- The risk of outbreaks of traditional diseases such as measles is concerning because people have not received routine vaccinations due to the pandemic. State and local officials, professional organizations, and others have made progress on reversing this trend, expecially in children, but much more needs to be done for both children and adults.

- HHS and its partners have raised awareness about catching up on childhood immunizations and increased access to vaccines. Children and communities are healthier when immunization rates are high. More resources are available at vaccines.gov.

Dr. Giroir concluded that he came to HHS with vaccination as one of his highest priorities and said he and NVAC have made progress together. He said it has been the honor of his life to work with NVAC and wished committee members the best as they continue their important work.

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

- Expressed appreciation for ADM Giroir's support for immunization and for NVAC over the past three years.
- Thanked the OIDP team for preparing a useful and informative meeting to address NVAC's final report based on ADM Giroir's charge.
- Noted that the virtual meeting was accessible to the public via live webcast at www.hhs.gov/live. Described technical logistics for committee discussion and public comments, noting that verbal comments would take place at 4:30 p.m. The public could submit written comments to nvac@hhs.gov.
- Provided an overview of the meeting agenda, including the following topics: how to proceed with COVID-19 vaccines for children, lessons learned from COVID-19 vaccine development, building confidence in the immunization system, public comment, and discussion of the charge and committee vote.
- Listed upcoming NVAC meeting dates: February 4-5, 2021; June 16-17, 2021; and September 15-16, 2021. He said more information is available at www.hhs.gov/nvac.
- Concluded by introducing the first speaker.

Perspective: Why Children Should Eventually Receive Vaccines Against SARS-2 Coronavirus
Dr. Stanley Plotkin, University of Pennsylvania (Emeritus)

Dr. Plotkin is a professor emeritus of pediatrics at the University of Pennsylvania's Raymond and Ruth Perelman School of Medicine and a consultant to vaccine manufacturers.

Dr. Plotkin said there is no doubt that while other populations need a vaccine against the coronavirus before children, the children ultimately should be included in vaccination.

He said the scientific literature indicates that pregnancy during COVID-19 is not primarily a problem of infection of the fetus, as with rubella or cytomegalovirus, but rather infection of the pregnant woman. He added that women who are late in pregnancy have less respiratory reserve than in the non-pregnant state.

Dr. Plotkin said that vaccinations tend not to be given during pregnancy based on concerns relating to the fetus. So far, it does not appear that there are such concerns with a SARS-2 vaccine, especially an activated vaccine. He added, however, that there is not a lot of evidence for

mRNA vaccines. They will have to be tested in pregnancy.

Dr. Plotkin pointed out that although children are largely asymptomatic as far as COVID-19, symptoms did appear in some, including cough, fever, pharyngitis, and other respiratory symptoms. He said studies consistently find that one to two percent of children with SARS-2 have significant disease. That incidence is in line with other childhood infections. If vaccinations are given against diseases such as Haemophilus influenza, that may be an indication for vaccinating children against COVID-19, he said. Results of one study found that 12 percent of newborns with SARS-2 became extremely ill. That may be an argument, he suggested, for vaccinating pregnant women in order to pass the antibodies to the fetus.

Dr. Plotkin concluded that eventually, children should receive vaccines against SARS-2 coronavirus for the following reasons:

- Although uncommon, serious C0VID-19 does occur in children.
- When children become infected, they excrete virus and could be the agents to infect parents, teachers, and other children.
- Because infection in children is often asymptomatic, there is no way of knowing which child is infected and capable of infecting other people.
- If a vaccine gives long-lasting immunity, or at least priming for accelerated response, a child will still be resistant after growing up.
- Because the U.S. cannot count on universal vaccination among adults, vaccination of children eventually will result in an immune population.

Assuming that SARS-2 becomes a permanent threat, children will have to be included in plans for vaccination, he said. The possibility of making vaccination mandatory is an important consideration. That is what the U.S. does with other vaccines to protect both children and the population at large. Although researchers are still learning about the disease, including which vaccines are most optimal, children eventually should be vaccinated, Dr. Plotkin concluded.

Discussion

Dr. Cooke asked **Dr. Plotkin** to leave the subject of childhood vaccination for a moment to comment on general lessons learned so far about how to innovate for vaccine development. Dr. Plotkin responded that he has been struck by two things:

- In part due to federal government financing, all platforms used to develop vaccines are engaged. This shows that when faced with an emergency, the scientific community can respond rapidly. The industry and academia will respond if they get enough financial support from governments.
- Organizations such as the Coalition for Epidemic Preparedness Innovations (CEPI) must continue their work to develop vaccines against emerging infections. CEPI is financing vaccine development for COVID-19, as well as many other infections for which there is no commercial interest. These organizations offer a way to address emerging infections at an early point before they become a pandemic.

Dr. Cooke added that there is an opportunity to have many different vaccine platforms—particularly new platforms such as mRNA and recombinant live virals—aim at the same target at the same time. He predicted that researchers will learn a tremendous amount about which platforms succeed quickly, cheaply, and can be stored at reasonable temperatures.

