MEETING SUMMARY

PRESIDENT'S CANCER PANEL

HPV VACCINATION AS A MODEL FOR CANCER PREVENTION

July 24, 2012
San Francisco, California

This workshop was the first in the President's Cancer Panel's (PCP, the Panel) 2012-2013 series, *Accelerating Progress in Cancer Prevention: The HPV Vaccine Example*. During the workshop, the Panel heard expert testimony and moderated discussions regarding the scientific basis for, current status of, and continuing efforts for effective vaccination against human papillomavirus (HPV)-related cancers. The agenda for the meeting was organized into five discussion sessions.

President's Cancer Panel

Barbara K. Rimer, Dr.P.H., Chair

Owen Witte, M.D.

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

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

Meeting Co-Chairs

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

Cosette Wheeler, Ph.D., Regent's Professor, Pathology and Obstetrics and Gynecology, University of New Mexico School of Medicine

Participants

Kevin Cullen, M.D., Director, University of Maryland Marlene and Stewart Greenebaum Cancer Center

Gary Dubin, M.D., Vice President and Director, Late Clinical Development, GlaxoSmithKline Biologicals

Denise Galloway, Ph.D., Head, Cancer Biology Program, Human Biology Division, Fred Hutchinson Cancer Research Center

Maura Gillison, M.D., Ph.D., Professor, College of Medicine, The Ohio State University

Richard Haupt, M.D., M.P.H., Section Head, Adult Vaccines Clinical Research, Merck Research Laboratories

Allan Hildesheim, Ph.D., Chief, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Lauri Markowitz, M.D., Medical Epidemiologist, Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, U.S. Centers for Disease Control and Prevention

Joel Palefsky, M.D., Professor, Departments of Laboratory Medicine and Medicine, University of California, San Francisco

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

Mark Schiffman, M.D., M.P.H., Senior Investigator, Division of Cancer Epidemiology and Genetics, National Cancer Institute

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

Claudia Vellozzi, M.D., Deputy Director, Immunization Safety Office, U.S. Centers for Disease Control and Prevention

OPENING REMARKS—DRS. BARBARA RIMER AND OWEN WITTE

On behalf of the Panel, Dr. Rimer welcomed invited participants and other attendees to the meeting. 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. She stressed the importance of actionable recommendations as a meeting outcome and, indeed, a series outcome. Dr. Witte provided background on the series and workshop and introduced the meeting co-chairs, Drs. Douglas Lowy and Cosette Wheeler. Dr. Rimer also introduced and welcomed Robert Mittman, who facilitated the meeting.

OPENING ROUNDTABLE

Participants introduced themselves and stated what they thought would be the most important interventions and/or activities for reducing the burden of HPV-related cancers. Most participants agreed that increasing the availability and uptake of the vaccine in the United States and around the world, particularly in developing countries, should be a top priority. Strategies mentioned for increasing availability and uptake included implementing free school-based vaccination, mandating vaccination, conducting a national campaign to promote vaccination, including dental professionals as vaccine providers, increasing provider awareness and understanding of HPV-related cancers, emphasizing the benefits of vaccinating males, developing a vaccine that could prevent all HPV-related cancers, developing a vaccine that requires fewer than three vaccine doses, and ensuring that children understand science and epidemiology. The need for an international surveillance system for monitoring vaccine safety also was cited.

SESSION ONE: OVERVIEW AND EPIDEMIOLOGY OF HPV-RELATED CANCERS

DR. DOUGLAS LOWY

HPV-RELATED CANCERS IN THE UNITED STATES AND AROUND THE WORLD

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 growth. The papillomavirus research is carried out in close collaboration with John T. Schiller, Ph.D., with whom he has co-authored more than 100 papers over the past 25 years. Their laboratory was involved in 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 global distribution of HPV-associated cancers differs from what is observed in the United States. In the developing world, cervical cancer accounts for more than 90 percent of HPV-associated cancers and less than 5 percent of HPV-associated cancers occur in males. In the United States, although cervical cancer accounts for the majority of U.S. HPV-associated cancer cases, notable proportions also are observed in the oropharynx, anus, vulva/vagina, and penis. Furthermore, at least

30 percent of HPV-associated cancers in the United States occur in men. Differences between the United States and the developing world have been driven in part by increases in HPV-positive oropharyngeal cancers and dramatic reductions in cervical cancer incidence brought about by widespread adoption of Pap screening. Given these patterns, in the developing world, the main goal of HPV vaccination is to prevent cervical cancer; in the United States, the goal of HPV vaccination is to prevent a broader spectrum of HPV-associated cancers.

- Pap screening is available for secondary prevention of cervical cancer, but for other HPV-associated cancers, vaccination is the primary validated approach for prevention (male circumcision or condom use also may be somewhat effective in preventing some of these cancers).
- Significant knowledge has been amassed regarding the natural history of anogenital HPV infections and subsequent progression to malignancy. However, significantly less is known about the natural history of oral and oropharyngeal HPV infection and how it leads to cancer. In addition, to date, premalignant oropharyngeal lesions have not been clearly identified.

DR. JENNIFER SMITH

OVERVIEW AND EPIDEMIOLOGY OF HPV-RELATED CANCERS IN THE UNITED STATES

BACKGROUND

Dr. Smith is research associate professor of Epidemiology, Gillings School of Global Public Health, University of North Carolina (UNC). Dr. Smith also is a member of the UNC Lineberger Comprehensive Cancer Center, UNC Center for AIDS Research and the UNC Center for Women's Health Research. She has a Ph.D. from the Department of Infectious Disease Epidemiology and an M.P.H. from the Department of Population Dynamics at The Johns Hopkins Bloomberg School of Public Health. Dr. Smith's research focuses on epidemiological studies of HPV and cervical cancer worldwide (primarily in North Carolina, China, and Kenya), with a focus on prevention via HPV self-screening and prophylactic vaccines. She is the principal investigator for the Multi-State Cervical Cancer-Free Initiative, a project aimed at preventing cervical cancer through vaccination against HPV and effective screening for early signs of cervical cancer in the United States. Dr. Smith has published over 150 articles in international peer-reviewed journals; the majority of these are focused on the epidemiology of HPV infection and HPV-associated diseases, including cervical, anal, vaginal, vulvar, and penile cancers. She is associate editor of *Sexually Transmitted Infections* and serves on the editorial board of *Sexually Transmitted Diseases*.

KEY POINTS

- In the United States, approximately 26,000 cases of cancer are attributable to HPV infection each year, with roughly 18,000 of these occurring in women. The most common HPV-associated cancer among U.S. women is cervical cancer (11,500 cases diagnosed per year), while oropharyngeal cancer is most common among U.S. men (nearly 6,000 cases diagnosed per year).
- There are differences in incidence rates among racial/ethnic groups in the United States for cancers that are commonly associated with HPV infection. Among women, blacks have higher rates of cervical and vaginal cancer than do whites, but lower rates of vulvar and anal cancer. American Indian/Alaskan Native women have lower rates of most HPV-associated cancers than do white women. Compared with white men, black men have higher rates of anal and penile cancers while American Indian/Alaskan Natives and Asians/Pacific Islanders have lower rates of oropharyngeal, anal, and penile cancers.

- Data on the presence of different HPV types within various types of cancer have been used to estimate the fraction of HPV-associated cancers that can be attributed to HPV 16 or 18. It may be useful to employ different approaches to refine these estimates.
- In the United States, women with lower levels of education have higher rates of cervical cancer mortality than do their more educated counterparts. This trend is observed among whites, blacks, and Hispanics. Perhaps even more troubling, while mortality rates have declined for many groups of women over the past several years, they have remained steady for both black and white women who have 12 or fewer years of education.

DR. DENISE GALLOWAY

HPV-SPECIFIC ANTIBODIES FOLLOWING NATURAL INFECTION

BACKGROUND

Dr. Galloway is a member of the Human Biology and Public Health Science Divisions and interim director of Human Biology at Fred Hutchinson Cancer Research Center. She also holds research professor positions in microbiology, pathology, and pathobiology at the University of Washington. Dr. Galloway's research focuses mainly on the role of viruses in cancer, particularly HPV and human polyomaviruses. Basic research in her lab has included mechanisms of oncogenesis, development of virus-like particles, and characterization of antibody responses following natural infection and vaccination. Collaborative studies with epidemiologists and clinicians have contributed to understanding the natural history of genital HPV infections and the risk of developing cancer. Dr. Galloway's work has been supported by NCI and the National Institute of Allergy and Infectious Diseases, including a MERIT Award.

KEY POINTS

- Cohort studies have provided insight into the natural history of HPV infection. One cohort comprised college women 18-20 years of age at enrollment who were followed at four-month intervals for a median of 3.5 years. At 24 months of follow-up, among women who were sexually active, approximately one-third tested positive for HPV DNA. However, for most of these women, HPV DNA was undetectable after two to three subsequent visits. Among women who had tested positive for HPV, 50 to 80 percent underwent HPV type-specific seroconversion; the reasons why some women do not undergo seroconversion are unknown.
- A subset of HPV-positive women from this cohort was followed for a longer period of time. A median of ten years later, fewer than 5 percent of identified infections were still detectable. Among those women who had previously undergone seroconversion, the persistence of seropositivity varied by HPV type. HPV 16 antibodies persisted in approximately 90 percent of women while persistence rates as low as 30 percent were observed for other HPV types. These differences were due in part to the fact that antibody levels for some HPV types (e.g., HPV 33) were very close to baseline detection levels; thus, small variations in antibody levels could change the outcome of serotesting. This finding has implications for researchers considering one-time testing for antibodies to assess HPV exposure.
- A second cohort comprised college men 18-20 years of age at enrollment who were followed at four-month intervals for a median of 2.5 years. At 24 months of follow-up, nearly two-thirds of men tested positive for HPV DNA. Although a higher percentage of men than women tested positive for HPV DNA, men were far less likely to undergo HPV seroconversion; depending on the HPV type, only 4 to 35 percent underwent type-specific seroconversion. These men exhibited high levels of antibodies against the BK virus, indicating that the low rates of HPV seroconversion did not represent an overall inability to produce antibodies in response to viral infection.

