

**MEETING SUMMARY**  
**PRESIDENT'S CANCER PANEL**  
**GLOBAL HPV VACCINATION: OPPORTUNITIES AND CHALLENGES**

April 23–24, 2013  
Miami, Florida

This workshop was the fourth in the President's Cancer Panel's (PCP, the Panel) 2012-2013 series, *Accelerating Progress in Cancer Prevention: The HPV Vaccine Example*. During this workshop, the Panel heard expert testimony and moderated discussions on strategies for increasing uptake of human papillomavirus (HPV) vaccines in the United States and around the world. Issues surrounding the development, implementation, monitoring, and evaluation of HPV vaccination programs were examined, as were the roles of programs, policies, financing, and disease surveillance in these processes. Participants included 22 individuals, including several representatives from vaccine programs in various countries, organizations involved in domestic and global vaccination efforts, academic centers, pharmaceutical companies, and others with expertise in immunization and public health.

***President's Cancer Panel***

Barbara Rimer, Dr.P.H., Chair

Hill Harper, J.D.

Owen Witte, M.D.

***National Cancer Institute (NCI), National Institutes of Health (NIH)***

Abby Sandler, Ph.D., Executive Secretary, PCP

***Meeting Co-Chairs***

Rima Khabbaz, M.D., Deputy Director, Infectious Diseases, Centers for Disease Control and Prevention  
Olufunmilayo Olopade, M.D., F.A.C.P., Director, Center for Clinical Cancer Genetics; Professor of  
Medicine and Human Genetics; Associate Dean for Global Health, The University of Chicago;  
Member, National Cancer Advisory Board

Edward Trimble, M.D., M.P.H., Director, Center for Global Health, National Cancer Institute

***Participants***

Jan Agosti, M.D., Senior Program Officer, Bill & Melinda Gates Foundation

Kenneth Alexander, M.D., Ph.D., Professor of Pediatrics; Chief, Pediatric Infectious Diseases Section,  
The University of Chicago

Joan Benson, M.D., Executive Director, Strategic Partnerships and Stakeholder Engagement, Merck  
Vaccines

F. Javier Bosch Jose, M.D., Ph.D., Director, Cancer Epidemiology Research Program, Catalan Institute of  
Oncology

Karen Canfell, Ph.D., Associate Professor, Lowy Cancer Research Centre, The University of New South  
Wales

Tania Cernuschi, M.S., HPV Vaccine Product Manager, Vaccine Implementation Team, GAVI Alliance

Eduardo Franco, Dr.P.H., Professor and Chair, Department of Oncology, McGill University

Maurice Gatera, M.P.H. Candidate, Director, Vaccine Preventable Diseases Division, Rwanda  
Biomedical Center

Bruce Gellin, M.D., M.P.H., Deputy Assistant Secretary for Health; Director, National Vaccine Program Office, U.S. Department of Health and Human Services

Rolando Herrero, M.D., Ph.D., Head, Prevention and Implementation Group, International Agency for Research on Cancer

Nathalia Katz, M.D., Médica Infectóloga, National Program of Control of Vaccine-Preventable Diseases, Ministry of Health, Argentina

D. Scott LaMontagne, Ph.D., M.P.H., F.R.S.P.H., Senior Technical Lead for HPV Vaccines, Vaccine Access and Delivery, PATH

Eduardo Lazcano, M.D., Ph.D., Executive Director, Research Center on Public Health, National Institute of Public Health, Mexico

Douglas Lowy, M.D., Deputy Director, National Cancer Institute

Lauri Markowitz, M.D., Team Lead, Epidemiology Research, Division of STD Prevention, Centers for Disease Control and Prevention

Daniel Rodriguez, M.B.A., Advisor, Revolving Fund, Comprehensive Family Immunization Project, Pan American Health Organization

Nathalie Schrameijer, M.D., Director, Global Medical Affairs for HPV-Related Diseases, GlaxoSmithKline Biologicals, Belgium

Jennifer Smith, Ph.D., M.P.H., Research Associate Professor, Department of Epidemiology, University of North Carolina Gillings School of Global Public Health

Susan Wang, M.D., M.P.H., Medical Officer, Immunization, Vaccines, and Biologicals, World Health Organization

## **TUESDAY, APRIL 23, 2013**

### **OPENING REMARKS—DR. BARBARA RIMER**

Dr. Rimer welcomed invited participants and other attendees to the meeting on behalf of the Panel. She introduced Panel members, provided a brief overview of the history and purpose of the Panel, and described the aims of the current series of meetings. Dr. Rimer also introduced meeting co-chairs, Drs. Rima Khabbaz, Olufunmilayo Olopade, and Edward Trimble, as well as Robert Mittman, the workshop facilitator.

### **SERIES OVERVIEW**

#### **DR. DOUGLAS LOWY**

#### **HPV VACCINATION: SUMMARY OF PREVIOUS PCP WORKSHOPS**

#### **BACKGROUND**

Dr. Lowy is Deputy Director of the National Cancer Institute and Chief of the Laboratory of Cellular Oncology in the NCI Center for Cancer Research. He received his medical degree from New York University School of Medicine and trained in internal medicine at Stanford University and dermatology at Yale. Dr. Lowy's research includes the biology of papillomaviruses and the regulation of normal and neoplastic cell growth. The papillomavirus research is carried out in close collaboration with John T. Schiller, Ph.D., with whom Dr. Lowy has coauthored more than 100 papers over the past 25 years. Their laboratory contributed to the initial development, characterization, and clinical testing of the virus-like particles that are used in the two U.S. Food and Drug Administration (FDA)-approved HPV vaccines. Dr. Lowy is a member of the National Academy of Sciences and is also a member of the Institute of

Medicine. He and Dr. Schiller have received numerous honors for their pioneering work, including the 2011 Albert B. Sabin Gold Medal Award.

## KEY POINTS

- The Panel held three previous workshops as part of the Panel's series on HPV vaccination. The first workshop focused on the science of HPV-associated diseases and vaccination. The second focused on ways to achieve widespread HPV vaccine uptake, and the third workshop involved discussion of ways to integrate HPV vaccination with cervical cancer screening programs.
- HPV causes several cancers, which often are divided into cervical and noncervical cancers. The burden of HPV-associated cancers varies in different parts of the world. Cervical cancer is the most common HPV-associated cancer worldwide and in developing countries. However, in the United States, there are more cases of HPV-associated noncervical cancers than cervical cancers. HPV also cause other non-cancer conditions, such as genital warts.
- In the United States, approximately 30 percent of HPV-associated cancers arise in males, compared with less than 5 percent in the developing world. This is, in part, because of the increase in oropharyngeal cancers over the past 25 years in the United States.
- In the developing world, the main goal of HPV vaccination is to prevent cervical cancers. In the United States, the goal of HPV vaccination is to prevent the spectrum of HPV-associated diseases, including several cancers, genital warts, and recurrent respiratory papillomas.
- With the exception of cervical cancer, HPV-associated cancers do not have validated intermediate markers or public health interventions for secondary prevention. HPV vaccination is the main validated public health approach to prevent noncervical HPV-associated cancers.
- HPV vaccines have excellent safety records, similar to those of other licensed vaccines. A prospective study based on Vaccine Safety Datalink data, which include control group data, found no evidence for increased risk of several prespecified adverse events following receipt of HPV vaccine.
- Clinical studies have found that among women who received all three doses of HPV vaccine and were HPV negative during the vaccination period, the efficacy of the vaccine with respect to various clinical endpoints was close to 100 percent. However, vaccine efficacy was substantially lower among women who were exposed to HPV prior to vaccination. These results provide evidence for the importance of vaccinating prior to sexual initiation.
- Clinical studies among men have found that the efficacy of the HPV vaccine for preventing warts and anal dysplasia was 75 to 90 percent.
- The duration of efficacy for both Gardasil and Cervarix is at least eight years and may be much longer.
- The goals of HPV vaccination are twofold: first, to directly reduce the risk of infection and disease and, second, to reduce the prevalence of HPV vaccine types in the general population through herd immunity.
- In Australia, there was a dramatic reduction in genital warts among young women and young heterosexual men between 2007 (when HPV vaccine was introduced for use in females) and 2010. However, a similar reduction was not observed among men who have sex with men. There also was a drastic reduction in cervical dysplasia among girls younger than 18 years old and a modest reduction among women 18 to 20 years of age. However, no reduction was observed among women older than 20, which likely reflects the decrease in efficacy when the vaccine is administered after HPV exposure.
- Australia experienced a significant fall in HPV prevalence following initiation of its national HPV vaccine program. A study of a group of women with HPV vaccine coverage rates of 75 percent for

the first dose and 55 percent for all three doses found a 75 percent decrease in prevalence of the HPV types included in the vaccines. This decline suggests that herd immunity is occurring even when vaccine coverage is incomplete.

- Several areas of research were suggested by participants in earlier workshops. The natural history of oropharyngeal HPV infection needs to be elucidated. In addition, second-generation vaccines with broader coverage against more vaccine types, lower cost, and fewer required doses could improve the vaccine and its uptake.
- Research is needed to examine the efficacy of fewer than three vaccine doses. Data from the Costa Rica Vaccine Trial indicate that one dose of Cervarix causes persistently high HPV antibodies in the serum for at least three years. Antibody levels were not as high as those in women who had received two or three doses, but they may be sufficient. Women who received only one dose of the vaccine were fully protected against the development of persistent HPV infection during the course of the study.
- High-quality data systems are essential to support vaccine monitoring and surveillance.
- Efforts should be made to increase HPV vaccine uptake in both males and females in the United States.
- Several factors may influence uptake of the HPV vaccine. There is a small, but vocal group of people who are concerned about sequelae of the vaccine, most especially, that the vaccine will result in sexual disinhibition among adolescents, although there is no evidence that this is the case. In addition, there is low awareness about the burden of HPV-associated diseases in males. In a study conducted by the Centers for Disease Control and Prevention (CDC), the reasons most commonly given by parents for not wanting their children to be vaccinated were: (1) the vaccine is not needed, (2) the child is not sexually active, (3) they had concerns about safety and/or side effects, (4) they lacked knowledge, and (5) the vaccine was not recommended by their health care providers. CDC also found that providers are less willing to strongly advocate for HPV vaccine than for other vaccines (i.e., vaccine hesitancy).
- Differences in HPV vaccine uptake have been observed among different demographic groups. In 2011, black and Hispanic girls were more likely than non-Hispanic white girls to receive the first dose of the vaccine, but black girls were less likely than Hispanic or non-Hispanic white girls to receive all three doses. Girls from households with incomes below the poverty level were more likely to receive the first dose of the vaccine than were girls from households with incomes at or above the poverty level.
- Many participants in previous Panel workshops said that it is important to educate providers in order to increase enthusiasm for the vaccine. It also was proposed that HPV vaccination be promoted as part of an integrated adolescent vaccine platform and as an anticancer vaccine. Pediatricians suggested that the vaccine doses be given over one to two years rather than within a six-month window. It also was suggested that the vaccine could be administered by providers other than pediatricians and primary care physicians (e.g., pharmacists, dentists). Another suggestion was to create incentives to encourage families to have their children vaccinated (e.g., insurance rebates). Many workshop participants pointed out that school-located vaccination would be useful for increasing uptake, although several barriers to this approach were discussed. Mandating vaccination for school entry, another strategy discussed, has generated considerable controversy in the United States.
- High HPV vaccine uptake will reduce the frequency of screening-detected, treatable cervical disease. This means that the benefit-to-harm ratio of cervical cancer screening will decrease because it is likely that the number of false positives will remain the same.
- High HPV vaccine uptake should allow women to begin cervical cancer screening at older ages and also enable the transition to HPV-based tests as the primary mode of screening.

