NVAC NATIONAL VACCINE ADVISORY COMMITTEE

September 12–13, 2018, Meeting Minutes

Committee Members in Attendance

Kimberly M. Thompson, Sc.D., Chair
Robert H. Hopkins Jr., M.D., MACP, FAAP; Incoming Chair
Steve Black, M.D. (by phone)
Jay C. Butler, M.D., CPE, FAAP, FACP, FIDSA
Melody Anne Butler, B.Sc.N., RN
Timothy Cooke, Ph.D.
John Dunn, M.D., M.P.H.
Leonard Friedland, M.D.
Ann Ginsberg, M.D., Ph.D.
Mary Anne Jackson, M.D., FAAP, FPIDS, FIDSA
Larry Pickering, M.D., FAAP, FIDSA
Melissa Martinez, M.D., FAAFP
Cody Meissner, M.D., FAAP
Geeta Swamy, M.D., FACOG (by phone)

NVAC Ex Officio Members

Amanda Cohn, M.D. (for Nancy Messonnier, M.D.) Centers for Disease Control and Prevention (CDC)
LT COL Chris Ellison (for Heather Halvorson, M.D., M.P.H., M.S.H.I., LT COL), Department of Defense (DoD)
Mary Beth Hance (for Jeffrey Kelman, M.D., M.M.Sc.), Centers for Medicare and Medicaid Services (*day two*)
Linda Lambert, Ph.D. (for Rick Bright, Ph.D.), Biomedical Advanced Research and Development Authority (BARDA)
Donna Malloy, D.V.M., M.P.H., U.S. Department of Agriculture (USDA)
Valerie Marshall, M.P.H. (for Marion Gruber, Ph.D.), Food and Drug Administration (FDA)
Justin A. Mills, M.D., M.P.H., Agency for Healthcare Research and Quality (*day two*)
Barbara Mulach, Ph.D., National Institutes of Health (NIH)
Narayan Nair, M.D., CAPT, Division of Injury Compensation Programs (DICP), Health Resources and Services Administration (HRSA)
Judith Steinberg, M.D., M.P.H., Bureau of Primary Health Care (BPHC), HRSA

NVAC Liaison Representatives

Rebecca Coyle, M.S.Ed., American Immunization Registry Association (AIRA)
Kristen R. Ehresmann, RN, M.P.H., Association of Immunization Managers (AIM)
Jean-Venable "Kelly" Goode, Pharm.D., BCPS, FAPhA, FCCP, American Pharmacists Association (APhA)
James David Nordin, M.D., M.P.H., America's Health Insurance Plans (AHIP)
Tiffany Tate, M.H.S., National Association of County and City Health Officials (NACCHO)

Acting Designated Federal Officer

Ann Aikin, M.A., Communications Director, National Vaccine Program Office (NVPO), Department of Health and Human Services (HHS)

Proceedings
Day One—September 12, 2018

Call to Order and Rules of Engagement—Ann Aikin, M.A., Communications Director, NVPO, HHS

Ms. Aikin called the meeting to order at 9:05 a.m. She announced that the current NVAC chair, Kimberly M. Thompson, Sc.D., is rotating off the Committee, and the incoming chair, Robert H. Hopkins Jr., M.D., MACP, FAAP, will begin his term on day two of this meeting (September 13). 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 NVPO staff for their support in organizing the meeting and called the roll.

Chair's Report—Kimberly M. Thompson, Sc.D., NVAC Chair

Dr. Thompson said she and Dr. Hopkins had been working closely together to facilitate a smooth transition of leadership. She said it had been an honor to serve and thanked all the NVPO staff and leaders who supported her and NVAC. During her tenure, NVAC published three important reports that Dr. Thompson hoped would have meaningful impact. She also initiated the practice of featuring one liaison or ex officio initiative at each meeting. Dr. Thompson expressed her appreciation for all the stakeholders in the vaccine enterprise and thanked all of those who help to ensure that people benefit fully from vaccines to prevent bad health outcomes.

The minutes of the February 7–8, 2018, meeting were unanimously approved by the NVAC members. Regarding the minutes of the June 25, 2018, teleconference, Cody Meissner, M.D., FAAP, took issue with a statement made by a public commenter that cervical cancer is "highly treatable." Most would not agree, he said. Cervical cancer causes 4,000 deaths per year and has a 75 percent 5-year survival rate, he noted. Ann Ginsberg, M.D., Ph.D., asked that a statement attributed to her be revised to improve the accuracy, as follows:

Current: Dr. Ginsberg raised concerns that the Gates Foundation and others are funding more of their own, internal research, which could have the effect of decreasing innovation and diversity of thought in the field. She concluded that increasing the amount of money spent on prevention, rather than cutting costs, should be taken seriously.

> **Proposed revision (*italics added to highlight changes*)**: Dr. Ginsberg raised concerns that the Gates Foundation and others are funding more of their own, internal research, which could have the *unintended* effect of decreasing innovation and diversity of thought in the field. She concluded that increasing the amount of money spent on prevention, rather than *only* cutting *treatment and diagnosis* costs, should be seriously *considered*.

NVAC members voted unanimously to approve the minutes of the June 25, 2018, meeting, with the proposed revision.

Dr. Thompson described the meeting proceedings and the agenda for this meeting. Written comments can be sent to the NVAC for consideration by e-mail (nvac@hhs.gov). The minutes and presentations of past meetings are available online at http://www.hhs.gov/nvpo/nvac/index.html. In 2019, NVAC is scheduled to meet virtually on February 5 and in person on June 4–5 and September 17–18. (See the appendix for a list of abbreviations used in this report.)

NVPO Update—Tammy R. Beckham, D.V.M., Ph.D., Acting Director, NVPO

Dr. Beckham is simultaneously serving as the Acting Director of the Office of HIV/AIDS and Infectious Disease Policy. She announced that NVAC's report, *Strengthening the Effectiveness of National, State, and Local Efforts to Improve HPV Vaccination Coverage in the United States: Recommendations of the National Vaccine Advisory Committee*, has been published online and will be printed in the November/December issue of *Public Health Reports*. She stated that NVPO is working on an action plan to implement NVAC report's recommendations. Dr. Beckham said several offices under the Office of the Assistant Secretary for Health (OASH) convened in August to discuss how to support the goal of improving HPV vaccine coverage. She said NVAC would receive updates on this group's progress. Dr. Beckham noted that she and ADM Brett P. Giroir, M.D., Assistant Secretary for Health (ASH), share a sense of urgency around HPV vaccination, and she looked forward to building on the momentum around this priority area.

In 2016, NVPO published the *National Adult Immunization Plan* and a corresponding implementation plan. Since then, NVPO has been working with HHS' regional offices to host public meetings around the country, engaging more than 300 diverse partners to talk about issues such as billing, immunization information systems (IIS), and other topics. Information about future meetings will be shared via the NVPO website. In July, the Healthcare Effectiveness Data Information Set (HEDIS) announced that two new quality measures—prenatal immunization and adult immunization—were being considered for 2019. If adopted, they can be used to evaluate health care service delivery and ultimately improve uptake.

In August, NVPO and the Office of Disease Prevention and Health Promotion launched a series of videos highlighting the importance of vaccines for whooping cough (pertussis), shingles (herpes zoster), and pneumococcal disease. Dr. Beckham said many liaison groups are already sharing the videos, and she invited the NVAC members and other participants to share them with their networks. They are available online at Vaccines.gov along with other resources.

Dr. Beckham thanked Dr. Thompson for her leadership and welcomed Dr. Hopkins as the new chair. She also thanked the NVPO staff for their efforts.

Opening Remarks—ADM Brett P. Giroir, M.D., ASH, HHS

ADM Giroir expressed strong support for NVAC, saying that he believes vaccines are the most important public health advance of modern times and have saved millions of lives. He recounted attending funerals of his pediatric patients who died from complications of measles, chicken pox, pneumococcal disease, and from influenza, and the disheartening knowledge that some of those deaths could have prevented.

NVAC is critical to the HHS' efforts, bringing together the brightest minds in the vaccine enterprise, said ADM Giroir. He thanked the members for their service, time, and effort. He was particularly grateful for NVAC's work to promote HPV vaccine coverage. Better uptake could prevent 30,000 to 40,000 cases of cancer per year in young women and men. ADM Giroir said NVAC's report arrived just as he chartered a group to address how to disseminate best practices and improve HPV vaccine coverage.

ADM Giroir also praised NVAC's attention to vaccine innovation, which is critical to tackling emerging disease threats. Innovation goes beyond targeting "bugs;" it also addresses new constructs, platforms, and distribution and delivery methods. Innovation is needed to better communicate the benefits of vaccines and their minimal risks, if any, associated with lifesaving

strategies. ADM Giroir noted that the 2017–2018 influenza season was severe and prolonged, and thousands died needlessly, underscoring that influenza is complex and difficult to predict.

Finally, ADM Giroir thanked Dr. Thompson for her leadership, which has had an enormous impact. He presented her with a plaque recognizing her outstanding service. ADM Giroir welcomed Dr. Hopkins, noting that Dr. Hopkins has high aspirations for NVAC.

Igniting Advances in Immunization: Funding Unmet Needs—Roula Sweis, M.A., Psy.D., Deputy Director, NVPO

The unmet needs initiative enables NVPO to identify gaps and respond to emerging needs and priorities, explained Dr. Sweis. The initiative is fueled both by NVPO's statutory charge to implement the National Vaccine Plan and the 21st Century Cures Act's directive to encourage vaccine innovation. For several years, NVPO's funding has remained steady at $6.4 million; about 25 percent of that ($1.5–$1.9 million) goes to funding unmet needs.

NVPO solicits nominations for projects from its federal partners. NVPO seeks projects that align with its priorities, are discrete projects that can be implemented in 1–2 years, offer measurable outcomes, and can be picked up by a partner who will continue or grow the project in the future. Dr. Sweis stressed that "unmet need" means no other source of funding is available.

For 2018, NVPO funded seven projects, all of which are administered by CDC. The projects address such topics as improving HPV vaccination coverage in the southeastern United States; better understanding racial and ethnic disparities in adult vaccine coverage; increasing knowledge about the burden of group B streptococcus, cytomegalovirus (CMV), and Lyme disease; and improving surveillance mechanisms.

For 2019, NVPO is considering projects overseen by CDC, FDA, NIH, and the U.S. Agency for International Development on a number of topics related to vaccine coverage, innovation, and safety. Dr. Sweis said awards should be announced in December 2018.

Discussion

Larry Pickering, M.D., FAAP, FIDSA, applauded the clarity of NVPO's initiative. He hoped future presentations would demonstrate how NVAC can support or align with the projects. Dr. Sweis noted that many of the projects build on ideas and concerns raised by NVAC.

Valuing Vaccines: Direct and Indirect Gains

Benefits of Vaccines—Sachika Ozawa, M.H.S., Ph.D., University of North Carolina at Chapel Hill

Dr. Ozawa outlined the methodology for determining what decision-makers most wanted to know about vaccines: the return on investment (ROI) for a specific population, which requires a broad look at all the related costs and benefits. She and her colleagues concluded that every dollar invested in vaccinating children yields an ROI of $16–$44. That finding sparked enthusiasm among world leaders and spread rapidly through social media. The worked helped to support, Gavi, the Vaccine Alliance, to raise $7.5 billion based on the ROI figures.

Dr. Ozawa stressed the importance of better communicating the benefits of vaccines, and she described evidence in six categories that can help support policy-making, which included some highlights:

- **Health:** In addition to direct prevention of the targeted disease, vaccination reduces the likelihood of premature birth, low birthweight, and long-term disability. Maternal immunization improves maternal and child health.
- **Education:** Childhood vaccination has been correlated with increased cognitive test scores and cognitive function and higher educational attainment.
- **Economic:** Vaccines are highly cost-effective and can avert the significant costs of treatment (a burden that may fall on individuals or governments or both).
- **Equity:** Vaccines can reduce gender, health, and wealth inequities by benefitting girls, people in poverty, and children who are immunocompromised.
- **Health Systems:** Vaccines could reduce pressure on the system by decreasing admissions. The infrastructure built to enable routine vaccination was leveraged to fight outbreaks of H1N1 pandemic influenza and Ebola virus. Vaccinations during infancy can provide an opportunity for early health and development screening.
- **Global Health Security:** Vaccines could control emerging infectious disease outbreaks and prevent them from spreading across borders; they may also reduce the impact of antibiotic-resistant disease.