- A case-control study of anal cancer provided additional insight into differences in HPV seropositivity among men and women. Among controls, women were much more likely than men to be seropositive for almost all HPV types tested. As expected, for most HPV types, rates of seropositivity were higher among women with anal cancer than among control women. Despite the low levels of seropositivity observed among control men, in most cases, men with anal cancer exhibited levels of seropositivity similar to those of women with anal cancer.
- Collectively, the data on HPV seroconversion in men suggest that the site of infection may determine whether men can mount an antibody response to HPV. Low levels of antibody responses observed among young men may have implications for their future susceptibility to HPV-related diseases—namely, oropharyngeal cancer.

DR. MAURA GILLISON

OVERVIEW AND EPIDEMIOLOGY OF HPV-RELATED CANCERS

BACKGROUND

Dr. Gillison is professor and Jeg Coughlin Chair of Cancer Research at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. She has made significant research contributions to the fields of tumor virology, cancer biology, and epidemiology. In 2000, Dr. Gillison pioneered a study that provided convincing molecular evidence that HPV is the causative agent for a defined subset of head and neck cancers. Her findings demonstrated, for the first time, that HPV-positive head and neck squamous cell carcinomas (HNSCCs) comprise a distinct clinical pathological disease at the molecular level. Dr. Gillison's research also has shown that HPV is the most important predictor of clinical response to tumor therapy status and prognosis for patients with head and neck cancers. As a result of these data, NCI has recommended that all clinical trials involving head and neck cancers be stratified by tumor HPV status. Additionally, the NCI task force on head and neck cancers has approved moving forward with a de-escalation of therapy clinical trial for "favorable" risk HPV-positive head and neck cancers under the Radiation Therapy Oncology Group. The objective is to decrease long-term morbidity of therapy without compromising survival. Dr. Gillison has published extensively in journals such as *The New England Journal of Medicine*, *Journal of the National Cancer Institute*, and the *Journal of Clinical Oncology*. Dr. Gillison's work is funded by NCI.

KEY POINTS

- There are at least two distinct types of head and neck cancers, which differ in their risk factors and prognosis. The first type, which is associated with HPV infection, is more common among younger men and is linked to sexual behavior. Head and neck cancers not associated with HPV infection are more common among older men and are linked to alcohol and tobacco use. Patients with HPV-associated head and neck cancers have a better prognosis than those whose cancers are not associated with HPV.
- In the United States, the overall rate of oropharyngeal cancer increased between 1988 and 2004. This trend was driven by increases in HPV-associated oropharyngeal cancers; rates of HPV-negative oropharyngeal cancer decreased over the same time period. In the mid-1980s, only about 16 percent of oropharyngeal cancers were HPV positive, compared with 72 percent between 2000 and 2004.
- In the United States, the burden of HPV-associated cancers is shifting. Although cervical cancer has been the most common HPV-associated cancer in the past, rates of cervical cancer have been declining for decades. If this trend continues, as is expected, and incidence of oropharyngeal cancer continues to increase at a similar rate, overall incidence rates for oropharyngeal cancer will surpass those for cervical cancer by 2025. Although registry data are not yet available, it is estimated that

incidence rates of oropharyngeal cancer among men, who are more likely to be diagnosed with the disease than are women, were similar to those for cervical cancer in 2010.

- The observed increase in oropharyngeal cancer also is occurring in many other developed countries. It is likely that, similar to what is being observed in the United States, these increases are due to rising rates of HPV-associated oropharyngeal cancers; in Australia and Sweden increasing rates of oropharyngeal cancer have been directly attributed to HPV. Rates of squamous cell carcinoma of the lung, which is associated with risk factors similar to those for HPV-negative oropharyngeal cancers, are declining in these countries.
- A number of factors have contributed to the success of primary and secondary prevention efforts for cervical cancer. Premalignant cervical lesions are well defined and accessible, making it feasible to do cervical cytology screening, which has led to population-level reductions in cervical cancer incidence. Also, the natural history of cervical HPV infection has been well described, which has led to the development of HPV testing as a complement to cytology screening. Finally, the histopathological progression of cervical cancer is known, providing well-described endpoints for vaccine clinical trials. In contrast, premalignant oropharyngeal cancers are poorly defined and inaccessible, which makes cytology screening for this disease infeasible. Oral HPV natural history studies have not been performed, so the utility of oral HPV detection for cancer screening is unknown. Also, the histopathological progression of oropharyngeal cancers has not been described, which has hindered pharmaceutical support for vaccine efficacy trials.

DR. ALLAN HILDESHEIM

HPV ANTIBODIES AS MARKERS OF RISK FOR SUBSEQUENT HEAD AND NECK CANCERS

BACKGROUND

Dr. Hildesheim received a Ph.D. in epidemiology from The Johns Hopkins School of Hygiene and Public Health in 1991. He has been at NCI since 1987 and is chief of the Infections and Immunoepidemiology Branch. Dr. Hildesheim's research focuses on understanding host and viral factors involved in the pathogenesis of DNA virus-related tumors and in the evaluation of efficacy and underlying immunological mechanisms associated with the recently licensed prophylactic HPV vaccines. Dr. Hildesheim’s team is conducting large-scale population studies on two groups of tumors: female gynecological cancers linked to HPV and nasopharyngeal cancer linked to Epstein-Barr virus. The Branch also is involved in the evaluation of the long-term impact of HPV vaccination and in elucidating immunological mechanisms involved in long-term vaccine efficacy. To this end, Dr. Hildesheim is the lead NCI investigator on a 7,465-woman community-based HPV 16/18 Vaccine Trial in Costa Rica. Initiated in 2004, this trial is designed to evaluate the safety and efficacy of the HPV 16/18 vaccine, examine broader questions of long-term population impact of vaccination, and explore cost-effective applications of HPV-based vaccination and screening. The trial involves active participant follow-up and includes a rich biological specimen collection component that allows for the added evaluation of numerous scientific questions of etiological and immunological interest.

KEY POINTS

- HPV 16 infection has been linked to a subset of oropharyngeal cancers. In some countries, such as the United States, a large proportion of oropharyngeal cancers are associated with HPV infection. However, there is limited knowledge about the natural history of HPV infection in the head and neck and there are no established precursor lesions for HPV-associated oropharyngeal cancers.

- The European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) includes more than 500,000 individuals from ten European countries. More than 380,000 EPIC participants have provided blood samples. Cancers occurring in participants are identified through linkage to registries or active follow-up.
- A nested case-control study involving 635 EPIC participants diagnosed with head and neck cancers (including 135 oropharyngeal cancers) and 1,599 matched controls was conducted. A multiplex assay was used to measure antibodies against 14 HPV genotypes in serum collected from participants. Overall differences between cases and controls were evaluated, as were relationships between serum measurements and time between blood collection and cancer diagnosis.
- One-third of those who had been diagnosed with oropharyngeal cancers were seropositive for antibodies against the HPV 16 E6 protein compared with only 0.6 percent of control participants (odds ratio = 274). HPV 16 E6 seropositivity was not significantly associated with cancers of the oral cavity or larynx. The association between oropharyngeal cancer and HPV 16 E6 seropositivity was similar regardless of the time that had passed between serum collection and cancer diagnosis (i.e., less than 2 years, 2 to 5 years, 5 to 10 years, more than 10 years). These data indicate that HPV 16 E6 seroconversion consistently occurs many years prior to cancer diagnosis and that HPV 16 E6 antibodies may be an early and specific marker of oropharyngeal cancer risk. Additional evaluation is under way to look at the HPV status of the oropharyngeal cancer cases within the EPIC cohort. Efforts are also under way to replicate this analysis in additional cohorts, including those that are part of the NCI's Cohort Consortium.
- The high specificity of the association between HPV 16 E6 seropositivity and oropharyngeal cancer and the extended time between seroconversion and cancer diagnosis may provide opportunities for screening. However, only a fraction of head and neck cancers are associated with HPV infection. An optimal screening assay would also include markers indicative of risk of head and neck cancers not associated with HPV infection.

SESSION ONE MODERATED DISCUSSION

KEY POINTS

- Cell-mediated immunity plays an important role in fighting HPV infection, which is evidenced by the fact that there are higher rates of HPV-related diseases among individuals with T-cell immunosuppression. However, most research studies have focused on anti-HPV antibody production, because antibody response can be more readily measured using currently available techniques, and because it has been shown that antibodies are sufficient to infer protection (i.e., protection can be transferred with transfer of antibodies).
- The EPIC nested case-control study of oropharyngeal cancer involved measurement of serum antibodies for various markers rather than assessing the presence of HPV at a specific site. It is possible that seropositivity for a given antigen is indicative of HPV infection at a site other than head and neck, but this is statistically highly unlikely.
- Unlike what was observed in the EPIC case-control study, patients who develop cervical cancer generally do not undergo seroconversion for HPV 16 E6 or E7 until late in the carcinogenic process. The reasons why seroconversion occurs more often and earlier in patients with HPV-positive oropharyngeal cancers compared with those with cervical cancer are not known. It is possible that this occurs because of the proximity of the oropharynx to the lymphoid-rich tissue in Waldeyer’s ring. Because of this proximity, immunosurveillance in the oropharynx is likely very different than it is in the cervix.
- In patients with Merkel cell carcinoma, antibodies to the polyomavirus T antigen generally decrease with treatment. Post-treatment increases in these antibodies are suggestive of recurrent disease. In

contrast, in head and neck cancer patients, levels of antibodies against HPV 16 E6 and E7 often remain stable for years, which limits their utility for disease monitoring.

