MEETING SUMMARY

PRESIDENT'S CANCER PANEL

CREATING AN INTEGRATED HPV VACCINATION AND SCREENING PROGRAM

November 16, 2012
Chicago, Illinois

This workshop was the third in the President's Cancer Panel's (PCP, the Panel) 2012-2013 series, *Accelerating Progress in Cancer Prevention: The HPV Vaccine Example*. During this workshop, the Panel heard expert testimony and moderated discussions on the potential health and economic impacts of human papillomavirus (HPV) vaccination, the potential impact of widespread HPV vaccination on cervical cancer screening practices, and tools and resources needed to support an integrated approach to HPV vaccination and screening.

President's Cancer Panel

Barbara Rimer, Dr.PH, Chair

Hill Harper, J.D.

Owen Witte, M.D.

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

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

Meeting Co-Chairs

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Marcus Plescia, M.D., Director, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention

Mona Saraiya, M.D., Medical Officer, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention

Participants

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

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Daniel Meyer, D.D.S., Senior Vice President of Science and Professional Affairs, American Dental Association

Debbie Saslow, Ph.D., Director, Breast and Gynecologic Cancer, Cancer Control Science Department, American Cancer Society

Diane Solomon, M.D., Senior Investigator, Division of Cancer Prevention, National Cancer Institute

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Cosette Wheeler, Ph.D., Regents Professor, Department of Pathology, University of New Mexico Health Sciences Center

OPENING REMARKS—DR. BARBARA RIMER

Dr. Rimer welcomed invited participants and other attendees to the meeting on behalf of the Panel. She introduced Panel members, provided a brief overview of the history and purpose of the Panel, and described the aims of the current series of meetings. Dr. Rimer also introduced the meeting co-chairs, Drs. Tamera Coyne-Beasley, Marcus Plescia, and Mona Saraiya, as well as Robert Mittman, the workshop facilitator.

SERIES OVERVIEW

DR. DOUGLAS LOWY

HPV VACCINATION: SUMMARY OF WORKSHOPS 1 AND 2

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 coauthored more than 100 papers over the past 25 years. Their laboratory contributed to the initial development, characterization, and clinical testing of the virus-like particles that are used in the two U.S. Food and Drug Administration (FDA)-approved HPV vaccines. Dr. Lowy is a member of the National Academy of Sciences and is also a member of the Institute of Medicine. He and Dr. Schiller have received numerous honors for their pioneering work, including the 2011 Albert B. Sabin Gold Medal Award.

KEY POINTS

- In the developing world, cervical cancer is the most common HPV-associated cancer. However, in the United States, the number of HPV-associated noncervical cancers is higher than the number of cervical cancers. In addition, males in the United States bear a larger proportion of the burden of

HPV-associated cancers compared with men in the developing world; 30 percent of HPV-associated cancers in the United States occur in men compared with less than 5 percent of cases in the developing world.

- Globally, approximately 85 percent of cervical cancer cases and 88 percent of cervical cancer deaths occur in the developing world.
- 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 the spectrum of HPV-associated diseases, including several cancers, genital warts, and recurrent respiratory papillomas.
- With the exception of cervical cancer, HPV-associated cancers do not have validated intermediate markers or public health interventions for secondary prevention. HPV vaccination is the main validated public health approach to prevent noncervical HPV-associated cancers.
- There is overlap between the cases of HPV-associated cancers that could be prevented through vaccination and the cases that could be prevented through cervical cancer screening, but a prevention strategy that includes both approaches would be more effective than one using either alone.
- The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) is the official U.S. group charged with making recommendations regarding vaccination. ACIP recommends Cervarix, the HPV vaccine manufactured by GlaxoSmithKline (GSK), as a routine vaccination for girls, and recommends Gardasil, the vaccine manufactured by Merck, as a routine vaccination for both boys and girls. The main target age for vaccination is 11-12 years of age, with catch-up vaccination recommended through 25 (Cervarix) or 26 (Gardasil) years of age.
- In contrast to ACIP, the American Cancer Society (ACS) recommends that catch-up vaccination be done up to only 18 years of age because of the lower cost-effectiveness of vaccinating older individuals.
- HPV vaccines have excellent safety records, similar to other licensed vaccines. A prospective study based on Vaccine Safety Datalink data, which include control groups, found no evidence for increased risk of several prespecified adverse events following receipt of the HPV vaccine.
- Clinical studies have found that among women who received all three doses of the HPV vaccine and were HPV negative during the vaccination period, the efficacy of the vaccine with respect to various clinical endpoints was close to 100 percent. However, vaccine efficacy was substantially lower among women who were exposed to HPV prior to vaccination. These results provide evidence for the importance of vaccinating prior to sexual initiation.
- In Australia, there was a dramatic reduction in genital warts among young women and young heterosexual men between 2007, when the HPV vaccine was introduced for use in females, and 2010. However, a similar reduction was not observed among men who have sex with men. There also has been a drastic reduction in cervical dysplasia among girls younger than 18 years old and a modest reduction among women 18 to 20 years of age. However, no reduction was observed among women older than 20, which likely reflects the decrease in efficacy when the vaccine is administered after HPV exposure.
- Recurrent respiratory papillomatosis (RRP), which is caused by HPV 6 and 11, should be prevented by Gardasil, although it is not currently listed as an indication. RRP is a rare disease but can be serious when it occurs in young children. Changes in RRP due to vaccination would likely be evident sooner than changes in cancer rates.
- It is highly plausible that the HPV vaccine will prevent HPV-associated oropharyngeal cancers. However, the natural history of oral/oropharyngeal HPV infection has not been fully elucidated, and no precursor lesion for HPV-associated oropharyngeal cancer has been identified to date. In contrast,

precursor lesions have been identified for each of the cancers included as indications for the HPV vaccine, and FDA approval for these indications was based on prevention of these precursor lesions.