The Role of Vaccines in the Prevention of Antimicrobial Resistance (AMR)—Kent E. Kester, M.D.

Dr. Kester served on the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), which highlighted the role of vaccines in its report, *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic Resistance*. He explained that addressing AMR requires creating new antibiotics and broadening focus beyond health-care-associated infections to include community-acquired infections. However, it also requires new attention to the role of vaccines, diagnostics, and other therapeutic approaches. In addition to their direct effects, vaccines can prevent development of related syndromes that typically require antibiotics. By preventing disease, vaccines can reduce inappropriate use of antibiotics prescribed, for example, for influenza that is interpreted as upper respiratory bacterial infection.

PACCARB recommended new and increased incentives for developing vaccines to stem AMR, optimizing regulatory interactions to bolster vaccine development, and creating incentives for uptake. More data are needed on the costs and social impact of generating new vaccines and the use of antibiotics for vaccine-preventable diseases. Europe is pursuing similar approaches to address AMR, Dr. Kester noted.

More surveillance and epidemiologic data are needed to better model the effects of vaccines so that policy-makers have more information on which to base decisions. Current models do not demonstrate the effects of vaccines on reducing co-infections or the related economic outcomes. Dr. Kester cited a number of large initiatives underway to support development of new vaccines to combat AMR, generation of evidence to demonstrate the value of vaccines, and communication of the benefits of vaccination. He concluded that many challenges remain, but there is a convergence of stakeholder effort around research and development (R&D), data generation, communication, and advocacy to address them.

The Economics of Polio Eradication—Kimberly M. Thompson, Sc.D., Kid Risk, Inc.

Dr. Thompson said not all audiences may not fully appreciate the factors that complicate modeling of the economic benefits of polio vaccination, including the costs and long-term impact of oral (attenuated) poliovirus vaccine (OPV) compared with inactivated poliovirus vaccine

(IPV). Economic literature demonstrates that, theoretically, high control of disease is not optimal if eradication is feasible.

When polio vaccine became available, uptake was rapid, and the number of cases dropped dramatically. Dr. Thompson presented the results of a study that estimated that U.S. investments in polio control and elimination resulting in a net savings of over $180 billion. Dr. Thompson emphasized that modeling only the benefits of vaccine to the individual vaccine recipient misses an important part of the story—the indirect economic benefits to society of preventing disease and stopping transmission.

Poliovirus transmission nearly stopped in the United States in the 1970s, and by 1988, the World Health Assembly and partners launched the Global Polio Eradication Initiative (GPEI). Economic analyses demonstrated that even in low-income countries, focusing intensively on polio eradication was a better option than targeting disease control alone. Despite pessimism about stopping polio in India, its polio eradication efforts ultimately succeeded in 2011, which energized other immunization activities in India and demonstrated that eradication is both feasible and effective.

Analysis of the GPEI found that investing in polio eradication increases costs in the short term but significantly reduces the burden or disease, resulting in an estimated net benefit of $40 billion to $50 billion, plus $17 billion to $90 billion more if the benefits of vitamin A delivered as part of polio vaccination campaigns are considered as well. A 2015 prospective analysis projected net savings of about $17 billion if wild poliovirus is eradicated and OPV is discontinued, assuming that governments adopt best practices such as maintaining immunity before OPV is discontinued and globally coordinating OPV cessation. Wild poliovirus persists in Afghanistan and Pakistan, and the GPEI partners have extended their strategic plan to 2019. Dr. Thompson said her collaborators are updating their model to support policy-making around the next phase of GPEI. She hoped the dynamic modeling approach could be applied to other diseases.

Questions and Answers (Q&A) with Dr. Thompson

Dr. Pickering described the initial resistance to switching from OPV to IPV. However, when the issue came up before the Advisory Committee on Immunization Practices (ACIP), parents brought their paralyzed children in wheelchairs—children who were infected after receiving OPV. That vivid example of the risks of OPV was influential in ACIP's decision to eliminate it in favor of IPV. Dr. Thompson added that the cost-effectiveness analysis for IPV was not favorable initially, but the safety concerns about OPV and the desire by public health officials to continue to achieve high coverage drove the decision with the U.S. remaining at risk from importation of live polioviruses from other countries.

Melody Anne Butler, B.Sc.N., RN, stressed the need for planning around sustaining polio eradication once it is achieved. Dr. Thompson agreed, adding that it is easy to see the cost of delivering vaccines but hard to show the costs averted as a result. Studies that show the economic benefits of vaccines are important, said Dr. Thompson.

Dr. Meissner noted several factors that complicate total eradication. Dr. Thompson agreed that containment is a major topic of discussion, and efforts are underway to catalog stored laboratory samples as one step. She emphasized the importance of continued, unrelenting attention to eradication and said lessons from the effort can inform other disease control and eradication efforts and research. When possible, eradication also presents the best opportunity to achieve health equity, Dr. Thompson noted.

Discussion

FULL VALUE OF VACCINES

Dr. Pickering appreciated that all the presentations highlighted the importance of modeling using multiple attributes to assess. He urged NVAC to use such multifactorial models to get a complete picture of direct and indirect effects to inform its recommendations. John Dunn, M.D., M.P.H., agreed, pointing out that much of the money for vaccines comes from government investment. More concrete estimates of costs averted can help paint a better picture of how much money is not available for other uses when it must be used to treat vaccine-preventable diseases, which may help build public support, said Dr. Dunn.

Timothy Cooke, Ph.D., said there is a strong link between the full value of vaccines and vaccine innovation. That is, if vaccines are not valued and used, innovation efforts will focus on other things. Dr. Cooke agreed that the cost savings of disease prevention may be difficult to visualize and does not carry the visceral appeal of curing disease. He wondered how the full value of vaccines could be translated to the public in a way that resonates emotionally. Dr. Thompson noted that AMR is a crisis with severe effects on individuals, yet it does not have the same emotional impact on people as seeing children with polio in wheelchairs and iron lungs. Dr. Ozawa said that individuals' stories are powerful for communicating a message. She also said that using specific data for a given country or population is effective. In countries where a vaccine-preventable disease is no longer visible, public health authorities should model the counter-factual to demonstrate the need for continued attention, said Dr. Ozawa.

Dr. Ozawa said that the ROI was calculated on the basis of the cost of illness and treatment as well as the full economic value of lives saved. Even higher-income countries benefit from continued prevention because of the high value of a life saved. Dr. Ozawa also pointed to the related benefits realized from vaccination, including stronger health systems and increased educational benefits.

VACCINES AND AMR

Steve Black, M.D., said that the United States lacks a good regulatory framework for demonstrating the benefits of vaccines in preventing AMR. Dr. Kester envisioned that vaccine manufacturers would present regulators with data on the effects of the vaccine on the target disease as well as potential effects on AMR or associated syndromes. Dr. Thompson said there is need for economic models that can capture the impact of vaccine on related conditions, such as antibiotics used for urinary tract infections (UTIs) or upper respiratory disease, and NVAC may want to discuss vaccine financing in relation to these other goals of vaccination.

Dr. Pickering said that the problem of antibiotic-resistant gonorrhea suggests that developing vaccines to address resistance will be impossible without a better understanding of the commonalities between gram-negative organisms and resistance. Dr. Kester appreciated the point and said that, for some organisms, the answer may still lie in better infection control and better antibiotics. Dr. Meissner said there are already some vaccines that can prevent more than one disease.

Dr. Hopkins noted that there were Pneumococcal vaccines available and licensed for use in the US in the 1940's; however, these vaccines were underused and eventually withdrawn due to the tremendous success of antibiotics [specifically penicillin] for treatment of pneumococcal infections. It may be important for us to consider the lessons learned from that experience in reverse in our current era of growing antimicrobial resistance.

Amanda Cohn, M.D., noted that the ACIP has adopted the evidence-to-recommendations framework, which should gather more information on noneconomic benefits. Such evidence may reveal the potential impacts of a vaccine on AMR.

Ms. Butler asked how European public health officials have improved AMR surveillance. Dr. Kester said surveillance in America is good but should be refocused to capture more data than can be used in R&D, communication, or advocacy to enhance uptake of current vaccines.

COMMUNICATING VALUE

Dr. Hopkins emphasized that communicating the benefits of vaccination means convincing different audiences and creating demand among individuals and health care providers for them. Jay C. Butler, M.D., CPE, FAAP, FACP, FIDSA, noted that it is also important to understand who receives the return from the ROI. Unfortunately, hospitals make money from disease, not prevention. In addition, the timeliness of returns is important; some expect instant returns that can be used to offset other costs immediately. Ms. Butler countered that that hospitals do not make money from, for example, catheter-associated urinary tract infections (CAUTI). Dr. Ozawa said she and her colleagues focused on the societal benefits of vaccination.

Leonard Friedland, M.D., particularly appreciated the infographics Dr. Ozawa presented. He called for more attention to visual representations of information that can be easily understood and digested by more people. Dr. Ozawa agreed that the infographics can be very effective in promoting vaccines, but they require significant investment.

As a way to draw attention to costs averted, Ms. Butler suggested highlighting the results of follow-up efforts after an outbreak to illustrate how well vaccination prevented disease in people who were exposed but had been vaccinated.

Leveraging Public-Private Partnerships to Move the Needle in Product Development

Industry Perspective on Vaccine Innovation Environment—Phyllis Arthur, Biotechnology Innovation Organization (BIO)

Ms. Arthur said the number of companies developing vaccines has increased substantially since the 1990s. The pipeline demonstrates that the vaccine portfolio is broad, which is exciting, but it is not deep, which is a problem. Companies consider various types of risk when determining whether to pursue vaccines, such as how to demonstrate effectiveness and the substantial capital needed just for manufacturing and testing the product. “Exit risk” describes the likelihood that a small or mid-sized company be acquired by a large company that can successfully take a product to market. Companies also consider commercial risks that affect demand and pricing, such as government purchasing decisions, ACIP recommendations, vaccine hesitancy, and insurance coverage and access.

The unique risks associated with vaccine development mean that companies may be more willing to invest in developing therapeutics, which present very different opportunities for ROI. The ecosystem for therapeutics rewards innovation by small biotech firms with early partnerships with larger firms, increasing the likelihood of getting a product to market. In the infectious disease arena, however, there are fewer large companies supporting vaccines, and often those companies do not partner with small firms until later in the development process—at the end of phase II trials or even the beginning of phase III trials.

Ms. Arthur noted that it takes 5–8 years and $700 million to $1 billion to set up a manufacturing plant approved by the FDA and international inspectors just to make the product needed for phase III trials. She also said that ACIP recommendations are very important for stimulating innovation.

Ms. Arthur outlined some of the most prominent partners involved in the vaccine enterprise, which include international, federal, and nongovernmental organizations. Much work is focused on emerging infectious diseases, where the marketplace for products is most uncertain. Ms. Arthur called for efforts to clarify the ACIP's thinking about its recommendations and for more sharing of epidemiologic and burden-of-disease data so that companies can determine which targets to pursue. She also called for continuing to strengthen the environment for adoption of vaccines across the lifespan.

Vaccine Research and Development: The Role of Public-Private Partnerships (PPPs) in Enabling Innovation—Annie Mo, Ph.D., NIAID, NIH

Dr. Mo explained that NIH is involved in research on all aspects of infectious disease and supports vaccine development at the earliest stages, mostly up to phase II clinical trials, at which point it expects industry partners or others to shepherd products through phase III trials and commercial development. NIH's goal is to facilitate R&D that improves existing vaccines and creates new ones. NIH advances vaccine development by partnering with various entities, including biotech and biopharmaceutical companies, and providing financial support, R&D, or access to intellectual property.

Financial support usually comes through NIH grants or contracts. Under contracts, the federal government is actively involved in directing the work. With grants, NIH funds solicited and unsolicited (known as investigator-initiated) proposals. Grants seek to spur creativity and innovation. Cooperative agreements are high-level, targeted grants that involve some government oversight. NIH can also support investigators by providing access to materials, intellectual property, and clinical trial networks. For example, the federal government may provide clinical trial sites and financial support, while a private entity provides the technology or product to be tested, and together the partners determine the trial design, protocols, and analysis. Dr. Mo described NIH's role in the development of a vaccine for Ebola virus as an example of an effective partnership. She also cited the partnership that led to an improved rotavirus vaccines as an example of innovation in vaccine licensing.