- Currently available data indicate that the natural history of HPV infection varies by site and gender. These differences likely depend on a number of variables, including immunological and biological factors (e.g., microbiome of sites). Research is needed to clarify the course of HPV infection at sites other than the cervix (e.g., anus, oropharynx), and gender-based differences must be considered.
- Gaps in knowledge about oropharyngeal cancer precursors have implications for vaccine testing, as precursor lesions were used as a surrogate endpoint in trials assessing the efficacy of vaccines in preventing cervical cancer.
- There are difficulties associated with studying the natural history of oropharyngeal HPV infection. The studies are very expensive, in part because of the lower prevalence of oral HPV infection. There are studies being conducted in high-risk populations (e.g., HIV-infected individuals, men who have sex with men [MSM]), but the extent to which the results of these types of studies are generalizable is unclear. The anatomic inaccessibility of oropharyngeal tissue also poses a significant barrier. It is unethical to look for precursor lesions in healthy individuals because the procedures are invasive; thus, the majority of precursor lesions identified to date have been in individuals with known or suspected cancer. These lesions are also very small and difficult to find; in some cases, experienced surgeons have difficulty locating established primary tumors.
- Natural history studies in the oropharynx would benefit from technologies that would allow noninvasive detection and characterization of lesions. It is possible to noninvasively check for HPV infection of the oropharynx using an oral rinse; however, because of the difficulty in characterizing and identifying precursor lesions, it has been difficult to correlate HPV positivity with cytologic abnormalities.
- In terms of elucidating the natural history of oropharyngeal HPV infection and progression to cancer, one approach is to conduct some studies that characterize events that occur around the time of infection and others that focus on the period of time when cancers are likely to be diagnosed.
- Valuable insights into the natural history of cervical HPV infection have been gained through randomized controlled trials of the HPV vaccines. Similar insights may be gained for the oropharynx if vaccine trials focused on this site are conducted.
- The age distribution of HPV infection prevalence differs between the oropharynx and cervix. In the cervix, prevalence of infection peaks in younger age groups, years before cancer occurs, while infection rates in the oropharynx peak in older adults (the same age group in which cancer is most likely to occur). The reasons for this difference are not well understood, but it does not mean that the period of time between infection and cancer is shorter for the oropharynx than for the cervix. The difference in the age distribution of prevalence may be because oropharyngeal infection is more persistent than cervical infection (which is often transient); if so, the higher prevalence among older people would be the result of fewer resolved infections over several decades rather than a higher number of new infections in older populations. It is also possible that current HPV prevalence rates are due to a birth cohort effect.
- Although prevalence of oropharyngeal HPV infection does not peak until older adulthood, it is not clear that it would be beneficial to promote vaccination among males between 25 and 40 years of age. It is likely that most of these men would already have been exposed to the virus by this time; thus, it would be better to vaccinate boys prior to their first sexual intercourse. It may be interesting to conduct a research study to assess the benefits of vaccinating seronegative men in their 20s and 30s; however, this would be a very large and expensive trial and would be unlikely to attract interest from industry.
- In addition to exhibiting different immunological responses to HPV infection, men also respond differently to vaccination. In one Merck trial, antibody responses to vaccination were lower in men

than in women (and even lower among MSM), although the vaccine was found to be efficacious in both men and women.

- HPV-associated cancers are more common in the oropharynx than in the oral cavity. It is likely that, similar to what occurs in the genital tract, HPV infection occurs throughout the airway but certain regions are more susceptible to HPV-mediated transformation. HPV is present in a small subset of oral cavity cancers (about 6 percent in one study); unlike the majority of oral cavity cancers, which are squamous in appearance, these lesions were basaloid.
- HPV-mediated malignancies can have different histological traits, even at the same site (e.g., squamous cell carcinoma and adenocarcinoma of the cervix are both caused by HPV). One question is whether these different histologies result from differences in differentiation following HPV infection of a single type of target cell or whether different cell types within a given site undergo HPV infection. In the cervix, it is thought that the reserve cells in the transformation zone are the cells that become infected with HPV and develop into cancer. The absence of a transformation zone in the perianal area suggests that the different types of HPV-associated tumors that arise in this area are likely due to the fact that there is a broader array of cell types that are susceptible to infection. Several different histological types of HPV-associated cancer have been identified in the head and neck (e.g., lymphoepithelioma of the oropharynx, small-cell carcinoma of the oropharynx); this indicates that if there is a single cell type that becomes infected in the head and neck, it is capable of differentiating along several different pathways.
- Since HPV is responsible for only a portion of the cancers that occur at most of the HPV-associated cancer sites (with the exception of cervix), vaccination will benefit only a portion of those at risk. Validated screening approaches are needed for these sites.

SESSION TWO: DURATION, SAFETY, AND EFFICACY OF HPV VACCINES

DR. CLAUDIA VELLOZZI

POST-LICENSURE HPV SAFETY MONITORING AND EVALUATION

BACKGROUND

Dr. Claudia Vellozzi is the deputy director of the Immunization Safety Office (ISO) at the U.S. Centers for Disease Control and Prevention (CDC). Dr. Vellozzi was responsible for leading the vaccine safety monitoring efforts within the CDC for the 2009 H1N1 virus and now guides ISO in all aspects of vaccine safety surveillance and research. She has extensive clinical and public health experience both domestically and internationally. Previously, Dr. Vellozzi worked with the World Health Organization (WHO) in Indonesia and Geneva, Switzerland. She also has worked with the Commonwealth Fund (New York City), conducting research in access to health care services for underserved women. Dr. Vellozzi completed her undergraduate studies at Loyola Marymount University in Los Angeles, California and received her M.D. at Loyola University, Chicago, Illinois; she also received an M.P.H. at The Johns Hopkins University in Baltimore, Maryland. Dr. Vellozzi is board certified in family medicine and preventive medicine.

KEY POINTS

- CDC obtains its vaccine safety data from two sources: pre-licensure clinical trial data and post-licensure safety monitoring. There are multiple post-licensure vaccine safety reporting systems within the U.S. Government. One system is the Vaccine Adverse Event Reporting System (VAERS), a passive reporting system co-managed by FDA and CDC. CDC's Vaccine Safety Datalink (VSD) is a large database that links ten managed care organizations, covering about 10 million patients. The

Clinical Immunization Safety Assessment (CISA) network provides subject matter expertise for clinically complex reports of an adverse event. The FDA's Mini-Sentinel project utilizes large health care plan claims data for monitoring. Industry also has post-licensure safety monitoring commitments.

- The quadrivalent HPV vaccine is the most widely distributed HPV vaccine in the United States. FDA pre-licensure safety data on the quadrivalent vaccine (combined from several clinical trials) reveals that the most common adverse events are headache, fever, nausea, dizziness, and discomfort at injection site; the occurrence of serious adverse events is rare (0.04% frequency). There are no differences in vaccine and placebo study arms for incident autoimmune disorders and death.
- There were a total of 20,805 VAERS reports (96.5% from females) submitted to CDC for approximately 46 million doses of the quadrivalent HPV vaccine distributed between June 1, 2006, and March 30, 2012. Of those reports, 7.2 percent were considered serious adverse events. The safety profile from these passive vaccine surveillance reports is consistent with the pre-licensure data, with the exception of disproportionate reporting for venous thromboembolism (VTE) and syncope.
- Within the VSD system, there were 600,588 quadrivalent HPV vaccine doses administered to females 9-26 years old. No significant risks were reported for eight pre-specified adverse events (including VTE and syncope).
- Unpublished industry data on 189,629 females who had received the quadrivalent vaccine revealed a favorable safety profile for the vaccine. There was no association with congenital anomalies, spontaneous abortions (SABs), autoimmune conditions, VTE, or death. However, an increased risk of syncope was identified. These data were presented at the CDC Advisory Committee on Immunization Practices.
- Industry pregnancy registry data show that rates of SAB and major birth defects following vaccination are less than or equal to those observed in the unexposed population.
- One of the challenges in HPV vaccine safety monitoring is the detection of rare adverse events. In order to the address the need for more rare adverse event data, the VSD is conducting extended surveillance for stroke and Guillain-Barré syndrome (both events are rare in females aged 9-26 years). The VSD and FDA's Mini-Sentinel systems are also assessing the risk of VTE. There are two large observational studies currently being conducted; VSD data should be ready by fall of 2012.
- Potential long-term outcomes of HPV vaccination, such as autoimmune disorders, also are difficult to study. VSD researchers are planning to assess the risk of autoimmune disease for up to three years following vaccine exposure. Industry commitments also are assessing long-term safety of HPV vaccination with respect to autoimmune conditions. An industry study, published in the *Journal of Internal Medicine* in 2011, found no correlation between vaccination and any of 16 prespecified autoimmune conditions.
- Simultaneous administration of the HPV vaccine with other adolescent vaccines also poses a challenge for surveillance of HPV vaccine outcomes. The HPV vaccine is frequently given with the meningococcal vaccine and the tetanus, diphtheria, and pertussis (Tdap) vaccine, making it difficult to identify the vaccine exposure responsible for an adverse event from observational data.
- One of the greatest challenges for HPV vaccine safety monitoring and reporting is communication—anecdotes are often more powerful than data. When the media reports on one adverse event submitted to a passive surveillance system, even if the event is rare or if it is not clear that the event is the direct result of vaccine exposure, it has a tremendous impact on public perception of the vaccine and its safety.

DR. JOEL PALEFSKY

HPV VACCINES FOR PREVENTION OF ANAL CANCER

BACKGROUND

Dr. Joel Palefsky is a professor of medicine at the University of California, San Francisco (UCSF) School of Medicine. He completed his undergraduate medical training and training in internal medicine at McGill University and completed his fellowship in infectious diseases at Stanford University in 1989. He then joined the faculty at UCSF, where he remains to this day. Dr. Palefsky is an internationally recognized expert on the molecular biology, treatment, pathogenesis, and natural history of anogenital HPV infections. He is director of the world's first clinic devoted to prevention of anal cancer, the Anal Neoplasia Clinic at the UCSF Cancer Center. He has pioneered diagnostic and treatment methods for anal intraepithelial neoplasia (AIN) and has been an advocate for screening and treatment of AIN in high-risk populations to prevent anal cancer.

