognitive function. However, previously researchers thought that immune system-mediated inflammation from vaccinations accelerated Alzheimer's Disease (AD) symptoms because the process by which immune cells release factors that destroy AD-related amyloid plaques can lead to accidental harm of healthy neurons over time, leading to cognitive decline. Based on observational data, researchers concluded that immune-mediated inflammation and general activation of the immune system in the periphery worsened AD. Immune-mediated inflammation may be caused by urinary tract infections, pneumonia, surgery, and vaccinations. However, research over the last several decades has demonstrated surprising benefits of several vaccines in preventing Alzheimer's Disease. Based on these updated findings, Dr. Schultz explained that physicians and researchers at the University of Texas Health Science Center at Houston have advised patients to get vaccinated against severe, sometimes fatal infections like influenza, shingles, and pneumonia.

Shingles Vaccination Reduces Risk of Alzheimer's and Parkinson's Disease—Steven Lehrer, M.D., Mount Sinai Medical Center, and Peter H. Rheinstein, M.D., J.D., M.S., Severn Health Solutions

AD and Parkinson's Disease (PD) show similar characteristics of progression in their advanced stages. For example, one cause of both diseases may be reactivation of processes and pathways silenced (i.e., shut down) at birth. Gene silencing and reactivation are controlled by histones—proteins wrapped around DNA that carry chemical modifications. With advancing age, these chemical modifications are disrupted by viruses, infections, and inflammation, and embryologic pathways and processes silenced at birth can be reactivated. For example, inflammation may trigger reactivation of cytokines expressed during embryologic development, causing these cytokines to adversely affect the same neuronal structures they formed in utero. Cytokines and growth factors in AD are also affected by neuroinflammation. In addition, cytokines and neurotrophins (proteins that induce the survival, development, and function of neurons) have a significant impact on PD and Lewy Body Dementia (LBD). By reducing the presence of viruses and prolonged infections and inflammation, vaccines can reduce the risk of AD. For example, data show

that flu and pneumonia vaccination reduce the risk of AD. One study showed that fewer influenza-vaccinated individuals developed AD compared to influenza-unvaccinated individuals at 46-months post study entry. A separate study observed a large reduction in AD risk in pneumonia-vaccinated individuals who were not genetically prone to AD.

Similarly, Herpes Zoster (shingles) vaccination prevents the activation of Herpes Simplex Type 1 virus (HSV1), which can produce neuroinflammation associated with an increased risk of AD. Herpes virus-induced reactivation of embryologic pathways silenced at birth may also lead to AD. Data from a study by Drs. Lehrer and Rheinstein suggest that the Zostavax shingles vaccine (licensed in 2006) also reduces the risk of dementia in 15 percent of vaccinated subjects. Drs. Lehrer and Rheinstein plan to repeat the study using the more recent Shingrix vaccine when a sufficient number of vaccinated patients meet the age criteria. Similar studies show a 20 percent reduction in AD risk in subjects vaccinated against shingles and reduced dementia incidence after varicella zoster vaccination. It remains to be seen if the AD-risk-reducing effects of flu, pneumonia, and shingles vaccinations are cumulative. Drs. Lehrer and Rheinstein also briefly presented data showing that shingles vaccination may also reduce risk of PD; the U.S. states with the highest rates of PD (lowest age-adjusted prevalence ranks) had the lowest proportion of adults aged 60 and over who had ever received shingles vaccination.

Risk of Alzheimer's Disease Following Influenza Vaccination— Avram S. Bukhbinder, M.D., University of Texas Health Science Center at Houston

Dr. Bukhbinder and colleagues studied the risk of developing AD after influenza vaccine by examining 1.8 million people with and without eventual AD in the general U.S. population. Optum Clinformatics collected data from 2009 to 2019 on a population of adults 65 or older with health insurance (private or Medicare) and no prior dementia, mild cognitive impairment (MCI), encephalopathies, or dementia medications. A propensity score matching analysis revealed that individuals 65 or older who were vaccinated against influenza at least once were 40 percent less likely to develop or be diagnosed with Alzheimer's in the four-year follow-up period. Individuals 75 or older who were vaccinated against influenza at least once were 25 percent less likely to develop or be diagnosed with AD in an eight-year follow-up period. Those who received more vaccinations (six versus three versus zero) were less likely to develop AD. Participants who received the Adjuvanted (Fluad) vaccine versus non-adjuvanted (excluding high-dose) vaccine were 54 percent less likely to develop AD. Researchers also found a link between dosage and the risk of developing AD. Individuals who received high dose were almost 20 percent less likely to develop AD than those who received the standard dose. Those who received Fluzone high-dose were 26 percent less likely to develop AD versus individuals who received any standard-dose influenza vaccine (except adjuvanted). However, the study may be biased towards health-oriented people with access to more vaccines and people with more health problems that visit a physician's office more frequently.

Other routine adult vaccinations are being tested for their protective effects against AD. Studies showed that Zostavax conferred a 25 percent reduced risk of AD and the Tdap (tetanus, diphtheria, and pertussis) vaccine conferred a 29 percent reduced risk of AD. Select pneumococcal vaccines (PCV-13 and PPSV-23) conferred 27 percent and 8 percent reduced risk of AD, respectively. Additionally, researchers in the United States and Israel currently studying bacille Calmette-Guerin (BCG) vaccination for bladder cancer report that early results indicate that BCG vaccination reduces the chances of developing AD.

Repurposing of Existing Vaccines for Alzheimer's Prevention— Svetlana Ukraintseva, Ph.D., Duke University

Major AD risk factors such as aging, genetics, and exposures can compromise immunity and increase the brain's vulnerability to infection by lowering immune response and increasing blood–brain barrier permeability and brain vulnerability to diverse pathogens. Viral, bacterial, fungal pathogens have been

linked to AD development. Therefore, therapies with broad beneficial effects on immunity may be protective against AD. Vaccines that have beneficial off-target effects on health and survival could be repurposed for AD prevention.

Using data from Health and Retirement Study (HRS) participants, Dr. Ukraintseva estimated associations of certain infections diagnosed between ages 65 and 75 (herpes simplex, herpes zoster, pneumonia, and recurrent mycoses), certain vaccinations received between the ages of 65 and 75 (shingles and pneumonia), development of AD and Alzheimer's Disease Related Dementias (ADRD) at 75 years old or older, and all-cause mortality risk. Dr. Ukraintseva found that the infections studied increased the risk of AD, whereas the vaccinations studied decreased risk of AD/ADRD. The association between herpes zoster, herpes simplex, pneumonia, recurrent mycoses and AD were stronger than for AD/ADRD combined.

In addition, results from the Cardiovascular Health Study (CHS) showed that a combination of vaccines and human genotypes affected development in AD. Pneumonia vaccination and the number of pneumonia vaccinations (with and without influenza shots) received between ages 65 and 75, were associated with lower odds of AD after age 75 in individuals who have the rs6859 A allele of the NECTIN2 gene (an AD risk factor). The pneumococcal vaccine may provide genotype-specific protection against Alzheimer's disease. Therefore, repurposing vaccines while considering genetic factors can be a promising approach to personalized prevention of AD.

Based on these findings, Dr. Ukraintseva suggested three questions of interest for future research: (1) how many existing vaccines provide off-target benefits for AD prevention, (2) why do some vaccines show negative off-target effects on all-cause mortality, and (3) why do live vaccines show more beneficial effects than non-live vaccines?

Discussion

In response to a question about additional benefits from multiple vaccinations and timing of vaccination to reduce AD risk, Dr. Ukraintseva explained that her lab studied the effectiveness of vaccines applied before diagnosis. However, Dr. Ukraintseva and her team plan to investigate administration of vaccine after diagnosis of AD in future research endeavors.

Dr. Daniel Hoft asked if there was a way to design a prospective trial with individuals diagnosed with AD/PD using vaccination status as the critical variable. However, he noted the ethical dilemma of withholding vaccines from patients. Dr. Schulz replied that this could be solved by using accepted animal models of AD and PD. The animals (in this case, mice) can be administered the infection directly; researchers then will be able to study results of infected mice and vaccine versus infected mice without vaccine in development of AD.

A Somber Milestone: COVID-19 Claims More Than 1 Million Americans

Trends in Mortality and Life Expectancy: Data from the National Vital Statistics System (NVSS)— Farida B. Ahmad, MPH, National Center for Health Statistics (NCHS), CDC

NCHS collects, codes, and disseminates U.S. vital statistics data, including births, deaths, and fetal deaths, as part of the NVSS. Mortality data in NVSS are based on information from all death certificate files in U.S, states, the District of Columbia, and U.S. territories. These data are released in one of two formats: 1) final annual data, which are released after all data have been received and reviewed for completeness and quality; and 2) provisional data, which is a sample of vital statistics data received and processed by NCHS by a specified cutoff date. NVSS currently contains final mortality data through 2020 and provisional data for 2021 and 2022 year-to-date.

Based on the provisional 2021 data, 60,000 more people died of COVID-19 in 2021 compared to 2020, and COVID-19 was the third-highest cause of death behind cancer and heart disease in both 2020 and 2021. The age-adjusted death rate increased by 0.7% from 2020 to 2021, with higher overall (i.e., not adjusted for cause of death) death rates among non-Hispanic American Indian, Alaska Native, and Black people. Percentages for other causes of death also changed during the COVID-19 pandemic; compared to 2019, 2021 saw increases in death rates for heart disease (5.5 percent), unintentional injury (29.9 percent), hypertension (17.2 percent), diabetes (17.8 percent), and chronic liver disease and cirrhosis (27.6 percent) and decreases in chronic lower respiratory disease (9.3 percent) and influenza and pneumonia (15.8 percent).

U.S. life expectancy declined by 1.8 years from 2019 to 2020 and by another 0.9 years from 2020 to 2021. Half of this decline in life expectancy is due to COVID-19 deaths, with sharp increases in drug overdose deaths during this period also contributing to declines in life expectancy. Changes in life expectancy differed among demographic groups, with larger decreases among non-Hispanic American Indian (6.6 years), Black (4.0 years), and Hispanic people (4.2 years) compared to non-Hispanic White (2.4 years) and Asian (2.1 years) people. Similar demographic in excess deaths occurred during early 2022 when compared to death rates between 2015 and 2019, illustrating that COVID-19 continues to disproportionately impact certain demographic groups.