- An NCI-conducted trial of Cervarix found that the vaccine prevents oral HPV infection with high efficacy (>90%) among women, but relevance of these results to oropharyngeal infection, men, and/or Gardasil is unknown.
- Some countries are implementing a two-dose schedule for the HPV vaccine, but key groups and organizations in the United States (e.g., ACIP, ACS) continue to recommend the three-dose schedule.
- Merck is conducting a Phase III trial of a nine-valent HPV vaccine. If successful, this vaccine could potentially prevent approximately 90 percent of cervical cancer cases.
- CDC data indicate that uptake of the HPV vaccine has lagged behind that of other adolescent vaccines. As of 2011, one in two females between the ages of 13 and 17 had received at least one dose of the HPV vaccine, but only one in three females in this age range had received all three recommended doses. Among males, 8 percent had received at least one dose by the end of 2011, although these data must be interpreted with caution since the vaccine was not approved by the FDA for use in males until 2009.
- Differences in HPV vaccine uptake also were observed among different demographic groups. Black and Hispanic girls were more likely than non-Hispanic white girls to receive the first dose of the vaccine, but black girls were less likely than Hispanic or non-Hispanic white girls to receive all three doses. Girls from households with incomes below the poverty level were more likely to receive the first dose of the vaccine than girls from households with incomes at or above the poverty level.
- Several factors may influence uptake of the HPV vaccine. There is a small, but vocal, group of people who are concerned that the vaccine will result in sexual disinhibition among adolescents, although there is no evidence that this is the case. In addition, there is low awareness about the burden of HPV-associated diseases in males. In a study conducted by CDC, the reasons most commonly given by parents for not wanting their children to be vaccinated were: (1) the vaccine is not needed, (2) the child is not sexually active, (3) concerns about safety and/or side effects, (4) lack of knowledge, and (5) the vaccine was not recommended by their health care providers. CDC also found that providers are less willing to strongly advocate for the HPV vaccine than for other vaccines (i.e., vaccine hesitancy).
- CDC has undertaken a number of efforts to increase rates of vaccine initiation, reduce disparities, and increase rates of completion. It is important to consider both initiation and completion of the HPV series.
- Several strategies for increasing rates of HPV vaccine uptake were discussed at the second workshop. Many participants said that it is important to educate providers in order to increase enthusiasm for the vaccine. It also was proposed that the HPV vaccine be promoted as part of an integrated adolescent vaccine platform and as an anticancer vaccine. Pediatricians suggested that the vaccine doses be given over one to two years rather than within a six-month window. It also was suggested that the vaccine could be administered by providers other than pediatricians and primary care physicians (e.g., pharmacists, dentists). Another suggestion was to create incentives to encourage families to have their children vaccinated (e.g., insurance rebate). Many workshop participants pointed out that school-located vaccination would be useful for increasing uptake, although several barriers to this approach were discussed. Mandating vaccination for school entry, another strategy discussed, has generated considerable controversy in the United States.

OPENING ROUNDTABLE

Participants introduced themselves and were asked to state the most important impact that widespread HPV vaccination would have on cervical cancer screening, clinical practice, and/or health economics.

Participants emphasized the potential of the HPV vaccine to improve the health and well-being of populations and to reduce the economic burden of cervical cancer. The vaccine also could help reduce health disparities both in the United States and globally if efforts are made to vaccinate those at highest risk for cervical cancer. However, current medical mistrust among some populations will need to be addressed in order to achieve widespread vaccine uptake. It was noted that there is still a need for effective therapies for HPV-associated cancers, particularly over the next few decades. Participants also discussed the need for providers to have access to their patients' medical histories in order to effectively integrate vaccination and screening; this will be facilitated through the adoption of interoperable electronic health records (EHRs). An organized system also is needed to facilitate population-based tracking of screening outcomes and any lesions that are identified. Participants indicated that with widespread uptake of the HPV vaccine, the age of initiation of cervical cancer screening could be raised and the frequency of screening reduced. The Canadian experience suggests that some women and their physicians will resist less frequent screening. It also may be possible to change current methods of screening (e.g., shift toward HPV testing). The lower demand for screening would necessitate changes in practice by hospitals and providers, who currently have financial incentives to perform procedures and may be resistant to changes in guidelines. It will be challenging to communicate with both providers and patients about the need to change current screening practices while maintaining well-woman visits for other purposes.