KEY POINTS

- In the United States, the incidence of anal cancer has increased by about 2 percent per year in both men and women since the 1970s. Other developed countries have similar anal cancer incidence trends.
- Since anal cancer largely has been studied in the MSM population, the disease has been misconstrued as a "gay cancer." While MSM are at higher risk for anal cancer than are the rest of the population, the incidence of anal cancer is actually higher in women than it is in men. The primary risk factor for anal cancer is receptive anal intercourse with acquisition of anal HPV, and the absolute number of people practicing receptive anal intercourse is higher in women than in men. In order to achieve effective primary prevention of anal cancer, universal HPV vaccination of all eligible males and females is needed.
- Vaccine efficacy study data, published in *The New England Journal of Medicine* in 2011, reveal that the quadrivalent HPV vaccine is effective at preventing HPV 6-, 11-, 16-, or 18-related AIN and anal cancer in MSM. In the per-protocol efficacy population (seronegative MSM who had HPV DNA-negative swab and biopsy specimens at day 1 for relevant HPV types), the quadrivalent HPV vaccine resulted in a 77.5 percent reduction in AIN associated with vaccine HPV types and anal cancer. In the intent-to-treat population (may already have been exposed to HPV), the vaccine resulted in a 50.3 percent reduction. These data highlight the need to promote vaccination before initiation of sexual activity.
- Immunocompromised individuals are at high risk of developing anal cancer. The population at highest risk for anal cancer is HIV-positive MSM. Data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study showed an anal cancer incidence rate of 131 per 100,000 HIV-positive MSM. This is higher than the highest incidence rates of cervical cancer in any patient population in the world.
- Following completion of the standard quadrivalent HPV vaccine regimen, MSM (including older, HIV-positive MSM) undergo seroconversion but have lower serum HPV 16 antibody titers than do heterosexual men. This may lead one to conclude that these individuals would not benefit from vaccination; however, a high proportion of HIV-positive MSM were both seronegative and HPV DNA negative to HPV 6 (60%), 11 (68%), 16 (62%), and 18 (78%) at study enrollment, suggesting that they may benefit from vaccination. Studies need to be conducted to determine the benefit with regard to prevention of incident high-grade disease and cancer in this population. In addition, the duration of protection needs to be studied in immunocompromised patients given the lower antibody titers present after vaccination.

- One issue that arises when determining how to best utilize resources for primary prevention of anal cancer is whether to target MSM since they are the patient population at highest risk. However, most MSM have not self-identified as such by the time they would benefit maximally from HPV vaccination. HPV vaccination is recommended for all males up to the age of 26, and MSM should be vaccinated through universal vaccination efforts for all men. School-based vaccination programs are one effective means by which to universally reach younger males.
- Vaccination of younger males and females (aged 4 to 6) may help improve overall vaccination rates since this is a time when other vaccines are given. However, much work needs to be done before HPV vaccination in this age group can be achieved. Namely, bridging immunology studies are needed to ensure the vaccine is efficacious in this patient population, as are studies on vaccine duration of protection.

DR. ALLAN HILDESHEIM

HPV VACCINATION: RECENT FINDINGS FROM THE NCI HPV 16/18 VACCINE TRIAL IN COSTA RICA

KEY POINTS

- Both the bivalent and quadrivalent vaccines have demonstrated high efficacy against new HPV infections and lesions in the genital tract caused by the targeted HPV types. There also is consistent evidence emerging that the vaccines may offer at least partial protection against phylogenetically similar HPV types. It is possible that the vaccines also are effective in preventing oral cavity infection, but there are not yet data to determine whether this is the case.
- The Costa Rica HPV 16/18 Vaccine Trial (CVT) is a community-based, randomized trial conducted by NCI in collaboration with investigators in Costa Rica. Approximately 7,500 women between the ages of 18 and 25 years were enrolled in the trial. Participants were randomized to receive either a control vaccine or the bivalent HPV vaccine manufactured by GlaxoSmithKline. The women were actively followed for four years. Cervical samples were collected at all visits, and anal, oral, and vulvar specimens were collected at the four-year visit. HPV testing was conducted using validated techniques.
- Analysis of the oral cavity specimens collected from CVT participants revealed that HPV 16 is far less prevalent in the oral cavity than in the cervix. The data also indicate that the bivalent vaccine is more effective in preventing HPV infection in the oral cavity than in the cervix; the reasons for this are not well understood, although biologic and/or behavioral factors may contribute.
- It would be beneficial to reduce the number of vaccine doses needed to impart protection for a number of reasons. A large proportion of individuals in the United States who begin the vaccination series do not receive the recommended three doses. In addition, the cost and logistics of the three-dose schedule present challenges in developing countries.
- Approximately 15 percent of CVT participants received fewer than three vaccine doses. Stratification of the data by number of doses received revealed that at four years after vaccination, participants receiving fewer than three doses were well protected against cervical infection with HPV 16 and 18.
- A follow-up study was conducted to determine whether protection would be expected to extend beyond four years. Throughout the course of the study (up to 48 months), all of the participants who had received at least one dose of the vaccine maintained serum HPV antibody titers significantly higher than those observed in naturally infected women. Furthermore, titers among all vaccinated women peaked around 12 months and remained relatively constant thereafter, which suggests durability of protection. Among women who received two doses, those who received the second dose

six months after the first dose exhibited slightly higher antibody levels than did those whose second dose was administered one month after the first dose.

DR. KEVIN CULLEN

HPV AS A CAUSE OF RACIAL DISPARITIES IN HNSCC: PROMISE AND PROBLEMS WITH HPV TESTING FOR OROPHARYNGEAL CANCER

BACKGROUND

Dr. Cullen is director of the University of Maryland Marlene and Stewart Greenebaum Cancer Center. Specializing in head and neck cancers, he is a professor of medicine at the University of Maryland School of Medicine and head of its oncology program. A graduate of Dartmouth College and Harvard Medical School, Dr. Cullen completed his internship and residency at Beth Israel Hospital in Boston and received additional training at the NCI. He served as interim director of the Lombardi Cancer Center at Georgetown University from October 2000 to September 2002 and was professor of medicine, oncology, and otolaryngology at Georgetown University School of Medicine. He came to the University of Maryland in January 2004. In 2008, the Greenebaum Cancer Center received NCI Cancer Center designation. Last year, *U.S. News and World Report* named the Center one of the top 25 cancer centers in America. Dr. Cullen is a member of the American Cancer Society National Board of Directors. Recently, he was appointed by President Obama to serve on the National Cancer Advisory Board.

KEY POINTS

- Patients with HPV-positive head and neck cancers have a much better prognosis than those with HPV-negative disease. The TAX 324 study, an international, randomized Phase III trial of patients with locally advanced squamous cell cancers of the head and neck, found that black patients had far lower survival rates than did whites, even when the data were corrected for stage of disease and treatment. An analysis of HPV infection found that whites in the study were 10 times more likely than blacks to be HPV positive (34% versus 3%); this difference fully accounted for differences in survival.
- These findings prompted University of Maryland researchers to look at oropharyngeal cancer cases that had been managed within the University system between 1993 and 2010, as well as other head and neck cases from 2000 to 2010. The analysis verified the disparity in survival between black and white oropharyngeal cancer patients (median survival 57 months for whites compared with 25 months for blacks), a difference that was not observed for oral cavity, laryngeal, or hypopharyngeal cancers. Similar to what was observed in the TAX 324 study, the differences in survival were completely attributable to differences in HPV infection status.
- The proportion of HPV-positive oropharyngeal cancers rose between 1995 and 2007 for both blacks and whites within the University of Maryland system. Between 1992 and 1995, just over 30 percent of oropharyngeal cancers in whites were HPV positive compared with nearly 55 percent in 2004 to 2007 (more recent data suggest that rates may now be as high as 75%). During that same time period, rates of HPV positivity among blacks increased from virtually zero to nearly 20 percent. Differences in HPV positivity are not explained by differences in sexual behavior between blacks and whites, although there are some small differences in age at initial oral sex and numbers of oral sex partners.
- Currently, there is no clinically detectable precursor lesion for oropharyngeal cancer. Screening for these cancers is based on physical examination. Existing studies based on oral HPV screening have not produced clear recommendations. One recent study found that 35 percent of oropharyngeal cancer patients are seropositive for HPV 16 E6 antibodies prior to diagnosis and that 23 percent of healthy individuals who were seropositive for these antibodies were diagnosed with oropharyngeal cancer

within ten years. Based on these data, it may be appropriate to perform enhanced screening on individuals who are seropositive for HPV 16 E6, but it is unclear what type of screening would be done and what the clinical implications of enhanced screening would be. Since the prognosis of HPV-associated lesions is very favorable, it is unclear whether screening and early detection would alter treatment strategies or survival.

SESSION TWO MODERATED DISCUSSION

KEY POINTS

- Definitive proof that one dose of the HPV vaccine could protect against infection would have major implications for clinical practice. However, the data from the CVT do not necessarily mean that one dose will provide adequate protection. Although women who had received one vaccine dose maintained serum antibody titers higher than those in women with natural HPV infection, the levels observed in naturally infected women provide only partial protection against reinfection. Thus, it is unclear whether the antibody levels induced by one dose will be sufficient to protect against HPV infection long term. There is an ongoing study in India that will provide additional insight into the efficacy of fewer than three doses of the vaccine. The study was originally designed to evaluate the efficacy of three versus two doses, but vaccination was halted earlier than planned, so there are a large number of girls who received only one dose. Other data related to one or two doses also will emerge as the vaccine is used in clinical practice.
- Serum samples from CVT participants who received fewer than three doses are being tested for HPV 18 antibodies, but the results of these measurements are not yet available.
- It is unclear whether fewer than three doses of the vaccine would result in cross-protection against any of the HPV types for which cross-protection has been documented with three doses. Data from CVT participants receiving fewer than three doses suggest that one or two doses will not result in cross-protection. However, the sample sizes are very small so it is difficult to rule out this possibility based solely on these data. In addition, analysis of the serum of a subset of CVT participants who received three doses revealed that cross-neutralizing antibodies did not emerge until all three doses were given. Additional follow-up data may be helpful in clarifying this issue. Efforts are ongoing to identify immunological markers of cross-protection, which should facilitate these types of studies.
- Consideration must be given to whether one or two vaccine doses would be acceptable if they provided somewhat less protection than the full schedule. A decreased schedule may allow more widespread implementation of the vaccines, but it is unclear if this would be worth sacrificing the additional protection afforded by three doses.
- Assays measuring memory B-cell response are becoming more reliable and may help provide an indication of vaccine-mediated protection against HPV infection. These assays may be useful in assessing the efficacy of one or two vaccine doses.
- One strategy that has been discussed for increasing uptake of the vaccine is to administer the vaccine to young children (4 to 6 years old), perhaps in combination with other childhood vaccines, rather than to adolescents. Some have speculated that this may reduce some of the social stigma that is currently associated with the vaccine. However, it would be a good idea to test whether this shift would influence social perceptions of the vaccine before investing in the research that would be required in order to make the necessary changes to the label. Validating the vaccines for this younger age group would have important global implications, as it may be easier to access younger children than adolescents in less-developed regions.
- Determining the effects of vaccinating younger populations would require bridging studies. Such studies are under consideration by pharmaceutical companies but are not under way. A vaccine trial in 4- to 6-year-olds with a virological endpoint would be difficult to conduct, in part because of the

length of time between vaccination and expected HPV exposure. In addition, small studies that look at vaccine efficacy with respect to immunogenicity or virological endpoints would provide interesting data but may not be sufficient to convince regulatory agencies to change the vaccine labels. It is important to consider what trial endpoints would be sufficient for regulatory approval of different indications or label changes. There also are ethical considerations associated with conducting bridging studies in young children; other countries may decide to vaccinate young children based on the results of bridging studies with immunologic endpoints, which could be problematic if earlier vaccination turned out to provide inadequate protection against infection.