- Electronic health records and vaccine registries linked to disease surveillance systems could help improve adherence to vaccination and screening guidelines, as well as facilitate monitoring of vaccine impact.

## **OPENING ROUNDTABLE**

Participants introduced themselves and were asked to state what they thought was the most important strategy for increasing global uptake of HPV vaccine. Several participants were enthusiastic about the opportunity for HPV vaccines to contribute to the eradication of cervical cancer and other HPV-associated diseases. To improve uptake, HPV vaccination should be integrated with other health services and incorporated into the activities of international organizations (e.g., United States Agency for International Development [USAID], United Nations Children's Fund [UNICEF], United Nations Population Fund [UNFPA]) whenever possible. In addition, HPV and hepatitis B vaccinations should be integrated into the cancer control plans of all countries. Efforts should be made to assist low- and middle-resource countries with cancer control and immunization program planning, including assessment of cost-effectiveness. The cost of HPV vaccination is a barrier in many areas of the world; costs should be addressed, and sustainable financing models should be developed. System-level changes should be made, as necessary, to make it as easy as possible to deliver and receive the vaccine. Multipronged delivery strategies likely will be needed to maximize vaccine uptake. This likely will include but not be limited to delivery through schools. Special consideration will need to be given to how to deliver the vaccine to hard-to-reach populations (e.g., adolescents in rural areas who do not attend school). Reducing the number of vaccine doses needed to confer protection against infection and disease would ease the logistical burden of vaccine delivery and likely enhance uptake. Programs should share their experiences so that others can learn from them.

## **SESSION ONE: OVERVIEW OF GLOBAL EPIDEMIOLOGY AND SURVEILLANCE OF HPV INFECTIONS AND RELATED DISEASES**

### **DR. OLUFUNMILAYO OLOPADE**

#### **GLOBAL HPV VACCINATION: OPPORTUNITIES AND CHALLENGES**

##### **BACKGROUND**

Dr. Olopade is Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics and Associate Dean for Global Health at The University of Chicago. Consistently listed among the Best Doctors in America, Dr. Olopade has held a number of leadership positions in the American Association for Cancer Research, the American Society of Clinical Oncology, and the African Organization for Research and Training in Cancer. She has received numerous honors and awards, including an honorary degree from Princeton University, the Doris Duke Distinguished Clinical Scientist and Exceptional Mentor Award, the American Cancer Society Clinical Research Professorship, the MacArthur Foundation "Genius" Fellowship, and the Officer of the Order of the Niger Award. Dr. Olopade currently serves on the Board of Directors for the American Board of Internal Medicine and the National Cancer Advisory Board. Dr. Olopade earned her medical degree from the University of Ibadan College of Medicine in Nigeria. She trained in internal medicine at Cook County Hospital in Chicago and in oncology and cancer genetics at the Joint Section of Hematology and Oncology at The University of Chicago.

##### **KEY POINTS**

- The 2012 World Oncology Forum in Lugano, Switzerland, culminated in the development of a ten-point message for the health care community. The cancer research community needs to do a better job implementing what it knows with respect to prevention, treatment, and care. It also needs to gain

knowledge more efficiently through use of new research models focused on patient benefit. Central mechanisms for achieving these changes include having a clear cancer strategy for each country, implementing universal health coverage to deliver high-quality cancer care, and waging a war on tobacco. The need to focus on prevention and the importance of national cancer control strategies are particularly relevant to global uptake of HPV vaccine.

- HPV is one of nine infectious causes of cancer that have been identified to date. Effective vaccines for these infections are paramount to cancer prevention.
- There are several opportunities to interfere with the progression of HPV infection to cervical cancer. Improvements in nutrition in the developing world could help reduce levels of persistent HPV infection by strengthening people's immune systems. Current vaccines could be improved by continued research on cervical cancer. There is also a need for improved screening and treatment for cervical cancer, particularly in low-resource areas.
- Deaths from cervical cancer have decreased in the United States, yet there are still many women who do not have access to affordable care and are unnecessarily dying from this disease. The mortality-to-incidence ratio of HPV-related cervical cancer needs to be reduced both in the United States and in developing countries.

## **DR. F. JAVIER BOSCH JOSE**

### **HPV AND CANCER EPIDEMIOLOGY**

#### **BACKGROUND**

Dr. Bosch Jose conducts epidemiological research focusing on cancers linked to infectious agents. His main research focus is on cancers of the head and neck, liver, cervix, skin, vagina, anus, and penis. He has also conducted studies on diet and colorectal cancer and headed a program of implementation and methodological research in cancer registration. He served as epidemiologist at the International Agency for Research on Cancer (IARC, 1982-1993) and was a visiting scientist at the National Cancer Institute (2002). He is Director of the Cancer Epidemiology Research Program at the Catalan Institute of Oncology (1994 to date) and Director of the World Health Organization (WHO)/Catalan Institute of Oncology Information Centre on HPV and Cancer. As co-principal investigator and organizer of the HPV and Cancer Program at IARC, Dr. Bosch Jose interacted with scientists on all continents, helped implement study protocols, assisted with technology transfer, and encouraged human mobility efforts. He is a meeting organizer of the International Papillomavirus Congress and a member of the advisory board of the International Papillomavirus Society.

#### **KEY POINTS**

- It is estimated that there are 500,000 cases of cervical cancer worldwide each year. However, this estimate is based on incomplete data. Only 13 percent of the world's population is covered by cancer registries. About 80 percent of the population in North America and Europe is covered by cancer registries; however, coverage is sparse in the rest of the world. In addition, the validity of registries is undermined in areas where people do not have access to health care services, which can result in many cancers not being diagnosed.
- Due to the incompleteness of cancer registries and the difficulty in establishing registries in developing countries, new approaches for estimating HPV-related cancer incidence are being developed. Dr. Bosch Jose and colleagues currently are working to create an algorithm that can predict cervical cancer incidence based on the prevalence of different biomarkers, including HPV DNA, HPV RNA, and p16, a protein involved in cell cycle regulation that is often highly expressed in cells transformed by HPV infected.

- An additional challenge to accurately estimating the incidence of HPV-related cancers is disease latency. A woman may receive a negative HPV DNA test result only to have the disease emerge later in life during periods of immunosuppression or menopause.
- In many areas of the world, HPV prevalence is highest among women less than 25 years of age and then steadily declines. However, a different pattern is observed in Latin America and Africa, where risk of cervical cancer is particularly high. In these regions, HPV prevalence is high among women under 25, declines for several decades, and then increases again as women age. It is possible that this second peak in prevalence represents new infections. However, it is also possible that the increased prevalence late in life is caused by reactivation of HPV contracted earlier in life. Major societal changes in sexual behavior during the mid-20th century generated increased opportunities for HPV infection at higher levels and in younger age groups. Women who were young at the time of the so-called sexual revolution now are entering menopause and experiencing increased opportunities for HPV reactivation.
- The presence of latent HPV that may become reactivated later in life has implications for evaluation of vaccine efficacy. A woman with latent HPV infection may test negative for HPV at the time of vaccination. If the virus reactivates and causes cervical disease, it might erroneously be interpreted as failure of the vaccine to prevent infection.
- The increase in HPV prevalence among older women also must be considered when making decisions about the age at which cervical cancer screening should be stopped.
- Based on studies of more than 10,000 cervical cancer cases worldwide, approximately 90 percent of cervical cancers worldwide are caused by HPV types that are included in the nine-valent HPV vaccine being developed by Merck. There is little geographic variability in the proportion of cervical cancers caused by these HPV types; thus, the vaccine likely would be similarly effective in most regions of the world. If the nine-valent vaccine results in cross-protection against additional HPV types, it may eliminate the need for screening.

## **DR. JENNIFER SMITH**

### **OVERVIEW OF GLOBAL EPIDEMIOLOGY AND SURVEILLANCE OF HPV INFECTIONS AND RELATED DISEASES**

#### **BACKGROUND**

Dr. Smith is a research associate professor in the Department of Epidemiology of the Gillings School of Global Public Health. She has over 150 articles published or in press, over 120 of which focus on epidemiological research related to HPV or cervical cancer. She earned her Ph.D. from the Department of Infectious Disease Epidemiology, and her M.P.H. from the Department of Population Dynamics, Johns Hopkins Bloomberg School of Public Health. Dr. Smith is a faculty member at the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center, UNC Center for AIDS Research, and the UNC Center for Women's Health Research. Dr. Smith's current research focuses on epidemiological studies of HPV and cervical cancer worldwide (primarily in North Carolina, China, Kenya, and South Africa), with a focus on prevention via screening and prophylactic vaccination.

#### **KEY POINTS**

- Among U.S. women with health insurance, the highest burden of precancerous grade 2 and grade 3 cervical intraepithelial neoplasms (CIN2 and CIN3) is in women 25 to 29 years of age. Prevalence of precancerous lesions may be even greater and occur in younger age groups among uninsured U.S. women and among women in developing countries. The global burden of these lesions is not well

understood due to a lack of cervical cancer screening in many areas. It is estimated that only 3 percent of eligible women in Kenya are screened.

- Based on data from U.S.-based Kaiser Permanente, it has been estimated that 63 percent of the cost of cervical cancer screening and treatment is in conjunction with routine screening. The cost of screening is substantially more than the costs of treating precancerous and cancerous lesions. HPV vaccination has potential to reduce the costs of cervical cancer control by reducing both the numbers of low- and high-grade lesions that require intervention and the need for screening.
- Measurement of HPV DNA in tumor samples has provided estimates of the proportion of various tumor types that are attributable to HPV infection, as well as the proportion that are due to HPV 16 and/or 18. HPV DNA analysis has suggested that virtually all cervical cancers are caused by HPV, with approximately 76 percent thought to be caused by HPV 16 and/or 18. HPV DNA data have also indicated that a significant proportion of other cancer types are caused by HPV, including cancers of the anus (90%), vulva (40%), vagina (66%), penis (40%), oral cavity (16%), oropharynx (25%), and larynx (24%). However, more recent studies looking at downstream markers of HPV activity, such as upregulation of p16 or the presence of HPV RNA, suggest that some of these estimates may be high.
- Additional research is needed to clarify the proportion of certain cancer types caused by HPV. Studies of the impact of widespread uptake of HPV vaccine may provide insight into this question.
- As efforts continue to promote uptake of HPV vaccine, it is important that lessons learned be identified and shared.

## **SESSION ONE MODERATED DISCUSSION**

### **KEY POINTS**

- Meta-analyses data indicate that approximately 11 percent of women in the world have HPV DNA in their cervical cells. The prevalence of HPV DNA varies by geographic region and population, with rates as low as 3 percent among Arab women in North Africa and higher than 20 percent in other parts of Africa and Latin America. It is possible that other biomarkers, such as HPV E6, may be better predictors of cancer risk than HPV DNA.
- A survey that collects information on HPV DNA and HPV type distribution for approximately 1,000 women should be sufficient to estimate the burden of cervical cancer in most countries. The data generated could be used to inform the development of an HPV vaccine program. These types of studies have been done in many, but not all, countries. It is recognized that measurement of HPV prevalence is not a perfect proxy for invasive cervical cancer, but it can provide valuable information.
- Data collected to date on the distribution of HPV types in cervical cancers indicate that current HPV vaccines and the nine-valent vaccine under development would be similarly effective in most regions of the world. However, there may be some isolated populations (e.g., populations in the jungles of Brazil) that may have significantly different patterns of HPV infection.
- Many countries are hesitant to invest in HPV vaccination programs in the absence of information about HPV and/or cervical cancer prevalence within their countries. However, they often delay or fail to conduct the studies needed to generate these data. Government officials should be told how little variation is observed worldwide and encouraged to implement programs based on existing data.
- The GLOBOCAN estimate of 500,000 cases of cervical cancer annually worldwide is calculated based on extrapolations from cancer registries and is thus subject to the limitations of cancer registries. Using HPV prevalence to estimate cervical cancer cases in areas where registries do not exist offers a different approach. In some cases (e.g., China), data on HPV prevalence suggest that cervical cancer incidence rates are higher than what is reported in cancer registries.