SESSION ONE: NAVIGATING THE FUTURE OF CERVICAL CANCER DETECTION: COORDINATING EVOLVING SCREENING PRACTICES WITH AN EMERGING HPV VACCINATION PROGRAM

DR. TAMERA COYNE-BEASLEY

NAVIGATING THE FUTURE OF CERVICAL CANCER DETECTION: COORDINATING EVOLVING SCREENING PRACTICES WITH AN EMERGING HPV VACCINATION PROGRAM

BACKGROUND

Dr. Coyne-Beasley is a tenured professor of pediatrics and internal medicine at the University of North Carolina at Chapel Hill. Her academic and community work has focused on improving adolescent health and access to health care and decreasing adolescent behavior that puts them at risk for sexually transmitted infections such as human immunodeficiency virus (HIV) and HPV. She is the founding director of the North Carolina Child Health Research Network and associate director for community engagement of the Child Health Core of the North Carolina Translational and Clinical Sciences Institute. She has been the principal investigator on several projects that examine knowledge and acceptability of the HPV vaccine and barriers to HPV vaccination. She also is developing interventions in partnership with health care providers, parents of male children, and young males to increase HPV vaccination among males. She currently works with the Center for Rural Health Innovations to develop a telemedicine and texting intervention to improve HPV vaccination uptake among middle school students through school-based health centers in rural communities. Dr. Coyne-Beasley is a voting member of ACIP, chair of the ACIP Adult Immunization workshop, and a member for the Measles, Mumps, and Rubella (MMR) and HPV workgroups of the ACIP.

KEY POINTS

- Incidence of cervical cancer in the United States has decreased more than 50 percent over the past 30 years due to widespread cytology screening. After introduction of the conventional Pap test in the 1950s, screening protocols remained unchanged for nearly 40 years. In 1988, the Bethesda system

was developed to standardize the terminology for describing abnormal cytology results. This system was subsequently updated in 1991 and 2001.

- In the 1970s, Harald zur Hausen postulated a role for HPV in cervical cancer. He discovered novel HPV DNA in cervical cancer biopsies, which was identified as HPV 16 in 1983. In 1984, he cloned HPV 16 and 18 from cervical cancer specimens and made them available to the scientific community. Dr. zur Hausen received the Nobel Prize in 2008 for his work in this area.
- Technological advancements and the discovery of the role of HPV in cervical cancer have led to changes in cervical cancer screening protocols in the past 20 years. Liquid-based cervical smear technology has facilitated better cytology analysis and allowed for the integration of HPV testing to determine cancer risk.
- Based on evidence accumulated regarding HPV infection, persistence of HPV infection, and progression of cervical lesions to cancer, three bodies—the American College of Obstetricians and Gynecologists; the U.S. Preventive Services Task Force; and a joint task force of ACS, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology—have issued updated cervical cancer screening guidelines. Currently, all of these organizations agree that there should be no change in screening recommendations if an individual has received the HPV vaccine.
- The quadrivalent HPV vaccine (Gardasil) was licensed in June 2006. Gardasil was recommended by ACIP as a routine vaccination for girls 11 and 12 years of age, with catch-up vaccination recommended for females 13 to 26 years old. In October 2009, the bivalent HPV vaccine (Cervarix) was licensed and recommended for routine use for girls 11 and 12 years of age, with catch-up vaccination recommended for females 13 to 25 years of age. At the same time, Gardasil was licensed for use in males, and ACIP issued a permissive recommendation for vaccination of males ages 9 to 26. In October 2011, ACIP recommended Gardasil as a routine vaccination for 11- and 12-year-old males, with catch-up vaccination recommended for males 13 to 21 years of age.
- Uptake of the HPV vaccine has been increasing slowly among U.S. females but still is below optimal levels. Early uptake among males also has been low, which may be in part because of difficulty communicating the risk of HPV-related disease in males. However, it was also pointed out that currently available data for males predate the ACIP recommendation that the HPV vaccine be a routine vaccine for males.
- Improvements in vaccine uptake are needed. Mandatory vaccination and/or school-based vaccination programs have been effective in other countries and may be possible strategies to promote uptake in the United States. It is possible that vaccine uptake will improve if the vaccine is shown to prevent additional cancers, such as oropharyngeal cancer, or if it is shown to be effective with only two doses.
- Efforts should be made to encourage vaccine uptake among populations at highest risk for cervical cancer so that existing disparities in cervical cancer are not made worse.
- Cervical cancer screening will continue to be necessary even if widespread HPV vaccination is achieved. Current vaccines protect against HPV 16 and 18, which collectively account for approximately 70 percent of cervical cancers, but other HPV types also can cause cancer.
- Widespread HPV vaccination could influence changes in cervical cancer screening protocols. For example, it may be appropriate to change the age of screening initiation or lengthen the time intervals between screenings.
- Cervical cancer screening may be enhanced by the inclusion of additional biomarkers in the future. For example, it may be possible to test for the E6 and E7 oncoproteins produced by HPV-infected cancer cells through self-sampling techniques. This type of approach could be applied for large-scale population screening.

DR. DIANE SOLOMON

INTEGRATION OF HPV VACCINATION AND SCREENING IN THE PREVENTION OF CERVICAL CANCER

BACKGROUND

Dr. Solomon is a senior investigator at the National Cancer Institute. Currently, she is working on an NCI-sponsored clinical trial of a prophylactic HPV vaccine in Costa Rica. She previously headed the ASCUS/LSIL Triage Study (ALTS) to determine the optimal management of equivocal and mildly abnormal Pap tests. Dr. Solomon led the development and evolution of the Bethesda system for communicating the results of cervical cytology and is editor of *The Bethesda System Atlas*, the internationally recognized standard text for reporting cervical cytology. She is the author or coauthor of over 140 scientific articles and texts and six book chapters and has presented over 250 lectures and workshops. Dr. Solomon's research and writing, as well as her leadership in key professional societies, governmental advisory committees, and national and international consensus conferences, have been instrumental in the development of new medical practice guidelines for management of patients with abnormal cytology results.