- Initial Phase III trials of current HPV vaccines were conducted among older adolescents and young adults; indications for both vaccines were extended to include individuals as young as 9 years old, based on bridging studies with immunogenic endpoints. This is conceptually similar to what is being suggested for younger children.
- Researchers should consider scientific, regulatory, social, and ethical issues when designing and conducting vaccine studies. These considerations may be different for the United States compared with less-developed countries.
- The United States has robust vaccine safety surveillance systems, but there is widespread misunderstanding of these systems among the public and within the medical field. There should be communications efforts to address this. CDC is preparing a summary of U.S. vaccine surveillance and safety systems, which should be helpful in this regard.
- Efforts should be made to target pediatrician-parent/patient communication to overcome misperceptions about the HPV vaccines. The American Academy of Pediatrics is implementing a vaccine safety component into its residency training program to help residents communicate more effectively with their patients. However, within the current health care system, pediatricians do not have incentives or time to have extensive conversations with parents on issues such as vaccine safety. Communication efforts targeted to physicians and the public may be more effective if they focus on vaccine safety and monitoring in general, although it may be necessary to do some outreach specifically related to the HPV vaccines.
- It may be beneficial to develop a communications campaign targeted to the MSM population. This population generally has been receptive to such interventions. However, a targeted campaign may perpetuate the idea that anal cancer is a "gay cancer."
- There is no guarantee that increased communication efforts will enhance vaccine uptake, but there have been past successes in modifying health-related behaviors (e.g., mammography, smoking cessation). Success depends on a multipronged approach, consistent messaging, and cooperation among stakeholders. It is also important to learn which messages facilitate changes in health behaviors. Cervical Cancer-Free America has found that promoting adolescent vaccines in general is more effective than specifically promoting the HPV vaccine.
- Data being collected in other countries also should be utilized to establish the safety of HPV vaccines. For example, the United Kingdom has extensive experience with Cervarix. The U.K. monitors vaccine safety and provides safety information on the web but has not yet published a peer-reviewed paper on this topic. Although publications from pharmaceutical companies on safety are helpful, it is preferable for peer-reviewed analyses to be published by independent parties (e.g., government agencies).
- Generating definitive data on the efficacy of the vaccines in preventing oropharyngeal HPV infections would be helpful from a communications standpoint because it would expand the benefit of the vaccine beyond the anogenital region to a region that is less associated with sexual behavior.
- A Healthcare Effectiveness Data and Information Set (HEDIS) measure was recently established for HPV vaccination, stating that females should receive three doses of the HPV vaccine between the ages of 9 and 13. This will provide some incentive for health organizations to promote vaccination,

but it is unclear if it will substantially increase uptake. It was suggested that it is unlikely that the potential for decreasing the future burden of cancer treatment will convince third-party payers to promote vaccination.

- There are at least two potential barriers to creating a combination vaccine that includes the HPV vaccine and one or more other adolescent vaccines (e.g., meningococcal, Tdap). First, there are formulation issues that would make it difficult to combine the vaccines; for example, the Cervarix vaccine includes a novel adjuvant that may not be compatible with the other vaccines. Second, the HPV vaccine schedule (i.e., three doses) is different from that of other adolescent vaccines. In addition, it is unclear whether creating a combination vaccine would solve the challenge of low vaccine uptake. Pharmaceutical companies would need to be convinced that there would be a benefit to creating a combination vaccine before they would be willing to invest in the expensive and often lengthy clinical development process of creating such a vaccine. Combination vaccines also raise additional safety concerns that must be monitored.
- It is unclear what data will be required to change the indications and/or policies related to vaccine use. From a regulatory perspective, data coming from other countries will likely be less compelling than data generated through trials for which the FDA has had design input. In terms of policy, post-licensure monitoring results are taken into account and should provide insight into issues such as duration of protection with fewer than three doses.

PUBLIC COMMENT

KEY POINTS

- A retired physician noted that Kaiser Permanente established quality markers-based evidence of vaccine efficacy. These markers were used within group practices to incentivize use of effective vaccines.

SESSION THREE: SECOND-GENERATION AND IMPROVED HPV VACCINES

DR. GARY DUBIN

CONSIDERATIONS FOR THE DEVELOPMENT OF IMPROVED AND SECOND-GENERATION HPV VACCINES

BACKGROUND

Dr. Gary Dubin received his M.D. in 1983 and is board certified in internal medicine and infectious diseases. He completed a research fellowship in molecular virology at the University of Pennsylvania School of Medicine and subsequently pursued his basic research interests in vaccines as assistant professor in the University of Pennsylvania's Infectious Diseases Division. Dr. Dubin has worked in GlaxoSmithKline (GSK) Biologicals since 1995, where he is vice president and director of Global Late Clinical Development. Dr. Dubin led development of the GSK candidate vaccine for genital herpes as well as the GSK HPV vaccine. In his current role, he oversees development of all GSK late-development-phase vaccines, including vaccines for seasonal and pandemic influenza, meningococcal diseases, streptococcus pneumonia, malaria, tuberculosis, rotavirus, measles/mumps/rubella/varicella, DTPa-based combination vaccines, herpes zoster, and HPV. Dr. Dubin is an adjunct associate professor of medicine at the University of Pennsylvania and has authored over 50 research papers, mostly on herpes simplex virus and HPV vaccine development.

KEY POINTS

- It is hoped that second-generation HPV vaccines will help achieve several goals, including higher efficacy in cervical, vulvar, vaginal, and anal cancer prevention, leading to a reduced need for screening and surgical intervention; improved prevention of low-grade lesions and the related psychological impact, intervention costs, and intervention-related side effects; prevention of other HPV-related cancers (e.g., head and neck, non-melanoma skin cancers); and additional efficacy against genital warts. It also would be beneficial to develop vaccines that have a therapeutic effect on established lesions.
- One strategy for accomplishing some of these goals is to create vaccines with expanded HPV coverage. Approaches being considered to achieve this goal are L1 virus-like particle (VLP)-based vaccines with additional HPV types and minor capsid lipid (L2)-based vaccines, including L1-L2 chimeric VLPs.
- Second-generation vaccines also should include administration improvements with potential to increase vaccine uptake and reduce costs (e.g., shorter vaccination schedule, fewer doses, needle-free administration, thermostable vaccines).
- Novel L1 expression systems may help to reduce the cost of vaccine production. Researchers have already demonstrated the ability to produce L1 proteins in both *E. coli* and plants. Preclinical work also has been done on plasmid-based L1 "naked" DNA vaccines.
- New routes of HPV vaccine delivery, such as oral/upper respiratory tract to induce mucosal immunity and needle-free administration, are being considered for second-generation vaccines. Therapeutic capability, which current HPV vaccines lack, would require a different technology platform. Potential approaches to a therapeutic vaccine include recombinant E6/E7 proteins or plasmid DNA-encoding E6/E7 fragments. The ultimate second-generation HPV vaccine would utilize a combined prophylactic/therapeutic approach (e.g., L1-E7 chimeric VLPs).
- The development of second-generation HPV vaccines presents challenges that may not have been faced during the development of first-generation vaccines. For example, clinical studies evaluating second-generation vaccines likely will need to use an active HPV vaccine comparator instead of a placebo control. Since there are no accepted immune correlates of HPV vaccine protection, use of simple immunologic endpoints may not be sufficient, depending on the second-generation technology used.
- Another challenge to second-generation vaccine development is the low incidence rates of lesions associated with "new" HPV types (HPV strains that were not included in the first-generation vaccine). Because of these low incidence rates, it is probable that clinical trials would have to rely on composite endpoints. Assignment of causal association with "new" HPV types also may be a challenge, although confounding events presumably will be less problematic since second-generation vaccines should prevent against infection with HPV 16 and 18.
- Determining the suitability of using surrogate endpoints for new target indications (e.g., head and neck cancers) also will be a clinical challenge for second-generation vaccines.
- Researchers also will encounter challenges specific to the technological approaches of second-generation vaccines. For L1 VLP approaches with additional HPV types, there is potential for immunological interference. For technologies not based on L1 VLPs, there is limited ability to "bridge" clinical data to currently licensed vaccines. The more a second-generation approach varies from a first-generation approach, the less researchers can rely on the vast databases that exist for currently licensed vaccines.

DR. RICHARD HAUPT

V503 (MERCK 9-VALENT HPV VACCINE)

BACKGROUND

Dr. Haupt is a 1979 graduate of the University of Maryland with a degree in biological sciences. He graduated from Harvard Medical School in 1983, and then completed his internship and residency at the Children's Hospital of Philadelphia, where he served as chief resident from 1986 to 1987. Dr. Haupt received his M.P.H. from The Johns Hopkins Bloomberg School of Public Health. After completing his pediatric training, Dr. Haupt was a general pediatrician in the Philadelphia area for 15 years. In his general practice, he also participated in clinical vaccine research. Dr. Haupt joined Merck in 2001 as senior medical director in the Policy, Public Health and Medical Affairs Department of the Vaccine Division. He served as the global medical director for adolescent vaccines from 2005 through 2007. Since 2007, Dr. Haupt has served as the section head for adult vaccines clinical research in Merck Research Laboratories. In this role, he is responsible for late-development clinical strategies for the HPV, shingles (herpes zoster), and staph aureus vaccines.