Disparities in COVID-19 Mortality by Occupational Sector and Occupation—Yea-Hung Chen, Ph.D., M.S., University of California

During the COVID-19 pandemic, shelter-in-place orders in most jurisdictions exempted essential workers (e.g., health care, agriculture), and reports of workplace outbreaks and inadequate protections were frequent in some workplace settings (e.g., meat-packing plants), leading to COVID-19 mortality potentially being higher in some occupations. However, few studies have examined potential occupational differences in COVID-19 mortality.

Dr. Chen and his research team examined COVID-19 mortality in California based on occupational sector and occupation. Because of potential concerns about underreporting of COVID-19 mortality, they also examined excess deaths by comparing death rates during the pandemic against pre-COVID mortality rates. During 2020, California had 11,462 excess deaths with significant differences in per-capita excess deaths among occupations, with higher rates among facilities, food, agriculture, and transportation and logistics compared to other occupation sectors. Specific occupations with highest relative excess death rates included sewing machine operators, cooks, agricultural workers, meat processing workers, couriers, and messengers. Health and emergency services employees had lower levels of excess mortality consistent with non-essential workers, which likely reflects more workplace protections and PPE in health care settings. These results aligned with data from a 2022 publication by Dr. Chen showing similarly high 2020 mortality rates across 46 states, with higher relative excess death rates among construction laborers, cooks, and sewing machine operators.

Dr. Chen and his colleagues also examined differences in excess death rates following the introduction and widespread availability of COVID-19 vaccines by examining excess deaths in California from March to November 2021. Compared to non-essential employees, high excess mortality occurred among agriculture, emergency services, facilities, and transportations and logistics employees. Similar to 2020 data, health care workers had few excess deaths compared to non-essential workers, and the higher rates among emergency services workers potentially reflect reduced vaccination rates among emergency services employees. Stratifying California mortality data by region based on vaccination rates showed significantly higher rates of excess mortality in regions with low vaccination rates. These results illustrate the need to 1) prioritize vaccine access for essential workers; 2) increase vaccine uptake in impacted occupations; 3) expand reporting of occupation in public health surveillance, and 4) expand structural policies such as sick leave to protect vulnerable occupations and populations.

COVID-19 Bereavement: Levels and Health Consequences— Emily Smith-Greenaway, Ph.D., University of Southern California

During the COVID-19 pandemic, many people minimized the social and health impacts of COVID-19 by emphasizing that most deaths occurred among older adults. However, each premature death due to COVID-19 affects a circle of people (e.g., children, spouses, siblings), and this bereavement can have significant physical and mental health challenges.

COVID-19-related bereavement was estimated using demographic microsimulations to computationally model U.S. family relationships and corroborate the model with existing survey data on living family of people who died from COVID-19. Based on this model, each person who dies from COVID-19 is a close family member (i.e., parent, grandparent, sibling, or child) of approximately nine people. This bereavement impacts all ages rather than just older adults. Based on this model, as of September 2022, approximately 8.5 million people in the U.S. had lost a close family member to COVID-19. Approximately 2.3 million people had lost a parent to COVID-19, including 82,000 children under the age of 18.

To assess the extent to which COVID-19 bereavement presents more difficulty than other forms of bereavement, Smith-Greenaway's research team examined data from the Survey of Health, Ageing, and Retirement in Europe (SHARE) on COVID-19 mortality, depression, loneliness, and trouble sleeping. Researchers then compared data collected from June through August 2020 with data from 2019 and 2017. Widows and widowers who had lost a spouse within the past three months due COVID-19 rated higher levels of loneliness and depression than respondents in 2017 or 2019 who lost a spouse within three months of the survey date. Navigating COVID-19 bereavement may pose additional challenges compared to other forms of bereavement for several reasons, including the perception that COVID-19 deaths are "bad deaths," separation at the time of death, disruption of mourning rituals, physical distancing, and lack of routine and traditional social supports. These results illustrate the need to address population health implications of COVID-19 bereavement, including additional research on social, economic, and health impacts.

Discussion

COVID-19 Bereavement

Dr. Hopkins highlighted that the COVID-19 pandemic significantly impacted health care providers, who experienced increased mortality and departures from the health care industry. He noted that the impacts of bereavement extend beyond immediate family members of those who died from COVID-19, and this larger societal bereavement may be a factor in increasing polarization in the United States.

Dr. Douglas noted that the increased difficulty of bereavement in 2020 may be due to increased isolation when shelter-in-place orders and other social distancing efforts were in effect. Dr. Smith-Greenaway agreed, and noted that her team is currently researching data from subsequent years of the COVID-19 pandemic to examine the extent to which impacts of bereavement are associated with the level of isolation and social distancing. The introduction of COVID-19 vaccines in 2021 may also change the nature and impact of COVID-19 bereavement, particularly if the deceased refused to get vaccinated.

Occupational Data on Death Certificates

Studies by Dr. Chen's research team on occupational differences in COVID-19 deaths have been cited in court cases regarding workplace protections, including during the U.S. Supreme Court's testimony in National Federation of Independent Businesses v. Department of Labor regarding COVID-19 vaccine mandates. Some states do not collect occupational data with death certifications, so NVSS is collaborating

with the National Institute for Occupational Safety and Health (NIOSH) to standardize reporting of occupational data on death certificates.

Role of COVID-19 Vaccination in Cardiac Arrest Deaths

Robert Schechter, M.D., M.Sc., asked whether the increase in cardiac arrests observed in 2021 was potentially due to post-acute sequelae of COVID-19 (PASC) (i.e., "long COVID"), and if so, whether COVID-19 vaccinations reduce this risk. Dr. Ahmad responded that NVSS mortality data do not include vaccination data. NVSS is examining potential standardized approaches for examining impacts of PASC, which may include examining impacts of vaccines.

Federal Agency and Liaison Representative Updates

Food and Drug Administration (FDA) —Jay Slater, M.D.,

On June 17, 2022 FDA approved an additional indication for VAXNEUVANCE for the prevention of disease caused by specific *Streptococcus pneumoniae* serotypes for individuals 6 weeks through 17 years of age. In July 2022, FDA approved eight influenza vaccines for the 2022-2023 influenza season. On July 8, COMIRNATY was approved for children ages 12 to 15 for the prevention of COVID-19. On July 13, the Novavax COVID-19 vaccine was given an EUA for the prevention of COVID-19 in individuals ages 18 and up. On August 9, an EUA was provided for the JYNNEOS vaccine via intradermal injection in individuals above 18 determined to be at high risk of for monkeypox. The EUA also allows the use of the vaccine in individuals younger than 18 years of age who are determined to be high risk, but the JYNNEOS vaccine must be administered by subcutaneous injection in these individuals. On August 19, FDA expanded the EUA for the Novavax COVID-19 vaccine, which is an adjuvanted recombinant protein vaccine for the prevention of COVID-19 in individuals ages 12 to 17. Previously, the FDA had authorized the vaccine for individuals ages 18 and up. On August 31, the FDA amended the EUA for Moderna and Pfizer-BioNTech COVID-19 vaccines to allow bivalent boosters (i.e., containing both WT and Omicron antigens) at least two months following the primary or booster vaccination.

Division of Injury Compensation Programs (DICP), Health Resources and Services Administration (HRSA)—Roxanna Diba, M.D.

The Vaccine Injuries Compensation Program (VICP) continues to process an increased number of vaccine injury claims. In fiscal year (FY) 2020, petitioners filed over 2,000 claims. Two hundred and eight million dollars was awarded to petitioners, with an additional thirty-six-and-a-half million dollars awarded to pay attorneys, attorney fees, and miscellaneous costs. In FY22, as of August 1, petitioners filed 736 claims and approximately 157 million dollars was awarded to petitioners. As of August 8, 2022, the VICP has had a backlog of about 1,500 claims alleging vaccine injury that are pending review.

The Countermeasures Injury Compensation Program (CICP) continues to process claims. As of July 1, 2022, petitioners filed 8808 claims alleging injuries and deaths from COVID-19 countermeasures, including approximately 5,700 claims alleging injuries and deaths from COVID-19 vaccines. In all, 31 claims have been denied. Dr. Diba noted that, although one claim was determined to be medically eligible for compensation, compensation has not yet been awarded.

Indian Health Services (IHS)—Uzo Chukwuma, MPH

IHS continues to confront the COVID-19 pandemic and its impact on population health and routine vaccination efforts. Since September 2022, the IHS COVID-19 task force has prioritized equitable access, distribution, and administration of COVID-19 vaccines throughout tribal communities. Participating federal and IHS tribal urban facilities administered over 2.3 million COVID-19 vaccines. According to

the CDC COVID-19 Tracker, among the estimated 2.1 million people served at IHS, 34 percent have received a booster dose. IHS is also actively engaged in distributing bivalent COVID-19 boosters for those ages 12 and up.

IHS continues to collaborate with CDC and engage tribal leaders to support vaccine confidence efforts among the American Indian and Alaskan Native population. In August, the chief medical officer conducted an outreach roadshow with various media and community engagements, promoting immunization across the lifespan for American Indian and Alaskan natives. To complement this outreach, IHS generated and updated tools and resources promoting immunization, which were distributed throughout the tribal country.

Additionally, the IHS immunization program continues to encourage vaccination among adults by providing training and webinars; they also promoted the adults' pneumococcal, Zoster, and Hepatitis B vaccines. IHS Tribal and Urban Indian Health Programs provided the influenza vaccine to Indigenous and Alaskan Native people and IHS is prepared to administer the COVID-19 bivalent booster.

IHS is also currently working with CDC and ASPR on the distribution and administration of monkeypox vaccine and associated countermeasures in tribal communities.

America's Health Insurance Plans (AHIP)— Christopher Regal, M.S.