- Some participants suggested that the Panel issue a strong statement about the possibility of eradicating cervical cancer, but others urged caution in this area. Those in favor of a statement about eradication pointed out that the tools to eradicate cervical cancer are available or likely will be available soon. There is a reliable diagnostic tool for cervical cancer, a vaccine that may be able to prevent 90 percent of cases, and screening tools that will allow detection of other cases. HPV is not known to have an animal reservoir, which means that elimination of the pathogen among humans would be sufficient to achieve eradication.
- Participants who were hesitant about issuing a statement about cervical cancer eradication pointed out that current tools would not permit elimination of oncogenic HPV from the environment, which is the definition of eradication used by the International Task Force for Disease Eradication. In addition, the term “eradication” suggests that intervention (e.g., vaccination, screening) is no longer necessary to prevent disease, which is not the case for cervical cancer. Participants also expressed concern that statements about eradication could damage the credibility of the scientific community and might be distracting. Given the lack of cancer registries in many areas of the world, it also would be difficult to confirm that cervical cancer had been eradicated.
- Setting a goal of reducing rates of HPV infection and cervical cancer would be more achievable and measureable than eradication of the disease. The WHO Western Pacific Regional Office created such a goal related to hepatitis B infection, which causes liver cancer and can be prevented with a vaccine. The current goal is for less than 2 percent of 5-year-olds to be hepatitis B positive. This goal eventually will be reduced to 1 percent.
- Even in the presence of widespread HPV vaccination, screening programs will be needed to monitor women who already have been exposed to HPV. It is important that vaccination and screening efforts be integrated.
- HPV vaccination of a subset of the population can result in herd immunity. For example, genital warts among males in Australia declined with widespread vaccination of females. However, high vaccination rates in certain subpopulations (e.g., a certain geographic region) will not necessarily benefit people in other subpopulations.
- Nations face a number of health challenges and, particularly in low-income areas, must make difficult decisions about how to prioritize their public health resources. Policymakers need data on which to base their decisions about how to allocate public health resources, and they often are not satisfied with data from another country or small survey studies. It would be beneficial if the United States helped develop reliable disease estimates for low-income countries. This could be done through HPV prevalence studies or creation of cancer registries; however, it was recognized that reliable cancer registries depend on the presence of a well-established health care delivery system.
- While countries prefer to have data based on their own populations, it sometimes may be possible to leverage data collected in nearby countries or regions. Nations may become more likely to adopt a vaccine if many or all of its neighboring countries have adopted it. No nation wants to be the last in its region to adopt an effective vaccine. For example, Brazil may follow Argentina’s lead in creating an HPV vaccination program.
- Australia created a registry to monitor HPV vaccination and dose completion. This registry now is being linked to state-based screening registries, which are linked to cancer registries. The linkage of these registries will facilitate monitoring of the impact of HPV vaccination on cervical precancerous lesions. Australia also is considering the collection of HPV type information for cervical cancers in order to evaluate the impact of HPV vaccination on those types associated with the cancer.
- Argentina has information on which girls have started and completed the HPV vaccine schedule. Most often, the girls who have not received the vaccine are those who do not have access to the health care system. Efforts are made to find and vaccinate these girls.

- Some low-income countries are monitoring HPV infection rates to monitor impact of vaccination programs. In Rwanda and Bhutan, the governments are monitoring vaccine uptake, and IARC is assisting with monitoring HPV infection rates. A urine assay is being used to monitor for HPV infection.
- Some countries decide to implement HPV vaccine programs first and then develop surveillance systems.
- Decision-making processes vary considerably among countries. While some lessons may be learned from looking at countries that have decided to implement HPV vaccine programs, it must be remembered that each country is unique. For example, Australia implemented an HPV vaccine program in the absence of concrete data about the impact of the vaccine.
- WHO has published several articles on the decision-making processes that resulted in implementation of HPV vaccination in various countries. In general, countries create a technical advisory group for immunization that gathers evidence and weighs the cost and potential benefits of a vaccination program. An array of factors (e.g., availability of vaccine donor, funding) determines whether a program is implemented.
- Cervical cancer has been discussed in World Health Assembly deliberations regarding noncommunicable diseases. Screening and HPV vaccination both have been discussed, although concern has been expressed about the cost of the vaccine and vaccine delivery.
- Rates of hepatitis B vaccination were relatively low in the United States for many years, at least in part because it was an adolescent vaccine. One of the motivations for making it a childhood vaccine was the hope that this would increase uptake. Globally, the hepatitis B vaccine had been introduced in relatively few countries until GAVI made it a priority. Many trends being observed for HPV vaccine uptake are similar to what occurred with the hepatitis B vaccine. Relevant lessons from the hepatitis B experience should be taken into account to try to achieve more rapid uptake of HPV vaccine.
- Uptake of HPV vaccine has been more rapid than uptake of some other vaccines. So far, 54 countries have introduced the HPV vaccine, and 20 to 30 other countries are conducting pilot programs or demonstration projects related to vaccination. Several other countries are beginning to think or talk about HPV vaccination programs. Overall, this represents promising progress; however, efforts must be made to ensure that HPV vaccine adoption continues at an acceptable pace, which will require adequate resource allocation and political will.
- It would be interesting to estimate what rates of cervical cancer would be in high-income countries (e.g., United States, Canada) if screening were not widespread.

## **SESSION TWO: INFLUENCE OF HPV VACCINE POLICIES AND FINANCING ON VACCINE UPTAKE**

**DR. RIMA KHABBAZ**

### **INFLUENCE OF HPV VACCINE POLICIES AND FINANCING ON VACCINE UPTAKE**

#### **BACKGROUND**

Dr. Khabbaz is Deputy Director for Infectious Diseases at the U.S. CDC. She is also Acting Director of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. She has served in leadership positions across CDC's infectious disease activities since the early 1990s. Dr. Khabbaz is a graduate of the American University of Beirut, Lebanon, where she obtained both her bachelor's degree (biology/chemistry) and her M.D. She trained in internal medicine and completed a fellowship in infectious diseases at the University of Maryland, Baltimore. In addition to her CDC position, Dr.

Khabbaz serves as Clinical Associate Professor of Medicine (infectious diseases) at Emory University. The author/co-author of more than 100 scientific articles, book chapters, and reviews, Dr. Khabbaz is a fellow of the Infectious Disease Society of America (IDSA) and member of the American Epidemiologic Society, the American Society for Microbiology, the Council of State and Territorial Epidemiologists, and the Institute of Medicine Forum on Microbial Threats.

## KEY POINTS

- In April 2009, WHO published recommendations on HPV vaccination. In May and July of that year, two HPV vaccines were WHO prequalified, which made it possible for United Nations (UN) agencies to procure vaccines.
- Between 2010 and 2013, WHO developed various standards and tools to aid in implementation of HPV vaccine programs. These tools are available to assist GAVI and individual countries in areas such as vaccine delivery, coverage monitoring, social mobilization and communication, cost estimation, program evaluation, and impact monitoring.
- By the end of 2012, 42 countries (including 3 developing nations) had introduced HPV vaccines into their national immunization programs.
- GAVI began accepting applications in 2012 from countries seeking support for national introduction of HPV vaccine or HPV vaccine demonstration programs. The first GAVI awards were announced in February 2013.
- WHO has recommended that each country have an independent body within its Ministry of Health that is focused on issues related to immunization and vaccine introduction (similar to the CDC Advisory Committee for Immunization Practices). The roles of these independent bodies, which WHO refers to as the National Immunization Technical Advisory Groups, are to act as a technical resource on vaccine introduction, evaluate evidence on disease burden and adverse events, review and balance potential benefits and harms, and provide evidence-based recommendations.
- The WHO Cervical Cancer Prevention and Control Costing Tool (C4P) is a generic costing and planning tool for cervical cancer prevention and control. The generic version of the Tool allows the user to define different vaccine delivery strategies (e.g., through schools, health facilities, or campaigns such as national immunization days). Furthermore, it allows subnational segmentation and extensive modification of input. It also provides access to transparent underlying calculations and assumptions. The tool is prepopulated with the required data and linked to data sources.
- GAVI's application requirements for its National HPV Vaccine Support in Low Income Countries program include a demonstrated ability to deliver a complete series of multiple vaccine doses to 9- to 13-year-olds (achieving at least 50 percent coverage); a high level of infant diphtheria-tetanus-pertussis (DTP3) coverage; cost analysis of the proposed delivery strategy; and detailed plans for communication and social mobilization.
- The Revolving Fund of the Pan American Health Organization (PAHO) is a mechanism for the joint procurement of vaccines, syringes, and related supplies for participating member states. PAHO requires that countries participating in the Revolving Fund have national immunization laws. In 2012, 17 countries introduced the pneumococcal conjugate vaccine (PCV), 14 introduced the rotavirus vaccine, and 4 introduced HPV vaccine.
- Middle-income countries are lagging behind high-income and GAVI-eligible, low-income countries when it comes to adoption of new vaccines. To address this issue, UNICEF has introduced a hybrid strategy focused on the introduction of new, high-cost vaccines (e.g., pneumococcal conjugate, HPV, rotavirus) in middle-income countries. UNICEF provides an aggregated vaccine demand forecast to manufacturers. It also pools procurement of vaccines and establishes reference pricing. UNICEF also

is working with the WHO Eastern Mediterranean Regional Office (EMRO) on a pooled vaccine procurement initiative for its middle-income countries.

## **MS. TANIA CERNUSCHI**

### **GAVI'S HPV PROGRAMME: AN OVERVIEW**

#### **BACKGROUND**

Ms. Cernuschi has worked for the past 11 years in design and management of development programs, focusing particularly on improving access to health technologies in poor countries. She manages the HPV program at GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation), after having worked on design and launch of the GAVI pneumococcal vaccine program through the Advance Market Commitment. Prior to this, Ms. Cernuschi worked in policy-making on innovative finance for development at the United Nations Department for Economic and Social Affairs in New York. She has held assignments with UNICEF, the Council of Europe, and the European Parliament at headquarters working on analysis of aid in social sectors. She conducted field work in Eritrea for civil society organizations and the Italian Ministry of Foreign Affairs, designing and managing projects in the areas of food security, water and sanitation, and health. Ms. Cernuschi holds a master's degree in development management from the London School of Economics and currently is pursuing a Master of Public Health degree from the London School of Hygiene and Tropical Medicine.

#### **KEY POINTS**

- To date, only three low-income countries (based on the GAVI definition) have launched national HPV vaccine programs: Rwanda, Uganda, and Lesotho. This is in part because of the high cost of HPV vaccine. GAVI launched its HPV program in 2012 to facilitate HPV vaccine adoption in countries with a per capita gross national income below \$1,550.
- Some challenges faced by HPV programs include a new target population (adolescent girls), untested delivery platforms (e.g., schools), different and higher delivery costs, potential impact on screening programs, and the need for more communication and social mobilization activities.
- GAVI has set up two separate HPV vaccine programs. The National Introduction Program provides support for countries that already have experience with HPV vaccination. The Demonstration Program is for countries with no experience vaccinating adolescents. Through the Demonstration Program, these countries vaccinate only in a few districts to determine whether national HPV vaccination is feasible. The HPV vaccine is the first vaccine for which GAVI has used the Demonstration Program model.
- Countries can apply for support through the National Introduction Program if they have at least 70 percent DTP3 coverage, demonstrated ability to deliver a complete series of vaccines to at least 50 percent of the target vaccination cohort in an average-size district, and 75 percent of the eligible population enrolled in school (if school-based delivery). Countries also must cofinance the vaccine costs, conduct a costing analysis, and have plans for communication and social mobilization. The Demonstration Program does not have co-financing requirements.
- The goal of the Demonstration Program is to evaluate coverage, feasibility, acceptability, and cost. The Program provides support for two years, with a maximum enrollment of 15,000 girls per year. Based on the information collected during this two-year period, countries can decide whether to introduce the vaccine nationally. The program also requires countries to conduct a review of other services being provided to the HPV vaccine target population to determine whether it may be feasible to integrate services. If the review indicates that integration of services may be feasible or efficient,

countries must do so in the second year of the program. The Demonstration Program also requires participating countries to either draft or improve existing cervical cancer screening strategies.