KEY POINTS

- Merck is developing a second-generation, nine-valent HPV vaccine called V503. V503 includes the four "original" HPV strains represented in the quadrivalent vaccine (HPV 6, 11, 16, and 18) in addition to five "new" types (HPV 31, 33, 45, 52, and 58).
- V503 has potential to prevent 90 percent of cervical cancer cases. Data from the laboratory of Dr. F. Xavier Bosch, Catalan Institute of Oncology, show that about 70 percent of all cervical cancers are attributed to HPV 16 and 18. HPV types 31, 33, 45, 52, and 58 account for roughly an additional 20 percent of cervical cancer cases worldwide. These cervical cancer rates are fairly consistent across all geographic areas.
- Similar studies on the prevalence of V503 HPV types in other anogenital and oropharyngeal cancers suggest that additional cancers of the anus, oropharynx, penis, vagina, and vulva could be prevented by the nine-valent HPV vaccine compared with existing vaccines. Oropharyngeal cancers would be the least impacted by V503 since these are primarily caused by HPV 16.
- Using Gardasil clinical trial data, Merck has calculated global V503 HPV type attribution estimates for ten precancerous lesions, including cervical intraepithelial neoplasias (CINs), the lesions detected through Pap screening. Approximately 25 percent of CIN1 lesions and 30 percent of CIN2/3 lesions are attributable to the five "new" HPV types. In countries where Pap screening is conducted, like the United States, the nine-valent vaccine could substantially reduce spending on follow-up for abnormal Pap screening results.
- Compared with Gardasil, the V503 vaccine includes increased amounts of VLP for all of the original HPV types except HPV 11. The ratio of aluminum adjuvant to VLP was kept similar to that of the quadrivalent vaccine by increasing the aluminum adjuvant in V503. The aluminum adjuvant used in V503 is more consistent with the adjuvant used in currently licensed vaccines such as the hepatitis B vaccine.
- Several Phase III trials of V503 have been completed or are ongoing. Gardasil-V503 immunobridging studies have been completed in 9- to 15-year-old girls and several other trials have looked at concomitant use of V503 with other vaccines as well as the effects of V503 in patients who had already received Gardasil. A large Phase III trial testing V503 efficacy, immunogenicity, and safety in more than 14,000 young women is ongoing and will be analyzed when the prespecified case count is reached, which should be soon.

- The nine-valent HPV vaccine has potential to have a great impact on public health. The vaccine could prevent about 90 percent of cervical cancer cases, as well as provide broader protection against other anogenital and oropharyngeal HPV-related cancers. V503 also could have a valuable health economic impact in countries where cancer screening exists and, potentially, have an impact on screening guidelines.

DR. JEFF ROBERTS

REGULATORY CONSIDERATIONS THAT INFORMED HPV VACCINE CLINICAL DEVELOPMENT

BACKGROUND

Dr. Roberts is a medical officer in the Office of Vaccines Research and Review at the FDA Center for Biologics Evaluation and Research. Dr. Roberts attended the University of Alabama School of Medicine and trained in obstetrics and gynecology at the University of Colorado Health Sciences Center. During a fellowship at NCI, Dr. Roberts performed basic research on HPV, concentrating on animal modeling of HPV infection. In 2008, he joined FDA as a clinical reviewer with a focus on HPV vaccines. As chief of one of the clinical review branches in the Office of Vaccines, Dr. Roberts manages the clinical review of a wide variety of licensed vaccines and vaccine products at all phases of development.

KEY POINTS

- Determining data that are required to change labels for current HPV vaccines will necessitate discussions among sponsors, researchers, and FDA. However, the regulatory history of these vaccines may provide insight into what might be required for changes.
- Cervical disease develops along a spectrum from normal histology to invasive carcinoma. Intermediate steps include mild dysplasia, moderate dysplasia, severe dysplasia, and *in situ* carcinoma. Each of these stages is well defined histologically and is associated with virological markers (e.g., E6/E7 production). These stages are potential endpoints for clinical investigations, with more advanced disease stages being associated with increased validity, reproducibility, relevance, and certainty of results. However, using more advanced stages as endpoints increases the size, complexity, and expense of trials and also raises ethical concerns because it takes longer to get results, which may delay introduction of the intervention into general use.
- In 2001, FDA convened the Vaccines and Related Biological Products Advisory Committee to discuss scientific questions surrounding vaccine development. At that time, many advocated a virological endpoint for vaccine trials based on the knowledge that HPV infection is "necessary and sufficient" to cause cervical cancer. However, the Committee ultimately recommended that a CIN2+ endpoint be used for trials of both vaccines. This was based, in part, on concerns that effective prevention of HPV 16/18 infection would result in more infections with other HPV types and that partial prevention of infection might not have a meaningful impact on dysplasia/cancer (i.e., that breakthrough infections would lead to cancer at a higher-than-expected rate). Based on subsequent HPV vaccine study data, both of these hypothetical concerns were rejected.
- AIN1+ was used as the endpoint in the study conducted to provide data for the addition of anal cancer/AIN prevention as an indication for Gardasil. Use of this less-advanced endpoint (compared with CIN2+), allowed this study to be much smaller in size: only 600 participants were needed compared with the 14,000-18,000 participants that were required for the cervical cancer studies. Although the study was conducted in men (specifically, MSM), the new indication also included women.

- Because vaccines intended to prevent disease generally are administered to healthy populations, risk/benefit considerations differ from those of other types of interventions that are administered to individuals with a diagnosed condition. In addition, vaccines often are administered to millions of people, a population far larger than would be expected to be exposed to most new drugs, which makes it even more important that efficacy is well established.
- FDA is often cautious about vaccine approval.

SESSION THREE MODERATED DISCUSSION

KEY POINTS

- As second-generation vaccines are developed, the efficacy and safety data of the first-generation vaccines will be taken into account. It will still be necessary to carry out post-licensure studies and do safety monitoring to ensure that the new vaccines are working as expected.
- Based on research and results of trials of first-generation vaccines in cervical cancer, many researchers recommend using a virological rather than a histologic endpoint (e.g., CIN1, AIN1) for trials of future vaccines. In many cases, persistent infection is thought to be a better indicator of vaccine efficacy than are histologic changes. Ultimately, FDA will make decisions about which trial endpoints are needed to establish efficacy for future vaccines and/or gain approval for new indications for approved vaccines. In general, less-extensive data will be needed to expand indications for existing vaccines, particularly if the sought-after indication relates to the same population covered by existing indications. More-extensive data may be needed for new vaccines, especially if the vaccine is of a new type (i.e., non-VLP). If the new vaccine is substantially different from licensed vaccines, new safety data will be needed, which usually requires a minimum of 3,000 trial participants.
- The most appropriate trial endpoint (virological versus histologic) may depend on the question being asked. Consideration should be given to what types of endpoints are appropriate for various types of evaluations (e.g., efficacy of vaccine in preventing infection, impact of vaccine on screening).
- Development of a thermostable vaccine would have considerable implications for administration of the vaccine in developing regions. Both current vaccines require refrigeration and lose potency after extended exposure to high temperatures. Use of alternative formulations to increase thermostability has been discussed by vaccine manufacturers, but there has not been any concrete progress in this area. A recent study found that silk polymers could be used in vaccine formulations to increase stability, but considerable work would be required to determine whether this approach would be appropriate and/or effective for HPV vaccines.
- Recent changes in cervical cancer screening guidelines and practices—including later initiation and longer interval between screenings—create challenges for studying the impact of vaccination on screening outcomes. One of the challenges related to changing screening guidelines for women who have been vaccinated is that it is difficult to confirm whether a woman has been vaccinated.
- There was discussion about whether the availability of a nine-valent vaccine would significantly increase uptake of HPV vaccines. On one hand, insufficient vaccine efficacy is not commonly given as a reason for non-vaccination, so expanded protection may not significantly influence physicians' and parents' decision making. However, if receiving the nine-valent vaccine allowed women to undergo Pap screening less frequently (or not at all), physicians may be more likely to recommend the vaccine and parents (particularly mothers) may be more likely to have their daughters vaccinated.
- Uptake might increase if physicians were informed about recent data about duration of protection offered by vaccines (some physicians may have been hesitant to promote the vaccine based on original trial results because duration of protection established by initial results was relatively short). Current data suggest that the duration of protection for existing vaccines is approaching 15 years.

Although HPV infections may be acquired later in life, a significant portion of cervical cancers are likely attributable to infections acquired during late adolescence and young adulthood, which would be prevented if vaccines were administered according to current guidelines. This represents a significant benefit to public health and should be communicated to physicians and parents.

- There is speculation that vaccine uptake would increase if vaccines were shown to prevent oropharyngeal cancers. Emphasizing the capability of vaccines to prevent genital warts also may enhance interest in the vaccine, particularly among boys/parents of boys.
- One reason parents may delay vaccination is that they do not think it is relevant for their children (for example, they do not believe their children are sexually active or likely to become sexually active in the near future). Data related to current vaccines indicate that the immune responses elicited by the vaccines are stronger in 9- to 15-year olds than in 16- to 26-year olds, which provides support for earlier vaccination. Perhaps efforts to improve vaccine uptake should focus on immunological factors rather than age at initiation of sexual activity as a reason for vaccinating at young ages.
- "Catch-up" vaccination has been recommended for some adolescents and young adults who did not receive the vaccine earlier. However, it is known that the vaccine is not effective if HPV infection has already been established. For this reason, it is preferable to focus on increasing vaccine uptake among adolescents rather than on catch-up vaccination.

SESSION FOUR: IMPACTS OF VACCINATION ON INTERMEDIATE CANCER MARKERS

DR. COSETTE WHEELER

MEASURING HPV VACCINE IMPACT: WHAT SHOULD WE CONSIDER?

BACKGROUND

Dr. Wheeler is Regent's Professor in the Departments of Pathology and Obstetrics and Gynecology departments at the University of New Mexico Health Sciences Center (UNM-HSC). For over 20 years, her New Mexico research group has contributed to understanding the molecular epidemiology of HPV in cervical precancer and cancer. She has overseen a number of large-scale multidisciplinary population-based projects to enable advances in primary (HPV vaccines) and secondary cervical cancer screening (Pap and HPV testing). Dr. Wheeler has led groups supporting clinical trials to assess the utility of HPV testing (NCI ALTS trial) and HPV vaccines (Merck Gardasil Phase I, II, and III and GSK Cervarix Phase II and III). Since 2006, Dr. Wheeler has led the New Mexico HPV Pap Registry (NMHPVPR), a statewide surveillance program. Under state regulations, the NMHPVPR captures all Pap and HPV tests and all cervical, vulvar, and vaginal pathology for individuals residing in New Mexico.