Dr. Plotkin said that the U.S. government must think how to be ready for emerging infections. He said the government's response to COVID-19 was disorganized at the beginning given recent past experience with diseases such as Ebola and Zika.

Dr. Holt said researchers need plenty of safety data for adults first before contemplating vaccinations in special populations. He asked Dr. Plotkin about timing; specifically, whether to start bridging trials as soon as possible after an emergency use authorization (EUA) is given or wait for licensure. Dr. Plotkin replied that trials should be started now because several have already produced sufficient evidence of safety in adults. Clinical data on children would then be available in the second half of 2021.

Dr Meissner asked Dr. Plotkin about the durability of the 95 percent effectiveness rate for the mRNA vaccines as compared with the waning effectiveness of vaccines for conventional coronaviruses. Dr. Plotkin answered that the correlate of protection for these vaccines is still unknown. The Oxford-AstraZeneca vaccine should allow researchers to determine the level of neutralizing antibody that is protective. There should be specimens available to measure neutralization after vaccination and look at who did and did not get infected. The mRNA vaccines have shown evidence of B cell memory, but researchers do not yet know what level of antibody is necessary. It could be that having memory means there is an anamnestic response at the time of exposure that allows protection to occur even though antibodies have waned. One of the arguments for human challenges is determining the duration of immunity after vaccination.

Approaches to Include Pregnant Women in COVID-19 Clinical Trials

Dr. Hopkins introduced the panel topic, noting that in addition to four panelists, two experts would be available to answer questions:

- **Dana Meaney-Delman, M.D., M.P.H, co-lead of the Vaccine Task Force on the CDC COVID-19 Response.**
- **Titi Oduyebo, M.D., M.P.H, CPH, medical officer on task force's Pregnancy Linked Outcomes Team**.

Sascha Ellington, PH.D., MSPH, CPH, CDC

Dr. Ellington is a member of the Pregnancy and Infant Linked Outcomes Team, Epidemiology Studies Task Force, CDC COVID-19 Response

She provided an update on the epidemiology of COVID-19 in pregnancy and the CDC's surveillance activities. It is well established that there are physiologic changes of pregnancy that may increase the risk of severe viral respiratory illness, explained Dr. Ellington. These include increased heart rate and oxygen consumption, decreased lung capacity, and a shift away from cell-mediated immunity.

A living systematic review and meta analysis published in September 2020 synthesized the literature during COVID-19 and pregnancy. The aim was to identify risk factors for severe COVID-19 during pregnancy and delivery and report on adverse outcomes among mothers and infants. Researchers detected differences in clinical manifestation of the disease in pregnant versus non-pregnant women with COVID-19:

- Fever and myalgia were less common among pregnant women.
- Pregnant women had an increased likelihood of admission to the ICU and increased need for invasive ventilation.
- Mortality due to COVID-19 was lower among pregnant women.
- Pregnant women with COVID-19 may have higher odds of a preterm birth.
- Neonates born to women with COVID-19 may have higher odds of admission to a neonatal intensive care unit.

Risk factors for severe COVID-19 during pregnancy include older maternal age, high body mass index, and underlying medical conditions, such as hypertension and pre-existing diabetes.

Dr. Ellington presented several CDC analyses of the effects of COVID-19 in pregnant women. After adjusting for age, race, ethnicity, and pre-existing conditions, the CDC found that when compared with non-pregnant women, the pregnant study subjects were:

- 3 times more likely to be admitted to the ICU compared to non-pregnant women,
- 2.9 times more likely to receive invasive ventilation.
- 2.4 times more likely to receive extracorporeal membrane oxygenation.
- 1.7 times more likely to die.

The CDC's weekly national surveillance data for COVID-19 among pregnant women reported 42,268 cases and 55 deaths at the time of Dr. Ellington's presentation. The CDC also collected data from the agency's Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET) — Adaptation for COVID-19. Surveillance data showed that 12.9 percent of infants were preterm, higher than the national figure of 10.2 percent. This suggests, said Dr, Ellington, that women with COVID-19 during pregnancy might be at risk for pre-term delivery. She noted that the CDC created a web page for monthly updates of SET-NET data.

The CDC is also supporting multiple investigations to better understand the impact of COVID-19 during pregnancy on both the mother and infant.

Based on the data so far:

- Pregnant women are at increased risk for severe illness from COVID-19.
- Pre-term birth is higher than expected.
- Still births may be higher than expected, although there have been limited data.

Ruth Faden, Ph.D., M.P.H., Johns Hopkins University

Dr. Faden is the Philip Franklin Wagley Professor of Biomedical Ethics and founding director of the Johns Hopkins Berman Institute.

She deferred to Dr. Ellington's presentation and those of upcoming speakers on the subject of how pregnant women are more likely to have severe outcomes with COVID-19.