- In 2012, GAVI received 15 applications to its HPV vaccination program. To date, eight Demonstration Program applications have been approved and two additional applications are pending approval. One country, Rwanda, has been approved for support through the National Introduction Program. The primary delivery strategy of the approved countries is school based. Up to 30 countries are forecasted to run demonstration projects by 2015, with up to 42 national introductions by 2020. The cost demand from GAVI countries will reach \$40 million in 2020.

## **SESSION TWO MODERATED DISCUSSION**

### **KEY POINTS**

- The cost of HPV vaccines can be a barrier to implementation of vaccination programs in low-income nations. The cost of manufacturing vaccines and lack of competition (only two companies manufacture the vaccines) are two factors that contribute to the high price of the vaccines. Pharmaceutical companies have committed to providing the vaccines to low- and middle-income countries at a reduced cost. For example, Merck provides GAVI with HPV vaccine for \$5 per dose. The price paid by countries varies depending on income level and is considerably lower—sometimes as low as 20 to 30 cents per dose.
- Many countries are struggling to make decisions about how to divide resources among several vaccines. A number of countries are focusing on introduction of pneumococcal conjugate and rotavirus vaccines because these vaccines are aligned with the UN Millennium Development Goal of reducing childhood mortality. In Latin America, the cost of immunizing a child for 12 basic antigens is about \$12. It costs \$13 dollars more to add the rotavirus vaccine and \$45 to add the pneumococcal conjugate vaccine. This often leaves little money to invest in HPV vaccination. For many countries, the price of the HPV vaccine is not the major barrier to program implementation. The cost of delivering the vaccine can be higher than that of the vaccine itself, particularly in countries with less-developed health care infrastructures. For example, Merck offered to provide Tanzania with HPV vaccine at no cost; however, challenges related to infrastructure, inadequate numbers of qualified health care workers, and other factors have deterred this country from implementing a program.
- A PATH study found that, on average, countries pay about \$2 per dose of HPV vaccine to implement a demonstration program. About half of this cost is for social mobilization. The costs of social mobilization and vaccine delivery are significant and must be taken into account when countries are creating their financing plans. The situation is even more complicated for countries that are close to exceeding GAVI limits on income. These countries also must factor in the entire cost of the unsubsidized vaccine in their financing plans since they likely will lose GAVI subsidies as their incomes rise.
- GAVI expects that most countries funded through the Demonstration Program will move forward with implementation of a national program within two to three years. However, it is possible that some of these countries will not immediately transition to a national program. GAVI is planning to do research in these countries to determine what factors influence the decision not to move forward with a national program.
- GAVI will be working with WHO to identify attributes that would be desirable for next-generation HPV vaccines. For example, a vaccine that is not dependent on a continuous cold chain would be beneficial.
- GAVI-funded countries are required to submit information on program implementation at the end of the first year of support. GAVI will analyze these data and use this information to advise countries on potential ways to improve their existing programs. These data also may be useful for helping

countries that are hoping to apply for GAVI support and will drive changes in the GAVI initiative as necessary.

- Many Latin American countries are participating in the ProVac Initiative, which is designed to help countries make evidence-based decisions about the introduction of new vaccines. These countries are using a tool called Survey Work to carry out a cost-effectiveness analysis. However, even when the survey results indicate that a vaccine would be cost-effective, it may be difficult to find the resources to pay for the program.
- The cost of HPV vaccine delivery was not a major factor in the decision making process for Argentina because adolescents in this country already were being given other vaccines (e.g., hepatitis B). The ability to build on existing infrastructure made the cost of the HPV vaccination program more reasonable.
- Some countries that are not capable of implementing national vaccine programs may roll out programs regionally (e.g., in certain states or provinces). In some cases, states in countries that are not eligible for GAVI support have reached out to Merck for help in introducing the HPV vaccine. Waiting until an entire country is capable of implementing a vaccine program may result in unnecessary delays.
- Decisions to support HPV vaccination are not always made on the national level. For example, the Canadian province of Prince Edward Island recently decided to publicly fund HPV vaccination for males. In addition, 50 municipalities in Brazil have provided support for HPV vaccination in the absence of national support.
- Many lessons have been learned during implementation of HPV programs to date. This information is disseminated to immunization program managers and others who are doing similar work in the regions through conferences or reports. However, it often is not published in the peer-reviewed literature, either because it is not considered to be scientifically robust or because the program may not have the resources to generate this type of paper.
- The GAVI tender process for HPV vaccines was open to all companies. Countries can express a preference regarding the vaccine they would like to use, and GAVI attempts to meet this preference. There are, however, some cases in which it is difficult for GAVI to meet country preferences (e.g., when a country switches its preference).
- A study funded by the Gates Foundation found that HPV vaccination would be cost-effective for most GAVI-eligible countries at current negotiated vaccine prices. In some countries, HPV vaccination would actually be cost saving; however, in other countries this savings would not occur because they currently do not spend resources on treating cervical cancer. In many cases, the costs of cervical cancer treatment are incurred by patients, not governments, so governments may not directly realize cost savings.
- Establishing the cost-effectiveness or cost-saving potential of an intervention is not the same as establishing its affordability. The deferred cost savings associated with vaccines may not be enough to drive uptake. It is often difficult for countries to secure financing for HPV vaccination programs, even if they are projected to be cost-effective. In low-income countries, finding a donor to cover the cost of the vaccine is generally more important in decision making than is cost-effectiveness.
- In high-resource settings, there is a strong link between the results of cost-effectiveness evaluations and decisions to move forward with a vaccination program. The role of cost-effectiveness analyses in low-resource settings has been quite different. This is in part due to lack of capacity within low-resource countries to carry out cost-effectiveness research in ways that would be useful for policymakers.
- Expertise in cost-effectiveness modeling currently is concentrated in very few groups around the world. Some participants suggested that the capacity for cost-effectiveness analysis be increased in

low- and middle-income countries, but it also was noted that these models are complex, and that it may not be realistic or necessary for all countries to have the expertise needed to do this type of work. The most important point is that there be local involvement in setting up the framework for cost-effectiveness analyses and decision making.

- Cost-effectiveness research in high-resource settings has overwhelmingly shown that HPV vaccination of females is cost-effective when integrated with cervical cancer screening programs. However, the cost-effectiveness of HPV vaccination of males may depend on coverage in females as well as the price of the vaccine.
- There are several cost-effectiveness models, each with different assumptions and parameters used for analysis. These models sometimes give different answers.
- It is often difficult to obtain the data needed for cost-effectiveness analyses for low- and middle-income countries. In addition, the assumptions made in these models may be inappropriate for these settings (e.g., related to screening costs), which reduces confidence in the results.
- The WHO costing tool helps countries test various scenarios for implementing a vaccine program (e.g., school-based delivery versus delivery in health centers). The budget estimates generated through this tool can be used to conduct cost-effectiveness analyses.
- The ProVac Initiative has developed a tool called CERVIVAC that assists in determining the cost-effectiveness of introducing HPV vaccination, as well as introducing HPV vaccination as a complement to cervical cancer screening.
- CERVIVAC is now being integrated into the UN OneHealth Model costing tool. This tool allows countries to see how costs for various health programs fit together. Some costs benefit multiple programs (e.g., health worker training, vehicles for transportation), while others are specific to certain initiatives. The ability to generate specific cost estimates can help countries mobilize resources.
- Sustainability of HPV programs is a concern. In many cases, donors are covering the entire cost of the vaccine. Countries need to consider how they will maintain programs in the long term.
- One way to reduce the cost of HPV vaccination, including both vaccine and vaccine delivery costs, would be to reduce the number of recommended doses from three to two. Even if a two-dose regimen is not approved by the U.S. FDA, it may be possible to gain approval from the European Medicines Evaluation Agency based on immunogenicity data.
- Fifty-four countries are eligible for GAVI support based on income. Of these, it is expected that 38 will carry out HPV vaccine demonstration projects by 2018 and that all or most of these will eventually implement national programs. Inadequate rates of DTP3 vaccine coverage are one reason countries may not receive GAVI support for HPV vaccine programs.
- Although middle-income countries are not eligible for GAVI support, there are some mechanisms available to assist them. As part of its ongoing tender process, GAVI also requested that HPV vaccine manufacturers quote a price for HPV vaccine for middle-income countries. The UNICEF Supply Division also is working on vaccine procurement for middle-income countries. Low-income countries that are on track to surpass the threshold for GAVI eligibility often make an effort to apply for GAVI support while they are still eligible.
- Vaccine price negotiations should be part of cost-effectiveness analyses. For example, in Australia, male HPV vaccination was initially rejected because it was not considered to be cost-effective. However, when the price of the vaccine was renegotiated, vaccination of males became cost-effective. The United States does not have the ability to negotiate vaccine prices.
- In settings with universal health insurance, there may be opportunities to develop innovative programs to increase HPV vaccination. Vaccination, including HPV vaccination, should be covered as part of basic preventive care.

- Several efforts are being made to expand access to cervical cancer screening in low-resource settings. One approach provides universal health care coverage at a low rate for individuals (approximately \$1 per month), which covers a basic package of health care interventions. The Gates Foundation has lobbied to include cervical cancer screening in this package of services in some areas. The Foundation also has looked at ways to provide access to low-cost cervical cancer screening through reproductive health networks (e.g., Planned Parenthood, Population Services International). These private networks serve more than 100 countries, in which they provide about half of the countries' reproductive services.
- In most developing countries, vaccination programs are nationally mandated and involve mass vaccinations at centralized locations on certain days. Most people in these countries receive vaccinations through the public sector, with only a small percentage receiving services through the private sector. However, in some countries, ensuring that patients utilizing private-sector health care services have access to HPV vaccine may help increase uptake.
- Most developing countries use an opt-out policy for vaccination, which is significantly different from the consent processes in the United States. With the opt-out approach, people are made aware of when and where vaccinations are being done (e.g., school, health center). On the vaccination date, it is assumed that all eligible people present will receive vaccines (e.g., children could be vaccinated even if they are not accompanied by a parent). The lack of a formal consent process removes an obstacle to vaccination.
- The opt-out policy may work well in developing countries, but it may be difficult to translate this approach for use in high-resource countries such as the United States, Australia, Canada, and the United Kingdom.
- High-income countries that have achieved high rates of HPV vaccination (e.g., Canada, Australia, the United Kingdom) have single-payer systems. Although most adolescents in the United States have coverage for vaccination through private insurance or the Vaccines for Children program, having multiple payers makes it more difficult to implement some types of programs (e.g., school based).
- Many people in the United States respond negatively to the term “school mandate.” The term “school requirement” is generally better received.
- Traditionally, U.S. school requirements have focused on vaccines that prevent diseases that could be acquired or transmitted at schools (e.g., polio). The first exception to this was the hepatitis B vaccine, but, for some reason, there was little resistance to creating a school requirement for this vaccine. Although HPV is not a virus that will spread in schools, it may be possible to justify school requirements for HPV vaccine based on the fact that it could reduce health disparities.
- Health disparities are a big problem in the United States, and efforts should be made to ensure that populations with high rates of cervical cancer have access to HPV vaccines. Focusing school-based vaccination initiatives among these high risk populations, such as girls in Appalachia and immigrants in Texas, might be one way to address this issue.
- Differences in HPV vaccination rates among racial/ethnic groups in the United States do not follow the pattern often seen for other health indicators. For example, African-American girls are more likely than white girls to receive the first dose of the vaccine, although the percentage of girls receiving all three doses is still relatively low. Any program for HPV vaccination should utilize an approach that helps adolescents receive all three recommended doses of the vaccine.