Throughout the COVID-19 pandemic, insurance providers have worked to provide equitable access to COVID-19 vaccines. Beyond COVID-19, health insurance providers have continued to inform members and provider networks about emerging vaccine-preventable diseases, such as monkeypox and polio, and provide members access to recommended vaccines. Insurance providers are also working with other partners, including health care providers and community groups, to disseminate accurate information on vaccines, especially vaccine safety information. AHIP has facilitated large-scale vaccination events, including mobile vaccination units and events that target specific communities, such as back-to-school events.

AHIP recently published two new briefs that address routine vaccines: 1) a document on the value of childhood vaccines, and 2) an issue brief describing insurance providers' actions to ensure members receive recommended vaccines.

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

AIM recently held a Leadership In Action conference, during which it distributed its annual awards. Molly Howell, the immunization program manager in North Dakota, received the Natalie J. Smith Excellence and Program Management Award. In early August 2022, AIM collaborated with CDC to distribute 28 champions awards, which recognize individuals who have been immunization champions in states and localities.

AIM released a new podcast series, Aiming to Reform, which features conversations with immunization program managers. AIM also recently conducted a webinar on translating vaccine confidence research into practice using three evidence-based models to increase vaccine confidence in communities. AIM launched a member assistance program focused on adult immunization, which features a business operations toolkit and other resources for public health immunization programs.

AIM continues to roll out the COVID-19 booster and conduct back-to-school immunization activities.

American Immunization Registry Association (AIRA)— Rebecca Coyle, M.S.Ed.

AIRA recently added a monkeypox response portion to their webpage. In addition, AIRA is in the process of assisting the RECOVER EHR project with Patient-Centered Outcomes Research Institute (PCORI) to evaluate immunization information system (IIS) data pertaining to individuals who had contracted COVID-19 and determine the role played by vaccines in PASC (i.e., "long COVID"). AIRA continues their measurement and improvement program, which evaluates key components of existing IAS systems, such as clinical decision support. In summer 2022, AIRA's advisory work group decided to move forward with the Data At Rest (DAR) project, which aims to perform quality checks on the data in the IIS database.

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

The American Pharmacists Association (APHA) is the one largest pharmacy organization in the United States and represents over 60,000 pharmacists, student pharmacists, and pharmacy technicians. APHA assists pharmacists with engagement training and education, as well as information and resources. APHA recently entered into a cooperative agreement with CDC to study vaccine confidence. In addition, APHA created free, on-demand continuing education materials regarding monkeypox administration.

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

ASTHO aims to increase the vaccination rates for children and adults through several approaches. For example, ASTHO collaborated with the APHA to lead the National Association's Leadership Council on COVID-19 vaccination planning and campaign implementation. ASTHO developed a recent brief on religious exemptions from state vaccination laws, as well as several podcasts that address influenza, COVID-19, and monkeypox vaccines. ASTHO also developed a blog describing the legal considerations for scaling monkeypox vaccination efforts.

ASTHO is also working on projects concerning data-sharing and partnerships between state information, immunization information systems, and health information exchanges, as well as projects concerning the reduction of vaccination rate disparities in racial and ethnic minorities. ASTHO is also working with community groups to increase knowledge and trust in vaccines. Along with Harvard University, ASTHO has been examining three different public opinion polls to gauge public perspectives on COVID-19 recommendations. ASTHO continues to support states as they roll out the bivalent COVID-19 boosters.

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

NACCHO continues to support local health departments with COVID-19 vaccine distribution through the Supporting Local Health Departments to Increase Vaccine Uptake through COVID-19 project as well as with monkeypox vaccine distribution. In addition, NACCHO recently released a report outlining the impact of the COVID-19 pandemic response on state and local health departments. This report highlighted that 80 percent of local health departments reassigned staff to respond to the COVID-19 pandemic. Limited financial and personnel resources hindered COVID-19 responses and forced many local health departments to suspend routine public health services, exacerbating health inequities.

In July 2022, NACCHO held a national stakeholder consultation regarding influenza vaccination in older adults and a separate workshop to discuss the Equipping Local Health Departments to Address Vaccine Hesitancy project. NACCHO has been assisting CDC with the Partnering for Vaccine Equity project, which aims to increase local health departments' capacity to improve adult vaccine coverage by identifying and implementing strategies to reduce racial and ethnic disparities. NACCHO has expanded the Equipping Local Health Departments to Build COVID Vaccine Confidence project by recruiting a new cohort of health departments.

Public Comment

No public comments were offered.

Adjourn

Dr. Hopkins thanked the participants and OIDP staff and recessed the meeting for the day at 5:00 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 September 23, 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.

Innovations in Vaccine Safety Data

Safety Platform for Emergency vACcines (SPEAC)— Robert T. Chen M.D., M.A., Brighton Collaboration

Unlike vaccine efficacy, vaccine safety generally cannot be measured directly, although relative safety can be inferred from number of adverse events following immunization (AEFI) compared to the size of the vaccinated population. Founded in 2000, The Brighton Collaboration launched with the goals to (1) build trust in the safety of vaccines via rigorous science and (2) develop internationally accepted standards for monitoring vaccine safety throughout the vaccine life cycle. Recognizing the need for standardized case definitions, the Brighton Collaboration delivered over sixty AEFI case definitions (e.g., Guillain-Barré Syndrome, seizures) tiered by three levels of evidence. These case definitions serve as guidance for collecting and reporting vaccine safety data, and have been endorsed by major partners, such as the FDA), European Medicines Agency (EMA), and World Health Organization (WHO). The Brighton Foundation and the Coalition for Epidemic Preparedness Innovation (CEPI) created the SPEAC program to further vaccine safety monitoring.

Dr. Chen emphasized that immunization safety activities start with hypothesis testing, followed by hypothesis clarification through standardized case definitions and clinical assessments, which leads to both passive and active surveillance of vaccines through adverse event monitoring; afterward, research results need to be communicated and vaccine technology developed to ensure new and safer vaccines. SPEAC created goals to enhance vaccine safety assessment across CEPI development programs, harmonize vaccine safety monitoring during CEPI preclinical studies and clinical trials, and provide a continuous improvement framework. Starting in May 2019 and ending in October 2022, SPEAC 1.0 consisted of five work projects: 1) create a data safety monitoring board (DSMB) to share safety findings and expand global pool of potential DSMB members; 2a) identify adverse events of special interest (AESI) for target pathogen vaccines and develop Brighton case definitions; 2b) create vaccine safety templates; 3) continue quality assurance; 4) assist scientific coordination, communication, and project management; 5) develop contingency plans for priority diseases. SPEAC 1.0 had several key achievements, including novel case definitions and companion guides for AESI, safety templates for five

new vaccine technology platforms, operational m-DSMB monitoring for all CEPI-funded trials, a DSMB training course in novel pathogen endemic regions, and AESI lists for pathogens targeted by CEPI.

A major goal for CEPI 2.0 is to reduce CEPI 2.0's COVID-19 vaccine development time from 300 days to 100 days. In addition to the points mentioned for SPEAC 1.0, SPEAC 2.0, which launched in November 2022 and is projected to be complete in December 2026, proposes creating an IT system to optimize vaccine safety data collection; foster a thorough understanding of disease pathophysiology and adversomics via International Network of Special Immunization Service and special populations (children, pregnant women, immunocompromised and medically at-risk individuals); and improve active vaccine safety surveillance in low- and middle-income countries. Building on lessons learned from SPEAC 1.0, the overall goal for SPEAC 2.0 is to assist CEPI 2.0 in meeting its goals. SPEAC 2.0 will maximize CEPI resources and integrate them, along with key vaccine safety activities under development by Brighton and others in the safety ecosystem, into a functional framework with the goal of collecting safety data in a meaningful manner to build public confidence in new vaccines.

The Brighton Collaboration's long-term goals include: 1) evaluating and updating the Brighton Case Definitions, given that the pathogenesis studies of AESI diseases will lead to prevention of vaccine injuries and vaccine-preventable disease; 2) building capacity for training vaccine safety researchers; and 3) replicating the pharmacovigilance seen in US and high-income countries in low- and middle-income countries, where new vaccines are likely to be introduced before high-income countries.

Safety Assessment to a New Vaccine - Moving Forward to Objective Evaluation— Yftach Gepner, Ph.D., Tel Aviv University

Despite the tremendous technological advances in recent years, objective assessment of physiological measures post-vaccination is rarely performed and rarely used as a safety assessment of vaccines; instead, many assessments are self-reported. Self-reporting may lead to many problems, including participant non-responsiveness and placebo effects. For example, placebo effects were demonstrated in a post-vaccination assessment of the Pfizer-BioNTech COVID-19 vaccine. For seven days after injection of either the vaccine or a placebo, participants self-reported specific local or systemic adverse events and use of pain medication. For the first dose, 90 to 93 percent of participants reported symptoms; however, for the second dose, only 75 to 83 percent of participants reported symptoms. Many of these symptoms were relatively common in both the vaccine and placebo arms, including fatigue, headache, and muscle pain.

Dr. Gepner emphasized that instead of relying on subjective self-reported symptoms, physiologists must utilize objective measurements because vitals and other objective parameters provide more accurate vaccine safety data. Dr. Gepner's team used continuous remote monitoring of participants' vitals (e.g., heart rate, stroke volume, cardiac output, and skin temperature) to monitor cardiovascular changes following Pfizer-BioNTech vaccine administration in healthy participants. The researchers also administered 14 days of self-reported questionnaires using an app that was developed for the study. Within the first 48 hours post-vaccination, many participants' vitals were elevated compared to baseline. Following the initial 48 hours, measurements slowly returned to baseline levels. However, only 30 to 50 percent of participants reported symptoms through the mobile application. Thus, objective physiological changes were observed even in presumably asymptomatic participants who did not self-report any local or systemic reaction.

In conclusion, this study provided support for objective evaluations of vaccine safety and may reassure those hesitant to be vaccinated due to concerns of potential adverse vaccination consequences. Dr. Gepner emphasized that the findings should encourage public health officials and regulatory agencies to complement self-report measures of adverse events with objective measures for vaccine safety evaluation.