KEY POINTS

- National statistics on HPV vaccine uptake do not reflect regional trends that may be important for cervical cancer prevention efforts. Many states with low rates of cervical cancer mortality have high rates of HPV vaccine uptake, which represents a redundancy of prevention efforts. In contrast, the lowest rates of vaccine uptake are observed in states with high rates of cervical cancer mortality. Efforts should be made to minimize redundancy, as it results in increased cost without commensurate reduction in cervical cancer mortality.
- Approximately 70 percent of cervical cancer cases potentially could be prevented with current HPV vaccines, which protect against infection with HPV 16 and 18. If the nine-valent vaccine currently under development proves to be effective, it could prevent up to 87 percent of the world's cervical cancer cases.
- Widespread HPV vaccination will reduce the benefits of cervical cancer screening because fewer abnormal Pap tests will be due to cervical cancer and/or high-grade precancerous lesions. Based on modeling data, widespread adoption of the HPV vaccines would result in a 17 percent overall decrease in abnormalities detected by screening, with the largest decreases being observed for higher-grade lesions. The model predicts an 8 percent reduction in atypical squamous cells of undetermined significance (ASCUS), a 23 percent reduction in low-grade squamous intraepithelial lesions (LSIL), a 45 percent reduction in high-grade squamous intraepithelial lesions (HSIL), and a 72 percent reduction in invasive cervical cancer.
- Potential harms associated with cervical cancer screening include anxiety regarding a positive screening test, discomfort from additional diagnostic and screening procedures, and increased risk of pregnancy complications related to treatment.
- In order to determine how cervical cancer screening practices should be changed, it is necessary to determine the risk of grade 3 cervical intraepithelial neoplasia (CIN3) among women who were vaccinated prior to initiation of sexual activity. This will require vaccine registries linked to pathology results. This type of study will help determine what level of vaccine uptake should trigger changes in screening guidelines. The potential benefit of having different guidelines depending on vaccination status also should be considered.
- Several strategies could help reduce over-screening as HPV vaccine uptake increases. It may be appropriate to start screening later among women who have received HPV vaccines. To do this, it is

necessary to determine the age at which the risk of CIN3 for a vaccinated individual is comparable to that of an unvaccinated 21 year old (the recommended start age for screening based on current guidelines). Modeling data using cervical cancer incidence rates in New Mexico indicate that initiation of screening could potentially be delayed several years for vaccinated women. The performance of existing and new screening tests also should be examined to determine which test or combination of tests provides the best indication of risk. It also may be necessary to institute a more conservative threshold for action based on screening test results if the risk of cervical cancer is lower.

DR. EDUARDO FRANCO

NAVIGATING THE FUTURE OF CERVICAL CANCER PREVENTION: COORDINATING EVOLVING SCREENING PRACTICES WITH AN EMERGING HPV VACCINATION PROGRAM

BACKGROUND

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

KEY POINTS

- Cervical cancer screening still will be needed even if the HPV vaccine is widely adopted. Current vaccines do not prevent infection with all high-risk types of HPV and are not 100 percent efficacious. However, changes in screening guidelines may be needed. Cervical cancer prevention activities are inherently a single process with multiple components, including vaccination and screening. Changes in one part of the process (e.g., increase in vaccination) will affect other parts of the process.
- A number of recent and pending activities have influenced or will influence cervical cancer prevention activities. Molecular HPV testing gradually has been introduced in North America and Europe. School-based vaccination has been successful in Australia, the United Kingdom, and Canada. A nine-valent HPV vaccine currently is being evaluated in a multicountry randomized clinical trial, and a pan-mucosotropic HPV vaccine also is being developed.
- Recent modifications to cervical cancer screening guidelines in the United States recommend less frequent screening. For women ages 30 to 65, the guidelines call for screening with cytology and HPV testing every 5 years.
- Some Canadian groups have concluded that cytology adds little value to HPV testing. In Ontario, HPV testing is the primary mode of cervical cancer screening; cytology is used as a follow-up for women who test positive for HPV. HPV tests have a number of benefits over cytology as a primary

screening method. For example, HPV tests are more sensitive, and interpretation of HPV tests is less subjective than cytology.

- It will not be possible to conduct a randomized controlled trial to compare cervical cancer screening strategies in vaccinated and nonvaccinated women because the sample size needed to enable reliable detection of differences in outcomes would be prohibitively large. Any differences in guidelines for these two populations should be based on observational data.
- A generic algorithm for cervical cancer screening was presented. This approach is modified on a province-by-province basis in Canada. Primary screening is conducted by testing for high-risk HPV types. Women with negative HPV tests are recalled to be screened again following an extended interval. Women who test positive for high-risk HPV types undergo either cytology testing or HPV genotyping. If the cytology test is normal or the genotyping test is negative for high-risk HPV types, testing is repeated in 12 months. If cytology is abnormal or high-risk HPV genotypes are detected, colposcopy and biopsy are performed. If the results of these procedures are normal, they are repeated in 12 months. If the results are positive, the woman is treated according to local guidelines.
- In high-resource areas, this approach to screening can be used as a surveillance system to measure the effects of vaccination (e.g., duration of protection, population effectiveness, cross-protection, type-risk replacement). This would require linkage between various components of the screening program, including vaccine registries, HPV outcomes registries, administrative health care databases, cytology and pathology registries, and population-based tumor registries. This type of organized system is in place in Canada but not in the United States.
- Research is needed to establish optimal follow-up strategies for women who test positively for HPV. Research also is needed to identify an appropriate age for initiation of screening for vaccinated women and to determine safe screening intervals for vaccinated and unvaccinated women. Efforts also need to be made to educate providers and patients about best practices.