Dr. Faden then discussed the activities of the COVID-19 Vaccine Ethics Research (COVER) Project, for which she is co-principal investigator. The project builds on 22 recommendations released in 2019 by the Prevent Working Group, an international team of experts across a range of disciplines brought together in the wake of the Zika crisis. The team addressed how to advance

the interests of pregnant women and their children in three areas—preparedness, R&D, and vaccine delivery for emerging and re-emerging diseases.

Dr. Faden explained that COVER aims for a world in which pregnant women and their offspring are not left behind as new vaccine products are developed and that women and children have access to safe and effective vaccines.

COVER calls the problem "presumption of exclusion," explained Dr. Faden. In this self-perpetuating cycle, pregnant women are by and large excluded from vaccine development for emerging and re-emerging infections. This is caused by concerns about ethics and viability, as well as an inertia in which researchers do not consider pregnant women in vaccine R&D. Lack of research data then leads to exclusion or delay of pregnant women from vaccine delivery programs.

COVER's solution is to strive for the appropriate inclusion of pregnant women in the research phase of vaccine development. This results in better evidence about safety and immunogenicity, which in turn allows the appropriate inclusion of pregnant women in vaccine campaigns. The vicious cycle becomes a virtuous cycle with greater knowledge about platforms, adjuvants, and vaccine technologies.

Dr. Faden emphasized that developmental and reproductive toxicity (DART) studies need to be initiated before any government regulatory body generally allows pregnant women to participate in evaluating an investigational vaccine. COVER recommends initiating DART studies at the end of Phase 1 of vaccine evaluation so that data is available when it becomes appropriate to include pregnant women. Dr. Faden noted that of the two COVID-19 vaccine candidates of most immediate interest, Moderna plans to report DART data in the first quarter of 2021. Pfizer has not indicated when its DART data will be available. The Oxford/AstraZeneca data is due out by the end of 2020.

Dr. Faden discussed factors to be considered in a risk/benefit analysis of pregnant women's participation in vaccine development:

- Prospects for vaccine protection – Pfizer and Moderna have reported efficacy of about 95 percent.
- Risk of harm from community-acquired infection – This is the "black box" issue, she said, with consideration analysis ongoing right now.
- Likelihood of infection – Pregnant women are not homogenous. They vary in the likelihood of becoming infected and whether they would become seriously ill if infected.
- Availability of alternative preventatives and treatments – Pregnant women also vary in the extent to which they can reduce infection risk. Women who live in crowded housing conditions and/or must work outside the home are not as able to shelter and physically distance themselves. These conditions fall disproportionately on disadvantaged groups such as low-income women, women of color, and women from poor communities. This raises the question of whether pregnant woman who are not yet cleared to take a vaccine should be at the top of the queue for treatments. It also raises the question of what is known about applying some of the newer treatments to pregnant women.

Dr. Faden concluded that any planning for inclusion of pregnant women in COVID-19 vaccine trials should include experts in maternal and prenatal health, pediatrics, research ethics, and public health ethics, as well as those who can speak directly for pregnant women.

Jeff Roberts, M.D., U.S. Food and Drug Administration

Dr. Roberts is associate director for scientific affairs in FDA's Office of Vaccines Research and Review.

He provided updates for several topics in FDA's June 2020 guidance for industry on clinical development of COVID-19 vaccines.

DART studies – The guidance document urged that studies be finished as soon as possible. They were nearing completion, but were not ready to be reviewed in time for Pfizer and Moderna EUA labeling.

Documentation of outcomes for pregnant women and infants – Pregnancy was an exclusion criteria in COVID-19 vaccine trials. Women were tested for pregnancy before being vaccinated. Nevertheless, there were a few women vaccinated very early in pregnancy during pre-licensure trials. Most of those pregnancies are not complete, so data is not yet available.

Including pregnant women in vaccine trials – FDA guidance recommended collecting two different sets of data on pregnant women. The first would include women in trials who are not actively avoiding pregnancy. The second would include specific studies in pregnant women. Both data sets are important but cannot be accomplished until DART data are available.

Evaluating safety post-EUA or post-licensure through study designs such as pregnancy registries – These approaches are under active discussion both within and outside FDA.

Labeling – When a vaccine label includes a contraindication in pregnancy, it is supported by data. In the absence of such data, FDA will not include a label recommendation. Labels generally are reserved for displaying data submitted to FDA and agreed upon with the manufacturer as being adequate to support the benefit/risk for use in a given population. The agency will label such data as it is received.

Linda Eckert, University of Washington, representing the American College of Obstetricians and Gynecologists (ACOG)

Dr. Eckert is a professor of obstetrics and gynecology at the University of Washington. She told NVAC that 95 percent of board-certified obstetrician-gynecologists are members of ACOG and attend 85 percent of deliveries in the United States.

ACOG convened an Immunization, Infectious Disease, and Public Health Preparedness Expert Work Group (IEIEWG) in 2010 as OB-GYNs were increasingly called to administer vaccinations. IEIEWG members are recognized experts in immunization and infectious disease. The group has been integral to ACOG's COVID-19 response and is currently working on recommendations for use of vaccines in pregnant women.