Strategy for Evaluation of Safety of a Novel Live Attenuated Oral Poliovirus Vaccine Type 2 (nOPV2)— Chris Gast, Ph.D., PATH

The GPEI eradicated Type 2 wild poliovirus in 2015 and then coordinated the removal of Type 2 poliovirus from oral polio vaccine (nOPV2) to ameliorate the risk of rare cases of Type 2 VAPP (VAPP caused by Type 2 poliovirus) and cVDPV2 (cVDPV caused by Type 2 poliovirus). As a result of the globally coordinated cessation of the nOPV2 vaccine, inadequate Type 2 immunity generated prior to cessation, inadequate IPV supply for global introduction, and limited nOPV2 supply to respond to outbreaks, cVDPV2 outbreaks occurred across WHO regions (Africa, East Mediterranean, Western-Pacific, and Europe) from 2017 to 2022. Dr. Gast emphasized the need for nOPV2 to halt poliovirus Type 2 outbreaks while reducing the risk of seeding new outbreaks resulting in paralytic poliomyelitis, and to reduce the risk of Type 2 VAPP.

Based on decades of prior research, the Bill and Melinda Gates Foundation funded a consortium of scientists to identify an nOPV2 candidate vaccine to be used for outbreak response; the new nOPV2 would have lowered risk of VAPP Type 2 and cVDPV2. Between 2011 and 2015, two candidates were selected; however, the removal of Type 2 from oral polio vaccines in 2016 did not allow for a full series of clinical trials for these new vaccine candidates. The consortium therefore included "prospective historical control" studies intended to be used as historical controls for nOPV2 clinical trials. Phase I and Phase II studies in adults, children, and infants spanned from 2017 to 2020. A Phase III study is ongoing for studying nOPV2 in children and infants. The Phase I and II trials employed typical endpoints: safety, solicited and unsolicited adverse events, immunogenicity, and measures of the frequency, duration, and quantity of fecal virus shedding. The first study was conducted in full containment for over a month in a purpose-built facility. Based on the evidence collected in this study, the Containment Advisory Group provided an exemption for nOPV2 to be used in clinical trials in additional trials.

Creating a novel polio vaccine without neurovirulence requires introducing mutations in Type 2 poliovirus that are resistant to reversion. Retention of these attenuating mutations can be monitored through genetic sequencing of shed virus. However, relatively few studies have examined the potential of nOPV2 to use other mutations to restore virulence. Therefore, development partners recognized the need for a phenotypic evaluation of genetic stability. In vivo evaluations of neurovirulence are required for the release of vaccine bulk batches, so researchers utilized the Monkey Neurovirulence Test (MNVT), an indicator of production consistency that is known to be sensitive to mutation associated with loss of attenuation, and the Transgenic Mouse Neurovirulence Test (TgmNVT), which was later used as a replacement of the MNVT. It is unknown how results of the MNVT or TgmNVT relate to absolute paralysis risk in humans, but their sensitivity to loss of attenuating mutations is well-understood. Therefore, relative neurovirulence was able to be quantified and compared. As a result of this study and other clinical data, nOPV2 was the first vaccine to receive WHO Emergency Use Listing because it is safe, produces similar immune responses as previous nOPV2 strains, has similar or lower viral shedding, and has a more stable genome than preceding oral poliovirus vaccines. Deployment of the vaccine began in 2021, and so far over 450 million doses have been administered. The experience from deployment is consistent with clinical trial observations.

Developing and Enhancing Algorithms to Identify Pregnancies in the Vaccine Safety Datalink (VSD)— Allison Naleway, Ph.D., Kaiser Permanente

Dr Naleway's team developed a Pregnancy Episode Algorithm (PEA), an algorithm that identifies pregnancies. Her team's PEA tracks pregnancies from 2002 onward and interfaces with VSD to identify pregnancy outcomes (e.g., live birth, stillbirth) and assigns start and end dates to each pregnancy. The PEA also includes an extensive list of diagnosis and procedure codes for pregnancy outcomes and pregnancy-related care. However, the PEA ran annually, only identified completed pregnancies, imputed gestational age for all non-live birth outcomes, and experienced data lags that make it challenging to perform real-time surveillance of vaccine safety related to pregnancy. Therefore, Dr. Naleway's team

enhanced the algorithm and named the new version the Dynamic Pregnancy Algorithm (DPA), updated the PEA to run on a weekly basis, and incorporated additional sources of gestational age.

The DPA has supported recent safety studies of maternal COVID-19 vaccination, including outcomes of spontaneous abortion and stillbirth. It interfaces with VSD to select samples of pregnant women for phone surveys about influence and COVID-19 vaccination uptake. Researchers have also used these algorithms to describe COVID-19 and influenza vaccination coverage in pregnant women in the VSD.

The use of the DPA led to several successes: the additional gestational age data sources reduced imputed dates compared to the original PEA; 100 percent agreement on outcome type and date and 97 percent agreement within 30 days for gestational age with manual medical record review for live births; and for pregnancy losses (spontaneous abortions, induced abortions, stillbirths), 98 percent agreement on outcome date and 75 percent agreement within 30 days for gestational age with manual medical record review. One perk of the DPA is that 80 to 90 percent of pregnancy episodes subsequently ending in live birth can be identified by the algorithm six or more months prior to birth; other pregnancy outcomes can also be inferred, allowing researchers to quickly conduct maternal vaccination safety studies.

Dr. Naleway noted that DPA still presented challenges. Its accuracy is lower for tracking pregnancy losses around 19 to 20 weeks' gestation. Additionally, the DPA is not adequately able to distinguish spontaneous abortion from stillbirth, meaning that non-live birth outcomes still require manual record review to collect precise information about diagnoses and exposures. DPA also does not capture very early pregnancy losses, and pregnancies or prenatal care that occur outside of the delivery system or at home.

Discussion

Dr. Dunn asked Dr. Chen about reassuring the public that vaccines were safe in the past, prior to the identification and use of modern-day vaccine safety measures. Dr Chan answered that, even though technology and knowledge have increased with each passing generation, researchers throughout history have strived to maintain rigorous vaccine testing standards.

Dr. Duchin asked panelists whether the work done by the CDC's public health data modernization initiative advances the ability to monitor and understand vaccine safety or whether other forms of enhancements are needed in public health surveillance and data systems to accomplish the task. Dr. Chen emphasized the need to make demographic information available for research purposes and added that the people in the vaccine safety domain are eager to work with the CDC and others in the initiative to further vaccine safety.

COVID-19 Vaccine Safety Review

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

The VaST Working Group provides 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), VSD, the FDA Biologics Effectiveness and Safety (BEST) System, Department of Veterans Affairs (VA), IHS, and DOD. International partners include the Public Health Agency of Canada and the Global Advisory Committee on Vaccine Safety.

From December 21, 2020 through December 21, 2022, VaST held 65 independent meetings to review COVID-19 vaccine safety data, 16 joint meetings with the Advisory Committee on Immunization

Practices (ACIP) COVID-19 Vaccines Work Group, and 19 ACIP meeting presentations or reports with VaST assessments. From June to September 2022, VaST met with ACIP to address the use of Moderna and Pfizer vaccines in younger children, use of Moderna vaccine in children and adolescents from 6 to 17 years old, use of Novavax vaccine in adults over the age of 18, and use of Moderna and Pfizer bivalent booster vaccines. On June 23, 2022, VaST used data from their VaST Assessment of Safety of COVID-19 Vaccines in Children and Adolescents in a meeting with ACIP to discuss the Moderna COVID-19 vaccine for children aged 6-17 years. On July 19, VaST met with ACIP to consider the Novavax COVID-19 vaccine for adults over 18. On September 1, 2022, VaST met with ACIP to consider the Moderna and Pfizer bivalent booster vaccines.

Myocarditis and pericarditis events are extremely rare. VaST found that risk is greatest in male adolescents and young adults (12 to 15 and 16 to 17 years old), and after the second dose of the primary series. Risk appears to decrease with age and the male-to-female predominance of cases attenuates with age. Potential risk of myocarditis and pericarditis is still being assessed in children younger than 12 years. Dr. Hopkins highlighted that the rate ratio of myocarditis and pericarditis was elevated in those vaccinated with Moderna versus Pfizer. Although the discrepancy was not statistically significant, a larger sample size may demonstrate a significant difference. Almost all cases were mild and resolved without complication; available information suggests that most individuals with myocarditis after mRNA COVID-19 vaccination recover by 3 to 8 months after diagnosis. Continued monitoring and natural history studies are needed for myocarditis and pericarditis following mRNA COVID-19 vaccination to understand rates, outcomes, risk factors and mechanisms. For booster doses, safety findings are generally consistent with those observed for primary series vaccination. VAERS reported that over 90 percent of events were non-serious for first mRNA COVID-19 booster doses in ages 5 to 11 and over the age of 12, as well as second booster doses in individuals above 50 years of age. Evidence suggests an increased risk for myocarditis following the first booster dose. VAERS found that, among individuals vaccinated with the first booster dose, reporting rates of myocarditis were highest in males ages 16-17; overall, reporting rates are low following the first booster dose versus the second of the primary series. In VSD analyses, myocarditis and pericarditis incidence following the first booster dose and the second dose of the primary series are similar, though case counts are small and confidence intervals around point estimates are wide.

VaST also examined COVID-19 vaccine safety as it relates to pregnancy and reproductive health. To date, there have been no concerning pregnancy and reproductive health outcomes following COVID-19 vaccination. Data on COVID-19 vaccine safety during pregnancy and reproductive health outcomes following vaccination will be presented at a future ACIP meeting.

Comparative Safety of COVID-19 mRNA vaccines: BNT162b2 versus mRNA-1273— Arin Madenci, M.D., Ph.D., Harvard T.H. Chan School of Public Health

Prior studies showed that mRNA COVID-19 vaccines are safe, as both Pfizer-BioNTech and Moderna vaccines had low SAE rates. However, head-to-head comparisons between the two had not been studied. Therefore, Dr. Madenci and his team created a two-step plan to study the risk of adverse events with Pfizer-BioNTech versus Moderna vaccines: 1) specify the hypothetical target trial protocol: eligibility criteria, treatment strategies, assignment, time zero and follow-up, outcomes of interest, causal contrasts, and data analysis; and 2) emulate target trial protocol as closely as possible using observational data.