In 2009, Dr. Wheeler became director of one of five U.S. National Cooperative Research Centers in Sexually Transmitted Infections—the UNM Interdisciplinary HPV Prevention Center funded by the National Institute of Allergy and Infectious Diseases. In 2011, she was awarded one of seven NCI-funded Specialized Cooperative Research Centers—the New Mexico HPV Outcomes, Practice Effectiveness and Surveillance (NM-HOPES) Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) Center, which is dedicated to improvements in cervical cancer screening. Dr. Wheeler's laboratory has acted as a reference laboratory for the World Health Organization and has developed international HPV DNA standards reagents for WHO. She has served as a research associate for the U.S. National Research Council and as a scientific fellow for both the U.S. National Science Foundation and the American Social Health Association, and has been an advisor to WHO, CDC, the Indian Health Service, and the American Cancer Society as well the International Agency for Research on Cancer (IARC), Cancer UK, and the Instituto Nacional de Salud Publica, Cuernevaca, Mexico, in support

of their efforts to understand and prevent cervical cancer. She is a recipient of the American Society of Colposcopy and Cervical Pathology Distinguished Scientific Achievement Award.

KEY POINTS

- A population-based study of the prevalence of various HPV types in cervical specimens was conducted among approximately 275,000 women in New Mexico. The goal of the study was to generate baseline prevalence measurements that could be used to determine the impact of widespread HPV vaccination. The peak prevalence of HPV (any type) was approximately 55 percent and occurred in women around 20 years of age. Similar patterns were seen for each HPV type, including the types targeted by the bivalent, quadrivalent, and nine-valent vaccines. Changes in HPV prevalence would be promising but would not necessarily reflect the clinical impact of the vaccines.
- Studying the impact of HPV vaccines is complicated by recent changes in screening guidelines. In New Mexico, screening among young women is declining, in part due to recommendations that screening not begin until age 21; thus, there will be less data on HPV prevalence and cervical cytology among these women. Also in accordance with guidelines, the interval between Pap tests is increasing. Similar trends are likely occurring in other states as well.
- Another factor that complicates attempts to evaluate vaccine impact is changing utilization of HPV testing across age groups within clinical practice. In addition, there is significant heterogeneity in the histopathological diagnosis of cervical lesions. In one study of 7,000 cervical lesions, an adjudication panel significantly downgraded the diagnoses made by community physicians.
- Getting estimates of population coverage of HPV vaccination will require use of billing/claims data or mandatory registries. Currently, registries are not mandatory so they are incomplete.
- Three types of endpoints can be considered when measuring impact of HPV vaccination: persistent infection, precancerous lesions, and cancer. In the short term, HPV DNA prevalence will likely be the best measure of vaccine impact. In the long-term, cancer registries will provide insight into changes in HPV-related malignancies.
- Population-based screening registries also would provide useful information. These could provide information on diagnosis, treatment utilization, and outcomes among the screened populations.
- Given complexities in assessing clinical impact of HPV vaccines, it is important to consider the limitations of the various approaches used for monitoring and evaluating vaccination programs.

DR. MARK SCHIFFMAN

LIMITED EARLY IMPACT OF HPV VACCINATION ON CERVICAL SCREENING

BACKGROUND

Dr. Schiffman received an M.D. from the University of Pennsylvania and an M.P.H. in epidemiology from The Johns Hopkins School of Hygiene and Public Health. He joined NCI as a staff fellow in 1983, and in 1996 was appointed chief of the Interdisciplinary Studies Section in the Environmental Epidemiology Branch, which later became the HPV Research Group in the Hormonal and Reproductive Epidemiology Branch. Dr. Schiffman joined the Clinical Genetics Branch in October 2009 to study why HPV is such a powerful carcinogenic exposure, akin to an acquired genetic trait with high penetrance for a cancer phenotype. Dr. Schiffman received a Fulbright Scholarship in 1977 to carry out epidemiologic studies in Senegal. He has received numerous awards for his work in molecular epidemiology, including the American Cancer Society Medal of Honor and the American Association for Cancer Research Prevent Cancer Foundation Award.

KEY POINTS

- It is likely that widespread adoption of HPV vaccines will reduce the positive predictive value of cervical cancer screening. Reductions in HPV 16/18 infections will reduce numbers of screening abnormalities detected, with the largest reduction being in the numbers of high-grade neoplasias.
- CVT data were analyzed to assess the impact of vaccination on cytology results from Pap screening. This analysis focused on the so-called naïve cohort—females from HPV and control vaccine arms with no indication of HPV exposure prior to vaccination (i.e., HPV DNA negative, serology negative, no abnormal cytology). As has been reported, those who received HPV vaccines had fewer cytologic abnormalities than did those who received the control vaccine. The reduction in high-grade squamous intraepithelial lesions (HSIL; 41.4% reduction) was larger than the reduction in minor cytologic abnormalities (low-grade squamous intraepithelial lesions [LSIL] and HPV-positive atypical squamous cells of undetermined significance [ASCUS]; 20% reduction).
- Differences in referral for colposcopy over the four study years also were assessed. Among the total vaccinated cohort (which includes those who may have been exposed to HPV prior to vaccination), there were fewer referrals for colposcopy among the HPV-vaccinated cohort than among the control vaccinated cohort beginning between 18 and 24 months after vaccination. Differences were subtle within the timeframe evaluated. In this cohort, patterns of referral in the first few years were driven primarily by infections already established at time of vaccination.
- A similar trend was also observed in the naïve cohort: differences in colposcopy referral between the HPV and control vaccinated groups emerged between 24 and 36 months after vaccination, although fewer overall referrals occurred because of the lower prevalence of disease in this population. In this cohort, the delay in the difference between the HPV-vaccinated and control groups occurred because many of the participants did not initiate sexual activity until after vaccination.
- Collectively, these data indicate that even with high coverage and excellent prophylactic vaccine efficacy, early impacts of vaccines on screening results will be subtle. Given this, type-specific HPV incidence may be a more attractive endpoint than cytologic abnormalities for early surveillance. The most appropriate endpoint may be different for different purposes (e.g., licensure versus surveillance).

DR. LAURI MARKOWITZ

IMPACTS OF HPV VACCINATION ON INTERMEDIATE CANCER MARKERS

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 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 and sexually transmitted infections. Since 2005, she has coordinated the HPV Vaccine Working Group of the Advisory Committee on Immunization Practices (ACIP) 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. Her current work includes evaluating the impact of HPV vaccine in the United States.

KEY POINTS

- Biological measures used to evaluate the impact of HPV vaccination include early outcomes, such as HPV prevalence and genital warts, which can be measured within years; mid-range outcomes, such as precancerous lesions, that become apparent in years to decades; and late outcomes (i.e., cancers), that are not manifest for decades. Use of each of these outcome measures is associated with challenges.

Measuring early outcomes would provide the earliest indication of impact, but the United States does not have extensive vaccine registries or information systems, which would facilitate this type of analysis. Similarly, use of precancerous lesions as an outcome is limited by the lack of screening registries. Cancer registries are available, but use of this late outcome requires a much longer surveillance period.

- Several ongoing efforts are directed at assessing the impact of vaccination on HPV prevalence. Different approaches have different benefits and limitations. The National Health and Nutrition Examination Surveys (NHANES) are nationally representative surveys done in two-year cycles. For females, cervicovaginal specimens and oral rinse specimens have been collected since 2002 and 2009, respectively. An NHANES pilot study tested the feasibility of measuring HPV prevalence in males in 2012; if successful, this component will be added to NHANES in 2013. In addition to providing data on HPV infection, NHANES collects information on behavior and vaccination. One limitation of using NHANES to look at the impact of HPV vaccination is that it includes a relatively small sample size of the age group of interest.
- HPV prevalence also is being monitored in a screening population within a managed care organization. The advantage of this approach is that there are excellent vaccine records linked to cytology outcomes within a defined population base. Limitations of this approach are a focus on one region and monitoring does not include behavioral data. The latter is of particular concern, because there are differences in behavior between those who receive the vaccine and those who do not.
- There are also several ongoing clinic-based studies to examine HPV prevalence as an indicator of vaccine impact. These studies generally target higher-risk individuals (e.g., young women, MSM). Clinic-based studies may include behavioral data but usually do not include representative sample populations.
- Genital warts also are being used as an early indicator of vaccine impact. Twelve sexually transmitted disease clinics are monitoring the relationship between genital warts and HPV vaccination. These clinics can reliably diagnose genital warts, but, as with all clinic-based studies, the individuals included are not necessarily representative of the HPV vaccine target population. For example, females are underrepresented because they have low prevalence of genital warts in the United States.
- Health care systems' administrative data also are being used to look at prevalence of anogenital warts before and after licensing of HPV vaccines (Gardasil was initially licensed in 2006). Use of these data facilitates access to a large population of insured individuals. Such data sets, of course, can be extremely valuable but results cannot be generalized to uninsured individuals. Inconsistent use of ICD-9 codes also sometimes presents a challenge. A study of the prevalence of anogenital warts among individuals in the Thomson Reuters MarketScan® database between 2003 and 2009 showed that diagnosis of anogenital warts among 15- to 19-year-old females began to decrease in 2007. Prevalence among 10- to 14-year-old and 20- to 24-year-old females remained constant from 2007 to 2009 while prevalence among older age groups increased during this time period. Prevalence among males increased in all age groups during this time period.
- Other studies are looking at precancerous lesions as an indicator of HPV vaccine impact. The HPV-IMPACT study involves population-based monitoring of CIN2+ and HPV typing. This effort began as a pilot in 2007 and includes sites in five U.S. states. The advantages of this approach are that it is population based, information on vaccine treatment and race/ethnicity are sought, and specimens are collected for HPV typing. However, it can be difficult to reliably obtain verification of vaccination, and changes in screening behaviors are creating challenges for analysis. In baseline data collected through the HPV-IMPACT study, prevalence of HPV 16/18 is higher in high-grade than in low-grade lesions, which is consistent with what has been observed in other data sets. HPV 16/18 are also more prevalent in lesions found in younger women (under 30 years of age) compared with older women. HPV 16/18 are more prevalent in lesions from non-Hispanic white women than in lesions from non-

Hispanic black and Hispanic women, which indicates that race/ethnicity should be taken into account in future monitoring efforts.