When asked by ACIP to make a comment on COVID vaccination, ACOG's considerations included:

- Pregnant patients are at increased risk of severe illness.

- They make up a significant portion of the top priority groups, including those facing increased risk due to systemic barriers within the healthcare system.
- mRNA vaccines are new and there is no background of historical data on safety and efficacy to fall back on.

ACOG made the following statement to ASIP:

- Pregnant and lactating individuals who otherwise fit the criteria for inclusion in a high-priority population should not be excluded from receiving a vaccine.
- The decision to vaccinate a pregnant patient should be based on a risk/benefit conversation with the patient and the clinical care team.
- Data on safety and effectiveness in pregnancy is urgently needed to help inform these conversations.

Dr. Eckert added that ACOG advises that pregnancy and lactation should be addressed as separate topics in vaccination discussions. The two have a very different risk profile.

Discussion

Dr. Meissner noted that Novavax published encouraging results in spring 2020 with a nanoparticle vaccine against respiratory syncytial virus (RSV) in pregnant women to boost maternal antibodies that are passed on to the fetus. Novavax is working on a SARS-CoV-2 vaccine that is also a protein antigen. Dr. Meissner asked Dr. Faden if the COVID-19 vaccine might be used in pregnant women based on the face that there is preliminary data about safety.

Dr. Meissner also asked whether Dr. Roberts is concerned that if mRNA vaccines are administered during pregnancy, the RNA could somehow become incorporated into the DNA of the fetus.

Dr. Faden replied that she will leave it to the experts to answer whether the Novavax vaccine is safter for pregnant women than mRNA vaccines because of prior use of a similar platform. The immediate ethics challenge is determining whether pregnant women—particularly those at high risk of infection—should be permitted to take the vaccines available now. Women cannot be told to wait for the Novavax vaccine.

Dr. Roberts noted that safety and DARTS data for mRNA products in previous clinical development programs, including Zika, have been reassuring with respect to RNA becoming incorporated into the DNA of the fetus.

Dr. Swamy pointed out that the Novavax RSV vaccine included an alum adjuvant vaccine, while the coronavirus vaccine under development has a proprietary Matrix-M™ adjuvant. The data may not allow experts to pick one vaccine over the other for pregnant women, but they should have the information to consider the options.

Dr. Friedland posted a comment that protein vaccines like HPV also have a strong history of safety experience in pregnant women.

Break

Vaccine Safety Systems and COVID-19

Arnold Monto, M.D., University of Michigan

Dr. Monto is the Thomas Francis Collegiate Professor of Public Health and professor of epidemiology and global public health at the University of Michigan School of Public Health. He represented FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC).

Dr. Monto told NVAC members that VRBPAC would meet on December 10th to review EUA for the Pfizer vaccine and December 17th for the Moderna vaccine. He said VRBPAC would use a process similar to that for other vaccines, but take into special consideration the issue of extraordinary need due to the pandemic's severity:

Efficacy Standard – A point estimate of 50 percent prevention of laboratory-confirmed SARS-CoV-2 infection. Based on media reports, efficacy is much higher than the guidelines. Confidence intervals are tighter and do not go down to 30 percent, which was the guidance to industry.

Safety Standard – Based on a median of two months of follow-up from the last vaccination. The safety consideration—but not the efficacy—is shortened because of emergency use. VRBPAC is not conducting its review any differently than for regular licensure, except for the timeline.

Peter Marks, M.D., Ph.D. U.S. Food and Drug Administration

Dr. Marks is director of the Center for Biologics Evaluation and Research, which is responsible for assuring the safety and efficacy of biological products, including vaccines.

FDA's EUA provisions define a floor of efficacy needed to make an investigational product widely available where there is a declared emergency by the HHS secretary, explained Dr. Marks:

- The medication must be thought to be effective.
- The known and potential benefits must outweigh the known and potential risks.
- There cannot be an approved and available alternative.

FDA's Office of Vaccines came up with a tougher standard to be used for COVID-19 vaccine EUAs that is closer to that for a licensed vaccine:

- Must demonstrate clear and compelling efficacy from large, well-designed Phase 3 clinical trials.
- Must undergo careful evaluation of quality, safety, and efficacy. Quality refers to how the vaccine is manufactured.
- Public advisory committee meetings must take plave before EUA authorizations.
- Enhanced post-deployment surveillance must take place. Researchers can get to endpoints through large trials, but they cannot magically compress time to get one or two years of safety follow-up in four or five months.

The FDA is collaborating with the CDC on a mutually reinforcing set of safety surveillance plans, continued Dr. Marks. FDA can ask for a post-market commitment for extra safety work as well as put in place post-market requirements if the agency sees a safety signal before or after a vaccine becomes available. This includes a mandate for additional trials.

Dr. Marks said that passive and active safety surveillance work best together. The FDA and CDC will collaborate on passive monitoring through the Vaccine Adverse Event Reporting System, which allows queries of databases. FDA will also use the Center for Biologics' Sentinel/Biologics Effectiveness and Safety (BEST) system, which links to tens of millions of electronic health records through the claims-based database. The system is especially important in refuting false safety signals. Citing the challenge of setting a baseline with which to compare incidence rates with COVID-19, Dr. Marks said the FDA has a variety of potential baselines and is trying to come to a conclusion about which would be best.