For the hypothetical target trial, the eligibility criteria for participation would be adult veterans with no previous COVID-19 infection or vaccination, no history of the adverse event of interest, and active use of the VA healthcare system. The two treatment strategies would be: 1) one dose of the Pfizer-BioNTech vaccine with second dose 21 days later and 2) one dose of Moderna vaccine at baseline with second dose 28 days later. Participants would be randomly assigned to a strategy at baseline and randomized following stratification for date, age, sex, race, urbanicity of residence, and geographic location. Follow-up would end on the day of the outcome of interest: SARS-CoV-2 infection diagnosis, 38 weeks, or end of the

study period. The following adverse events would be assessed individually: neurologic events, hematologic events, hemorrhagic and ischemic stroke, myocardial infarction, other thromboembolic events, myocarditis or pericarditis, arrhythmia, kidney injury, appendicitis, autoimmune events, herpes zoster or simplex, arthritis or arthropathy, and pneumonia. Researchers emulated the target trial with clinical data from the VA EHR database. SARS-CoV-2 infections were identified with VA COVID-19 National Surveillance Tool. Approximately 370,000 individuals had received the Pfizer-BioNTech vaccine and were eligible for subsequent analyses and around 400,000 individuals had received the Moderna vaccine and were eligible for subsequent analyses. After matching of covariates of interest (e.g., age, sex, race), 216, 836 individuals were included in each cohort. Results showed that recipients of the Moderna vaccine (compared to Pfizer-BioNTech) had lower 38-week risk of stroke, myocardial infarction, thromboembolism, and kidney injury. Although adverse event risks differed significantly between Moderna and Pfizer-BioNTech vaccines, these differences amounted to less than 0.2 percent. In conclusion, both vaccines had low absolute risks of the studied adverse events.

Reactogenicity of Simultaneous COVID-19 mRNA Booster and Influenza Vaccination: V-safe— Anne M. Hause, Ph.D., M.S.P.H., CDC

CDC recommends that all persons aged 6 months and older be vaccinated against COVID-19. COVID-19 vaccinations may be administered without regard to timing of other vaccines (e.g., seasonal influenza vaccines), enabling simultaneous vaccinations. Utilizing simultaneous vaccinations to eligible individuals at the same visit increases the likelihood that they remain current on all recommended vaccines.

Dr. Hause's team compared reactions and health impacts reported to v-safe in the week following simultaneous seasonal influenza vaccine and an mRNA COVID-19 booster versus an mRNA COVID-19 booster alone. Data were collected from September 22, 2021 through May 1, 2022. Individuals were excluded from the analysis if they reported: a) simultaneous administration of mRNA COVID-19 booster dose, influenza vaccine, and additional vaccine(s); b) booster dose prior to authorization; and c) Moderna vaccination in persons less than 18 years or Pfizer-BioNTech vaccination in persons aged less than 12 years. Preliminary findings indicate that injection site pain and systemic reactions are more frequently reported following simultaneously administered mRNA COVID-19 booster vaccine and seasonal influenza vaccine than mRNA booster alone. The increase in reporting frequency of injection site pain and systemic reactions was modest (8 to 11 percent) There was no evidence for a difference in severity. CDC will continue to monitor the safety of COVID-19 vaccines.

Discussion

Dr. Cooke asked whether the Pfizer-BioNTech and Moderna cohorts had been compared with a non-vaccinated group. Dr. Madenci answered that controlling for non-vaccination would have been difficult as the analysis was designed to emulate a randomized clinical trial without a vaccine placebo group. Due to ethical concerns, a vaccine placebo group should not exist in a randomized clinical trial, and thus was excluded.

Monkeypox Vaccine Safety Review

Monkeypox: CDC Vaccine Safety Monitoring— Jonathan Duffy, M.D., M.P.H., CDC

JYNNEOS is a live, non-replicating monkeypox vaccine initially licensed for subcutaneous injection in adults and later expanded by an EUA for intradermal administration in adults and subcutaneous administration in minors. As of September 13, 540,150 JYNNEOS doses had been administered, the majority being first doses due to limited supplies. The majority of vaccinees have been men aged 25-39.

CDC monitors the safety of JYNNEOS using three systems:

1) Vaccine Adverse Event Reporting System (VAERS): Public system for reporting vaccination administration errors and SAEs.
2) VSD: Includes vaccine safety data from nine participating integrated health care organizations on more than 12 million people. For monkeypox, VSD will monitor for adverse events of special interest (e.g., anaphylaxis, Guillain-Barré Syndrome) identified in JYNNEOS's EUA.
3) V-safe: smartphone-based survey platform created for COVID-19 vaccination program. Based on positive feedback from that program, CDC is currently developing a new module for monkeypox vaccines.

Under JYNNEOS's EUA, vaccination providers are required to report vaccination errors, SAEs (regardless of whether they are linked to vaccination), cardiac events (e.g., myocarditis, pericarditis), thromboembolic events, and neurovascular events. As of September 16, 856 adverse events have been reported through VAERS, 849 (99.2 percent) of which are non-serious adverse events. Common adverse events include incorrect route administration (e.g., intramuscular instead of subcutaneous), injection site erythema and swelling, urticaria (i.e., hives), injection site pain, and dizziness. Based on this reporting, CDC has not identified any new safety concerns to date regarding the JYNNEOS vaccine.

ACAM2000™: Use & Safety Data in the DoD Monkeypox Vaccine Safety Review—Limone Collins, M.D., Defense Health Agency (DHA), Department of Defense (DOD)

ACAM2000 is a replication-capable live Vaccinia virus vaccine first licensed in 2007 to replace Dryvax® for DOD smallpox vaccinations. ACAM2000 is delivered through multiple punctures of the skin by a bifurcated needle containing the vaccine; as the virus replicates at this site, a lesion forms over the next 21 days that eventually turns into a pustule with a crust (i.e., scab). Vaccination symptoms begin about one week after vaccination and can include redness, warming, and itching at the vaccination site as well as swollen lymph nodes, fever, muscle aches, and fatigue. These symptoms are often more pronounced in people who have not previously been vaccinated for smallpox using Dryvax or ACAM2000.

Until the crust forms over this lesion (about 21 days after vaccination), live virus from this lesion can be spread to other parts of the body or to other people through contact with the vaccination site. This ability of the live virus to spread requires people administering the vaccine to be previously vaccinated. Potential adverse events range from mild events (e.g., erythematous reactions, accidental infection of others) to serious and potentially fatal SAEs (e.g., eczema vaccinatum, progressive Vaccinia infections). SAEs are more likely among people with eczema (i.e., atopic dermatitis) and compromised immune systems. Additionally, some vaccine recipients may experience serious cardiac complications (e.g., myocarditis, pericarditis), so the American Heart Association recommends cardiac monitoring and exercise restrictions for vaccine recipients for 21 days following inoculation.

DHA monitors recipients of ACAM2000 vaccines to monitor the wound site and potential adverse events and ensure the recipient properly bandages and maintains the wound site to reduce the risk of accidental infections. Among Service Members, accidental infection of others most commonly occurs due to contact sports and other close contact. DHA also examines immunological profiles of potential recipients as immunocompromised people have higher risk of serious or fatal adverse events.

Discussion

Given the large number of monkeypox vaccines already administered, Dr. Schechter asked whether launching the v-safe monkeypox module can be accelerated to provide another avenue for reporting potential safety concerns. Dr. Duffy replied that CDC had already planned to expand v-safe to diseases outside COVID-19 before the current monkeypox outbreak. CDC continues to refine v-safe to enable quicker launching of modules for other vaccines, including for future infectious disease outbreaks.

Dr. Schechter also asked whether VSD can be used to monitor safety of vaccines outside the network of participating health care providers. Dr. Duffy responded that VSD is limited to the current network of providers. He noted that, for the current monkeypox outbreak, VSD can provide information on vaccinations administered by participating providers.

Evaluating Evidence to Address Safety Questions

Vaccine Safety Issues at the Turn of the 21st Century— Zunera Gilani, M.P.H., Ph.D., CDC

Immunization is one of the most effective ways to reduce infectious disease risk. However, global advances in vaccination coverage have been threatened by antivaccination sentiments and misinformation perpetuated through social media and public figures. Public trust in vaccine safety is necessary for continued gains in global vaccination programs. The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 by WHO to respond to vaccine safety issues of global or regional importance. The group includes experts in a variety of fields (e.g., epidemiology, statistics, infectious disease, public health), who provide independent advice to WHO on vaccine safety issues and review safety issues relevant to all vaccines and vaccine-specific issues.

Dr. Gilani summarized reviews by GACVS conducted from 1999 to 2019 on six key public concerns that have been at the center of controversies regarding vaccine safety during the early 21st century: 1) aluminum adjuvants; 2) thiomersal; 3) purported links between routine vaccinations and autism spectrum disorder (ASD); 4) autoimmune disorders; 5) immune overload; and 6) nonspecific effects. Each issue has been linked to reduction of public trust in vaccines and vaccination.

Aluminum Adjuvants

Aluminum is found everywhere in the environment and is a component of many consumer products, including in the form of aluminum hydroxide and soluble aluminum salts, which act as adjuvants in vaccines to enhance immune responses. Although high intravenous levels of aluminum are associated with encephalopathy, developmental delays, adverse neurological outcomes, and autoimmune disorders, the concentrations of aluminum in vaccines are lower than exposure from inhaling air particulates or antacid consumption. Multiple clinical and epidemiological studies indicate that children who receive aluminum adjuvant-containing vaccines do not have aluminum levels in blood or hair above minimum risk levels established by the Agency for Toxic Substances and Disease Registry and are not at increased risk of adverse neurodevelopmental outcomes. GACVS concluded that public concern regarding aluminum adjuvants is fueled by poorly designed studies and inaccurate extrapolation from such studies.