## **PUBLIC COMMENT**

- Clyde McCoy from the University of Miami School of Medicine urged the Panel to consider the populations in the United States that often experience health disparities, including Native populations, people in Appalachia, immigrants, and minorities.



## **SESSION THREE: HPV VACCINATION PROGRAM DEVELOPMENT**

### **DR. EDWARD TRIMBLE**

#### **NCI CENTER FOR GLOBAL HEALTH**

##### **BACKGROUND**

Following graduation from Harvard College and the Johns Hopkins University School of Medicine, Dr. Trimble trained in obstetrics and gynecology at the Vanderbilt University Medical Center. He earned a Master of Public Health degree from the Johns Hopkins School of Hygiene and Public Health, then completed a fellowship in gynecologic oncology at Memorial Sloan-Kettering Cancer Center. He is board-certified in obstetrics, gynecology, and gynecologic oncology by the American Board of Obstetrics and Gynecology. In September 2011, Dr. Trimble was appointed Director of the NCI's new Center for Global Health. Between 1991 and 2011, he was Head of Gynecologic Cancer Therapeutics and Quality of Cancer Care Therapeutics, Clinical Investigation Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI. His duties involved scientific liaison with the Gynecologic Oncology Group and the American College of Surgeons Oncology Group, as well as oversight of issues involving the elderly, minorities, women's health, international collaboration, cost, cancer health disparities, health-related quality of life, and patient-reported outcomes in NCI-sponsored treatment trials. For his work at NCI he has received two Public Health Service Commendation Medals, six NIH Merit Awards, and the NCI Director's Gold Star Award.

##### **KEY POINT**

- NCI is trying to leverage the increased global attention to noncommunicable diseases in its effort to help promote HPV vaccination and control. NCI has been working closely with CDC to ensure that the new WHO action plan for noncommunicable diseases includes promotion of HPV vaccination. NCI also has been working closely with other organizational partners on cervical cancer control plans.

### **DR. SUSAN WANG**

#### **HPV VACCINE INTRODUCTION IN DEVELOPING COUNTRIES: KEY ISSUES AND WHO'S ROLE**

##### **BACKGROUND**

Dr. Wang received her A.B. from Harvard College in Cambridge, Massachusetts, and her M.D. and M.P.H. from Columbia University in New York City. She completed internal medicine and pediatrics training at Duke University Medical Center in Durham, North Carolina, and is board-certified in both specialties. She was a primary care physician in North Carolina before she joined the U.S. CDC in 1996. She is a fellow of the American Academy of Pediatrics and a member of the American College of Physicians. At CDC, Dr. Wang's areas of work included outbreak investigations, infection control, injection safety, HIV postexposure prophylaxis, U.S. and global surveillance of antimicrobial resistance of *Neisseria gonorrhoeae*, public health responses to Severe Acute Respiratory Syndrome (SARS) and influenza, U.S. and global perinatal hepatitis B prevention, and integrated monitoring of health services (e.g., family planning, hepatitis B vaccination, sexually transmitted disease [STD] and HIV screening) for adolescents in nontraditional venues. Since December 2008, Dr. Wang has been a medical officer for new vaccines in the Expanded Programme for Immunization (EPI) at the World Health Organization in Geneva, where she provides technical and strategic support to countries and global partners for the

introduction of new vaccines. She leads the WHO work for HPV vaccine implementation in countries and advises GAVI on HPV vaccine program implementation.

## KEY POINTS

- The WHO Noncommunicable Diseases Global Monitoring Framework was developed to enable global tracking of progress in preventing and controlling major noncommunicable diseases (e.g., cardiovascular disease, cancer, chronic lung diseases, and diabetes) and their key risk factors. The Framework comprises 9 global targets and 25 indicators and will be up for adoption by member states during the World Health Assembly in May 2013. Three elements of the framework—cervical cancer screening, hepatitis B vaccination, and HPV vaccination—relate to cancer.
- WHO provides review of and advice on immunization and vaccine issues to GAVI, UNICEF, UNFPA, the United National Joint Programme on HIV/AIDS [UNAIDS], and other organizations that are starting to work with HPV vaccine.
- Three challenges unique to HPV vaccine introduction are the target population (9- to 13-year-old girls), vaccine delivery, and costs (of the vaccine and delivery). The target population is not a group that routinely has been served by most immunization programs. Understanding the demographics of this population is a difficult undertaking. The vaccine requires delivery of three doses over the course of six months. In most developing countries, similar health services that currently are provided to the target population (e.g., deworming, malaria, HIV prevention) do not require health workers, injections, or cold chains. HPV vaccination requires new routine delivery services and more social mobilization. WHO-PATH analysis suggests that for GAVI-eligible countries, start-up costs for vaccine delivery are about \$3-5 per girl, and operational costs for delivering three doses are about \$4-6 per girl.
- HPV vaccine introduction provides the opportunity to establish primary care for a new age group of patients, which would ultimately strengthen health systems. Additionally, there are new stakeholders and partners that will bring added experience and expertise outside of traditional child health partners.
- WHO recommends that countries perform Post-Introduction Evaluations of immunization programs following new vaccine introduction. WHO has led HPV evaluations in five countries in four world regions. When implementing HPV vaccination, every country, regardless of development status, has an array of problems to solve. The size and location of target populations often are revised after the first and even after the second year of HPV vaccine use; delivery strategies also often need modification. Investments in information, education, and communication are critical to successful HPV vaccine implementation.
- When schools are used for vaccine delivery, success and affordability are dependent on good coordination between the Ministry of Education and the Ministry of Health, engagement and education of local school and health staff, and high school attendance among girls. It is helpful to make use of any existing infrastructure, such as a school health coordinator or school immunization teams. In the absence of existing infrastructure or ongoing additional funding support, the logistics and costs of using schools for delivery may not always be sustainable.
- A country cannot rely solely on school-based delivery to vaccinate the girls who are least likely to access cervical cancer screening later in life. Data from Niger show that about 60-70 percent of urban 9- to 13-year-old girls attend school compared with 20 percent of rural girls. Similarly, about 60 percent of the wealthiest girls attend school compared with 20 percent of the poorest girls.

## **MR. MAURICE GATERA**

### **ACHIEVING HIGH COVERAGE IN RWANDA'S NATIONAL HPV VACCINATION PROGRAM**

#### **BACKGROUND**

Mr. Gatera is Director of the Vaccine Preventable Diseases Division of the Rwanda Biomedical Center. He is responsible for overseeing and coordinating all immunizations in Rwanda and has supervised the rollout of vaccines for rotavirus, measles, and rubella. Mr. Gatera is also a member of the GAVI Alliance Global Accelerated Vaccine Initiative HPV subteam. Prior to his position with the Vaccine Preventable Diseases Division, Mr. Gatera was in charge of the Expanded Program on Immunization's Target Diseases Surveillance Program at the Ministry of Health, where he implemented an acute flaccid paralysis surveillance system. Mr. Gatera has extensive experience in leadership, research, program implementation, and monitoring and evaluation, having worked in immunization programs for the past eight years. He has earned degrees in population studies and public health management. He also received a certificate in vaccinology from the Regional Institute of Public Health in Ouidah, Benin. Mr. Gatera currently is pursuing his M.P.H. degree in field epidemiology and laboratory training at the National University of Rwanda.

#### **KEY POINTS**

- Rwanda has introduced the HPV, pneumococcal conjugate, and rotavirus vaccines within the past five years, resulting in a 50 percent reduction in child mortality between 2005 and 2010.
- Implementation of Rwanda's HPV vaccine program revolved around three key factors: systematic inclusion of all stakeholders, school-based delivery, and a multiphased vaccine delivery strategy.
- A Technical Working Group including representatives from government ministries, clinicians and other health experts, and key development partners was formed to ensure systematic inclusion of stakeholders. Subcommittees were created to address several aspects of vaccine program implementation, including cold chain logistics, social mobilization, and program monitoring and evaluation. Systematic inclusion also involved a communications strategy that included speeches by important figures such as the First Lady, technical assistance, and a public-private community partnership among local leaders, community health workers, and teachers.
- Utilizing a school-based strategy required a partnership with the Ministry of Education, since vaccine coverage could be maximally targeted at the 98 percent of Rwandan girls who attend primary school. "Health days" is the term used for vaccination days. On these days, local health care providers and teachers also discuss hygiene, nutrition, infectious diseases, and reproductive health with parents and students. Vaccination is completely voluntary in Rwanda, so parents/guardians are instructed to accompany their daughters to school for the purpose of giving consent.
- Year one (2011) of the multiphase vaccination strategy targeted girls in primary grade 6 to receive the full three-course dose of Gardasil®. Years two and three targeted the same group of girls, but added a "catch-up" phase targeting girls in secondary grade 3. Years four and beyond of the vaccination strategy will target girls age 12 in any grade and in the community.
- Three major challenges were encountered in implementing the HPV vaccination program in Rwanda. First was the public's understanding of eligibility for vaccination. Parents wanted all children to be immunized and female schoolteachers also wanted to receive the vaccine. Solutions to this problem included radio and onsite informative communication and an announcement by the Ministry of Health acknowledging the benefits of vaccinating adult women while emphasizing that the national program was for girls before sexual debut.

- The second challenge was vaccinating girls absent from school. Some girls were sick or otherwise absent from school on vaccination days. A small number were not enrolled at the time of vaccination. To address this problem, community health workers were mobilized to trace missing girls. Identified girls then were vaccinated at the local health center if parental/guardian consent was given.
- The third challenge was resistance from the international community over initial high fixed costs and concern that HPV may distract from more cost-effective child health interventions. Solutions to this resistance included development of a systematic noncommunicable diseases program, Merck's provision of free vaccines for the first three years of the program, and high-level leadership commitment to a long-term cervical cancer control program.
- A well-established vaccine delivery system, including cold chain, transportation, human resources, and monitoring capacity, is needed to implement a successful HPV vaccination program. It is also important to have a health system with strong communication capacity and collaboration between public and private institutions.
- In August 2012, Rwanda submitted a proposal to GAVI for HPV vaccine support. The application was accepted with clarification. GAVI support will begin in 2014 and continue through 2017. Merck has lowered the price of Gardasil® to \$5 per dose for GAVI-eligible countries. In addition, Rwanda is ready for co-financing according to GAVI's co-financing policy.