Dr. Marks described the Center for Biologics Evaluation and Research (CBER) Surveillance Program Collaborative as a diverse set of federal agencies—including the Centers for Medicare and Medicaid Services (CMS), Veterans Administration (VA), and Department of Defense (DoD)—along with a variety of other academic and corporate partners. The diversity is meant to allow access to as much information as possible.

Dr, Marks listed partners in FDA's BEST system, including:

- Healthcare data providers, academic organizations, and scientific collaborators.
- FDA Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) partners, which include Optum, HealthCore, Healthagen, and Humana.
- A variety of healthcare settings, such as inpatient, outpatient, and emergency departments. Dr. Marks added that skilled nursing facilities will soon be included.
- Electronic healthcare data from multiple partner organizations. This includes claims, health records, and claims-electronic health record linked data.

Dr. Marks concluded that FDA will post protocols on the BEST website (https://www.bestinitiative.org/) for public comment, then post results. The aim is to get a good sense of the safety profile of COVID-19 vaccines after deployment.

Tom Shimabukuro, M.D., M.P.H., M.B.A, Centers for Disease Control and Prevention

Dr. Shimabukuro is deputy director of the CDC's Immunization Safety Office, which conducts post-licensure safety monitoring of U.S. vaccines.

He updated NVAC members on COVID-19 vaccine post-authorization safety monitoring, asserting that the U.S. vaccine safety system is strong and robust and that agencies are adding new systems for COVID-19 vaccines:

U.S. government vaccine safety monitoring systems, timeline, and covered populations

Active Surveillance – Includes the CDC's new v-safe smartphone-based, text monitoring to web surveillance process system, created specifically for COVID-19.

Passive Surveillance – The Vaccine Adverse Event Reporting System (VAERS) is co-managed by the CDC and FDA. There are other spontaneous reporting systems that feed into VAERS from manufacturers, DoD, the VA, and others.

Adverse events – The CDC examines unusual or unexpected adverse events reported by healthcare providers who reach out to the agency for review.

Large-linked database monitoring systems – These include surveillance programs from the CDC, FDA, CMS, VA, DoD, and Genesis, which is a new initiative through the National Institutes of Health (NIH) and Brown University that covers long-term care facility residents.

This combination of systems will cover the initial 1A priority vaccination groups, which include healthcare workers and long-term care facility residents.

V-safe

Dr. Marks described the CDC's new smartphone-based monitoring program for COVID-19 safety:

- Uses text messaging and web surveys to check in with vaccine recipients after vaccination. Participants can also report side effects and health impact events.
- Includes active telephone follow-up by the CDC for reports of significant health impact.
- Captures information on pregnancy status and enables follow-up on pregnant women.
- Conducts electronic health check-ins with vaccine recipients daily for the first week post-vaccination, then weekly thereafter, until six weeks post-vaccination.
- Conducts additional health checks at three-, six-, and 12 months post-vaccination.
- This timeline resets when an individual receives a second dose.

The CDC asks that health departments help spread the word on the importance of v-safe enrollment and distribute one-page information sheets at the time of vaccination. The sheet includes a URL and a scannable QR code that individuals use to register, after which the CDC starts the text messaging process and electronic health check-ins. The CDC also has an electronic version of the v-safe information sheet.

Dr. Marks called on public health and healthcare partners to promote vaccine safety, participation in v-safe, and reporting to VAERS

Sonali Kochhar, M.D., University of Washington

Dr. Kochhar is clinical associate professor in the Department of Global Health at the University of Washington and scientific researcher in the Department of Public Health at Erasmus University.

Dr. Kochhar discussed the global coordination and innovation of COVID-19 vaccine safety monitoring.

BRAVATO Templates

One tool to promote global coordination is templates for benefit- risk assessments of COVID-19 vaccines. Dr. Kochhar led template development for the Brighton Collaboration Benefit-Risk Assessment of Vaccines by TechnnolOgy (BRAVATO) Working Group. Templates are available for all COVID-19 vaccine platforms.

The objective is to improve the ability of regulators, public health officials, the general public, and other key stakeholders to anticipate potential safety issues, interpret safety data, and facilitate improved public acceptance of vaccines. The hope is that vaccine developers will complete

templates and submit them to BRAVATO for peer review, publishing, and updating when new information becomes available.

SPEAC Project

CEPI funded the Brighton Collaboration Safety Platform for Emergency Vaccine (SPEAC) project to harmonize the safety information on candidate vaccines, including COVID-19. The project defined 18 safety outcomes of interest for COVID-19 based on landscape analysis and literature review.

Development is underway for case definitions, risk factors and background rates, and ICD MeddRA codes for adverse events. The aim is to help standardize information regardless of whether from clinical trials or epidemiological studies.