Thiomersal

Hesitancy regarding the use of thiomersal, a mercury-based preservative with antiseptic and antifungal properties, in (primarily non-live) vaccines stems from concerns about fetal exposure to methylmercury, which has adverse effects on neurodevelopment. Thiomersal is eventually metabolized into ethylmercury, which has different pharmacokinetic properties than methylmercury. After conducting comprehensive reviews of pharmacokinetic studies on ethylmercury and epidemiological studies of neurodevelopmental outcomes, GACVS determined that published research does not demonstrate a link between thiomersal-containing vaccines and increased risk of adverse neurophysiological outcomes or ASD. Despite thiomersal having been removed from routine pediatric vaccines in most high-income countries as a precautionary measure, the prevalence of neurodevelopmental disorders has continued to increase in these countries.

Purported Links Between Vaccines and ASD

ASD is a developmental disability that can cause significant social, communication, and behavioral challenges. The alleged link between vaccines and ASD came to prominence based on a study published in 1998 by Dr. Andrew Wakefield that suggested a linkage between the MMR vaccine and ASD—although this paper has since been retracted. Proponents of the vaccine-ASD link highlight anecdotal observations of ASD symptoms developing shortly after vaccination and the purported "ASD epidemic" coinciding with increasing numbers of recommended childhood vaccines. However, multiple large cohort studies have demonstrated no association between ASD and administration of vaccines, thiomersal, or aluminum adjuvants. Instead, an increasing body of evidence suggests that ASD is a predominantly genetic disorder.

Autoimmune Disorders

Purported associations between vaccination and chronic autoimmune conditions (e.g., multiple sclerosis, thyroid disease autoimmune encephalitis) are largely based on the concept of molecular mimicry, which refers to a similarity between vaccine antigens and human proteins, which may lead to the immune system targeting human proteins, resulting in autoimmune damage. The alleged link between vaccination—especially against HPV—and autoimmune conditions have been extensively explored via controlled trials, observational studies, and epidemiological analyses in multiple countries and subpopulations. In 2013, GACVS review of available data found no increased risk of autoimmune diseases among girls who received the HPV vaccine compared with those who did not.

Immune Overload

Immune overload, the concern that multiple simultaneous vaccinations can overload the immune system and increase vulnerability to other infections, has led to delayed or alternative vaccine dosing schedules due to parental concerns, particularly in high-income countries. A 2006 GACVS report concluded that available data did not support the hypothesis that multiple vaccines weaken or harm the immune system and reassured confidence in infant immunization programs.

Non-specific effects

Evidence for nonspecific effects (NSE) of vaccines, which are believed to induce protection from or susceptibility to infections not targeted by the vaccines, is lacking. GACVS reports from 2002 to 2008 stated that current evidence was not sufficient to warrant changes in global immunization policy. Furthermore, a systematic review conducted in 2016 found no evidence to support presence of clinically relevant, geographically generalizable NSE after BCG, DTP, or MCV vaccination.

Discussion

In response to a question from Dr. Dunn about whether CDC had created a training module on the information presented geared toward educating health care providers and personnel, Dr. Gilani replied that a training module based on the GACVS review paper has not yet been created.

A Boost of Protection: Booster Doses and Strategies

Variant Vaccines for COVID-19: COVID-19 Variant Immunologic Landscape Trial (COVAIL)— Nadine Rouphael, M.D., Emory University

The COVAIL trial examines how different COVID-19 vaccine boosters impact immune response and nAb production. The trial includes monovalent (i.e., containing or encoding one variant's spike protein) and bivalent (i.e., containing or encoding spike proteins from two different variants) boosters as well as

comparisons of the initial prototype (i.e., first introduced in early 2021) vaccine boosters against variant-specific (e.g., Delta, Omicron) boosters. Sera from these boosters are tested against pseudoviruses (i.e., viruses only able to replicate once, used for testing vaccines) with antigens for different variants, including D614G (i.e., WT COVID-19 with the D614G mutation, which became prevalent in summer 2020), Beta, Delta, and multiple Omicron subvariants (e.g., BA.1, BA.4/BA.5). Dr. Rouphael presented results from participants who received Moderna initial doses and boosters, but she noted that COVAIL has other study arms for other vaccines (e.g., Pfizer, Sanofi).

Initial data showed that different boosters (e.g., prototype, Omicron BA.1 + prototype) elicited similar nAb levels against D614G pseudoviruses, but boosters encoding Omicron BA.1 (monovalent or bivalent) induced significantly higher levels of nAbs against Omicron pseudoviruses than prototype boosters. Boosting with prototype Moderna vaccines elicited nAbs against both D614G and Omicron pseudoviruses by 29 days post-inoculation, but Omicron nAbs declined faster by Day 90 compared to D614G nAbs, suggesting that prototype boosters offer less long-term protection against Omicron. These results are similar to data released by Moderna.

Examining different Omicron BA.1 boosters (monovalent or bivalent) showed that BA.1-containing boosters produced similar nAbs to the prototype booster for non-Omicron variants (e.g., Beta, Delta), but BA.1 boosters produced significantly more nAbs for Omicron than the prototype vaccine. However, testing against pseudoviruses with BA.4/BA.5 antigens showed that both monovalent prototype and bivalent boosters containing BA.1 produced approximately 33 percent less nAbs compared to BA.1 and BA.2 pseudoviruses, suggesting that more recent Omicron subvariants (e.g., BA.5) have significantly different antigens than earlier Omicron subvariants (e.g., BA.1). This difference between earlier and more recent Omicron variants was confirmed through antigenic mapping (i.e., measuring distances between antigens) by the Smith laboratory. These results may suggest that boosters with antigens from more recent Omicron sublineages may offer more protection than BA.1 antigen boosters. COVAIL is currently examining effects of boosters containing BA.4/BA.5 antigens.

Homologous and Heterologous Platform Boost Study: Rapid Decline in Vaccine Boosted Neutralizing Antibodies against Omicron Variant— Kirsten E. Lyke, M.D., University of Maryland

By April 2021, three COVID-19 vaccines (Janssen/Johnson & Johnson, Pfizer-BioNTech, and Moderna) were available through EUAs. Concerns about potentially limited supplies and about the safety of multiple adenoviral-vectored vaccine doses (i.e., Janssen/Johnson & Johnson) prompted the Infectious Diseases Clinical Research Consortium (IDCRC) to launch the "Mix and Match" study in May 2021. Participants who had already received at least one of the three COVID-19 vaccines and were not previously infected with SARS-CoV-2 received one of the boosters, either homologous (same as their first dose) or heterologous (different from their first dose) boosters at least 12 weeks after their first vaccine dose. Participants were then monitored for nAb production and potential adverse events.

All three boosters elicited anamnestic immune responses (i.e., production of nAbs that target the original antigen encountered). Heterologous boosters elicited similar or higher immune responses compared to homologous boosters. mRNA vaccine (Moderna and Pfizer-BioNTech) boosters resulted in higher nAb titers compared to the Janssen/Johnson & Johnson booster. None of the boosters, whether homologous or heterologous, posed any safety concerns. Based on these data, FDA authorized the mixing and matching of vaccines for booster shots.

The IDCRC also recently examined the effects of different boosters on immune responses to Omicron sublineages. Boosters of any of the three vaccines significantly increased nAb production by Day 29. Whereas D614G-nAbs remain present through 180 days, Omicron-nAbs decline after Day 29, with greater declines among participants who received both mRNA initial vaccine doses and boosters than

participants who received at a Janssen/Johnson & Johnson booster. Antibody binding against BA.4 and BA.5 (i.e., more recent Omicron sublineages) was 5-12 times lower than binding against BA.1 (i.e., the initial Omicron sublineage identified), suggesting reduced efficacy of these boosters against more recent Omicron sublineages. Among participants who initially received mRNA vaccines, those who received a Janssen/Johnson & Johnson booster had higher levels of nAbs at Day 90 compared to those who received an mRNA booster. These results suggest that Janssen/Johnson & Johnson may provide longer-lasting protection than mRNA vaccine boosters.

COVID-19 Variants and Vaccines: Where is the Science Taking Us?—Andrew Pekosz, Ph.D., Johns Hopkins University

The NIH SARS-CoV-2 Assessment of Viral Evolution program monitors emerging SARS-CoV-2 variants, examines SARS-CoV-2 viral genome sequence data for potential mutations, monitors variants of concern, and performs in vitro and in vivo analyses of different viral strains on immune responses to inform public health decisions. This work is crucial given the large amount of variation among SARS-CoV-2 strains, including among specific sublineages (e.g., BA.5).

Compared to previous variants (e.g., D614G, Delta), Omicron had multiple mutations in the spike protein that significantly increased transmission, enabled the virus to replicate in other tissues, and changed the structure of the spike protein, enabling it to escape many antibodies elicited by previous strains. In addition to enabling escape from nAbs, spike protein mutations can also impact binding by non-neutralizing antibodies, receptor (e.g., ACE2) binding and affinity, and transmission. Even if they have mutations that enable them to escape antibodies, mutations that reduce fitness (e.g., reduced transmissibility) can prevent new strains from becoming dominant. Therefore, further research is needed to improve understanding of how mutations impact transmissibility.

Omicron sublineages continue to emerge, but these sublineages typically differ from the original Omicron sublineage (BA.1) by only one or two mutations in the spike protein gene as well as some other viral genes rather than multiple mutations within the spike protein. This indicates that Omicron sublineages continue to evolve in a manner similar to other respiratory viruses such as influenza. Population immunity can also drive viral evolution and vaccine selection. Differences in population immunity, both within the U.S. and throughout the world, will also impact SARS-CoV-2 evolution and should be considered when selecting COVID-19 vaccination strategies.

Dr. Pekosz outlined seven key considerations for guiding COVID-19 vaccination strategies:

1) Level of pre-existing immunity.
2) Vaccination strategies for people without any pre-existing immunity, such as infants and young children.
3) Balancing short-term and long-term protection.
4) Previous SARS-CoV-2 infections can significantly strengthen and alter immune responses elicited by vaccines.
5) Impacts of vaccines on mucosal immune responses.
6) Selection of vaccines to protect against serious illness versus protection from infection.
7) Immunological imprinting (i.e., production of antibodies that match the original antigen exposure) may be a positive with COVID-19 due to potential cross-reactivity.