Dr. Mo said successful PPPs require the following:

- Aligned goals
- The capacity for partners to leveraging comparative advantages
- Shared risk, responsibility, and accountability
- Careful strategic planning
- Flexible mechanisms

BARDA and PPPs—Linda Lambert, Ph.D., BARDA, Office of the Assistant Secretary for Preparedness and Response (ASPR)

Dr. Lambert said BARDA makes medical countermeasures available by forming unique PPPs that employ its flexible, nimble authorities; multiuse funding mechanisms; and access to exceptionally talented subject matter experts with experience in the private sector. In just over a decade, through collaboration with over 200 partners, BARDA has helped 40 products achieve FDA approval, licensing, or clearance. With industry partners, BARDA established three Centers of Innovation and Advanced Development and Manufacturing in response to the need for more

domestic capacity to manufacture vaccine in case of a pandemic disease. The Centers also support product testing and training.

BARDA's Other Transactional Authority agreements allow companies to propose candidates for funding and apply a managed portfolio approach, so that companies can shift their attention as needed to advance the most promising candidates. The CARB-X initiative to accelerate innovation around AMR currently has 35 candidates in development, of which five are in the testing phase. For every dollar committed to CARB-X by funders (public and private), $7 to $8 in private equity follows. From 2016 to 2021, CARB-X is committed to invest $500 million.

BARDA's new Division of Research, Innovation, and Ventures (DRIVe) offers several approaches, including an innovation acceleration effort, solution mapping, and a focus on sustaining access to needed products, especially when there is no commercial market for them. DRIVe will link companies to venture capitalists. It seeks to address significant public health threats, such as sepsis, which is a factor in many deaths in hospitals. Dr. Lambert explained that BARDA aims to foster innovation in all different aspects of public health response, from the initial situational awareness, through design, production, and administration. Strong PPPs along with financial support from Congress have enabled BARDA to make significant gains.

PPPs: Successes and Failures in Financing Vaccine Innovation—David C. Kaslow, Ph.D., PATH Essential Medicines

Dr. Kaslow summarized PATH's support for vaccine development and its goal of getting vaccines and other products to people who need them all over the world. PPPs are particularly important for products for which there is no commercial market, so mechanisms are needed to share the risks and costs of development. PATH plays different roles depending on the nature of the product, the market, and the economic capacity of the countries where the product is needed. For example, Dr. Kaslow noted, some vaccine products (such as those targeting cholera) will never be in high demand in high-income countries, so they will always need some support to bolster the business case for private development.

PATH's principles for global access underscore how it works with private sector partners to develop products: availability, accessibility, affordability, acceptability, and, sustainability. The development of meningococcal conjugate vaccine for Africa represents a recent success, said Dr. Kaslow, but if access to the vaccine is not sustained, a new epidemic will emerge in the future.

PATH is also concerned about what Dr. Kaslow called "the second valley of death." Once a vaccine clears the first "valley of death" (i.e., getting from clinical testing to the market), before low-income countries have access to it, the vaccine must go through additional review by, for example, the World Health Organization (WHO) and its Strategic Advisory Group of Experts and Gavi (for financing and procurement). GSK's malaria vaccine, Mosquirix, was approved in Europe after 30 years in development, but the WHO and others recommended further evaluation of issues beyond safety and efficacy, such as the feasibility of a four-dose regimen. Dr. Kaslow said PATH hopes to construct the "highway of life" for vaccines to cross the second valley of death.

Biotechnology Company Perspective—Timothy Cooke, Ph.D., NovaDigm Therapeutics

Biotech companies would not exist without PPPs, said Dr. Cooke. He described the investment considerations that underpin biotech financing. For example, venture capitalists make money when small companies are acquired by large companies or become publicly traded companies. In addition to the risks already described by BIO, barriers to private investment in biotech firms that

develop vaccines include the lack of a robust commercial market, product pricing limitations, and the potential for higher returns in other areas of biotech.

On the surface, biotech firms have seen a boom in investment over the past 5 years, with much growth in the area of infectious disease. For vaccines, however, investment has been relatively flat, with the exception of two spikes, one related to an acquisition and the other around one product. Thus, PPPs are more important than ever to fill the funding gaps, said Dr. Cooke. Getting products past the valley of death and into the market requires good commercialization options, robust investment from big pharmaceutical companies, and government policies that lower the risks of product development.

The two most valuable biotech firms in the field, Emergent BioSolutions and Bavarian Nordic, were supported by push and pull incentives from BARDA, demonstrating that government intervention can make a difference. The best pull mechanism, Dr. Cooke observed, is a robust commercial market.

Pfizer's Commitment to Vaccine Innovation—Joanna Wolkowski

Ms. Wolkowski said Pfizer's portfolio targets infectious diseases across the lifespan, and its pipeline is robust. Its investment decisions take into account many factors and apply to numerous therapeutic products other than vaccines. Ms. Wolkowski outlined the quantifiable factors used in decision-making:

- **Risk:** The success rate of bringing a product in development to market is about 5 percent.
- **Cost:** In addition to dollars, the company must invest its resources, and resources dedicated to one effort are not available for others.
- **Time:** Products require about 10–15 years on average to reach the market.
- **Value:** The ROI is important, as is the impact of the product on the lives of people who use it.

Nonquantifiable factors that affect decisions include regulatory commitments, the potential benefit to users, strategic considerations, and platform capabilities. For every program, Pfizer assesses the value and compares it with all of its other products in development to determine where to allocate money and resources, and many tradeoffs must be taken into account.

Ms. Wolkowski pointed out that developing vaccines often costs more than developing other products, primarily because clinical trials must be much larger to demonstrate efficacy. On the other hand, the probability of success with vaccine products is higher than for other products, because numerous preclinical models are available to test them. Ms. Wolkowski concluded that Pfizer's strong partnership with Gavi helps get its products to the people who need them.

Discussion

Given the amount of government funding that goes into vaccine development, Dr. Meissner asked, are there mechanisms for manufacturers to pay back the government when products become successful and profitable? Dr. Mo said NIH's mission is to minimize the risks associated with early development, but it is up to the private sector to move products through to completion and commercialization. She did not think that NIH had a mechanism to receive money from private companies that benefit from NIH's efforts. NIH does have some licensing agreements that generate royalties for the agency, which go back into intramural research funding.

Dr. Lambert said that BARDA partnerships focus on cost-sharing, so that industry partners have a stake in product development. The DRIVe program allows for third-party investment, and BARDA shares in the ROI from those efforts, which it then uses to support other projects. This strategy will effectively expand the dollars BARDA has available to invest. To recoup some of its investment, Dr. Kaslow said that PATH asks companies to donate doses of the final product, which it uses to accelerate introduction and uptake of the product.

Dr. Ginsberg asked the panelists for suggestions on how to help propel products from early- to late-stage development. Dr. Kaslow said that in the development process, more attention should be given to the full value proposition of the product and the factors that can create a second valley of death—such as feasibility of dissemination and the financing needed to get the product where it is needed. Ms. Wolkowski said Pfizer looks for ways to improve any of the quantitative or qualitative factors that affect value—for example, by accelerating development, better understanding the likely appeal to the ACIP, ensuring that clinical trials have endpoints that can provide the data that matter, and leveraging new technology for communication to facilitate clinical trial enrollment and processes.

Dr. Cooke said there should be more emphasis on the value of prevention. In addition, biotechs need a stronger commercial market and higher revenue for their products (either from higher prices or higher volume of sales). With more federal funding, BARDA could buy more vaccines, which would be a very effective pull incentive. Investing in new antibiotics to address AMR is problematic, because the goal is to use fewer antibiotics; on the other hand, vaccines that target AMR are well positioned, because they do not generate AMR, said Dr. Cooke.

Melissa Martinez, M.D., FAAFP, asked what could be done with current PPPs and resources to further lower the costs of vaccines and make them more affordable. Dr. Cooke said that from the production perspective, lowering the price could drive investors to other areas of development. Focusing on the full value of vaccines, he said, would better address the problem. Ms. Arthur added that a better market would draw more investment from multinational players. She called for more attention to issues of access (e.g., coverage, cost, public payment policies), which drive uptake and brings developers and manufacturers to the market. Dr. Mo said decisions about which products to support should take into account downstream issues, such as potential funders and private-sector partners.

Dr. Mo said that one way to overcome barriers to the market is to seek out manufacturers in developing countries that will use the product, as was done with rotavirus vaccine. Similarly, Dr. Lambert encouraged developers to start with the end in mind, anticipating what will be required to attain recommendations from the WHO, the ACIP, and others. Dr. Lambert encouraged NVAC to consider devising an innovative communication strategy to encourage vaccine uptake, which would incentivize vaccine development.

Dr. Kaslow called for prioritizing the unmet need (e.g., identifying targets) and clarifying what is needed to demonstrate the value. In addition to dollars, there is a need to build the infrastructure to support development. Finally, there must be efforts to sustain products, so that companies who develop them are not left holding the bag. Ms. Wolokowski said the more transparent and visible the process, the more confidence Pfizer can have in investing.

Social Media for Hypothesis Testing: The Good, the Bad, and the Ugly—David A. Broniatowski, Ph.D.

Social media offers the opportunity to identify public perceptions and behavior quickly, potentially facilitating more rapid responses to emerging public health issues. He summarized some of his research team's work relevant to vaccines. He noted that early efforts to analyze Google searches to determine the spread of seasonal influenza turned up some misleading results, as investigators failed to distinguish those who had influenza symptoms from those who were simply seeking information. Since then, however, investigators have been analyzing Twitter messages with filters that better identify people with influenza symptoms.

Social media platforms are effective for gauging awareness of disease. Compared with traditional surveys, social media oversamples people with cell phones (rather than landlines, who tend to be white and rural.) Social media can provide data more quickly, but the validity of that data is less clear.

Dr. Broniatowski explained that public health messages can be conveyed by facts and by the "gist"—that is, the underlying meaning. Fuzzy trace theory states that individuals take in both the facts and the gist, but unless a message includes both, they will draw their own conclusions. Individuals may hear the gist, and it may be evidence-based, but it may not be correct. They may hear the risk in statistical terms and conclude that it does not apply to them.

Dr. Broniatowski's analysis of media coverage found that stories are effective if they communicate a gist, and not effective if they do not. Stories with statistical data are more likely to be shared on social media than those without. Stories communicating a gist and that express both sides of a debate are shared much more often than those without. Dr. Broniatowski proposed that communication include both statistics and factual data as well as a gist—and that there be a link between the two, because the gist should be based in evidence.

Evaluation of the sources of online misinformation (and disinformation) about vaccines found that much of it comes from bots (automated posters that masquerade as humans) and content polluters (which exist to send spam and transmit malware). These senders do not seek to communicate a message but rather to promote discord, steal private information, or sow confusion. Analysis of the content of messages and the sender determined that Russian trolls (bots seeking to promote discord) sent equal amounts of pro- and anti-vaccination messages. Content polluters sent significantly more anti-vaccination messages.

Dr. Broniatowski concluded that despite the consensus in science and public health that vaccines are safe and effective, organized misinformation and disinformation campaigns have different agendas that can undermine public health. He and his colleagues hope to better understand how to communicate successfully and avoid "feeding the trolls."

Discussion

Mary Anne Jackson, M.D., FAAP, FPIDS, FIDSA, asked how individual providers can protect their practices from malicious attempts by bots to ruin their reputations. Dr. Broniatowski said the issue highlights the importance of good cybersecurity practices to prevent infiltration. He said counter-attacking trolls is generally a losing proposition, and ignoring them may be effective. If it is not, it may be necessary to engage law enforcement. Dr. Broniatowski recommended the Online Harassment Field Manual, created for journalists, as a resource that could be adapted for public health providers and communicators.

Dr. Thompson asked for insights on how to craft an effective gist or otherwise improve communication. Dr. Broniatowski encouraged communicating positive messages and not engaging with misinformation efforts. Shining a light on the source of misinformation can be

effective, however. More detailed research is needed on what constitutes an effective gist, but there are many examples from many years of medical decision-making and communication. In general, in any domain, about two or three gists will resonate with a given audience because they are consistent with that audience's values and beliefs, said Dr. Broniatowski. Good communication comes down to targeting audiences and tailoring messages while ensuring that communication remains evidence-based, he said.