SESSION ONE MODERATED DISCUSSION

KEY POINTS

- The consensus reached by three organizations issuing cervical cancer screening guidelines is notable and encouraging. However, there is evidence that obstetricians/gynecologists (OB/GYNs) are less likely to follow guidelines than are other types of providers. Efforts should be made to engage OB/GYNs and convince them of the risks of over-screening. It is possible that they will be more willing to conform to current guidelines both because of the consensus reached by the issuing organizations and because of the integration of HPV testing as a screening tool.
- System-level changes may promote adherence to guidelines. This was the case with mammography. The addition of mammography to Healthcare Effectiveness Data and Information Set (HEDIS) measures prompted providers and organizations to modify their systems to increase the likelihood that mammographies would be performed.
- Concerns about liability influence provider behavior. Tort reform is needed to ensure that clinicians are not penalized for following evidence-based guidelines. It is also important that physicians and patients understand that all tests and procedures are associated with errors and that not all cervical cancers will be prevented by screening.
- Reimbursement policies also drive clinical practices. Well-woman visits will be covered as a preventive service under the Affordable Care Act, but screening does not need to be a part of all of these visits. If screening procedures that do not fall within guidelines are not reimbursed, the number of excess procedures will decrease. Requiring patients to pay out-of-pocket for undergoing screening more frequently than is recommended also may reduce the number of unnecessary procedures.

- Patients often expect annual screening and may feel that having more procedures means that they are receiving good care. Education efforts are needed to inform patients about the adverse consequences of over-screening and let them know that there are other benefits of annual well-woman visits. Consideration should be given to whether the annual visit should be with a primary care physician or an OB/GYN.
- It is important to reduce over-screening, but it is equally important to continue and increase efforts to reach women who are currently not being screened at all. This includes both insured and uninsured women.
- Trained community health workers and *promotoras* would be able to help deliver information about screening and guidelines to patients. This approach may be particularly effective for women from underserved populations who may not have regular providers.
- Age of initiation of cervical cancer screening has been increasing among U.S. women in recent years. The interval between screenings also is beginning to lengthen.
- It is technologically feasible for physicians to link to information in state-based immunization registries using their office-based EHRs. For example, a provider could open a patient's record and be told that the patient is unvaccinated and/or due to be screened for cervical cancer. In Michigan, this system is in place for childhood immunizations; providers can access information about immunizations and other required screenings using their office-based EHRs, or they can access the state registry directly. Setting up this type of system requires collaboration among different stakeholders, but it is feasible and desirable. These services will be available to more physicians as adoption of EHRs increases.
- As the United States considers how to change cervical cancer screening guidelines in the future, it may not be necessary to depend solely on the outcomes of large clinical trials. Informative data will be generated in Canada and Australia, which have higher rates of HPV vaccine uptake and/or different screening practices. Observational data also can be derived from large databases maintained by large health systems. There is also increasing acceptance of modeling data.
- Potential changes in cervical cancer screening recommendations should be considered on both the individual and population levels. Making decisions on a patient-by-patient basis will require integrated data systems that allow providers to access each patient's vaccination and screening history. This would be possible within some closed health care systems but would not be feasible for much of the U.S. population at this time. The issues related to the individualized approach are different than those associated with modifying guidelines based on high uptake of the vaccine across the whole population.
- Patients should be involved with their providers in a shared decision-making process regarding screening and other medical care. Patients' ownership and control of their medical information should be discussed.
- When considering changes to U.S. cervical cancer screening guidelines, it probably makes the most sense to focus first on increasing the age of screening initiation because there are already some data supporting this change and it will affect the age cohort that has had access to the HPV vaccine.
- Many other countries have considered or are considering increasing the age of initiation of cervical cancer screening to 25—4 years later than the current U.S. guidelines. It is reasonable to consider increasing the screening age to 25, even among unvaccinated individuals, although there are significant differences between the health care systems of the United States and other countries.
- Data from the Danish Cohort Study reveal that HPV type affects the rate of development of CIN3 and higher-grade cervical lesions. Women infected with HPV 16 or 18 have the highest risk of developing a lesion that is CIN3 or worse over the next 12 years. Those infected with HPV 31 or 33 have intermediate risk, while those infected with other HPV types have relatively low risk over the same

time period. A single HPV test does a good job of predicting increased risk of CIN3 based on HPV type. If there were a vaccine that protected against HPV 16, 18, 31, and 33, these data indicate that it would be appropriate to increase the age at which women begin cervical cancer screening because high-grade lesions caused by other HPV types are unlikely to appear in younger women.

- Valuable data regarding outcomes in vaccinated patients can be accessed through the Kaiser Permanente database and the New Mexico Pap Registry. Kaiser data also can be used to study the effects of increasing the age of initiation of screening and lengthening screening intervals.