Discussion

Dr. Cooke noted that the FDA recently approved bivalent boosters that encode BA.4/BA.5 antigens. Dr. Lyke noted that human studies on the effect of these BA.4/BA.5 bivalent boosters have yet to be published, but initial in vitro neutralization analyses show that these boosters may be effective against current Omicron sublineages. However, more research is needed on whether bivalent boosters increase

the breadth of memory B cell responses across different strains, which can offer broader protection against future sublineages and variants.

Dr. Cooke asked whether COVID-19 boosters may eventually become required annually similar to seasonal influenza vaccines. Dr. Pekosz responded that the need for annual boosters will depend on whether bivalent boosters induce a broader range of protection against different SARS-CoV-2 strains than monovalent boosters, which requires additional research on how different boosters alter T cell and memory B cell responses. mRNA vaccines may also offer broader protection against different strains than most current seasonal influenza vaccines.

In response to a question about whether any SARS-CoV-2 variants tend to recur on a cyclical basis (e.g., seasonal prevalence), Dr. Pekosz hypothesized that convergent evolution may lead to many strains having the same few amino acid substitutions within the spike protein, which may reflect regions where mutations and amino acid mutations do not significantly reduce viral fitness. Bivalent boosters may induce broader immune responses across these variable regions of the spike protein, which may slow SARS-CoV-2 evolution. Dr. Lyke disagreed, noting that vaccine coverage is still very low in regions such as sub-Saharan Africa and Asia where large immunocompromised populations (e.g., people living with HIV) may enable SARS-CoV-2 to accumulate multiple mutations before spreading to other populations and geographic regions. Improving vaccine availability and uptake in these regions, including among immunocompromised populations, can reduce the risk of new variants with multiple mutations and significant antigenic differences.

Regarding whether the benefits of the Janssen/Johnson & Johnson booster may be due to the adenovirus vector, Dr. Lyke explained that the "Mix and Match" study did not intend to evaluate differences between vaccine platforms; but she noted that high nAb titers induced by heterologous boosting with the Janssen/Johnson & Johnson may increase interest in adenoviral boosters.

Dr. Lyke also explained that the Novavax vaccine's current EUA is for first doses only and does not include its usage as a booster, but the Mix and Match study has some initial data on people who received first Novavax vaccine doses followed by a different booster, and IDCRC should publish these data soon.

Protecting Rural Americans: Addressing Gaps in COVID-19 Vaccination Coverage

Disparities in COVID-19 Vaccination Coverage Between Urban and Rural Counties—United States, December 14, 2020-January 31, 2022—LaTreace Harris, Centers for Disease Control and Prevention

As reflected in the National Immunization Survey, disparities in COVID-19 vaccination rates have resulted in higher COVID-19 incidence and mortality in rural compared urban communities. Between December 14, 2020 and January 31, 2022, 75.4 percent of residents of urban counties received at least one COVID-19 vaccine dose compared to 58.5 percent of residents of rural counties. Furthermore, this disparity has widened over time: between April 2021 and January 2022, the gap between urban and rural vaccination rates doubled from 7 percentage points to 16 percentage points.

To determine the gap between urban and rural counties across America, CDC utilized state level IIS and Vaccination Administration Management System (VAMS) data. Participants' county of residence was matched to one of six urban-rural categories according to the 2013 NCHS Urban-Rural Classification Scheme; the urban category included four subcategories (large central metropolitan, large fringe metropolitan, medium metropolitan, and small metropolitan); the rural category included two categories (micropolitan and noncore).

A total of 46 states had higher COVID-19 vaccine uptake in urban counties compared to rural counties. Arizona is the only state that started with (slightly) higher COVID-19 vaccine uptake in rural areas. Three

states (New Hampshire, Rhode Island, Delaware) and the District of Columbia were not included in this analysis as they do not have rural counties under (NCHS) definitions.

Vaccination coverage is also affected by age and sex. In both urban and rural counties across the country, women are slightly more likely to receive vaccinations than men. The largest vaccination rate differences were noted among children and adolescents, with 64.95 percent of 12- to 17-year-olds vaccinated in urban areas versus 38.7 percent in rural areas. Furthermore, 5- to11-year-olds had the lowest rate of vaccination overall; however, this is likely because they were the last group to receive the vaccination. For children in the youngest age group, the urban populations have double the rate of vaccination over rural areas (30.5 percent versus 14.7 percent). A similar gap is seen in older adults; the difference in vaccination rates for individuals 65 and older in urban and rural populations was as wide at 92.7 percent and 83.2 percent, respectively.

National Governors Association—Brittney Roy, National Governors Association

The National Governor's Association (NGA) provides bipartisan strategies to fifty-five governors in U.S. states and territories. During the COVID-19 pandemic, CDC contracted NGA to work on the CDC's Vaccinate With Confidence strategic framework, which aims to strengthen vaccine confidence and prevent outbreaks of vaccine-preventable diseases in the United States. The team increased vaccine uptake in rural populations by assisting immunization managers, the governor's office, the health department, and health officials involved with the COVID-19 crisis. NGA collaborated with states to increase vaccine availability by improving access, streamlining systems, and increasing outreach efforts.

Ms. Roy's team faced multiple challenges, including lack of facilities (e.g., pharmacies, medical clinics, and vaccination centers) and decentralized health departments that make it difficult to include local health departments in vaccine roll-out. In Alabama, Ms. Roy's team overcame these challenges by having the decentralized Alabama Department of Public Health partner with the education center office to set up five regional vaccination sites.

Ms. Roy emphasized the positive role of trusted messengers and community health partners (e.g., EMS workers, local pharmacists) in the dissemination of vaccine information in small towns, especially those with vaccine mistrust. Behavioral scientists, who collaborated with state health departments and city mayors to develop communication strategies about vaccines, were also helpful. Yet, the information was not trusted by the public. Ms. Roy noted that her own family members distrusted vaccine information disseminated by the government but changed their minds when she shared vaccine information from other sources. Eventually, they became comfortable with being vaccinated and came to trust organizations like the CDC and the Biden administration.

Arizona COVID-19 Vaccine Strategy—Siman Qaasim, Arizona Department of Health Services

In reaction to the COVID-19 pandemic, Arizona incorporated a data-driven strategy to boost vaccination across rural areas of the state. The strategy included three steps: 1) work with the Geographic Information System (GIS) team and in-house data equity coordinator to create a vaccine-planning tool that identifies regions of interest based on Social Vulnerability Index (SVI) and vaccine rate at census tract level, as well as other demographic variables ("layers"); 2) select the three census tracts per county with the highest SVI and lowest vaccine rate to target with a multi-million-dollar media campaign; and 3) provide one-on-one assistance to rural counties and data sharing agreements with partners. They also mobilized on-the-ground community partners: a Disparities Grant focused on rural counties and Tribes, Mobile Vaccine Program led by Vaccine Equity Coordinator, Vaccine Equity Task Force, Mayo CEAL (vaccine hesitancy focus groups with racial ethnic minorities to examine drivers of hesitancy and effective communications), community health workers and representatives, the Arizona Center for Regional and Border Health, and the Arizona Center for Rural Health MOVE-UP Program.

Ms. Qaasim emphasized the strong community response of Arizona tribes to COVID-19 vaccination. Arizona has a population of 22 native tribes, the third largest American Indian population in the country. She highlighted Navajo County, part of the Navajo Nation (one of the largest tribes in the U.S.), where the vaccination rate for 5- to 11-year-olds was 50 percent (versus 31 percent nationally), and the vaccination rate for 12- to 19-year-olds was 76 percent (versus 60 percent nationally). Ms. Qaasim associated high vaccination rates in Navajo County with five factors: 1) the tribes' strong history of vaccines; 2) tribal sovereignty and ability to enact independent vaccine strategies; 3) COVID-19 deaths among tribe members, especially elders; 4) transparency and communication across all twenty-two tribes; and 5) a value system that favors community responsibility.

Many tribes already had highly coordinated strategies in place for vaccine rollout. The Navajo County Public Health Services District already had on-the-ground partners mobilizing for flu vaccine distribution through Points of Dispensing (POD) clinics, which they expanded by collaborating with fire departments, nursing students, and paramedics. During COVID-19, this sophisticated orchestrated infrastructure helped roll out vaccines across the nation, especially in hard-to-reach rural areas. Other campaigns around vaccine emphasized community values. An example is the Izee' Baa Gowah San Carlos Apache Healthcare For You, For Me, For All campaign, which utilized Native voices: rodeo stars for campaigns aimed at youth, elder voices, which urged younger generations to assist in vaccination, and other culturally relevant messages. Other efforts included communication to community through tribal council meetings two months before vaccine arrival, COVID-19 case, infection, and community updates, and vaccine roll-out plans, nurse call line for calls related to the vaccine, establishing the COVID-19 vaccine call line, and cash incentives for vaccinated individuals. At the Tuba City Regional Health Center, tribal community members were engaged to create pro-immunization messages, which proved particularly effective in the community.

In LaPaz Country, which has a Latinx/Native American population with a high SVI, vaccination rates increased through the Regional Center for Border Health's efforts to disseminate mobile clinics and vaccinate farmworkers at events before and after work hours. In Southern Arizona, the University of Arizona Center for Rural Health utilized a mobile vaccine program separate from the state effort, which targeted communities with high incidence of poverty, essential health workers, migrants, seniors, and individuals living in low-income housing to achieve high vaccination rates. Ms. Qaasim emphasized the importance of considering a county's total workforce to maximize vaccination rate. For example, in the county of Santa Cruz the vaccination rate for the workforce exceeds the number of workers documented in the area, because individuals, usually agricultural workers, cross the border from California and Mexico to work in Arizona during the agricultural season.