## **DR. D. SCOTT LAMONTAGNE**

### **SUCCESSFUL HPV VACCINE DELIVERY STRATEGIES: EVIDENCE FROM THE PATH DEMONSTRATION PROJECTS**

#### **BACKGROUND**

Dr. LaMontagne is a Senior Technical Officer for HPV vaccines at PATH. For the past five years, he was Research Manager for PATH's HPV vaccine demonstration projects, which vaccinated more than 65,000 girls in India, Peru, Uganda, and Vietnam. He serves as a member of the GAVI Alliance HPV subteam and holds an affiliate assistant professor position with the Department of Global Health at the University of Washington. Prior to joining PATH, Dr. LaMontagne was lead scientist and member of the executive management team for the National Chlamydia Screening Program in England. His career has focused on bridging the gap between research and policy by focusing on evidence-based decision making in program implementation. He has over 17 years of experience in infectious disease surveillance, operations and implementation research, public health program implementation, monitoring and evaluation, and project management for government and nongovernment agencies at local, state, and national levels in developed and developing countries. He is a specialist in surveillance and epidemiology of HPV, *Chlamydia trachomatis*, other sexually transmitted infections, and tuberculosis. Dr. LaMontagne has a Ph.D. from Middlesex University in London, an M.P.H. degree from Yale University, and a bachelor's degree in Japanese studies from the University of Washington.

#### **KEY POINTS**

- PATH conducted five-year HPV vaccine demonstration projects in India, Uganda, Peru, and Vietnam. The effort was funded by the Bill and Melinda Gates Foundation, with vaccine donations from Merck and GlaxoSmithKline. Vaccine demonstration programs provide countries with a learning opportunity prior to initiating a national vaccine strategy.
- Vaccine programs were designed for each country after a period of formative research with the government. Most countries utilized more than one delivery strategy. Peru, Uganda, and Vietnam used a school-based approach as one of their delivery strategies, which targeted 10- to 11-year-old

girls enrolled in primary grade 5 or 6. Health centers were also a delivery location for Peru and Vietnam.

- In Peru, Uganda, and Vietnam, vaccination days were predefined and required mobilization of the community to give and receive the vaccine on those days. Having defined vaccination days helps countries avoid the need to store the vaccine long term, which reduces the impact on health systems. Each delivery strategy also employed “mop-up” sessions. These are secondary vaccination strategies used to vaccinate girls who were either absent from school on the vaccination day or do not attend school at all. Mop-up days occur at schools, health centers, or fixed outreach sites.
- PATH evaluated the coverage, acceptability, feasibility, and cost of each vaccine program. On average, all but two of the delivery strategies achieved 70 to 80 percent coverage. The two strategies that did not achieve as high coverage were the Child Days Plus strategy in Uganda, which selected girls based on age, and the health-center-based strategy in Peru.
- In Vietnam, Uganda, and Peru, over 98 percent of all eligible girls were attending or enrolled in school. In India, where a significant proportion of the eligible population was out of school, there was only a 10 percent difference in coverage between out-of-school girls and those attending or enrolled in school.
- One of the critical factors in vaccine uptake was parents’ acceptability. Parents who received information about the vaccine only via flyers or the radio were significantly less likely to have their children vaccinated compared with parents who had conversations about the vaccine with health workers, teachers, other parents, or family members.
- High uptake of HPV vaccine was achievable in the demonstration projects. A variety of delivery strategies are feasible with strong coordination and careful planning between the health and education sectors. Eligible populations should be easily identifiable by age or grade to effectively deliver the vaccine.
- The most critical aspect of successful vaccine programs was government endorsement. The demonstration projects were not PATH-run programs; they were conducted by each country’s government, using their own workers, systems, and resources. Embedding HPV vaccination into government programs results in credibility and efficient delivery by using existing human resources and infrastructure.

## **SESSION THREE MODERATED DISCUSSION**

### **KEY POINTS**

- When implementing an HPV vaccine program, it is important not to underestimate the power of the media. Communication plans should be developed before program launch and should include consideration of the media. Governments should assess the media presence in their countries, including whether they are supportive of health and vaccination programs, and should leverage the media as warranted. In some cases, it is beneficial to begin circulating positive messages about HPV vaccination via radio, newspaper, and/or television before launching a program in an effort to foster a welcoming environment.
- Medical journalists can play a significant role in public perception of health programs. Governments should consider partnering with news outlets to promote dissemination of positive messages about HPV vaccination, although this approach may not be appropriate in all settings.
- Negative media coverage in Fiji had a detrimental effect on the HPV program. The program was suspended for approximately three years due to misinformation spread by the media in that country.
- Negative messages from other sectors of society also can be detrimental to program success. In some European countries, groups of scientists and policy makers have voiced opposition to the vaccine.

Some of the arguments against vaccination are based on ethics and religion, which can be difficult to counteract with scientific data.

- Many HPV programs have very high early success rates. However, it is important to continue evaluating programs over time (e.g., six months, one year, two years) to determine whether the success can be maintained. It is important that programs be capable of maintaining momentum when the strong enthusiasm that often surrounds the launch of a new program wanes.
- Champions have helped to promote HPV vaccine programs in several countries. These have included the Queen Mother of Bhutan and the First Lady of Rwanda. The most effective champions are those capable of leveraging political power and resources.
- Establishing trust is important when launching a new vaccine program. In some areas, targeting adolescent girls for HPV vaccination has caused suspicion that programs are providing family planning services. There also may be a lack of trust among some subpopulations (e.g., African-American community in the United States). Suspicion often can be overcome if leaders exhibit support for their programs (e.g., being immunized or having family members immunized). One participant shared an example of when he was talking to parents about an HPV immunization program being launched on the south side of Chicago. One parent was suspicious of the effort to immunize young African-American girls. The participant was able to address this concern somewhat by responding that he had had his own adolescent daughters vaccinated.
- For PATH-supported HPV vaccine programs, consent processes have been dictated by the policies of the home country's Ministry of Health. In some cases, formal consent has been used, but in other cases an authorization or community consenting process has been employed. PATH found that utilizing a formal consent process in settings where formal consent was not the norm raised suspicions about the program among communities, teachers, and health workers.
- PATH-supported HPV programs have used a variety of approaches to raise community awareness of the programs. All of the programs developed leaflets for parents that included key messages, questions and answers, and information about the program schedule. Some programs also have utilized radio programs, parent education sessions, or speeches by champions or local leaders. Awareness-raising activities are most important early in program implementation. It may be possible to reduce communications efforts as the program becomes routinized. For example, the HPV program in Uganda, which is in its fifth year, no longer conducts community awareness campaigns because the community has come to expect HPV vaccination to occur at certain times each year.
- Physician-directed communications often are not a major part of communication strategies in low-resource countries. In contrast with the situation in the United States, physicians in these countries generally do not influence decision making about vaccination. Community health centers, not private physician offices, are the primary mode for distributing vaccines. However, in some settings, it is important to educate physicians about HPV vaccine and vaccination programs so they will be able to communicate with parents or patients who come to them with questions.
- Some programs that utilized school-based delivery of HPV vaccines conducted educational sessions with teachers prior to launching their programs. Parents sometimes participated in these sessions. This approach offered the opportunity for exchange among health workers, teachers, and parents prior to vaccination. The support of teachers can be important if vaccines are delivered in schools.
- WHO conducted a communications assessment of the HPV programs implemented in Latvia, Malaysia, and Rwanda. The assessment identified a number of things done well in Malaysia. Malaysian newspapers tend to be sensationalistic; to counteract the expected negative messaging, the Malaysian government posted factual information in the same newspapers. They also made use of social media outlets such as Facebook and Twitter. In addition, they were cognizant of potential concerns of the Muslim population in the country. They had the vaccine authorized as halal and

developed posters showing mothers and, perhaps more importantly, fathers being supportive of having their daughters vaccinated.

- Programs need to be prepared to counteract negative messaging about HPV vaccination (e.g., about adverse events). These negative messages can begin circulating even before the program is launched and can be detrimental to uptake.
- The patents for current HPV vaccines will expire in the coming years. There is not a generic vaccine manufacturing industry, so it is unlikely that generic versions of the vaccines will become available and influence their price. However, there may be opportunities to reduce costs. The price of the hepatitis B vaccine declined substantially when the vaccine began to be regionally manufactured. Regional manufacturing also may contribute to regional development efforts.
- HPV vaccines that are distinct from the VLP-based vaccines manufactured by GlaxoSmithKline and Merck are being developed. These vaccines are at various points in development but may become available in the next several years.
- Merck is developing a nine-valent vaccine that would include HPV types that account for up to 90 percent of cervical cancer cases in the world.
- GlaxoSmithKline and Merck both are working on development of a two-dose schedule for their respective HPV vaccines. A two-dose schedule may help improve compliance; however, it should be implemented with caution. If two doses are eventually found to be insufficient to provide protection, it would be very difficult to recall girls to receive a third dose.
- Simplifying vaccine delivery through new modes of administration (e.g., needleless) or reduced dosage requirements would undoubtedly make it easier to implement vaccine programs, particularly in low-resource settings. However, it is possible that technological advancements that are unfamiliar may cause hesitancy about vaccination. For example, there was resistance to using the nasal spray influenza vaccine when it first became available.
- Efforts should be made to understand local factors that contribute to vaccine hesitancy. The WHO Strategic Advisory Group of Experts on Immunization has created a working group to look at vaccine hesitancy. One issue that should be anticipated is the potential of anecdotal accounts of adverse events to cause vaccine hesitancy. Formal adverse event monitoring can help counteract this problem.
- In PATH-supported programs, the percentages of girls who have failed to complete the HPV vaccine series are between 0.5 and 12 percent, with 12 percent being an outlier. The high rates of completion have been due largely to the dedication of community health workers, who have gone above and beyond what they were asked to do to ensure that every girl receives each vaccine dose. Data on three-dose coverage in Bhutan and other WHO-supported countries are being collected.
- Increased use of community health workers may represent an effective strategy for increasing HPV vaccine uptake in the United States. However, differences in the structure of health care systems between the United States and low-resource countries may affect how this approach can be translated. In low-resource settings, community health workers deliver a broad array of services, and it is often relatively easy to add HPV vaccination to the list of services they provide. Providers in the United States are generally more specialized, so it might be more expensive and/or logistically challenging to use community health workers in this setting.
- Cost analyses for HPV vaccine programs in various countries are under way. Argentina is using the PAHO ProVac tool to estimate costs associated with its program. Cost data have been generated for PATH-supported programs. Uganda piloted two delivery strategies for HPV vaccination and compared the costs of the approaches. The first approach involved school-located vaccine delivery on a series of dedicated dates at a cost of approximately \$6 for a three-dose regimen. The second approach involved delivery of two of the three HPV doses through an ongoing program that provided other vaccines, deworming, and vitamin A supplementation twice a year. The third HPV vaccine dose

was provided in schools. This approach cost only \$1.50 for a three-dose regimen. Uganda is planning to adopt the latter strategy as it rolls out its national program.

- A repository for best practices related to HPV vaccine program development and implementation would be helpful.
- Reporting of adverse events following vaccination is different in low-resource areas than it is in the United States. Surveys have found rates of adverse events that are similar to those found through passive reporting in higher-resource settings. However, many of the minor events that occur in low-resource areas are not reported to national registries. This creates some difficulty in evaluating adverse events in developing countries.
- The NCI Center for Global Health is interested in promoting uptake of HPV vaccine globally. The global emphasis on noncommunicable diseases, which include cancer, provides an opportunity to do this.