SESSION TWO: PREDICTING HEALTH AND ECONOMIC IMPACTS OF WIDESPREAD HPV VACCINATION

DR. MONA SARAIYA

PREDICTING CANCER-RELATED IMPACT OF HPV VACCINATION

BACKGROUND

Dr. Saraiya is a cancer epidemiologist at the CDC Division of Cancer Prevention and Control (DCPC), which is involved with cervical cancer screening research and policy. She provides technical expertise to the CDC Breast and Cervical Cancer Program, national surveillance of Pap testing, adherence to guidelines, and monitoring of impact of HPV types in cancers. Dr. Saraiya is an active member of the CDC HPV Workgroup, the CDC HPV Vaccine Workgroup, the CDC ACIP HPV Working Group, and the ACIP writing group for the HPV vaccine. She has provided a cancer perspective on the areas of HPV testing for cervical cancer and provided technical assistance on several public and provider education brochures and media. Dr. Saraiya works collaboratively within CDC and with external partners. She recently was appointed the lead for international cancer prevention activities, with a focus on cervical cancer screening, HPV vaccine's impact on screening, and cancer registries. Dr. Saraiya completed her medical school training at Rush Medical College and earned her master's degree at Emory University. She is board-certified in preventive medicine.

KEY POINTS

- U.S. cancer registries cover 100 percent of the population, a critical factor in studying cancer and specific populations.
- Study of the impact of HPV vaccination would benefit if cancer registries included information about HPV type and precancerous HPV-associated lesions. As new EHR reporting requirements are implemented, cancer registries will have the capability to obtain HPV genotype information if those data are included in a patient's EHR. There has been some experience collecting information about precancerous lesions, including carcinoma *in situ*, CIN3, and grade 3 anal, vaginal, and vulvar lesions. However, changes in classification systems will be occurring, which will present some challenges in collecting these data. In some cases, it now is possible to link cancer registries with state vaccine registries.
- It is estimated that HPV 16 and 18 cause 15,000 cancer cases among women and 7,400 cancer cases among men in the United States each year. Among men, the majority of these cancers occur in the oropharynx.
- An ongoing CDC-supported project involving seven cancer registries is conducting population-based HPV typing of specific cancer types, including cervical, vulvar, vaginal, anal, penile, oropharyngeal, and oral cavity cancers. The goal is to develop infrastructure for systematic population-based monitoring of HPV types in cervical cancer and other HPV-associated cancers. Four of the registries are working with pathology labs, and three are using Surveillance, Epidemiology, and End Results

(SEER) repositories. Baseline HPV typing data were collected for approximately half of the eligible invasive and *in situ* cancers in the registries using a standardized assay. Based on preliminary data, 78 percent of the cancers analyzed were HPV positive. For many of the cancer types, HPV prevalence was higher than expected based on previous studies.

- The results of the CDC project were analyzed based on the HPV types covered by current vaccines (HPV 16 and 18) and by the additional types included in the nine-valent vaccine currently being developed (HPV 31, 33, 45, 52, and 58). These results indicate that more than 80 percent of CIN3 and cervical cancer lesions are associated with HPV types that are included in one or both of these vaccines. In addition, 67.3 percent of oropharyngeal cancers are associated with these HPV types. These data may help inform future modeling efforts.
- The study revealed differences in the distribution of HPV types across racial/ethnic groups. While similar proportions of cervical cancers in white, black, and Hispanic women were found to be associated with HPV 16/18 and HPV 31/33/35/52/58, different patterns are observed for CIN3. Among white women, 66.7 percent of CIN3 lesions were associated with HPV 16 or 18 and 16.3 percent were associated with HPV 31, 33, 35, 52, or 58. Among black women, the percentages were 27 percent and 36.8 percent, respectively, and among Hispanic women, the percentages were 49.9 percent and 26.3 percent, respectively. Based on these data, a smaller proportion of CIN3 lesions would be prevented by the current HPV vaccines among black and Hispanic women than among white women.
- There were also differences between blacks and whites in the HPV types found in oropharyngeal cancers. Among whites, 65.1 percent of oropharyngeal cancers were associated with HPV 16 or 18, compared with only 29.1 percent of cases among blacks.
- It is possible that some of the racial/ethnic differences and patterns of HPV type distributions may be due to regional differences since these data are drawn from only seven registries.
- CDC conducted a pilot study to determine the feasibility of collecting CIN3 data using a standardized protocol. The initial effort included registries in three states and found rates of CIN3 incidence per 100,000 women to be 77.9 in Kentucky, 54.7 in Louisiana, and 57.2 in Michigan.
- A study conducted in Michigan found that it was feasible to link data for preinvasive cervical lesions with data from vaccine registries. This was done by linking both preinvasive cervical lesion cases and vaccine registry records to birth records and then crosslinking the registries. In 2015, when a cohort of girls who have been vaccinated reaches screening age, a study will be done to compare incidence rates of CIN3 and cervical cancer between vaccinated and unvaccinated individuals. This effort can be expanded to other states and could include other preinvasive lesions as well.
- Several areas should be addressed through modeling and/or other types of studies. These include the role of the HPV vaccine in preventing noncervical cancers, the roles of the additional HPV types included in the nine-valent vaccine in HPV-associated lesions, and the impact of adherence to screening guidelines on clinical outcomes. Consideration also should be given to how racial/ethnic and/or geographic differences in HPV type prevalence may impact the effectiveness of HPV vaccines or screening technologies.