World Health Organization (WHO) Safety Surveillance Manual

WHO has developed a safety surveillance manual for COVID-19 vaccines aimed at global, regional, and national staff for immunization programs, regulatory authorities, partners, and pharmacovigilance centers. Content includes:

- Key safety considerations for COVID-19 platforms, priority populations, and immunization strategies.
- Adverse events following immunization (AEFI), adverse events of special interest (AESI), and monitoring tools,
- Global and regional preparedness for COVID-19 vaccine introduction.
- Stakeholders' mapping, platforms, and resources for pharmacovigilance.
- How establish AEFI surveillance systems.
- Data management and monitoring safety surveillance.
- Recommendations for safety communication. The manual does not cover dealing with vaccine hesitancy.

Critical Areas for Global Safety Surveillance

The WHO highlighted the following areas, particularly during the early phase of vaccine introduction, when spontaneous reporting is inadequate:

Active vaccine safety surveillance

- Incidence rate calculations and background rates.
- Implementation in diverse populations.
- Use of a similar methodology so that data can be pooled and have better sensitivity.
- Globally coordinated implementation.

Country implementation requires close collaboration between the national regulatory authorities, national immunization programs, and pharmacovigilance centers.

- History of close collaboration is often lacking.
- A combination of critical data from all parties is needed.
- The combined expertise from all parties is required for analysis and response.

Common platform for information sharing:

- All key stakeholders need access to the same data from global safety surveillance.
- There should be reconciliation of global, regional, and national databases.
- Reconciliation of data is needed from active surveillance and spontaneous reporting systems.
- Inconsistent information can lead to confusion and rumors.

Coordinated, comprehensive communication strategy:

- Inform the media and the public of the responsibilities of key stakeholders early and often.
- Coordinate stakeholder public statements to avoid confusion.
- Carefully explain the concept of a coincidental event.

Global Safety Surveillance Landscape

WHO designed a master plan for a coordinated global vaccine safety surveillance system:

- WHO sent a survey to key organizations that work in the vaccine safety ecosystem.
- Results show that most areas are covered at global, regional, and national levels by one or more organizations.
- WHO organized a COVID-19 Vaccine Safety Ecosystem workshop to identify the gaps and overlaps for vaccine safety activities.

European Medicines Agency (EMA) Projects for COVID-19 Vaccine Safety

EMA projects include:

ACCESS (vACCccine COVID-19 Monitoring readinESS) Project. Twenty-two European research centers use data sources and epidemiological methods to monitor the safety, effectiveness, and coverage of COVID-19 vaccines. Objectives include:

- Identify and characterize a Europe-wide network of data sources that could provide continuous monitoring of the safety, effectiveness, and coverage of COVID-19 vaccines and investigate specific research questions.
- Provide background rates of AESIs and other relevant conditions.
- Make common protocols for safety studies and network of data sources available to marketing authorization holders (MAHs) and other stakeholders for joint post-authorization safety studies.
- MAH applicants submit vaccine-specific protocols to be endorsed by the PRAC and CHMP committees.
- The CONSIGN (COVID-19 infectiOn aNd medicineS in preGNancy) project collects data on the impact of COVID-19 in pregnancy to help guide decision-making about vaccine indications, vaccination policies, and treatment options.

EMA's Core Requirements for Risk Management Plans for COVID-19 Vaccines:

- Safety in pregnant women, the elderly, children, and patients with severe comorbidities, including the frail and vaccinees with auto-immune diseases.

- Observation of interaction with other vaccines.
- Reactogenicity data, including the impact on the safety profile and necessary risk minimization measures. This also includes looking at subgroups, such as frail vaccinees or patients with chronic inflammatory conditions. Differences with a second or subsequent dose are important, as are aspects of the formulation and preparation of the vaccine that may increase the risk of adverse drug reactions.
- Risk of vaccine dropout for second doses.
- Long-term follow-up with adequate pharmacovigilance activity.

Dr. Kochhar concluded that a coordinated and collaborative approach is critical for the success of COVID-19 vaccine safety monitoring.

Discussion

Dr. Marks confirmed for **Ms. Martinez** that the FDA's December 10 advisory committee on Pfizer's vaccine would be public, open, and live-streamed on Facebook and Twitter. Company and FDA briefing materials were available in advance on FDA's website.

Dr. Douglas asked about the v-safe program development timeline, the timing for rollout, and whether vaccinees could participate on an opt-out basis. **Dr. Shimabukuro** replied while a complex surveillance system normally takes time develop, test, and roll out, the CDC compressed the v-safe timeline to several months in order to be ready when vaccines are available. The agency is conducting long-term testing and will adjust the system if bugs arise. All scenarios for v-safe are opt-in, said Dr. Shimabukuro, although the CDC may explore ways to increase enrollment by making the process easier.

Dr. Friedland asked how the v-safe system will know which vaccine a participant is receiving. Dr. Shimabukuro explained that during registration, participants see a screen with manufacturer vaccine types displayed, then tap on the appropriate one. If the vaccinee forgets which type he or she received, a prompt will direct the person to check the shot card. The CDC will collect details such as the vaccine's lot number and expiration date if a patient reports an adverse health impact. v-safe is not linked to an immunization information system.