## **SESSION FOUR: HPV VACCINATION PROGRAM MONITORING AND EVALUATION**

### **DR. EDUARDO FRANCO**

#### **HPV VACCINATION PROGRAM MONITORING AND EVALUATION IN CANADA**

##### **BACKGROUND**

Dr. Franco is the James McGill Professor, Director of the Division of Cancer Epidemiology, and interim Chair of the Department of Oncology at Montreal's McGill University. Since 1985, his research has focused on the epidemiology and prevention of cancers of the uterine cervix and anogenital tract, upper aerodigestive tract, and prostate, along with childhood cancers. He has published over 350 articles, 55 chapters, and 2 books, and has proffered over 560 invited lectures. Dr. Franco has served on the editorial boards of the *American Journal of Epidemiology*; *Cancer Detection and Prevention*; *Cancer Epidemiology, Biomarkers & Prevention*; *eLife*; *Epidemiology*; *International Journal of Cancer*; *Medical and Pediatric Oncology*; *PLoS-Medicine*; and *Preventive Medicine*. His distinctions include: Fellow of the Canadian Academy of Health Sciences (2012); Fellow of the Royal Society of Canada (2011); McLaughlin-Gallie Award, Royal College of Physicians and Surgeons of Canada (2011); Lifetime Achievement Award, American Society for Colposcopy and Cervical Pathology (2010); Honorary President, EUROGIN Congress, Monaco (2010); Women in U.S. Government's Presidential Leadership Award (2008); Canadian Cancer Society's Warwick Prize in cancer control research (2004); Medical Research Council of Canada's Distinguished Scientist (2000); Educational Excellence at McGill University (2000); and Montreal Convention Centre's Ambassadeur émérite (2007).

##### **KEY POINTS**

- The first HPV vaccine was approved in Canada in December 2006, about six months following approval by the U.S. FDA. The Canadian HPV vaccine program was launched in September 2007. As of March 2013, 4.3 million doses of the quadrivalent vaccine had been administered in Canada; worldwide, over 100 million doses had been administered. About 79 percent of the vaccine distribution in Canada was delivered via its school-based program; 21 percent of the administered doses were in the private sector. Prince Edward Island will begin to vaccinate sixth-grade boys in the fall of 2013.
- Year-to-year vaccine coverage has slightly decreased since implementation in many of Canada's provinces. This decrease is partly due to negative public messages about HPV vaccination.
- In 1999, the Canadian National Advisory Committee on Immunization recommended establishment of a network of immunization registries. Immunization registries are the cornerstone of surveillance.



They capture vaccination data at the individual level, thus accurately measuring coverage and evaluation of adverse events. The Canadian Immunization Registry Network was established to coordinate the development of standards and facilitate knowledge sharing.

- Canada has considerable public and professional support for a national immunization registry. The 2003 SARS outbreak prompted increased funding for immunization programs and use of electronic health records across all provinces. There is an effort to harmonize the use of barcodes on vaccines to capture and centralize immunization data. Nevertheless, challenges remain in implementation and integration of Canadian immunization registries.
- Registries in Canada are managed by the provinces and territories. Most of the provinces and territories have registries in place for cancer, cervical screening, immunization, and HPV immunization. The next step will be to link these registries.
- Canada is working to increase interoperability among the registries of its provinces and territories to allow data to be captured at a national level. To compensate for the current lack of a national network of immunization registries, the Public Health Agency of Canada conducts telephone surveys via random-digit dialing to assess immunization coverage and provide data to WHO. Drawbacks to this approach are that it is costly and there is responder bias. Random-digit dialing is becoming a biased approach to collect information due to the increasing incidence of cell-phone-only households.

## **DR. NATHALIA KATZ**

### **UNIVERSAL HPV VACCINE INTRODUCTION IN ARGENTINA: PROGRAM MONITORING AND EVALUATION**

#### **BACKGROUND**

Dr. Katz is a physician working in the area of scientific recommendations for the National Program of Control of Vaccine-Preventable Diseases (ProNaCEI, in Spanish) of the Ministry of Health of Argentina. Her work includes introduction of new vaccines to the national vaccination schedule, creating scientific guidelines, training, supervising distribution logistics, and monitoring coverage and events attributable to vaccination and immunization. Dr. Katz also coordinates the influenza and HPV vaccines, as well as the universal vaccine against hepatitis B, among others. She collaborates in the design and execution of research studies to measure the impact of the introduction of the HPV and influenza vaccines. Furthermore, she coordinates the vaccination of adults and adolescents, including training, intensive scientific recommendations, and actions to improve and encourage vaccination at these stages of life. Dr. Katz specializes in internal medicine and infectious diseases. She is a member of the Infectious Diseases Society of Argentina, currently participating in the Vaccines Commission. In her private practice, she is devoted to general clinical infectology and to the control, treatment, and monitoring of HIV-positive patients in particular. Dr. Katz has been invited to various national and international conferences to convey Argentina's experience in the introduction of new vaccines, specifically the HPV vaccine.

#### **KEY POINTS**

- The population of Argentina, a country with a land area of 2.78 million square kilometers, is over 40 million. Politically, Argentina is subdivided into 24 provinces. In 2011, there were 750,000 new births.
- The HPV vaccine was introduced in Argentina in October 2011. The target population for immunization is 11-year-old girls. Argentina purchased the vaccine through PAHO's Revolving Fund. The main goal of the vaccine program is to reduce cervical cancer incidence and mortality. Each year, 2,000 Argentinian women die due to cervical cancer.

- The HPV vaccination program in Argentina involves interaction between several groups, including the Program for the Control of Immunopreventable Diseases, the Argentinian National Cancer Institute's Program for Cervical Cancer Prevention, and the PAHO Regional HPV Reference Laboratory.
- For girls born in 2000 or 2001, there has been 81 percent vaccination coverage for the first dose, about 65 percent for the second dose, and 42 percent for the third dose.
- Argentina is utilizing a passive surveillance system for adverse events one year following immunization. With almost 1.3 million doses administered, there have been 150 reported adverse events per year. The adverse event rate is 11.65 events per 100,000 doses. The rate of adverse events is higher for the first dose compared with the second and third doses. The severe adverse event rate is 0.62 per 100,000 doses. Severe adverse events have included five syncopal seizures, one generalized rash, and two bronchospasms.
- Argentina is evaluating the effectiveness of its HPV vaccine program on three levels: HPV genotype prevalence; incidence of precancerous lesions; and cervical cancer incidence and mortality. Fifteen to 20 years are needed to assess the effect of the vaccine on cervical cancer incidence and mortality, but the midterm goals (reductions in HPV prevalence and precancerous lesions) can be evaluated earlier.
- Argentina is preparing to launch a prospective project to monitor the prevalence of 12 HPV genotypes with the PAHO Regional HPV Reference Laboratory. This project, HPV Genotype Prevalence in Adolescents: A First Step Toward Infection Surveillance in Argentina, will determine type-specific HPV prevalence in sexually active adolescent females (15-16 years old) from cervical samples obtained between May 2013 and May 2014. In the second stage of the project, samples will be collected between May 2017 and May 2018. Results from both stages will be compared to detect type-specific prevalence shifts in the population.
- Challenges in implementing the HPV vaccine program have included immunizing adolescents, sustaining high coverage levels, completing the full three-dose schedule, elaborating the impact of introduction projects, and maintaining a comprehensive approach.

## **DR. EDUARDO LAZCANO**

### **EXPERIENCE IN PRIMARY PREVENTION OF CERVICAL CANCER IN MEXICO**

#### **BACKGROUND**

Dr. Lazcano has a Ph.D. in epidemiology in addition to a medical degree. He has over 15 years of experience working in studies related to HPV that have led to new health policies in Mexico. He also has worked on HPV studies in other countries, including Brazil and France. As Director of the Center for Population Health Research, National Institute of Public Health, in Cuernavaca, Mexico, Dr. Lazcano facilitated the design, implementation, and analysis of population studies that led to the establishment of HPV vaccination protocols.

#### **KEY POINTS**

- Mexico's National Institute of Public Health has received funding to conduct clinical trials of the efficacy of the bivalent and quadrivalent HPV vaccines. The Institute also has received donations from Digene, QIAGEN, and Roche to develop HPV testing at the population level.
- Since August 2012, Mexico has had universal coverage of HPV vaccine in girls 10 years of age (primary grade 4); 1.3 million girls are included in this cohort. Mexico utilized an alternative vaccination scheme—0, 6, and 60 months—to increase coverage and evaluate whether only two doses would be necessary for vaccine efficacy.

- From 2006 to 2012, the Mexican government decreased the cost of the quadrivalent vaccine from 80 to 12 Mexican dollars per dose. In 2013, the bivalent vaccine was offered at the discounted rate, requiring studies of interchangeability.
- The National Institute of Public Health was commissioned to evaluate and monitor the bivalent and quadrivalent vaccines in a clinical trial of 2,500 girls in three comparison groups. The bivalent and quadrivalent vaccines also are being compared in women 18-25 years of age. Study results have shown that a possible plateau is reached at 20 months with the bivalent vaccine. Recent evidence suggests that the plateau lasts longer when the age at vaccination is younger and the spacing of the second dose is between 6 and 12 months after the first dose.

## **DR. LAURI MARKOWITZ**

### **HPV VACCINATION PROGRAM MONITORING AND EVALUATION**

#### **BACKGROUND**

Dr. Markowitz received her medical degree from Albert Einstein College of Medicine and completed her residency training in internal medicine at the University of Pennsylvania. She currently is the team lead for epidemiology research in the CDC Division of STD Prevention. Over the past 25 years, Dr. Markowitz has worked on a variety of vaccine-preventable diseases as well as sexually transmitted infections. Since 2005, she has coordinated the HPV Vaccine Working Group of the Advisory Committee for Immunization Practices and spearheaded the development of recommendations for use of HPV vaccine in the United States. Dr. Markowitz has provided consultation related to HPV vaccine to a variety of national and international groups, including the HPV Vaccine Advisory Committee of the World Health Organization.

#### **KEY POINTS**

- Vaccine monitoring and evaluation can address a variety of issues. The most important aspect is evaluation of the vaccine delivery program, which includes coverage in the target population, feasibility, acceptability, and cost. Monitoring also includes safety (adverse events following immunization) and vaccine impact. Evaluating the impact of a vaccine involves looking at morbidity and mortality rates, effectiveness in a real-world setting, and epidemiologic patterns of disease after vaccine implementation.
- WHO recommends HPV vaccine coverage monitoring be conducted by dose and year of age. This allows comparison of coverage trends over time and geographic areas. A challenge to this strategy is determining the denominator to assess coverage.
- WHO is developing HPV Vaccine Coverage Monitoring Guidance that will include tally sheets and an immunization coverage cluster survey. There also is an annual WHO-UNICEF Joint Reporting Form used to collect vaccine coverage data for other vaccines. Since 2010, WHO has recommended that countries report on HPV vaccine doses administered so that vaccine administration can be assessed and standardized.
- WHO also recommends that countries conduct Post-Introduction Evaluations approximately 6-12 months after introducing any new vaccine. Five Post-Introduction Evaluations have been conducted to date, in Bhutan, Rwanda, Latvia, Macedonia, and Mongolia.
- In 2009, WHO held a consensus meeting on HPV vaccine coverage and impact monitoring. WHO concluded that monitoring is not a prerequisite for vaccine introduction. However, two potential endpoints for monitoring impact were suggested: HPV prevalence monitoring in young women and cervical cancer registries. Monitoring HPV prevalence among sexually active young women in one or two select settings would provide an important early indication of HPV vaccine impact. However,

because this approach requires considerable resource commitment for at least five to ten years, WHO has not broadly encouraged its implementation. Rather, it has indicated that all countries should consider establishing or improving reporting to cervical cancer registries in order to measure impact of HPV vaccination.

- HPV prevalence monitoring has been initiated in Rwanda and Bhutan. The approach being used involves collection of cervical cells in women aged 18-69 in 2012 and 2013; repeat cervical cell surveys of women under 29 years of age in 2016 and 2021; and collection of urine from 18- and 19-year-old women in 2013, 2015, and 2017.
- There has been a dramatic decrease in the number of women under 21 years of age in Australia with genital warts since introduction of the vaccine in 2007. There also has been a decrease in the 21- to 30-year-old age group. HPV prevalence also has decreased about 80 percent in women 18-24 years of age attending family planning clinics since introduction of the vaccine.
- HPV vaccine coverage in the United States has not been as high as in Australia—only 49 percent for the first dose and 32 percent for all three doses in 13- to 17-year-olds in 2010. However, even with this low coverage, there has been a significant decline in the prevalence of HPV vaccine types among 14- to 19-year-olds.
- There are a variety of challenges involved with impact monitoring. Cervical cancer registration is recommended, but there are few functioning registries in developing countries. There are efforts to establish regional hubs for general cancer registries, but it will take a long time before the impact of HPV vaccination on cancer rates becomes apparent. Prevalence monitoring also is challenging because it requires proper population selection, standardization of methods to ensure comparability of results, and acquisition of expensive reagents for sample extraction and testing.