NVAC Liaison and Ex Officio Updates

Agency Highlight: Strengthening the Capacity of Local Health Department (LHD) Immunization Programs—Tiffany Tate, M.H.S., NACCHO

Ms. Tate presented some of the findings of NACCHO's 2017 survey of LHDs. More than half of the respondents represented small or rural organizations, and NACCHO stratified the results by geographic type (rural, urban, or suburban). Rural health departments were more likely than others to have small immunization staffs (one or two full-time staff members), and they were also less likely to experience reductions in staff.

The top five most common program activities across LHDs were hosting clinics, conducting outreach and education, collaborating internally, vaccinating children and adolescents, and conducting communication campaigns. Rural LHDs were less likely than others to offer a broad range of services, but the most commonly offered services were similar across department types. Across all types, LHDs often partnered with schools, other health departments, individual health care providers, clinics, and hospitals. Urban LHDs had a larger variety of partners than others. Rural LHDs were much more likely to partner with professional associations.

Across LHDs, the top five priorities were increasing vaccine rates, increasing vaccine confidence, establishing partnerships, improving IIS, and providing technical assistance. In terms of billing capacity, 80 percent had the ability to bill public payers, but only 56 percent could bill private insurers, so there is opportunity for improvement in both areas, said Ms. Tate.

On the basis of these data, NACCHO offered five recommendations to better support vaccinations in LHDs:

- Increase funding to support immunization.
- Facilitate capacity-building for LHDs to address barriers and challenges.
- Leverage existing partnerships and explore new ones.
- Improve data systems to enhance vaccine delivery.
- Further explore rural immunization programs.

Recently, NACCHO hosted a webinar on rural health that featured a speaker from USDA. It continues to support the grantees of the now-completed HPV vaccine demonstration projects. New members were recently named to NACCHO's Immunization Advisory Group. NACCHO provided members with a comprehensive communications campaign and toolkit for recognizing National Immunization Awareness Month.

Liaison Member Updates

AHIP—JAMES DAVID NORDIN, M.D., M.P.H.

AHIP informally surveyed member health plans about their HPV vaccination activities. Responses generally fell into the category of communication to members (e.g., targeted mailings with reminders, information about vaccine safety and cancer prevention, and education to dispel myths about the vaccine) or to providers (e.g., information about cancer prevention, lists of

eligible members, templates for letters to patients). Provider communication also included newsletters and other internal communication channels to highlight clinical research and address public perceptions. Some of the plans have internal performance metrics for HPV vaccine delivery, and some offer financial incentives for high quality as measured by targeted indicators. Some strongly encourage providers to routinize vaccination for tetanus, diphtheria and pertussis (Tdap); HPV; and meningitis together.

Dr. Nordin said that clinics in his area have seen the Minnesota Department of Health's outstanding video on how to communicate about HPV vaccination, which emphasizes cancer prevention. He said the approach has been very effective in his practice.

AIM—KRISTEN R. EHRESMANN, RN, M.P.H.

AIM's Adolescent Resource Guide now includes an adolescent immunization toolkit pertinent to HPV. AIM participated in a summit highlighting provider practices to increase adolescent immunization coverage rates that was hosted by the American Academy of Family Physicians in July. AIM continues to hold quarterly HPV call-to-action webinars; the next will take place in September. AIM is speaking with members about managing the hepatitis A outbreaks that have been occurring across the country and working with members to prepare for the possibility of such an outbreak.

AIRA—REBECCA COYLE, M.S.ED.

In August, AIRA held its sixth national meeting in Salt Lake City, where much discussion centered on sustainability of systems as new vaccines come out and efforts to ensure that the uptake and coverage gets measured. In addition to the growing interest domestically, there appears to be a growing global interest in IIS or registries. A number of sessions at the national meeting focused on global perspectives of IIS.

Through its measurement and improvement initiative, AIRA is measuring exactly what IIS do in response to test messages. AIRA has been working on this project for a couple of years and has completed its first round of validation reports that focus on interoperability. A meeting in June focused on the next step, which will be looking at the clinical decision support pieces.

APHA—JEAN-VENABLE "KELLY" GOODE, PHARM.D., BCPS, FAPHA, FCCP

APhA continues to be involved in training, education, information, resources, and recognition. It holds webinars following each ACIP meeting to inform members about relevant discussions. APhA has information on herpes zoster and meningitis B that is available to support pharmacists in delivering vaccines for those diseases. In July, it published the results of a survey on pharmacy-based immunization delivery in the United States. The APhA is calling for nominations for its Immunization Champions award. Earlier in September, at an international meeting of pharmacists in Glasgow, Scotland, APhA delivered its immunization training program to representatives of more than 20 countries and held a panel discussion on international policy and advocacy. At that meeting, the APhA Foundation received an award for its Project ImPACT immunization effort.

ADVISORY COMMISSION ON CHILDHOOD VACCINES ACCV—CODY MEISSNER, M.D., FAAP

At the 107th quarterly ACCV virtual meeting on September 6, 2018, the Commission heard updates from its Process Work Group, the DICP, and the Department of Justice. As part of its mandate, the Commission reviewed revisions to the CDC vaccine information statements for meningococcal (MenACWY) and diphtheria, tetanus, and pertussis (DTaP) vaccines and provided comments to the CDC staff. Finally, the Commission heard program updates from the

CDC's Immunization Safety Office, the NIH's National Institute of Allergy and Infectious Diseases (NIAID), FDA's Center for Biologics Evaluation and Research, and NVPO.

Ex Officio Member Updates

BARDA—LINDA LAMBERT, PH.D.

BARDA's new division, DRIVe, has put out a solicitation, called an EZ BAA (broad agency announcement), which seeks very short proposals and offers a rapid review (applicants will get feedback within 30 days). Also, DRIVe has put out a request for information for a new concept around innovative space, in which a partner would provide resources such as laboratory space or network capability. BARDA is supporting the ASPR in a formal listening session on medical countermeasures, including vaccines. BARDA Industry Day takes place at the end of October; those interested can register on the BARDA website.

CDC—AMANDA COHN, M.D.

Dr. Cohn said Nancy Messonnier, M.D., could not attend this meeting because she and several hundred others representing CDC partners are participating in the CDC pandemic influenza functional exercise. In partnership with the Association of Public Health Laboratories and the WHO, CDC is hosting the Southern Hemisphere 2019 Vaccine Strain Selection Meeting on September 24–26 in Atlanta. The resulting announcements are scheduled for September 27, 2018.

CDC is responding to hepatitis A outbreaks among adults in nine states. As of August 22, there have been more than 4,000 cases, more than 2,500 hospitalizations, and 42 deaths. At the outset, there had been some vaccine supply constraints due to high demand, but CDC has been able to work with the manufacturers, who have made a lot of progress in getting vaccines to the states that had early outbreaks.

Regarding the supply of the new vaccine for shingles, Shingrix, CDC is developing some guidance for physicians, primarily focused on reminder-recall notices when the vaccine is available for providers as well as reminding people that they can get their second dose even if it has been more than six months since the first dose. Dr. Cohn hoped the guidance would be available in the next week or two.

At its upcoming October 24–25, Dr. Cohn anticipates the ACIP will vote on the childhood immunization schedule for 2019, the adult schedule for 2019, and adding homelessness as a potential risk factor that merits hepatitis A vaccination. CDC is modifying the ACIP schedules to make them easier to read, with particular focus on the footnotes.

DOD—LT COL CHRIS ELLISON

LT COL Ellison said that although there are forthcoming organizational changes within the military health system in accordance with the National Defense Authorization Act, there are no significant changes related to immunization procurement and delivery. Work continues towards bidirectional flow of immunization health records between the readiness systems and the electronic medical records (EMRs). The Immunization Health Branch's educational outreach to beneficiaries continues via its public-facing web page at health.mil/vaccines, a recently updated toolkit booklet, on-site assessments of practices at immunization sites, and online and on-site educational courses hosted by the Immunization Health Branch.

The vaccine redistribution program continues to be widely successful. Individual DoD immunization sites can communicate expiring vaccine surplus or vaccine deficit through their Immunization Health Branch personnel within the Defense Health Agency. The Immunization

Health Branch then reaches out to other immunization sites and redistributes vaccines as needed. In fiscal year 2018, $567,000 worth of vaccines was successfully redistributed.

HRSA-BPHC—JUDITH STEINBERG, M.D., M.P.H.

HRSA's Community Health Center (CHC) program aims to provide accessible, affordable quality health care, especially for underserved and vulnerable populations. As of 2017, HRSA is funding nearly 1,400 CHCs, operating at more than 11,000 sites in every U.S. state and territory. These sites serve more than 27 million people, including one in three people living in poverty and one in nine children in the country. The CHCs provide comprehensive primary care that includes preventive services and chronic disease management.

CHCs provide data annually through HRSA's Uniform Data System, which includes clinical quality measures. From 2013 through 2015, the system measured completion of the entire series of vaccines recommended by age 36 months, and there were seven vaccines. Under that metric, 77 percent of children completed the series. In 2016, the timeframe was revised to 24 months, and the number of vaccines has since increased to 10. In 2016, 43 percent of children completed the series, and in 2017, the figure declined to 40 percent. Before the switch, the CHCs had been in line with national benchmarks. Dr. Steinberg invited others to share any national benchmarks that align with the new childhood immunization measure.

HRSA also tracks information about service provision for a host of immunizations (grouped together) and a separate assessment of influenza vaccination. In 2017, the CHCs provided selected immunizations to nearly 4 million clients in about 4.7 million visits. About 4 million clients received influenza vaccination at 4 million visits. HRSA also funds technical systems and training entities, including the Health Center Controlled Networks, which support health centers around information technology and thus facilitate capturing immunizations.

HRSA- VACCINE INJURY AND COMPENSATION PROGRAM—NARAYAN NAIR, M.D., CAPT

The VICP continues to process a large number of claims. In fiscal year (FY) 2017, 1,243 claims were filed, and $252 million was awarded to petitioners, plus $29.8 million in attorneys' fees. (Attorneys' fees apply to compensated and dismissed cases and include interim fees and costs.) So far in FY 2018, as of July 16, the program has awarded $172 million in compensation to petitioners and attorneys' fees. Information and the most recent data can be found on the program's website. HRSA is seeking public comment on a notice of proposed rulemaking that would add to the Vaccine Injury Table a category for vaccines that are recommended for routine administration to pregnant women. A public hearing will be held September 17 for public comments, and the deadline for written comments is October 1.

Dr. Pickering asked about the top three conditions for which the program is seeing claims. Dr. Nair noted that the program used to see most claims filed on behalf of children; now, claims are predominantly for alleged injuries to adults. The top three claims from adults are for shoulder injuries related to vaccine administration, Guillain-Barre syndrome, and influenza and other neurologic conditions related to Guillain-Barre syndrome that are not Guillain-Barre syndrome. Dr. Thompson encouraged NVAC members to comment on the proposed rule regarding maternal immunizations, as NVAC supported that addition to the Vaccine Injury Table.

FDA—VALERIE MARSHALL, M.P.H.

FDA has approved a supplement for the biologics license application for seasonal influenza vaccines to include the 2018–2019 U.S. formulation and associated labeling revision. On October 3, 2018, the Vaccines and Related Biological Products Advisory Committee will meet in an open

session to discuss and make recommendations on the selection of strains to be included in an influenza virus vaccine for the 2019 Southern Hemisphere influenza season.

NIH—BARBARA MULACH, PH.D.

In February 2018, NIAID published a strategic plan for developing a universal influenza vaccine in the *Journal of Infectious Diseases*. NIAID has several funding opportunity announcements related directly to that strategic plan. It also has a contract solicitation for the Collaborative Influenza Vaccine Innovation Centers. These Centers will support improvements in immunizations and in the durability of seasonal influenza vaccines but will also look at innovative influenza vaccine approaches and a more iterative vaccine design approach. NIAID recently renewed program announcements for research to advance vaccine safety in collaboration with the CDC.

NIAID is talking with the community about ways to improve its infectious disease clinical research networks. It hosted a webinar in May and has posted questions and answers on its website. NIAID is considering a new structure for the Vaccine and Treatment Evaluation Units and the related clinical network. Later this fall, NIAID will post a solicitation for the new iteration. The NIAID Council meets Monday, September 17, and open sessions will be webcast, including an open session with NIAID Director Anthony Fauci, M.D.

Dr. Jackson asked for comment on a recent publication that described a surprising loss of immunity to influenza vaccine of 16 percent per every 28 days after vaccine. Dr. Cohn said she was not familiar with the article, but the ACIP influenza work group discusses timing of vaccination almost every year. That work group recognizes the challenges of implementation and the importance of maximizing the immune response when it is not known when the influenza season will start. The data are constantly being reevaluated. Dr. Meissner said the latest CDC publication on the upcoming influenza season addressed the issue and explained the complexities of its recommendations for seasonal influenza vaccine.