Dr. Meissner asked what the effect would be on long-tern safety assessments if placebo recipients drop out of a trial so they can receive a vaccine. Dr. Marks said the effect will depend on how many participants cross over and when additional vaccines become available. The situation is complicated. Researchers will make use of as much placebo control data as they can get, augmenting it with observational data. Dr. Shimabukuro said that CDC will attempt to follow individuals in Phase 4 trials for a year after their final vaccine dose. He said the agency has the opportunity to conduct studies on long-term safety through large-linked database systems like the vaccine safety datalink.

Dr. Hopkins asked if there have been discussions about shared definitions and issues of concern between the United States and its international partners. Dr. Shimabukuro replied that CDC has been in contact with WHO colleagues to share information on adverse events of special interest, pre-specified conditions for active surveillance, and standardized case definitions. Dr. Kochhar noted that templates for benefit-risk assessment have been published and shared with all vaccine developers. She said there is a considerable amount of global coordination taking place.

No Co-Pays: Coverage for COVID-19 Vaccines

Jeff Wu, J.D., M.B.A., Centers for Medicare & Medicaid Services

Mr. Wu is the deputy director for policy at the Center for Consumer Information and Insurance Oversight. He coordinates CMS efforts on COVID-19 vaccines and treatment.

Mr. Wu explained that CMS put out an interim final rule at the end of October for a reimbursement infrastructure to support vaccination work under Operation Warp Speed:

- Clarified that CMS will view any kind of authorization, including an EUA, for COVID vaccines as equivalent to a license for purposes of Medicare reimbursement. Medicare will cover the vaccine without cost sharing for the duration of the public health emergency. There is an exception for people covered by a very limited Medicaid Plan, but the Provider Relief Fund will reimburse providers who administer the vaccine to people covered by this plan.

- Clarified that people covered under Medicare Advantage plans will have access to COVID-19 vaccines without cost sharing. The interim rule also clarifies billing procedures for providers. Mr. Wu noted that Medicare will be a huge payer for the populations targeted for the vaccine, particularly at early stages.

- CMS and the Departments of Labor and Treasury regulate group health plans and insurance coverage across the private sector. The interim rule requires that all major medical forms of commercial coverage must cover COVID vaccines without cost sharing, copays, deductibles, or coinsurance from an enrollee. For the duration of the public health emergency, all plans must provide this coverage even for out-of-network vaccinations. These provisions are backed up by provider agreements under Operation Warp Speed for those who will receive a free supply of the vaccine.

The interim rule intends to make the back-office reimbursement process completely invisible to the consumer. People will walk into to their provider, receive the vaccination, and get a card telling them when to return, with no money exchanged and no bills, regardless of vaccinees' coverage status.

CMS has created online toolkits, which are updated as new information is available for providers, payers, states, and beneficiaries.

Discussion

Dr. Hopkins asked whether the provider relief fund will cover uninsured populations. Mr. Wu confirmed that a portion of the fund has been dedicated to paying for vaccinating the uninsured.

Report Overview

Dr. Hopkins provided an overview of NVAC's report in response to the charge questions from ADM Giroir. That charge centered on three major elements:

1. What should HHS do before, during, and after the COVID-19 vaccination campaign to improve confidence in the vaccines and the nation's immunization system, especially within communities that are underserved and comprised of racial and ethnic minorities?

2. ADM Giroir is particularly interested in how to approach vaccination of children, given that there will be relatively little data available and a low reported case fatality rate. What is the appropriate approach and timing of generating the needed data and proceeding to potential childhood vaccination?

3. What lessons can be learned from COVID-19 vaccine development to more broadly promote innovation and shorten timelines to increase the availability of new vaccines to the American public?

Dr. Hopkins outlined the process for adopting the final report on ADM Giroir's charge and thanked the OIDP staff for facilitating this process. He listed the roster of topics and experts who presented at NVAC meetings in September, October, and the current meeting and thanked the experts for their presentations. He noted that NVAC would discuss and vote on the draft report after public comment.

Dr. Hopkins then read NVAC draft recommendations in response to the three questions in ADM Giroir's charge.

He concluded by opening the meeting to public comment, noting that NVAC members also had been sent the three written comments received prior to the start of the meeting,

Public Comment

Catharine Krebs, Ph.D., medical research specialist at the Physicians Committee for Responsible Medicine

Dr, Krebs urged HHS on behalf of the Physicians Committee to shift away from funding and reliance on animal-based COVID-19 research and testing and immediately prioritize development of approaches and policies that advance protections for human subjects from vulnerable populations.

She said that federal research agencies have acknowledged the limitations of animal-based experimental systems in replicating human biology and predicting health outcomes. Nevertheless, little has been done to achieve a shift towards more human-based research and testing strategies.