## **SESSION FOUR MODERATED DISCUSSION**

### **KEY POINTS**

- A number of cervical cancer screening programs are shifting from cytologic screening to HPV testing as the primary mode of screening. In Australia and Canada, this transition could take place within the next few years. This could provide a way to monitor the impact of HPV vaccination on the distribution of HPV types. The potential value of vaccine impact monitoring likely is not sufficient to warrant a shift from cytologic screening to HPV testing; however, if HPV information is collected through screening practices, either alone or in combination with cytologic testing, it should be used to monitor vaccine efficacy.
- Studies correlating markers of immune response to HPV vaccination with protection from disease are under way. This could potentially provide another option for measuring HPV vaccine impact. However, it is unlikely that immune-based monitoring would provide an advantage over HPV testing or screening for precancerous lesions.
- Monitoring and evaluation of HPV vaccine impact in low-resource settings could benefit from advancements in laboratory techniques. In general, however, the technological advances are driven by the demand of the industrialized world. These tools may be modified for implementation in low-resource settings, but development of tools specifically tailored to the needs of low-resource areas likely would require establishment of some financial incentive.
- There was initially concern about using HPV prevalence as a measure of HPV vaccine impact. Concerns were related to the fact that HPV16 and 18 account for a small percentage of HPV infections, and it was unclear whether the vaccine would prevent any infection or only persistent infection, which would be more difficult to detect. However, the data indicate that HPV vaccination does reduce overall HPV prevalence.

- The cost of monitoring and evaluation can be very high. Some countries may need to weigh the expenses of these efforts against the possible value of greater investment in increasing vaccine uptake.
- Research on urine-based testing for HPV is being conducted in Bhutan and Rwanda.
- Herd immunity refers to reduction of disease or infection among unvaccinated individuals. From a financial perspective, it would be beneficial to take herd immunity into account when establishing targets for vaccination (i.e., only the number of individuals needed to achieve population protection would be vaccinated). Lower levels of vaccination are likely needed to achieve herd immunity against a sexually transmitted infection like HPV than for infections transmitted through other modes (e.g., respiratory). One challenge with predicting herd immunity is the fact that vaccination and HPV transmission are not random within the population.
- Initial indicators of the impact of HPV vaccination, including the study of genital warts in Australia, have been based on ecological data. More-formal linkage analyses using vaccine and screening registries are ongoing in Australia. In addition, researchers in Australia are conducting individual-level studies on genital warts. Research efforts also are under way to investigate HPV infection at other sites.
- Adoption of a two-dose HPV vaccine schedule is being considered in multiple locations. Based on current data from the 0-6-60-month study, Mexico is planning to move to a two-dose schedule. Quebec also is looking into the possibility of administering only two doses; this decision will be based on serological markers of vaccine activity.
- Asking patients for their HPV vaccination status at the time of cervical cancer screening was discussed as a possible approach to studying vaccine impact. Some of the programs in Canada do collect this information at the time of screening. However, in the United States and Australia, this is not routine, in part because of the length of time between vaccination and screening. Australia will depend on linkage of its vaccination and screening databases to measure impact.
- In the United States and Canada and other high-income countries, linked immunization and cancer registries are the gold standard for monitoring the impact of HPV vaccination. However, this level of monitoring is not necessary or realistic in all settings.
- From a scientific standpoint, randomized controlled clinical trials provide the most convincing evidence of the effectiveness of an intervention. Cohort and case-control studies are also informative. However, these types of studies do not need to be repeated in every location around the world. Generating level-one data on the efficacy of an intervention in a few places should be sufficient. Ecological studies, which are less resource-intensive, can be done in other locations.
- Organizations that currently are supporting vaccination programs in low- and middle-income countries will not continue to provide support indefinitely. Efforts should be made to help low- and middle-resource countries develop sustainable infrastructures so they can conduct their own research and make improvements to their health care systems. Building local capacity will lead to long-term, sustainable vaccine programs and the ability to monitor the impact of those programs. Efforts like the recent NCI request for applications calling for U.S. cancer centers to partner with cancer centers in low- to middle-income countries may help accomplish this.

## **PUBLIC COMMENT**

- There was no comment from the public.

## **CLOSING REMARKS**

Mr. Mittman informed participants that the second day of the workshop would focus on discussion of priorities to be considered by the Panel as it prepares its annual report. Panel members thanked the participants for their contributions to the first day of the workshop.

## **WEDNESDAY, APRIL 24, 2013**

## **OPENING REMARKS**

Dr. Rimer welcomed participants back for the second day of the workshop and acknowledged ongoing work by several organizations related to global HPV vaccination. Mr. Mittman explained the framework for the discussion and identification of potential recommendations. Participants were asked to discuss two main topics: (1) how lessons learned in other parts of the world can be applied to increase HPV vaccine uptake in the United States and (2) how the United States can promote global HPV vaccine uptake.

## **IDENTIFYING PARTICIPANT PRIORITIES**

Key themes discussed throughout the workshop were identified, including strategies for increasing HPV vaccination in the United States and globally. Participants discussed which strategies and activities should be given priority. Top priorities listed below are those that were supported by the highest number of participants. Priorities recommended by the participants will be considered by the Panel as it develops recommendations for inclusion in its annual report.

## **PRIORITIES TO INCREASE HPV VACCINE UPTAKE IN THE UNITED STATES**

### **TOP PRIORITIES**

- Champions should be recruited to promote HPV vaccination within the United States.
- The United States should develop an integrated campaign that uses multiple evidence-based strategies to increase HPV vaccination and integrate vaccination and cervical cancer screening. It is important to collect the data that will be needed to appropriately integrate vaccination and cervical cancer screening once vaccination rates are higher. These data will help in developing good disease models that can characterize levels of risk among different cohorts depending on vaccine uptake and other factors.
- The United States should more effectively engage its health care providers to increase HPV vaccination. This should include adding HPV vaccination to practice guidelines, integrating HPV vaccination rates into quality indicators for health care practices, structuring reimbursement to incentivize vaccination, developing tools to help providers communicate with patients, and other efforts to ensure that providers strongly encourage vaccination of adolescents.
- The United States should support research with potential to simplify the logistics of vaccine administration, reduce costs, and increase uptake. For example, research should be done to determine whether fewer than three doses of HPV vaccine is sufficient to impart protection. System-level changes should be made, as necessary, to make it as convenient as possible for adolescents to be vaccinated. Community-based vaccination programs that make it convenient to get HPV vaccine have been most successful in achieving high rates of vaccination. Schools are a convenient location for vaccination, as well as for education and communication. One barrier to implementing school-located vaccination programs is difficulty billing insurance companies for the cost of the vaccine and vaccine administration.
- The United States should develop stronger public health messages regarding HPV vaccination. Areas of priority related to communication and public health messages include:

- Government-sponsored messages based on evidence are preferable to messages from other organizations (e.g., pharmaceutical companies, advocacy organizations).
  - The media should be engaged to assist in communication efforts about HPV vaccination.
  - Communication strategies for HPV vaccine should focus on specific target times for vaccination. For example, a “back-to-school” campaign could urge adolescents to get HPV vaccine and other recommended vaccines at the beginning of the school year. Alternatively, a certain week or month could be designated for awareness of cervical cancer and/or HPV vaccination.
  - Communication strategies related to HPV vaccination should strongly emphasize that the vaccines prevent cancer rather than focus on HPV as a sexually transmitted disease.
  - Messages surrounding vaccination cannot be based only on communicating facts and statistics. To be effective, they also should include narrative and appeal to adolescents’ and parents’ emotions.
- Efforts to increase HPV vaccination should focus primarily on populations at high risk of cervical cancer.

## **OTHER PRIORITIES**

- U.S. federal agencies should take a stance against the messages of antivaccine activists.
- HPV vaccine should be made available within schools and other locations, such as pharmacies, particularly for the second and third doses. One option would be federal funding for a national school-based vaccination program.
- The success of programs being implemented in the United States should be monitored so that best practices can be identified and shared within the United States and with other countries.
- The introduction of HPV vaccination in males should be evaluated.
- The United States should observe the outcomes of the ongoing work by GAVI and other organizations around the world to determine whether some of the lessons learned can be applied in the United States.

## **PRIORITIES TO INCREASE HPV GLOBAL VACCINE UPTAKE**

### **TOP PRIORITIES**

- The United States should continue its collaboration with and support of GAVI. Additional support should be provided as necessary and appropriate to scale up implementation of HPV vaccination programs. Efforts also should be made to increase demand for the vaccine in order to help lower costs.
- The United States should support research with potential to make vaccine delivery more affordable and sustainable. This would include research on the vaccine (e.g., reduced dosage) as well as health delivery systems research. Research on health care delivery should address how to effectively combine HPV vaccination and other health services.
- The United States should encourage low- and middle-income countries to make HPV program implementation a higher priority than surveillance, monitoring, and evaluation. The evidence collected to date has overwhelmingly shown that HPV vaccination is effective for preventing cervical cancer, and it is unlikely that research in different geographical areas will yield significantly different results.

- The United States should focus its resources on supporting HPV vaccination in countries that are not currently supported through other mechanisms (e.g., middle-income countries not eligible for GAVI support). Such efforts should include financial and technical assistance.
- The United States could help countries develop national strategic plans for cervical cancer control, as well as corresponding budgets for these plans. This would help these countries apply for GAVI support.

## **OTHER PRIORITIES**

- There should be a rallying call to bolster global support for cancer control efforts, including but not limited to efforts to reduce the burden of cervical cancer through HPV vaccination and screening. Sustainable financing models are needed to support implementation of programs to achieve these goals.
- The United States should help build research capacity in low- and middle-income countries. Many countries would be able to carry out high-quality research if they received financial and technical support from the United States.
- Some countries would benefit from U.S. funding to support research to measure the impact of HPV vaccination. Support for development of cancer registries would help accomplish this in some countries.
- U.S. and international regulations that restrict flexibility in HPV vaccine pricing should be revisited so that more appropriate prices can be determined based on each country's ability to pay.
- The United States should advocate for price reductions for HPV vaccine and other vaccines (e.g., pneumococcal, rotavirus).
- The HPV vaccine price negotiation process should be more transparent. This would help countries with their decision making about implementing HPV vaccine programs.
- The United States should support development of a science-based social media campaign that countries can modify and incorporate into their efforts to promote HPV vaccination.
- The United States should support HPV awareness and education efforts through the International Papillomavirus Society.
- The United States should promote regional production of the vaccine in other areas of the world. This would have the added benefit of creating jobs in these areas.

## **PUBLIC COMMENT**

- There was no comment from the public.

## **CLOSING REMARKS**

Panel members thanked the participants for their valuable contributions. Dr. Rimer asked participants to submit any additional input via email.



## **CERTIFICATION OF MEETING SUMMARY**

I certify that this summary of the President's Cancer Panel meeting, *Global HPV Vaccination: Opportunities and Challenges*, held April 23-24, 2013, is accurate and complete.

Certified by:

Date: June 27, 2013

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Barbara K. Rimer, Dr.P.H.  
Chair  
President's Cancer Panel