USDA—DONNA MALLOY, D.V.M., M.P.H.

In August, USDA's Animal and Plant Health Inspection Service (APHIS) began its 2018 field evaluation of oral rabies vaccine for raccoons, skunks, and other wildlife in five states. This year's evaluation is part of a multiyear study addressing operational questions related to bait density and effectiveness. The National Rabies Management Program, which works to prevent the spread of rabies in wildlife, currently uses a different vaccine to control the disease in raccoons, coyotes, and foxes, but this evaluation is testing a vaccine to see whether it more effectively controls the disease in skunks and raccoons.

The oral rabies vaccine bait is a blister pack filled with vaccine and coated with a sweet attractant. The animal bites it, and the bait releases the vaccine in an adequate dose to confer immunity to rabies. In August, APHIS will distribute more than 2.8 million oral rabies vaccination baits in parts of Vermont, New Hampshire, New York, Ohio, and West Virginia to test the targeted wildlife. APHIS personnel will sample raccoons and skunks prior to and following bait distribution to determine effectiveness. This effort is a cooperation among APHIS, CDC, the vaccine manufacturer, and state departments of agriculture, health, and natural resources. Oral rabies vaccine has been used in the United States since 1990. Currently, 16 states distribute oral vaccines for raccoons; Texas also distributes them for gray foxes and coyotes.

OTHER ENTITIES

Written reports were submitted by the Association of State and Territorial Health Officials and the Public Health Agency of Canada.

Public Comment

Dennis Friedman began his comment by stressing that he is not anti-vaccine and believes that millions of lives have been saved because of vaccines. He said his daughter received the HPV vaccination, then four days later she passed out. Two weeks later, she was unable walk down the street or go upstairs, and she has developed severe digestive problems. She has been diagnosed with dysautonomia and noted that many dysautonomia specialists feel that vaccination is a cause. He is very concerned about the methodology used to identify safety signals, and he gets the impression that public health authorities are relying simply on the Vaccine Adverse Events Reporting System (VAERS). Many, many more people out there have symptoms of dysautonomia, said Mr. Friedman, and doctors do not know how to diagnose or appreciate these symptoms, frequently believing that these are psychologically caused. Mr. Friedman said he did not know whether a solution exists, but he asked for comments or any help available to deal with this difficult situation that has devastated the lives of his daughter and family. He added that he is a recently retired physician, so he can take care of his daughter, but he hoped that somebody has a conscious and a heart out there who can help.

Theresa Wrangham of the National Vaccine Information Center (NVIC) clarified comments she made at the June 25 NVAC meeting that cervical cancer is highly treatable. Her statement is based in fact and comes from the CDC's and Johns Hopkins University's websites. However, she said, NVIC does not want to minimize the lives of those impacted and those who were lost to cervical cancer. The statement was made to request balance in policy decisions and messaging about HPV vaccines and the public's right to access accurate information when making vaccine decisions. In that same context, NVIC offers comments on vaccine innovation, economic modeling, and ROI.

Earlier in the meeting, a member asked how the vaccine enterprise can compete with the images of children in wheelchairs. Regarding NVAC's role, the law states, "The Secretary shall establish in the Department of Health and Human Services a national vaccine program to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines." Therefore, NVIC believes that rather than competing with the injured, efforts should be made to show the public the science and give a choice. There should be transparency in the public messaging on vaccines, and the messaging must include that vaccination is not without risk, as demonstrated by science and the law. Vaccines, like many pharmaceutical products, carry the risk for injury and death—some known and some unknown.

Findings by the Institute of Medicine in more than 25 years of reports demonstrate significant gaps and misunderstandings, resulting in over 90 percent of claims for the VICP being litigated. It is also widely acknowledged by research that vaccine-related adverse events are underreported, and federally commissioned reports on the VICP indicate that few are aware of this program's existence.

Ms. Wrangham asked where the messaging and transparency for the public is and what is being done to assure that existing vaccines are providing optimal prevention of vaccine injury and death given the acknowledged research on underreporting and vaccine risk and lack of awareness of the VICP that result in lack of compensation to those who are injured and have faithfully vaccinated.

Absent from the conversation on vaccine innovation is discussion on the human right to exercise informed consent. People do not want to be treated like numbers and are not owned by the government. Utilitarianism should not be the foundation for public health law and policy, and policy cannot be made based solely on economic models that treat the vaccinated as acceptable collateral damage for the greater good. The right and responsibility for making medical risk-taking decisions such as vaccination rightly falls to the person taking the risk, not public health officials.

Finally, NVIC has long supported access to vaccines as well as the critical need for an independent federal agency to monitor vaccine safety and oversee vaccination safety research. Ms. Wrangham asked how the inherent conflicts of interest created by PPPs to promote vaccine innovation would be addressed given the lack of such an agency.

Wrap Up and Adjournment—Kimberly M. Thompson, Sc.D., NVAC Chair

The meeting concluded for the day at 4:22 p.m.

Day Two—September 13, 2018

Welcome from the Incoming Chair—Robert H. Hopkins Jr., M.D., MACP, FAAP

Dr. Hopkins thanked Ms. Aikin and the NVPO staff for their support of NVAC, ADM Giroir for his leadership, and Dr. Thompson for her mentorship. Following the first day of the meeting, one take-home message is that communicating the value of vaccines is not a one-size-fits-all proposition; different messages are needed for different audiences, Dr. Hopkins observed. Tackling AMR may require a different value assessment. Polio eradication efforts have been successful but are not yet complete. NVAC should discuss how to make the value case for individual vaccines and for specific populations.

Regarding PPPs, Dr. Hopkins said NVAC has a role in defining and communicating the full value of vaccines and devising an innovating communication strategy. There is a call to prioritize needs and goals and to champion infrastructure development and vaccine use. A transparent view of the market is needed not just for pharmaceutical companies but for public health broadly. The presentation on social media demonstrated the importance of understanding the gist as well as the facts and the need to communicate positive messages on social media. Dr. Hopkins outlined the agenda and introduced the speakers for the day.

Exploring the Pipeline: CMV Vaccines

Burden of CMV Infection and Disease in the United States—Tatiana M. Lanzieri, M.D., M.P.H., CDC

Dr. Lanzieri described the prevalence of CMV infection at infancy, pointing out that Black and multiracial infants have higher rates of infection than White, non-Hispanic White, and Asian infants. From 12,000 to 20,000 infants are born infected with CMV each year. Of those, 10 percent, or 1,200–2,000, have symptoms at birth ranging from mild or transient signs that would not be diagnosed without screening to severe, life-threatening disease. Antiviral therapy is available to treat moderate to severe disease. The mortality rate for neonates with CMV is 5 percent, translating to 60–100 neonatal deaths per year.

Of the 10 percent who are symptomatic at birth, 50–70 percent will have neurologic impairment, such as cerebral palsy, intellectual disability, vision loss, or deafness, although these sequelae may be underreported as a result of incomplete evaluation or insufficient follow-up. Of the 90

percent who are asymptomatic at birth, 10–15 percent will have isolated hearing loss, and about half of them will have congenital hearing loss that should have been detected with newborn screening tests. Among the 10–15 percent with hearing loss, 500–900 will have severe hearing loss within 1 year, and 200–360 will have profound loss by age 4 and need cochlear implants. Dr. Lanzieri pointed out that hearing is important for the development of speech and language. The remaining 75 percent of asymptomatic, infected neonates will have no long-term health or related intellectual or developmental problems.

Dr. Lanzieri presented estimates of the high costs of caring for children with symptomatic congenital CMV or related hearing loss. A clinically sensitive test would identify infants with symptoms or sequelae of congenital CMV, while an analytically sensitive test would identify all infected infants. A project comparing the clinical sensitivity of dried blood spots (DBS) versus saliva for screening newborns for CMV aims to test 30,000 newborns. So far, 8,000 newborns have been screened, and both methods have fairly high analytic sensitivity. Newborn screening for CMV remains a public health challenge because there is no standard, high-throughput test for public health laboratories. Screening could identify more infants who would benefit from early intervention, even without tests with analytic sensitivity.

Q&A with Dr. Lanzieri

Dr. Pickering asked whether the risk of CMV is higher among infants born to women who have previously had an infant with CMV. Dr. Lanzieri did not know but said young children without congenital CMV can acquire it early because it is so easily shed by those infected. The risk of infection increases when women spend time around toddlers.

Dr. Meissner asked whether valacyclovir was used to treat infants with CMV. Dr. Lanzieri said valacyclovir is only used for those with severe disease. Other interventions target hearing loss and educational development. Dr. Meissner asked why some infants suffer from severe disease. Dr. Lanzieri said some studies show the severity of disease is linked to viral load; DBS screening determines the viral load in blood, which may identify those at higher risk for sequelae. It is not clear why some infants are asymptomatic, but that may be related to the timing of maternal infection during pregnancy or preconceptional maternal immunity.

Dr. Jackson said salivary polymerase chain reaction (PCR) testing has a high false-positive rate, especially when the mother is breastfeeding and whether the study described is looking at that relationship. Dr. Lanzieri said that most of the false-positive results from salivary PCR in the study so far appear to be the result of contamination with breastfeeding.

Gaps and Challenges in CMV Vaccine Development—Cristina Cassetti, NIAID, NIH

Dr. Cassetti said that, at a recent NIH workshop focused on CMV, participants agreed on the need for a CMV vaccine that is safe, durable, and offers broad protection, and they expressed optimism about the feasibility of vaccine development. Dr. Cassetti briefly outlined work underway by several companies to develop vaccines for organ transplant or congenital CMV. She noted that all of the major pharmaceutical companies are actively pursuing CMV vaccine.

Despite all the ongoing research, several challenges remain. There are limited animal models, and few primate colonies are CMV-negative, which makes it difficult to assess vertical transmission in primate models. The correlates of protection against CMV are not known, and the relative role of antibodies versus T-cells is not well understood. In pregnant women, it is difficult to distinguish primary infection from reinfection and reactivation, so it is not clear what a vaccine should target or the correlates of protection. The role of anti-gB antibodies in controlling infection is unclear. Because CMV is mostly cell-associated, rather than the classic viremia, so it

takes longer to see the impact of vaccine candidates in testing. As with other fields, there are no standardized immunological assays or diagnostics, so all the makers are using different approaches.

The epidemiology of CMV infection is not well understood, Dr. Cassetti continued, making it difficult to design trials, and the seroprevalence varies by geographic region. The sample size for clinical trials must be very large. The path to licensure is complicated, because manufacturers will have to demonstrate the benefits of the vaccine in seropositive women, for whom the correlates of protection are not known. If the vaccine targets toddlers, the longevity of the vaccine will have to be demonstrated.

Dr. Cassetti said NIH has a robust program around CMV research across several institutes. NIH is assisting vaccine developers with epidemiologic data and studies of the natural history of hearing loss in children infected with CMV. A study in Latin America is monitoring pregnant women who may have been exposed to Zika virus and their infants. It will provide thousands of neonatal samples that can be used to better understand CMV infection. In addition, to aid companies in phase III clinical trials of CMV vaccines, NIH awarded contracts to five companies to develop diagnostics to identify seronegative women, and four have succeeded in creating viable candidates for further funding toward the goal of commercialization.

Q&A with Dr. Cassetti

Dr. Meissner clarified that most infants with CMV are born to women who were seropositive before conception. Therefore, an effective vaccine would have to work in seropositive women. Dr. Cassetti agreed, noting that many more women are seropositive than seronegative. However, it may be difficult for vaccine developers to demonstrate the benefits of vaccine in seropositive women who already have high blood titers. NIH's Zika in Pregnancy trial is one effort to identify useful markers. Some companies are targeting seronegative women, but the product may not be very attractive if it only benefits the seronegative population.

Ms. Butler asked whether the target is only found in human hosts and thus may be a candidate for eradication. Dr. Cassetti said it is limited to humans but an effective vaccine is so far away that it is too soon to consider eradication. Philip Krause, M.D., noted that CMV is a herpes virus that resides in the body for life and can be shed at any time, so eradication would take many, many years.