She said that far too often, nonclinical safety testing fails to predict trial outcomes because the testing is largely conducted using animal-based experimental systems rather than more predictive human biology-based models, such as tissue chips and organoids. This poses a risk to vulnerable populations such as minorities, the elderly, pregnant women, and people with medical comorbidities who need to be included in clinical trials. More predictive nonclinical testing also presents an opportunity to fill the data gap on the vaccination of children.

Virginia Bader, M.B.A, Students Assist America

Ms. Bader explained that Students Assist America is a coalition of 11 health education associations. The coalition has access to institutions that are training one million future healthcare practitioners.

She noted that medical, nursing, pharmacy, and physician assistant students already participate in flu vaccine efforts across the United States. She said that students are a critical way to ensure access to vaccines, particularly in rural and underserved communities, which is a major concern for COVID. These students are not part of Operation Warp Speed, however, and are only mentioned in a handful of state vaccine distribution plans. Students Assist America asked NVAC to encourage all states to do three things:

1. Enter into agreements now with health education institutions to enable faculty and students to help vaccinate for COVID-19 and waive liability for those institutions, as is typical of a pandemic situation.
2. Expand the definition of what types of students are eligible to vaccinate to include all health professions who are trained to give injections with supervision.
3. Give students who are in clinical environments priority access to the COVID-19 vaccines so they can continue their training without additional delay, then safely vaccinate others.

More information is available at http://aacom.org/mobilize.

Diana Zuckerman. Ph.D., National Center for Health Research

Dr. Zuckerman is director of the center, a nonprofit think tank that scrutinizes the safety and effectiveness of medical products. She presented the following points:

- The importance of studying diverse groups of children and pregnant women to learn as much as possible prior to making COVID-19 vaccines widely available to them.
- The importance of a targeted EUA for the COVID-19 vaccine without off-label uses, particularly prior to studies of pregnant women and children. Dr. Zuckerman acknowledged that it may be crucial to invoke FDA's expanded access program for an urgent use to include some people off-label.
- The importance of continuing randomized clinical trials and not changing who is in the placebo group until researchers gather at least a few more months of data.

Aileen Marty, M.D., Distinguished University Professor, Infectious Diseases, Herbert Wertheim College of Medicine, Florida International University

Dr. Marty asked NVAC to consider three points regarding COVID-19 vaccines:

1. COVID-19 has a significantly greater negative impact on the elderly and those from historically underrepresented populations, such as Black, Latinx, and Native Americans. Long-term care facility residents, one of the first vaccine target groups, are disproportionately white and do not generally represent underrepresented communities. Dr. Marty urged NVAC to recommend that vaccine doses be provided to long-term care facilities only if they agree to vaccinate all persons 75 years of age or older who live within a seven-mile radius of the facilities, whether or not such persons are patrons.

2. Data are not currently available for how effective vaccines are at preventing a vaccinated person with asymptomatic COVID-19 from transmitting the infection to others. This raises the question of whether Phase 4 trials will include identification of the transmission risk from vaccinated people and whether it will alter the percentage of the population that needs to be vaccinated for herd immunity.

3. Pregnancy is known to alter metabolism and immune response, which can impact vaccine effectiveness. Dr. Marty asked NVAC to demand that T cell and B cell subclass responsiveness in pregnant women be part of the trial to determine vaccine efficacy for pregnant and lactating women.

Committee Discussion and Vote

Dr. Hopkins explained that the committee would discuss the charge questions and recommendations in numerical order, beginning with Question 1 and Recommendations 1.1 through 1.7.

Dr. Goode asked whether the recommendations needed to specifically mention healthcare provider receipt of vaccines or if providers are covered under "stakeholders." **Dr. Hopkins** said providers are well covered in the stakeholder piece, not only for vaccination, but for developing educational pieces to help facilitate that group.

Question 2 and Recommendations 2.1 – 2.6, dealing primarily with issues of including patients in trials, specifically children and pregnant women.

Dr. Douglas expressed concern that the wording may cause confusion over whether the committee recommends that childhood trials should be delayed until post-marketing surveillance is complete.

Dr. Hopkins noted that the Pfizer study included children 12 years of age and up. He said he has heard of at least one other vaccine trial that includes older children. He expressed hope that the NVAC report will encourage more discussions between FDA, other federal partners, and the vaccine manufacturers to begin evaluating trials in children. Dr. Hopkins said he has also heard of work going on to develop trial models for pregnant women,

He continued that NVAC has tried to walk a fine line between pushing too hard or stepping back too far. He expressed hope that the report can push those discussions forward without being too forceful.

NVAC members had no questions or comments on Question 3 and Recommendations 3.1 – 3.6.

Dr. Meissner moved to approve the NVAC recommendations as presented. **Dr. Fleming** seconded the motion. NVAC members present unanimously approved the recommendations, with three members absent.

Dr. Hopkins thanked committee members, federal partners, and the OIDP team for their hard work on the response to ADM Giroir's charge during a time of disruption to the U.S. healthcare and vaccination systems. He wished everyone a happy holiday season and adjourned the meeting.