COVID-19 Vaccine Equity in Marin County: Lessons from the Last Mile — Dr Matt Willis, Marin Health and Human Services

Before the COVID-19 pandemic, Marin County had one of the lowest vaccination rates among California counties. Dr Willis noted that only 75 percent of their incoming kindergarteners received routine immunizations. Marin County also had the highest rate of personal belief exemption submissions against required vaccinations in the San Francisco metropolitan area as well as whooping cough cases in record numbers and measles cases in 2015. However, after community engagement, increased communication, and policy changes, 95 percent of Marin County children going into kindergarten now are fully vaccinated, and the county now has one of the highest vaccination rates against COVID-19 in the nation.

Dr. Willis described how vaccination was achieved in Marin County. First, Dr. Willis's team examined barriers to vaccination in rural areas (i.e., language barriers, technology gaps, lack of transportation, knowledge gaps, lack of trust, and lack of healthcare access). He emphasized that access to vaccines and trust in the healthcare system are equally necessary to increasing vaccination rates. In addition, the greatest influences on families were surrounding communities and local agencies. He noted that state and

federal agencies were not important influencers, as it was difficult for state and federal agencies to access and gain trust through direct communication with families. Based on his assessments, Dr. Willis's team formed four COVID-19 Community Response Teams (CRTs) in the four hardest hit communities in West Marin (part of Marin County), one of which was rural West Marin, to support the health departments of these counties by:

1) utilizing local data for local action (ensuring that no city or town has a vaccination rate of 10 percent below the county average or lower)
2) communicating for impact, including communications with from federal and state agencies, Marin public health officials, community partners, and families; weekly meetings with CRTs, schools, hospitals, care facilities, volunteers, law enforcement to discuss pandemic updates, videos, press releases, and social media messages
3) building partnerships between family members and trusted community agencies, such as schools, health clinics, libraries, churches, food banks, and employers, in order to spread vaccine-positive messages.

The efforts put forth by the CRTs resulted in the full vaccination of 98% of Latinx residents in western part of Marin County by August 2021 and a reduction of racial disparities in vaccination rates. In 2020, Latinx individuals were seven times more likely to be infected, whereas now they are infected at the same rate as their white counterparts. Dr. Willis reported that achieving high vaccination rates equitably required a focus on building trust while removing barriers to vaccination through data-sharing, communication, and partnership-building.

Fabulous Ladies Book Club Lincoln County Vaccine Clinic— Dr. Keri Rath, M.D., The Fabulous Ladies Book Club

Dr. Keri Rath is a practicing obstetrician and gynecologist (OB-GYN) in rural Lincoln County, NM. In the summer of 2020, Dr. Rath's husband, Dr. Stephen Rath, was deployed for COVID response with the NM Air National Guard, where he became acquainted with Dr. Aja Sanzone, coordinator of infectious disease response for the New Mexico Department of Health (DOH). In December 2020, at the urging of Dr. Sanzone, Dr. Rath and her husband began to expand vaccine services to their town but initially experienced several barriers to vaccine delivery: location, labor, and supply. To mitigate the location issue, Dr. Rath utilized her husband's medical office as a vaccine delivery area. For labor, she enlisted the members of her book club, The Fabulous Ladies Book Club, and their spouses to distribute vaccines. Dr. Rath and the Fabulous Ladies Book Clube received a supply of Pfizer vaccines from the NM DOH, which they were able to store in Dr. Rath's husband's clinic freezer.

Dr. Rath's team also experienced a multitude of challenges. Due to a leak of the registration codes, individuals who were not eligible for the vaccine (i.e., not part of the current vaccine allocation phase) were able to register for vaccine appointments through the NM DOH scheduling portal. To avoid wasting vaccine doses, Dr. Rath's team vaccinated all registered patients. This error in the scheduling codes led to the local governor's office publishing an article that Dr. Rath and her team were purposefully providing vaccinations to ineligible people during specific vaccination phases, nearly causing state leadership to stop vaccination efforts. However, after clarifying communications, Dr. Rath and her team received additional doses and continued their vaccination efforts. In addition to access issues, the computer-based scheduling system was challenging for elderly patients to use. Dr. Rath also noted that equitable distribution was a challenge; the online registration and scheduling software lacked Spanish-language support, and those who did not own computers had to phone a call center to book appointments because most public libraries were closed. Dr. Rath's efforts resulted in early high vaccination rates in New Mexico. By January 27, 2021, more than 8 percent of New Mexico residents had received at least one vaccine dose. Dr. Rath's story garnered media attention: an article about her and the book club's vaccination efforts was published in the Washington Post, and was then retweeted by Michelle Obama,

Glennon Doyle, and Reese Witherspoon. She was also interviewed by CBS Evening News and the BBC. The public showed their gratitude by providing Dr. Rath and the Book Club with meals from local eateries. They were also awarded the Chamber of Commerce Healthcare Heroes Award for their efforts. In total, Dr. Rath's team fully vaccinated 3,281 people.

Discussion

Molly Howell asked Ms. Harris if CDC examined the impact of political affiliation of rural counties on vaccination rates. Ms. Harris answered that early in the pandemic political affiliation impacted vaccination rates across the country, but the CDC has not yet in vaccination rates among political affiliations. She noted that this difference might be a topic of future analysis at CDC.

Ms. Howell suggested that state departments and organizations should decrease the minimum quantity of vaccines required for shipments to rural areas to conserve vaccine supply. Ms. Harris agreed, adding that vaccine allocation and distribution strategies should be customized to meet the needs of a given community. Dr. Willis added that his team modified their labor allocation strategy accordingly and sent larger teams to rural communities to maximize vaccine advocacy and information dissemination.

Dr. Dunn asked the panelists whether they believed that the current national and federal vaccination framework gives health departments and local community partners enough flexibility to enact independent vaccination strategies post-COVID-19. In response, Ms. Qaasim emphasized the importance of promoting the health equity principles of power-sharing and codesign as successful strategies to lowering vaccination disparity. She also noted the importance of providing funding to community organizations to assist them in vaccination efforts. Dr. Rath agreed and added that, during a pandemic, trust and respect need to be present between the government and public to ensure a quick vaccination response. Without trust and respect healthcare workers will need to find alternative methods to efficient ensure vaccine access, such as reaching out to community partners and attempting opportunistic strategies, such as vaccinating children at their schools, instead of medical clinics.

Public Comment

No public comments were offered.

Adjourn Meeting

Dr. Hopkins thanked the participants and NVAC members and adjourned the meeting at 2:27 p.m.

Appendix: Abbreviations List

ACCV	Advisory Commission on Childhood Vaccines
ACIP	Advisory Committee on Immunization Practices
AD	Alzheimer's disease
ADRD	Alzheimer's disease related dementias
AESI	adverse events of special interest
AHIP	America's Health Insurance Plans
AHRQ	Agency for Healthcare Research and Quality
AIRA	American Immunization Registry Association
APHA	American Pharmacists Association
APHIS	USDA Animal and Plant Health Inspection Service
ASD	Autism Spectrum Disorder
ASPR	Administration for Strategic Preparedness and Response
ASTHO	Association of State and Territorial Health Officials
BARDA	Biomedical Advanced Research and Development Authority
BCG	bacille Calmette-Guerin
BEST	FDA Biologics Effectiveness and Safety
CBO	community-based organization
CEPI	Coalition for Epidemic Preparedness Innovation
CDC	Centers for Disease Control and Prevention
CHS	Cardiovascular Health Study
CMS	Centers for Medicare and Medicaid Services
COVAIL	COVID-19 Variant Immunologic Landscape Trial
COVID-19	Coronavirus disease 2019
cVDPV	circulating vaccine-derived poliovirus
DHA	Defense Health Agency
DOD	Department of Defense
DPA	Dynamic Pregnancy Algorithm
DTP	diphtheria-tetanus-pertussis
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FY	fiscal year
GACVS	Global Advisory Committee on Vaccine Safety
GIS	Geographic Information System
GPEI	Global Polio Eradication Initiative
HA	hemagglutinin
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HPAI	highly pathogenic avian influenza
HPOP	Health Partner Order Portal
HPV	human papillomavirus
HRS	Health and Retirement Study
HRSA	Health Resources and Services Administration
HSV1	Herpes Simplex Type 1 virus
IDCRC	Infectious Diseases Clinical Research Consortium
IHS	Indian Health Service
IM	intramuscular
IN	intranasal
IPV	inactivated poliovirus vaccine
IVR	Influenza Vaccines Roadmap

LGBTQ	lesbian, gay, bisexual, transgender, and queer
LPAI	low pathogenic avian influenza
MCI	mild cognitive impairment
MCM	medical countermeasure
MCV	measles-containing vaccines
MMR	measles, mumps, and rubella
MSM	men who have sex with men
NA	neuraminidase
nAb	neutralizing antibody
NACCHO	National Association of County and City Health Officials
NCHS	National Center for Health Statistics
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
nOPV2	novel live attenuated oral poliovirus vaccine Type 2 vaccine
NSE	nonspecific effects
NVAC	National Vaccine Advisory Committee
NVSS	National Vital Statistics System
NYC	New York City
NYSDOH	New York State Department of Health
OIDP	Office of Infectious Disease and HIV/AIDS Policy
PASC	post-acute sequelae of COVID-19
PEA	Pregnancy Episode Algorithm
PEP	post-exposure prophylaxis
PEP++	expanded post-exposure prophylaxis
POD	Points of Dispensing
PPE	personal and protective equipment
PrEP	pre-exposure prophylaxis
R&D	research and development
RCA	Rapid Cycle Analysis
SAE	serious adverse event
SAVE	SARS-CoV-2 Assessment of Viral Evolution program
SNS	ASPR Strategic National Stockpile
SPEAC	Safety Platform for Emergency vACcines
SVI	Social Vulnerability Index
TgmNVT	Transgenic Mouse Neurovirulence Test
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VAMS	Vaccination Administration Management System
VAPP	vaccine-associated paralytic poliomyelitis
VSD	Vaccine Safety Datalink
VTrckS	CDC Vaccine Tracking System
WHO	World Health Organization
WT	wildtype