Dr. Jackson asked whether the vaccine makers are assessing the potential effects on infants in terms of sequelae. Dr. Cassetti said makers will have to design phase III trials that can assess neonatal outcomes, and she was not sure that any are designing trials of sufficient power to measure the protection against sequelae. Dr. Jackson asked whether there is consideration of epigenetics, specifically genetic predisposition. Dr. Cassetti responded that there has been discussion of incorporating maternal inmmunogenetics into the studies; however, even the Zika in Pregnancy study may not be large enough to assess the issue.

Dr. Pickering asked whether there has been consideration of vaccinating pregnant women. Dr. Cassetti said there has been some discussion, but pregnant women may not be the main target. Dr. Krause said congenital disease is most likely caused by infection very early in pregnancy; it may not be possible to vaccinate pregnant women early enough to have an effect.

Regulatory Considerations for CMV Vaccines—Philip Krause, M.D., FDA

Because demonstrating efficacy with traditional approaches may not be feasible in all settings, regulators have established alternative pathways to product approval, such as the accelerated

approval processes, to evaluate surrogate endpoints that appear reasonably likely to predict clinical benefit, Dr. Krause explained. In 2012, several federal agencies met and talked about appropriate surrogate endpoints for CMV vaccine trials, with much discussion of whether to target toddlers (i.e., children under 2 years old). Immunizing toddlers would more rapidly impact CMV than targeting adolescent girls or women who intend to become pregnant. Typically, mothers are infected with CMV through virus that rapidly spreads in child care settings. Notably, immunizing toddlers means the duration of effect of the vaccine does not need to be very long—just past the time of diaper changes and other exposures likely to infect the mother. Most toddlers are seronegative, making it easier to determine if the vaccine is effective.

Many companies are considering targeting vaccines toward adolescent girls to prevent infection among those who go on to become pregnant. In this population, duration of efficacy is a bigger issue. To demonstrate a clear impact on congenital CMV, trials would have to target women of childbearing age. Determining the effect of vaccine on congenital CMV could involve looking at the rates of neonatal infection, which may be missed or difficult to detect. Studies seeking to reveal correlates of protection for congenital CMV could identify surrogate endpoints. Some researchers could choose to evaluate elective or spontaneous terminations of pregnancy to assess findings that suggest CMV infection, but the approach is complicated and could be easily confounded.

Several stakeholders have proposed that preventing maternal infection should be a good enough marker for demonstrating that a vaccine can prevent congenital infection. However, it may be much easier to prevent congenital infection than maternal primary infection, and not every maternal infection will result in congenital infection. Reducing the impact of infection on the pregnant woman might have a major impact on congenital infection, but that would not be identified if the only endpoint were preventing maternal infection. As mentioned earlier, in seropositive women, it is difficult to distinguish primary infection from reinfection or reactivation, so maternal infection rates would not be an applicable endpoint for them. Dr. Krause noted that even if a vaccine only reduced maternal infection rates and did not affect congenital infection, it would decrease the number of elective terminations, which could be seen as a public health benefit.

Dr. Krause said that CMV disease is more severe in the infants of seronegative women, and in this country, seropositive women do not outnumber seronegative women by very much. Targeting only seronegative women would be reasonable and could have a significant public health benefit.

The opportunities are increasing to gather real-world, observational data in selective circumstances with mechanisms to minimize or at least understand bias, Dr. Krause said. He concluded that FDA is committed to working with product sponsors to identify the right endpoints to determine the efficacy of a CMV vaccine. He reiterated that immunizing toddlers would be the most effective way to stem disease, but the approach raises questions about who benefits from the vaccine.

Q&A with Dr. Krause

Dr. Meissner pointed out that, in general, vaccinations are not given to people who do not benefit directly from the vaccine. Dr. Krause countered that rubella vaccine was initially targeted toward adolescent girls but was not successful; when it was given to toddlers, public health authorities were able to get control of the disease. CMV is difficult to diagnose except in severe cases, he added, and symptoms sometimes take a long time to manifest. Dr. Krause estimated that CMV costs at least $1 billion per year and so represents a huge public health concern. He also pointed

to transmission-blocking malaria vaccines, which could be used to prevent transmission while not benefitting the individual who receives the vaccine.

Dr. Meissner said that giving toddlers a live, attenuated vaccine could cause latent infection, which could be a problem if the child eventually becomes immunocompromised. Dr. Krause said FDA and others would have to have great confidence in the safety of any vaccine before it is recommended for toddlers. Most of the candidates in development are not live, attenuated vaccines, he added.

Dr. Dunn said that in addition to uncertainty about the ACIP's willingness to recommend a CMV vaccine for toddlers, there is also concern about public acceptance in general. Providers already have a difficult time getting the public to accept the number of vaccines recommended for young children. Every additional vaccine is going to meet with resistance, he predicted especially those targeting infections that are not perceived as a widespread problem. Therefore, Dr. Dunn suggested raising awareness, especially among parents, about CMV and its potential effects before rolling out a vaccine. Dr. Krause said that manufacturers typically start advertising when they are close to achieving licensure.

Dr. Pickering asked whether recommendations from the 2012 meeting had been achieved. Dr. Krause said he considered the 2012 meeting a success because of the number of manufacturers pursuing CMV vaccine, which he believes came about because the meeting clarified the landscape around CMV. A great deal of recommended research was funded following the meeting, but it takes time to analyze and understand the results.

Discussion

Dr. Cooke said the presentations demonstrated how federal agencies work together with industry to address tough problems. Federal efforts to address predictable paths forward and potential targets are an example of how the government can lower the risk that companies take on when they invest in vaccine development.

Dr. Friedland stressed the importance of ensuring that clinical trials have adequate samples to assess the effect of the vaccine on those disproportionately affected by it (i.e., Black and multiracial infants), as described by Dr. Lanzieri.

Dr. Hopkins said more discussion is needed about the challenge of acute CMV in immunosuppressed people receiving transplants. He also hoped for consideration of the CMV vaccine in relation to the aging immune system and to inflammation associated with chronic infection.

Dr. Meissner expressed concern about alternative paths to licensing vaccines that rely on correlates of protection rather than demonstrating effectiveness directly. Dr. Krause said such paths are limited to very specific circumstances in which the disease is serious and the candidate product shows a clear advantage over existing therapies. Some new influenza vaccines have been approved on the basis of serologic endpoints, and the effectiveness of those products was later confirmed with clinical endpoints. No vaccines have been approved under an accelerated process that have failed confirmatory studies, which usually occur at the time of licensure. The accelerated process requires confirmatory studies, and licensure can be revoked if the studies do not confirm benefit.

The accelerated process may sound vague, Dr. Krause continued, but it involves insights from experts in the field and requires a lot of supporting data. The products are also reviewed by

advisory committees and others to confirm that there is general agreement among experts about the reasonable likelihood of benefit. It is increasingly clear that for some diseases, investigators will never be able to conduct traditional studies, so alternative approaches are needed.

Dr. Pickering noted that DBS samples are collected from every newborn in this country; he asked Dr. Lanzieri how she and her colleagues would use the information if CMV were added to standard newborn screening panels. Dr. Lanzieri responded using DBS to assess CMV would be ideal, because there is already a public health platform in place to support it. However, more work is needed to standardize definitions of symptomatic CMV infection and understand the prognostic markers of sequelae, including hearing loss.

Newborn screening can be extremely beneficial for identifying conditions early, Dr. Lanzieri continued. Identifying hearing loss early, for example, allows for interventions that can mitigate the impact. However, there is still a long way to go to ensure that affected children get sufficient follow-up and intervention after diagnosis, said Dr. Lanzieri.

Advances in Vaccination Technologies

Update on Two-Dimensional (2D) Vaccine Barcode Scanning—Kenneth Gerlach, M.P.H., CDC

Mr. Gerlach explained that 2D barcodes capture a product's lot number, expiration date, and National Drug Code (NDC) number. CDC first piloted the 2D barcodes in 2011, but several years passed before they became widely used. Currently, 98 percent of vaccines used in public health clinics have a 2D barcode. Early pilot programs sought to assess implementation of 2D barcode scanning in multiple sites with numerous practice settings that had no common EMR or administrative links. A more recent pilot took place in a single health system and focused on compliance with scanning to assess barriers to scaling up the use of the barcode systems.

Analysis found that using the scanners to read the 2D barcodes increased the accuracy of the data entered and saved time (21 seconds per vaccine). The highest rates of scanning occurred among those staff who not only received training but also took part in multiple other adherence strategies, such as commitment cards, posted reports of individual compliance, and visits from the study designers. Staff experienced less eye strain and had fewer hand- or joint-related problems when they used the scanners (compared with manual entry). Once a vaccine was scanned, staff could dispose of the bottle and syringe immediately (rather than hold on to them for later entry), which improved safety. Some roadblocks to scanning persisted: scanning difficulties, scanner location, limited buy-in, and unclear expectations or protocols.

Scanning improved the accuracy of data in all settings, but compliance was highest among pediatric practices and vaccination clinics (where vaccination volume is high) and lowest among family and internal medicine practices. At the high-volume sites, each of the adherence strategies had a similar effect; at the low-volume sites, each intervention improved scanning rates significantly, with stepwise improvement from training only through the combination of interventions.

Mr. Gerlach said the next steps are to share the study results and refine an implementation guide for those considering adopting scanners. Maintaining the NDC crosswalk table is an important step, because in some cases, the unit of purchase differs from the unit of use. CDC will also maintain its Functional Capabilities Report, which is used by software developers. Mr. Gerlach noted that EMR vendors probably will not include scanning capacity in their systems until

providers request or demand it. The Drug Supply Chain Security Act passed in 2013 may also impact the use of barcodes and scanners.

Advances in Cold Chain Handling: Global Temperature Control—Geoffrey Glauser, Geoffrey Glauser LLC

Mr. Glauser described some current technology used to monitor temperatures of sensitive products, some of which are relatively expensive and have limited capacity to provide information. Miniaturization in electronics is spurring development of new, smaller products with more capacity. For example, some new products are programmable, have a long battery life, can record during long periods of storage, and can transfer data wirelessly to other technology. Some have built-in USB capacity. Some are calibrated to federal measurement standards, but even those that are not are more accurate than the chemical-based indicators, which cannot be validated at the level that pharmaceutical makers want.

Mr. Glauser presented a breakthrough tiny new device, just coming on to the market (in late September), that can transmit information wirelessly and has a 4-year battery life. It can be affixed to a package so that the product can be monitored through its expiration date. The data collected can be transferred to a cell phone. The monitor costs less than $6. Manufacturers and others have long sought a device that can gather data continuously for the life of a product. This monitor can be programmed by the manufacturer with the parameters for stability; Mr. Glauser said that feature is important, because manufacturers have been reluctant to share all of their stability data.

Other new products designed specifically to protect vaccines are emerging:

- A container with reusable interior panels that can be reconfigured quickly to prevent a product from freezing or overheating (Mr. Glauser noted that in the United States, vaccines are more likely to be exposed to extreme cold during shipping than extreme heat.)
- Vacuum-insulated panels for shipping that are thinner than current container construction and are reusable, recyclable, and competitively priced.
- For large shipments of pallets, battery-powered containers that maintain temperatures (When shipped by air, to comply with federal requirements, the power shuts down, and the container uses panels sensitive to temperature changes to ensure adequate temperature control.)
- Containers that can maintain desired temperatures even when transporting vaccines in sub-Saharan environments.

Q&A with Mr. Glauser

Dr. Pickering said a common problem is that devices may warn about temperature deviations (e.g., the power goes out in an office storage refrigerator) on a weekend, and no one knows about it. Mr. Glauser said new devices would provide a visual indication that a product temperature has deviated from the safe zones. With miniaturization, he noted, sensors could be applied to individual products. Mr. Glauser said he would like to see microchips embedded into product labels that could be scanned to provide information.

Advances in Vaccination Technologies: The Microneedle Patch—Šeila Selimović, Ph.D., National Institute of Biomedical Imaging and Bioengineering (NIBIB), NIH

Dr. Selimović said NIBIB has supported the development of microneedle patches, about the size of a quarter, that use miniature needles to puncture the skin and deliver a drug. Some have solid

needles coated with drug, while others use hollow needles that contain the drug. Both products, once removed, must be treated as sharps and carry drug residue. Recently, investigators have created microneedles that dissolve on application, so there are no sharps to deal with once the patch is removed from the skin. Several vaccine developers have expressed interest in the technology.