- Four central cancer registries are collecting data on CIN3 diagnosis. These registries are statewide, which is advantageous, but it is difficult to link diagnosis data with information about screening and vaccine history.
- Administrative data also are being used to conduct surveillance for HPV-associated precancerous lesions. However, similar to the studies on anogenital warts, these large studies are limited by the fact that they include only insured individuals. Also, ICD-9 codes for these outcomes are not as clear-cut as for anogenital warts, which can complicate analyses.
- There are ongoing efforts to monitor the impact of the HPV vaccine outside the United States. Vaccine manufacturers are continuing to monitor participants from their Phase III trials. In Australia, studies are looking at genital warts as well as HPV prevalence. Researchers in Nordic countries are utilizing registries that link screening and vaccine data. Other European countries also are using a variety of approaches to evaluate the impact of the vaccine on genital warts and HPV types in precancerous lesions.

SESSION FOUR MODERATED DISCUSSION

KEY POINTS

- One of the difficulties in monitoring the effects of HPV vaccination is accurately determining who has been vaccinated. Within research settings, it is sometimes possible to distinguish vaccinated from non-vaccinated/naturally infected individuals using serology or saliva-based measurements. Vaccinated individuals have higher serum levels of antibodies to some HPV types than do naturally infected individuals. Higher levels of HPV antibodies also can be detected in the saliva of vaccinated individuals compared with naturally infected individuals for up to one year after vaccination. Another approach would be to measure the presence of antibodies to two or more HPV vaccine types as an indicator of vaccination status. If the nine-valent vaccine is licensed, antibodies to HPV 52 would likely provide a good indication of vaccination because naturally infected individuals have very low HPV 52 antibody titers.
- Assays to distinguish vaccinated from naturally infected individuals have applications in research, but it also may be useful to have a commercially available assay that could be used in community practice, particularly if the results could be used to guide decisions about screening. Such an assay would need to be validated, inexpensive, and highly reliable.
- One major drawback of using an antibody-based assay to determine whether someone has been vaccinated is that a positive result does not mean that the individual was vaccinated prior to HPV exposure. For example, some women are vaccinated after they receive an abnormal Pap result; this type of "catch-up" vaccination is unlikely to be protective and would confound analysis based on assay results.
- If current cervical cancer screening practices continue and use of the HPV vaccine expands, screening will become progressively less efficient. Fewer high-grade lesions will be found, and a higher proportion of interventions will be performed on women with ASCUS and LSIL lesions. This may be frustrating to physicians and to women. If a serology-based test or some other type of assay could be used to reassure women and physicians that less screening is needed, this would help preserve the integrity of the screening process.
- Universal HPV vaccination will not preclude the need for cervical cancer screening, in part because current vaccines do not protect against all oncogenic HPV types. However, it may be sufficient for vaccinated individuals to begin screening later and/or to be screened less frequently than population guidelines recommend (e.g., every five to ten years with an HPV-based assay). Appropriate screening

intervals and approaches will be different if the nine-valent vaccine is widely adopted. Conducting screening efficiently is difficult in a heterogeneous population (i.e., mixture of unvaccinated individuals and individuals vaccinated with different vaccines).

- Changes in screening recommendations should be based on evidence generated through surveillance and other studies. It would be possible to create additional venues for collection of these data (e.g., screening or vaccination registries). Investing in screening and vaccination registries would facilitate integration of data related to vaccination and screening and would help achieve rational changes in screening guidelines in less time than might otherwise be the case. These registries could be state based or established by health maintenance organizations. It would be helpful, but not essential, to collect specimens for HPV genotyping as part of these efforts.
- Another approach for determining if there is decreased effectiveness or value in cervical screening for vaccinated individuals might be to assess whether lesions removed from vaccinated women via loop electrosurgical excision (LEEP) are low risk (and thus removed unnecessarily). Showing that vaccinated women have been exposed to risks due to overtreatment might provide an impetus for changing screening guidelines.
- The total cost for HPV-related diseases and screening in the United States is estimated to be $8 billion per year. Most of this—approximately $6.5 billion—is spent on Pap screening and follow-up. These estimates do not take into account the long-term effects experienced by some women who undergo follow-up for an abnormal Pap result (e.g., cervical stenosis, infertility, preterm birth) or the indirect/nonmedical costs borne by individuals undergoing cancer treatment (e.g., employment issues, psychosocial effects).
- The option of studying women screened through the CDC Breast and Cervical Cancer Early Detection Program to determine the impact of HPV vaccination was discussed. However, these women are not an optimal vaccine cohort, in part because they are older than target age groups.
- Expanded use of electronic health records (EHRs) would likely benefit efforts to monitor the impact of HPV vaccination because it would be easier to determine if an individual has been vaccinated. However, even with recent federal incentives, adoption of EHRs remains low in office settings so it may be some time before this benefit is realized.
- Monitoring efforts may be enhanced if precancerous lesions and/or positive tests for high-risk HPV types are included on lists of notifiable diseases and conditions. These lists are established at the state level through a variety of processes.
- Vaccine registries exist in some states, although most are not mandatory. Vaccine registries include the date of vaccination and the number of doses received. In the United States, there is a resistance to establishing mandatory vaccine registries. An effort to establish a state-based vaccine registry in Washington failed because of inability to secure funding. Registries in all 50 states are not necessary to evaluate the vaccine; it would be sufficient to have comprehensive registries in a few locations.
- Resources should be devoted to sustaining current surveillance efforts, which will provide valuable information about the impact of HPV vaccination. However, the addition of sites in different regions of the United States would make the data more generalizable. It also would be useful to have data generated by a non-government body. One of the limitations of current surveillance projects is that they are not linked to screening data.
- Data on male vaccination should be collected, in part to allow evaluation of the effects of male vaccination on cervical disease among females. The vaccine registry in North Carolina collects data on male HPV vaccination because it focuses on all adolescent vaccines, not just the HPV vaccine. Recent data indicate that vaccination rates among males are increasing. For example, in New York City, the number of vaccine doses distributed to males was higher than the number distributed to females; this was in part because the HPV vaccine was made available through the Vaccines for

Children Program and was actively promoted as a way to prevent genital warts. CDC data on 2011 vaccine coverage for males and females will be released in August 2012.

- There are potential ethical considerations in conducting placebo-controlled trials to assess whether HPV vaccines prevent persistent HPV infection of the oropharynx. The study would be feasible but very large (possibly including up to 10,000 participants) and likely expensive.
- Although no definitive data have been generated to date, most participants felt there was a strong possibility that HPV vaccines would reduce the risk of oropharyngeal cancer.

SESSION FIVE: IDENTIFYING PARTICIPANT PRIORITIES

Key themes that emerged during the workshop were identified, including knowledge gaps that should be addressed through research, strategies for determining the impact of HPV vaccines, and approaches for increasing vaccine uptake. Invited participants discussed which gaps and activities should be given priority in efforts to reduce the burden of HPV-associated disease. The priorities recommended by the invited participants will be considered by the Panel as it develops recommendations for its annual report.

KEY POINTS

- Efforts should be made to increase vaccine uptake, particularly among males. The *Healthy People 2020* goal that 80 percent of females should receive three doses of vaccine by 13 to 15 years of age should be endorsed and also expanded to include males, as gender-neutral policies related to vaccination are more likely to be effective. School-based vaccination programs (possibly as part of a broader school-based adolescent health initiative) could be implemented to increase vaccine uptake. There is good evidence that school-based vaccination programs are effective. A small number of participants also suggested that requiring the vaccine for school entry should be considered.
- Outcomes of ongoing studies on the efficacy and duration of protection based on fewer than three vaccine doses should be monitored. These data may influence changes in vaccination recommendations and policies.
- Data systems should be created and expanded to support vaccine monitoring and surveillance (e.g., vaccine registries, screening registries).
- Strategies and tools should be developed to facilitate communication with physicians (specifically, pediatricians) and the general public about vaccine safety and the benefits of vaccination. These tools/strategies should not be specific to HPV vaccines.
- Research is needed to address gaps in knowledge regarding the natural history of oropharyngeal HPV infection.
- Guidelines should be developed regarding types of endpoints that are appropriate for addressing various scientific questions related to HPV vaccines.
- Bridging studies are needed to assess immunogenicity of HPV vaccines in younger age groups.
- There is a need for validated screening approaches for HPV-associated cancers other than cervical cancer. Efforts should be made to develop biomarker-based assays capable of identifying individuals at risk of HPV-associated cancers. It also would be helpful to characterize precancerous lesions for oropharyngeal cancers and noncervical anogenital cancers.
- Serological assays that assess vaccination status should be developed.
- It may be beneficial to conduct some future vaccine studies in high-risk populations. Even if the results are not fully generalizable, they will be informative.

PUBLIC COMMENT

KEY POINTS

- Data from the initial clinical trial of the Merck vaccine indicated that women who had abnormal Pap test results prior to vaccination had worse outcomes than women who had not been vaccinated (i.e., more likely to present with CIN). If this finding is true, it has implications for whether catch-up vaccination should be done. It is important to resolve this issue because physicians and women may have a tendency to suggest or undergo vaccination after an abnormal Pap result.
- Although it is important to promote use of the HPV vaccine among those who will benefit from it, it is also important to promote screening among those who have already been exposed to HPV and to improve treatments for those who have been diagnosed with HPV-related cancers.

CLOSING REMARKS

Drs. Rimer and Witte thanked the participants for their contributions to the workshop. Dr. Rimer also urged participants to submit any additional input via email.

CERTIFICATION OF MEETING SUMMARY

I certify that this summary of the President's Cancer Panel meeting, *HPV Vaccination as a Model for Cancer Prevention*, held July 24, 2012, is accurate and complete.

Certified by: _____ Date: November 1, 2012

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