DR. DONATUS EKWUEME

ECONOMIC EVALUATION OF HPV VACCINATION IN LOW-INCOME POPULATIONS IN THE UNITED STATES

BACKGROUND

Dr. Ekwueme is the lead senior health economist in the Division of Cancer Prevention and Control of the CDC National Center for Chronic Disease Control and Health Promotion. He has worked as a health

economist conducting economic research on international and domestic public health issues in several national centers within CDC. Within DCPC, he provides leadership and direction for applied economics research projects and policy analysis on the burden of cancer disease in the United States. In addition, his research focuses on using various modeling approaches to understand the interplay between human behavior, economics, and the prevention and control of cancer, and in developing methods to collect economic cost data to accurately evaluate and estimate the economics of the national cancer prevention and control programs. From 1998 through 2000, Dr. Ekwueme was a consultant to the World Health Organization and worked in several sub-Saharan African and English-speaking Caribbean countries. Dr. Ekwueme received his master's of science and a doctorate in economics from Wayne State University. Prior to receiving his doctorate, he was a faculty member in the Department of Economics at Eastern Michigan University, where he taught labor and microeconomics. Dr. Ekwueme has authored or coauthored peer-reviewed publications and technical reports on the use of public health economics to improve program performance and effectiveness.

KEY POINTS

- Data on the long-term impact of HPV vaccination are not yet available. The full benefits of HPV vaccination and other efforts to prevent cervical disease will not be realized for decades. Modeling can be used to provide insight into the effects of HPV vaccination in the meantime.
- Prior modeling studies have demonstrated that HPV vaccination can significantly reduce future cervical abnormalities and the incidence of cervical cancer and that vaccination can be a cost-effective prevention strategy. However, modeling studies have not yet measured the impact of HPV vaccination on medically underserved, low-income populations in the United States. This information may be helpful in guiding policy decisions.
- A modeling study was done to estimate the long-term public health impact and cost-effectiveness of the introduction of HPV vaccination on medically underserved, low-income women who are participating in the CDC National Breast and Cervical Cancer Early Detection Program (NBCCEDP). The effort also was designed to determine optimal cervical cancer screening strategies for NBCCEDP participants in the presence of an HPV vaccination program.
- An individual-based, open-population model that permits estimation of the impact of interventions in populations with various combinations of characteristics that affect uptake of cervical cancer screening was developed. The model simulates a proportion of the U.S. low-income female population and follows each woman through different infection and cervical disease states (e.g., susceptible, infected, immune, cervical lesion, cancer) for five classes of HPV genotypes (i.e., 16, 18, 6/11, 31/33/45/52/58, other oncogenic HPV types). The model consists of three modules: the natural history module, the screening and treatment module, and the vaccination module. The natural history and screening modules are used to replicate current population outcomes, while the vaccination module is used to predict the effect of the HPV vaccine.
- The natural history and screening modules have been developed and are undergoing validation. The screening parameters are based on patterns observed in the NBCCEDP population. Coding has been developed for the vaccination module. Once validation of the natural history and screening modules is complete, the vaccination module will be integrated, which will allow predictions to be made about the impact of HPV vaccination on the health effects and cost-effectiveness of cervical cancer screening.
- There have been several challenges associated with developing this model. The natural history of HPV is complex; there are multiple HPV types, each with a different disease progression. There are also multiple stages of disease and a long lag time between infection and disease. It is difficult to estimate some parameters because of the lack of data on age, race/ethnicity, and the natural history and transmission of the various HPV types.

DR. JANE KIM

MODEL-BASED COST-EFFECTIVENESS OF HPV VACCINATION AND SCREENING

BACKGROUND

Dr. Kim is an assistant professor of Health Decision Science in the Department of Health Policy and Management at the Harvard School of Public Health. Her research focuses on the development and application of mathematical modeling methods to evaluate health policy issues related to women's health. Dr. Kim has developed and used models to perform cost-effectiveness analyses of cervical cancer prevention strategies for informed decision making in the United States, Europe, and less-developed regions. Her methodological interests include capitalizing on different methods of operations research to inform health decision making in low-resource settings, such as packaging health services at opportune moments and quantifying the impact of budget and human resource constraints on program effectiveness. Dr. Kim received the Association of Schools of Public Health/Pfizer Young Investigator's Research Award in 2010 for an analysis evaluating the cost-effectiveness of HPV vaccination of boys in the United States. She holds a master's degree in health policy and management from the Harvard School of Public Health (2001) and a Ph.D. in health policy and decision sciences from Harvard University (2005).

KEY POINTS

- There are opportunities to improve the cost-effectiveness of cervical cancer screening. Results of one modeling study indicated that the following strategy would be cost-effective if implemented among U.S. women who had not received the HPV vaccine: cytology-based screening with triage based on HPV testing every three years beginning at age 21 and a shift at age 30 to HPV testing every three years with triage based on cytology testing. Other studies have identified cost-effective strategies for screening in Canada, Spain, the Netherlands, Sweden, and Australia.
- Numerous studies covering several developed countries have indicated that HPV vaccination of preadolescent girls is cost-effective.
- Modeling studies have indicated that changes to screening guidelines for women who have received the HPV vaccine could increase cost-effectiveness. One study indicated that the most cost-effective screening strategy for vaccinated U.S. women would be cytology-based screening with triage based on HPV testing every five years beginning at age 25, with a shift to HPV testing and triage based on cytology results every five years beginning at age 35. Other studies in various countries also have found that cost-effectiveness of screening is increased when screening intervals are lengthened and the age of initiation of screening is delayed.
- In Australia, cervical cancer screening guidelines state that women aged 18 to 69 years should be screened using conventional cytology every two years. However, these guidelines soon will be changing. The three strategies currently being considered are: (1) conventional cytology beginning at 25 years of age, with a three-year screening interval for women 25 to 49 years of age and a five-year screening interval for women 50 to 65 years of age; (2) liquid-based cytology beginning at 25 years of age, with a three-year screening interval for women 25 to 49 years of age and a five-year screening interval for women 50 to 65 years of age; and (3) HPV DNA testing at least every five years for women 25 to 64 years of age. Australia currently is not considering different guidelines for vaccinated and unvaccinated women; however, the situation in Australia differs from that in the United States because Australia has achieved very high levels of vaccine uptake.
- The cost-effectiveness of HPV vaccination changes depending on the populations that utilize the vaccine. Among the scenarios considered in one modeling study, the highest cost-effectiveness was achieved if vaccine uptake and screening coverage were assumed to be random. However, if vaccine uptake was assumed to be low among women who would never undergo screening or if vaccination