The patches look similar to adhesive bandages and could be self-applied. The microneedles are designed to reach the dermis, but the dimensions (e.g., the depth of penetration) could change on the basis of the vaccine being delivered. Because of skin's high immunogenicity, patches are effective for delivering drugs and may require lower doses than intramuscular injection. In contrast with hypodermic needles for vaccination, microneedle skin patches are easily self-applied (requiring no medical personnel), minimally invasive, induce a stronger immune reaction, and cause no pain. The patch keeps the vaccine thermostable (and there is no need to reconstitute vaccine). The patch is versatile and could support different types of vaccines. It could be mass-produced at low cost and with no cold-chain requirements.

A phase I trial found the microneedle patch safe and effective for influenza vaccine administration. The product is being commercialized by Micron Biomedical. CDC and Micron are also working on a patch that would co-administer rotavirus and polio vaccine and one for rubella vaccine.

Some technical considerations to address include the possible need for new vaccine formulations compatible with the patch; the potential for slow-release materials rather than multidose vaccines; and the need for quick-dissolving (i.e., less than 1 minute) materials. More research is needed around packaging, storage, and durability of the product in various conditions. Self-administration eliminates the need for highly trained medical personnel but raises questions about potential misuse, so related policies and regulations must be considered. Dr. Selimović said the microneedle patch could be used for other applications, and some are testing it for contraception.

Discussion

Dr. Butler asked how 2D barcodes are being used to track vaccine safety, effectiveness, distribution, and uptake. Mr. Gerlach said those areas pose big challenges. When the barcodes were introduced, he and others did not anticipate that providers' EMR systems would play such a critical role. Dr. Dunn said 2D barcodes could address the challenges, but many providers are waiting for a standard to emerge before they adopt the technology. He asked for any cost-savings data that would help make the case for the barcodes, but Mr. Gerlach said CDC has not looked at costs. Mr. Glauser said the Drug Supply Chain Security Act mandated that all vaccines eventually must have a 2D barcode with the lot number, expiration date, NDC, and 20-digit serialization code for tracking products, and ultimately those data will be included in patients' EMR.

Ms. Coyle asked that manufacturers pay close attention to the problems that can arise when the lot numbers vary between a unit of sale and a unit of use. The NDC and lot number should match the unit of use consistently. Mr. Glauser said the challenge is to compress all of the needed information into a small space that fits on a label and can be scanned using a cell phone. Dr. Jackson noted that some vaccines include two components that must be combined to constitute the vaccine; Mr. Gerlach said the situation poses a challenge, but the manufacturer should be able to identify both products with the 2D barcode in case of a recall.

In response to Dr. Pickering, Dr. Selimović said microneedle patches have not yet been tested in children or infants, but there is motivation to develop the technology for those populations, because it is less painful than vaccinating with traditional needles. In response to Dr. Jackson, Dr.

Selimović said there has not yet been assessment of possible skin reactions or the feasibility of using microneedle patches in people with underlying skin diseases, but she agreed that such research is very important. Dr. Pickering suggested NVAC analyze lessons learned from the rollout of other novel technology and determine what might be relevant to patches.

Dr. Meissner noted that aluminum salts are added to some vaccines to prevent reactions if intramuscular administration does not go deeply enough into the muscle. Dr. Selimović said the role of aluminum salt in microneedle patches has not yet been studied; however, she said, because the patch may require a lower dose of vaccine, it may also require a lower concentration of salt. The fabrication process offers a lot of room to include adjuvants and stabilizers with the vaccine, so nothing precludes adding salts if needed.

Dr. Ginsberg pointed out that vaccines like Shingrix are given intramuscularly with a reactogenic adjuvant; she asked how intradermal application might affect the immune response and thus efficacy of a vaccine. Dr. Selimović said the microneedle patch has only been tested with influenza vaccine so far. It is possible that is not ideal for all vaccines, but in principle, there is no reason why it would not be compatible with a given drug or vaccine, she concluded.

From Innovation to Implementation: The Journey of a New Shingles Vaccine—Leonard Friedland, M.D., GSK

Dr. Friedland described shingles, the makeup of the new Shingrix vaccine, and lessons learned related to the licensure and marketing of the vaccine. Shingrix was licensed by the FDA in October 2017 and almost immediately recommended by the ACIP for prevention of shingles in adults 50 years and older. It was also recommended for those who had already received zoster vaccine live (Zostavax) and determined to be preferable to Zostavax. So, within days of approval, more than 115 million U.S. adults became eligible to receive Shingrix. Within 4 months of FDA approval, Shingrix was covered by most Medicare pharmacy and commercial insurance plans and stocked by most retail pharmacy chains. The pace of uptake and the demand were unprecedented, said Dr. Friedland. Early demand was driven predominantly by pharmacies, where most people over 65 have received the vaccine. Most of those under 65 have received it through their health care providers.

Within weeks of Shingrix becoming available, GSK began hearing about errors in storage, administration, and reconstitution of the vaccine because providers were treating it the product the same as Zostavax. GSK took a comprehensive approach to educating providers about the unique storage requirements, reconstitution process, and administration of Shingrix. It disseminated information and provided training directly to providers and retailers and also collaborated with professional organizations like APhA to ensure that information got out. In addition to messaging through all types of media and providing education in person and on demand, GSK created an elasticized tag to keep vials together so that reconstitution would be easier. It simplified package labeling to highlight storage requirements and created materials for providers and patients about dosage, administration, and other topics of interest.

The rapid and unprecedented demand has posed challenges for the manufacturer, but GSK is ramping up production. It has adopted guiding principles for fair and equitable distribution. For example, it is supporting providers who ordered the product early and have patients who have already received their first dose by ensuring that they get the second dose of vaccine as soon as possible. It is working with wholesalers and distributors to ensure customers get the vaccine through their preferred channels. GSK has mechanisms to remind providers and patients when the second dose is due. Notably, the FDA has agreed that GSK can work through CDC to deliver the

message that people can get their second dose even if it has been more than 6 months since the first dose.

Dr. Friedland said the Shingrix vaccine exemplifies the goals of the vaccine enterprise, as outlined in the National Vaccine Plan. NVAC should take note of the following:

- Innovative vaccines can result in immediate and strong consumer demand.
- There is an adult vaccine infrastructure in place and it can work, but challenges remain around Medicaid Part D financing and access. Retail pharmacies are important for adult vaccinations.
- Shingrix succeeded by effectively addressing problems in real-time, with transparency and through collaboration with partners and patients. Best practices should be shared to assist other innovators.
- The successful implementation of the new vaccine demonstrates that the vaccine enterprise works well.

Discussion

Dr. Dunn said that, in contrast to the proposed CMV vaccine, people were aware of shingles when Shingrix arrived on the market, which translated into immediate demand for the product. The awareness enhanced community uptake.

Dr. Jackson asked about the magnitude of errors of administration and whether GSK targeted guidance to practices where errors occurred. Dr. Friedland said the number of errors was not much different than is seen with any new vaccine, but administration errors were seen as vaccine uptake increased. GSK worked with pharmacy associations and others to educate providers about the differences between administering Shingrix and Zostavax. Dr. Friedland said that FDA typically reviews advertising materials after products are approved, so educational videos about how to reconstitute Shingrix were not immediately available to providers. When administrative errors were reported, GSK was able to give providers data about reactogenicity from its study of subcutaneously administered Shingrix.

Dr. Martinez said vaccines with adjuvants may have more side effects, but the public will likely accept the side effects if they are aware of them in advance. She suggested GSK clearly communicate the potential side effects. Dr. Friedland agreed on the importance of ensuring that people know what to expect. Doing so not only increases acceptance and allays fears but also helps to ensure people return for the needed second dose of vaccine, he said.

Dr. Steinberg asked about the extent of Medicaid coverage of Shingrix. Dr. Friedland said the rapid approval of Medicaid coverage for Shingrix demonstrated that all the stakeholders in the vaccine enterprise saw the value of the vaccine for maintaining health. He said access to the product (specifically, insurance coverage) is not the problem; rather, individuals need to check with their providers and pharmacies to confirm availability of the product. Dr. Martinez pointed out that Shingrix is not covered for all Medicare beneficiaries; it depends on the individual beneficiary's plan type. Dr. Friedland agreed that coverage under Medicare Part D is critical. Data clearly support that anything that reduces copays improves vaccine coverage rates. Dr. Nordin noted that people over 65 are getting vaccinated at pharmacies because current payment policies prevent providers from being reimbursed for vaccines administered at clinics.

New Approaches to Analyzing National Immunization Survey (NIS) Data—Jim Singleton, Ph.D., CDC

Dr. Singleton explained the rationale for switching the methodology of the NIS child component to a birth cohort analysis. The current approach samples children across a wide age range, making it difficult to interpret year-to-year changes in the results. Survey response rates are dropping, which affects the accuracy of results each year.

CDC has developed a mechanism to evaluate birth cohorts that will be implemented beginning in 2019. For 2018, it will report the cohorts it has created from previous data, which will include some overlaps. For the proposed annual estimates, CDC will assess vaccination status by key milestones to improve interpretation and make fair comparisons. Dr. Singleton gave several examples of how data would appear using the new approach.

Dr. Singleton recognized some of the limitations of the new method. For example, estimates vaccine coverage and confidence intervals may differ from previous years' data if survey weights specifically designed for birth cohort analysis were used. However, the new approach is expected to improve the value of NIS-Child data to immunization programs in this age of increasing use of IIS, relatively stable vaccine coverage rates nationally over time, decreasing survey response rates, and better understanding of the limitations of survey estimates in a given year.

Estimates by survey year can lead to false conclusions about immunization program performance. The birth cohort approach more directly assesses performance and makes it easier to identify and interpret trends. It will also provide a larger sample size and better precision. Moreover, the new approach is more consistent with widely used quality measures and can more easily be used for making comparisons with IIS data. Dr. Singleton said it will take time for CDC to communicate the change and for stakeholders to adjust to it, and there will be some overlap during the transition period. New survey weights designed for birth cohort analysis are needed, and the analytic method applied is more complex than previous analyses.

Feedback from immunization programs about the change has been mostly positive. During the implementation, CDC will publish results this year using the current format along with information about the changes to come, and it will consider how to handle the data for Healthy People 2030 and the ChildVaxView website. CDC is working closely with IIS partners and will accelerate efforts to ensure that it provides accurate, comparable estimates of vaccine coverage at all levels that can be used to monitor disparities.

Fourteen states have enrolled in a CDC program to enhance the 2019 sample, although one dropped out because of state laws prohibiting it from sharing data. CDC is rolling out new cooperative agreements and considering the need for revised agreements or legislative changes to facilitate data sharing. Dr. Singleton said CDC is grappling with the question of how to collect accurate data as fewer people respond to phone surveys. In theory, big data from EMRs and claims databases could provide insights but would require mechanisms to minimize bias and assess validity.

Discussion

Dr. Dunn said the quality and accuracy of data have improved in recent years as more states incorporate IIS data into the NIS survey. He asked how many states have IIS data that could be combined with NIS. Dr. Singleton said CDC has not yet defined what constitutes sufficient IIS data. However, he believes that about half of states have data that are close to being usable. Dr. Hopkins also supported the integration of data from IIS, EMRs, and other sources. Dr. Singleton said he hopes to create a dashboard using data from the Medicaid claims database.

Dr. Nordin appreciated the new approach, because it better assesses what really happens in primary care practice around the timing of vaccinations for toddlers. Ms. Coyle said AIRA is working with CDC to identify best practices related to integrating IIS data with other data.

Opportunities in HPV Cancer Prevention

Coordinated Efforts to Strengthen HPV Vaccination—Judy Mendel, M.P.H., NVPO

Ms. Mendel described the group formed by the OASH to increase HPV vaccine uptake, which will use the recent NVAC report on HPV vaccination as framework for its efforts. Currently, the group includes representatives from NVPO, the Office of Adolescent Health, the Office of Minority Health, the Office of Population Affairs, the Office on Women's Health (OWH), and HHS' regional offices. Ms. Mendel hoped the group would expand to include many other stakeholders and partners, including some specifically recommended by NVAC in its report.

The OASH influences stakeholders through data and information-sharing mechanisms, outreach that builds awareness around ASH priorities, and partnerships that support innovation and change. In discussions, three NVAC report recommendations have bubbled up to the top so far:

- Recommendation 1.1 suggesting the ASH encourage further development, dissemination, and implementation of evidence-based practitioner resources and support collaborative relationships
- Recommendation 4.1 suggesting the ASH request further research to better understand the needs of rural providers and to identify barriers to vaccination in rural settings
- Recommendation 4.3 suggesting the ASH support a stronger HHS-wide social media presence to improve the reach and effectiveness of communication strategies

Vaccination Coverage Among U.S. Adolescents: Results from the 2017 NIS-Teen—Jim Singleton, Ph.D., CDC

Dr. Singleton provided some NIS-Teen data on vaccines for adolescents. He outlined the purpose and methodology of the survey. From 2016 to 2017, HPV vaccination rates for those ages 13–17 years old increased about 5 percent for both the first dose and second (or final) doses. Coverage remains higher for females than males, but the year-to-year data show that vaccination rates in males are starting to catch up with those of females. Dr. Singleton noted that Tdap and meningococcal vaccine rates are plateauing among adolescents, but HPV vaccination remains lower than both.

The rates of first dose and final dose of HPV vaccination by age 13 are rising but lag significantly behind the vaccine rates for Tdap and meningococcal vaccine. Dr. Singleton noted that Tdap vaccination is required by schools. As expected for HPV vaccines, vaccination rates increase with age.

There is no difference in Tdap or meningococcal vaccine rates among adolescents by poverty status. However, teens living below the poverty level have higher rates of first and final doses of HPV vaccination. Vaccination rates for Tdap, meningococcal, and HPV vaccine are highest in urban areas and lowest in rural areas. Black adolescents are more likely than White, non-Hispanic, and Hispanic adolescents to have received the first or final dose of HPV vaccine. Teens who are covered by Medicaid are more likely than others to have received HPV vaccine.

In the survey, parents expressed slightly different reasons for refusing HPV vaccine depending on whether their child is a girl or a boy, but the most common reasons were concerns about safety and side effects and the perception that HPV vaccine is not needed nor consistently recommended. Parents of both boys and girls cited a lack of knowledge about the vaccine and the fact that they did not think their child was sexually active as reasons for refusal.

The Rationale Behind the Next President's Cancer Panel (PCP) Report—Abby Sandler, Ph.D., PCP Executive Secretary, National Cancer Institute (NCI)

Dr. Sandler summarized PCP's 2012–2013 report to the President to accelerate HPV vaccine uptake, which recommended reducing missed opportunities for vaccination, increasing acceptance, maximizing access, and promoting global uptake. The report also called for research on dosing, scheduling, and preventing HPV-related cancers. Since the report was published, support for the PCP's recommendations and for HPV vaccination in general has come from professional societies, federal entities (e.g., NCI-Designated Cancer Centers), NVAC, and others.

A few of NCI's Designated Cancer Centers received a small amount of supplemental funding to craft a joint statement on HPV vaccine, and all of the Centers meet annually to discuss ways to collaborate to improve vaccination rates. The National HPV Vaccine Roundtable formed to bring stakeholders in the fields of cancer and vaccination together to work toward increasing vaccination. The Cancer Moonshot Task Force and a White House Blue Ribbon Panel recognized HPV vaccination as an urgent public health priority. The PCP called for updated HEDIS recommendations to include boys and to require providers to report all three adolescent vaccines together.

Research funding led to the development of a new HPV vaccine that provides expanded protection and to ACIP recommendations to decrease the number of doses required. Current research is considering whether a single dose may be sufficient.

Despite progress, attainment of the Healthy People 2020 goal for HPV vaccination remains elusive. While the PCP usually changes focus every few years, it has remained engaged around HPV vaccine and will issue a follow-up report on the barriers to higher vaccine uptake. The report will be released in late October.

The Talk: HPV Awareness Campaign—Marla Dalton, National Foundation for Infectious Diseases (NFID)

Ms. Dalton described NFID's partnership with the online teen advocacy platform DoSomething.org, which has about 5 million members ranging in age from 13 to 25 years and encourages them to take nontraditional approaches to grassroots campaigns. Ms. Dalton said the goal of the joint campaign was to empower teens with information (digitally) and encourage them to initiate conversations about HPV vaccine with their parents. She described the uptake of the effort as "tremendous," saying that organizations like hers may have been underestimating the power and interest that teens have in HPV vaccination.

The first step was defining the issue in clear language, emphasizing that HPV vaccination prevents cancer. Then, information resources were developed. Greeting card templates were provided for teens to tailor and present to their parents as a way to start the discussion. Armed with resources and knowledge, teens became subject matter experts. All of the products are digital. Most teens used text messages as the medium for their invitations to their parents.

So far, the web page for the campaign has received 42 million impressions, and the campaign has gained more than 21,000 subscribers, 30 percent of which are new to DoSomething.org. Teens have shared their cards on social media broadly. To encourage participation, DoSomething.org is offering a $3,000 scholarship to the creator of the best card. Participants are demographically diverse. Ms. Dalton said she was most moved by how the campaign drove teens to action. She gave an example of a teen who said he knew nothing about the vaccine but then read the materials, presented them to his parent, and insisted on getting vaccinated. NFID is now discussing how to sustain the momentum.

HPV Vaccination Campaign Targeting Young Adults—Jill Wasserman, M.P.H., OWH, HHS

Ms. Wasserman outlined the upcoming HPV vaccine campaign, noting that the award for the project has not yet been made. Through its websites, help lines, programs, publications, and campaigns, the OWH educates and motivates women and girls to live healthier lives. HPV vaccination rates are improving but many young women still either do not get vaccinated or do not complete the series. Many initiatives focus on educating providers and parents rather than young adults. HPV vaccination rates vary across the nation, with an increased HPV-related cancer burden in women of color and also in the southern Unites States. To address the gaps in coverage, the OWH proposes to target HPV vaccine completion rates among women and men ages 18–26 years in the South, where rates of cervical cancer are high and HPV vaccine coverage low.

The campaign specifically aims to increase awareness about a) the effectiveness of the vaccine and b) HPV-associated cervical cancer. It seeks to increase the vaccine completion rate among the target audience. Ms. Wasserman anticipated that the award to conduct the program would be announced by the end of September. It will build on a literature review and the work of two expert panel meetings hosted by the OWH, which will provide research-based recommendations on the best strategies to communicate with the target population about HPV vaccine effectiveness. The campaign will use evidence-based communication strategies to address barriers to HPV vaccination and series completion; these may include digital public service announcements and social media sites.

The OWH will work with partners and potential ambassadors and conduct marketing and media outreach. The project also includes a phase-out design, a sustainability plan, and a tracking and evaluation mechanism.

National HPV Vaccination Roundtable—Noel Brewer, Ph.D.

Dr. Brewer described the structure and goals of the roundtable, which hosts annual stakeholder meetings, monthly meetings of task groups, and webinars as needed on urgent or emerging issues. In its efforts to increase information exchange, the roundtable has invested in social media platforms, where it seeks to present a single, positive voice on the benefits of HPV vaccination to counter the steady drumbeat of negative information on social media.

The roundtable catalyzes the work of its member organizations. For example, members identified the importance of first-person accounts from people affected by HPV-related cancers. So, the roundtable has put out video testimonials from cervical cancer survivors, which can be a powerful antidote to anti-vaccine conversations. It has also put out a video explaining oropharyngeal cancer. Another video—HPV Vaccine Champion Yoga—began as a joke and went viral; it demonstrates yoga poses and ties them in with an HPV vaccination message. The roundtable has facilitated more than 300 new collaborations among its members.

Among its major activities, the roundtable has created action guides and toolkits targeting different health care provider types. An ongoing campaign seeks to encourage organizations to identify and commit to specific efforts around HPV vaccination. Another, the Power to Prevent Cancer campaign, has been taking place throughout the summer, when HPV vaccine uptake peaks. It also focuses on different provider types each week and uses digital media to raise awareness about HPV vaccination.

Discussion

Dr. Hopkins particularly praised NFID's efforts to encourage teens to initiate conversations with their parents. Dr. Dunn said he was impressed with the variety of work going on around HPV vaccine; he noted that if the field had been working to raise awareness about HPV 10 years ago, the ground would be more fertile for the acceptance of HPV vaccine now.

Dr. Dunn asked whether experts had any insights on which age groups to target to increase overall HPV vaccine coverage. None of the presenters could identify any particular age that should be targeted.

Dr. Friedland said that in an effort to cultivate new ideas, GSK hosted a vaccine hack-a-thon to bring together programmers and others to generate new ideas around vaccine education. The participants came up with products, and GSK selected three to support. Dr. Friedland encouraged others to look at novel channels and engage people from outside the field who think differently. He expressed strong support for continued focus by NVAC on HPV vaccination.

Ms. Aikin asked whether NFID had data on how much teens shared information among their peers as a result of the DoSomething.org campaign. Ms. Dalton said the campaign is still going on, and DoSomething.org and NFID will collect data about it. Later in September, DoSomething.org will launch a survey about the HPV vaccine campaign. Anecdotally, Ms. Dalton said, NFID is hearing about peer-to-peer education.

Dr. Hopkins asked Ms. Wasserman to keep NVAC updated on the OWH campaign to increase vaccination in high-need areas.

Public Comment

Ms. Wrangham of the NVIC said her organization's mission is to prevent vaccine injury and death through public education and to defend informed consent. Regarding self-administration of vaccination through microneedle patches, NVIC encourages NVAC to begin discussing how federally required vaccine information statements would be distributed with such technology and how consumers would be educated about vaccine reactions and injuries, how to report injuries, and other issues that may arise with this technology.

Regarding the NIS data and IIS systems, NVIC receives many complaints and concerns from the public regarding the lack of privacy associated with being forced to participate in IIS systems. Ms. Wrangham raised concerns about sharing sensitive medical information without specific consent. NVIC has learned that many do not want to participate in NIS phone surveys due to privacy concerns. Medical procedures such as vaccinations used to take place in the context of a private conversation with a health care provider, but new technology is eroding privacy, often without consent. Ms. Wrangham did not believe that NVAC had ever addressed the public's privacy concerns. NVIC encourages discussion about privacy and consideration of policy that would require IIS to default to an opt-in rather than opt-out approach.

Data from the ACIP February meeting indicate it may be decades before it is known how the HPV vaccine impacts prevention. In addition, HPV resolves without complication in over 90 percent of infected individuals within 2 years. HPV-associated cancers make up a small percentage of total cancer cases in the United States; for some associated cancers, highly successful screening methods are in place, and the conditions are highly treatable. HPV also continues to be one of the most expensive vaccines on the market today, Ms. Wrangham concluded.

Wrap Up and Adjournment—Robert H. Hopkins Jr., M.D., MACP, FAAP, NVAC Chair

Dr. Hopkins thanked the NVPO staff and all those who contribute to NVAC and the vaccine enterprise. Dr. Hopkins adjourned the meeting at 3:57 p.m.

APPENDIX: Abbreviations

2D	two-dimensional
ACCV	Advisory Commission on Childhood Vaccines
ACIP	Advisory Committee on Immunization Practices
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMR	antimicrobial resistance
APHIS	Animal and Plant Health Inspection Service
ASH	Assistant Secretary for Health
ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development
BIO	Biotechnology Innovation Organization
BPHC	Bureau of Primary Health Care
CDC	Centers for Disease Control and Prevention
CHC	community health center
CMV	cytomegalovirus
DBS	dried blood spots
DICP	Division of Injury Compensation Programs
DoD	Department of Defense
DRIVe	Division of Research, Innovation, and Ventures
DTaP	diphtheria, tetanus, and pertussis
EMR	electronic medical record
FDA	Food and Drug Administration
FY	fiscal year
HEDIS	Healthcare Effectiveness Data Information Set
HHS	Department of Health and Human Services
HRSA	Health Resources and Services Administration
IPV	inactivated poliovirus vaccine
LHD	local health department
NACCHO	National Association of County and City Health Officials
NCI	National Cancer Institute
NDC	National Drug Code
NFID	National Foundation of Infectious Diseases
NIAID	National Institute of Allergy and Infectious Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NIH	National Institutes of Health
NIS	National Immunization Survey
NVAC	National Vaccine Advisory Committee
NVIC	National Vaccine Information Center
NVPO	National Vaccine Program Office
OASH	Office of the Assistant Secretary for Health
OPV	oral (attenuated) poliovirus vaccine
OWH	Office of Women's Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCP	President's Cancer Panel
PCR	polymerase chain reaction
PPP	public–private partnerships
R&D	research and development
ROI	return on investment

Tdap	tetanus, diphtheria and pertussis
USDA	U.S. Department of Agriculture
VAERS	Vaccine Adverse Events Reporting System
WHO	World Health Organization