was limited to the population most likely to undergo frequent screening, the cost-effectiveness of vaccination declined dramatically.

- Priorities for future work related to the cost-effectiveness of HPV vaccination include continual integration into models of emerging data on HPV burden, screening patterns/behaviors, and systems barriers. It is also important to evaluate strategies to improve the efficiency of screening by minimizing under- and over-screening and improving management of women with abnormal screening results. The cost-effectiveness of screening also could be improved through the integration of innovative technologies and approaches (e.g., self-sampling, genotype testing, nine-valent vaccine). Efforts also should be made to improve coordination and data sharing among independent modeling groups and to enhance the communication of cost-effectiveness data to stakeholders.

SESSION TWO MODERATED DISCUSSION

KEY POINTS

- In the United States, there is not an established threshold for cost-effectiveness, but an intervention is generally considered to be cost-effective if it costs between $50,000 and $100,000 per life-year or quality-adjusted life-year saved. Many U.S. policymakers are hesitant about using cost as a consideration in decision making. Cost-effectiveness values often are used to illustrate the relative value of one intervention compared with another intervention rather than as a way to indicate the absolute cost of an intervention.
- In addition to cost-effectiveness, it may be beneficial to evaluate the potential cost savings associated with various interventions. Given current concerns about health care spending in the United States, information about cost savings may resonate with policy makers and the public. However, the differences between cost savings and cost-effectiveness must be considered; an intervention could be associated with cost savings but still not be cost-effective. In addition, messaging related to cost savings must be carefully considered. Discussions should focus primarily on improving the quality of patient care rather than on cost; if cost is the focus, the motivation for making changes is questioned. The Choosing Wisely campaign was created to help improve appropriate utilization of medical tests and procedures and has made efforts to facilitate communication between providers and patients in this regard.
- Researchers need to be able to communicate to the President, elected officials, and the public about cost-effectiveness in understandable and meaningful terms. The data need to be communicated with respect to tangible factors, such as cervical cancer deaths and the potential harms of cervical cancer screening. Although cancer-related benefits should be highlighted, it is important that the other benefits of following guidelines for vaccination and screening are made clear. The public needs to understand that less-frequent screening will not lead to worse clinical outcomes and that over-screening can increase the occurrence of unintended negative outcomes such as preterm birth.
- Health economists can provide information on the number of life-years saved by an intervention and/or the lives that would potentially be saved with a certain increase in investment. However, it is often difficult to interpret these numbers if they are not presented in a format that allows comparison to the return that would be expected from a similar level of investment in another area; the benefit of the cost per quality-adjusted life-year is that it facilitates this sort of comparison to determine what investment will provide the highest return.
- The most recent CDC statistics indicate that 26,000 new cancers are attributed to HPV in the United States each year, with 18,000 of these occurring in women and 8,000 occurring in men. Assuming the HPV vaccine could prevent three-quarters of these cases, vaccination could prevent as many as 20,000 cases of cancer in the United States each year.

- Managed care organizations are actively considering the integration of HPV vaccination and cervical cancer screening. These organizations are thinking about ways to lengthen screening intervals in order to offset the cost of the HPV vaccine. The resource limitations present in managed care settings are also present in other sectors, although they may not be as obvious in the short term.
- The committees responsible for developing the most recent sets of cervical cancer screening guidelines for ACS and the U.S. Preventive Services Task Force were explicitly instructed not to consider cost. Cost-effectiveness and cost savings should be considered as part of these types of discussions.
- The United States is lagging behind many other countries with respect to HPV vaccine adoption. The Panel should consider highlighting the speed at which many other countries are working to increase rates of HPV vaccination based on evidence of population benefit. However, the current U.S. health care system may not be conducive to programs that have worked in other countries.
- The United States currently spends approximately $6.5 billion per year on cervical cancer screening. One participant estimated that it would cost less than $1 billion to vaccinate 75 percent of the approximately 4 million children born in the United States in a given year. If the cost of screening could be decreased by 15 percent or more, this would offset the cost of vaccination. The cost of screening could be reduced by increasing the age of screening initiation and/or lengthening the screening interval.
- The decreased cost-effectiveness that results from low vaccine uptake among those least likely to be screened for cervical cancer is concerning, particularly in light of data showing that vaccine uptake is low in many states with high rates of cervical cancer mortality. Uneven uptake of the vaccine could increase existing disparities in cervical cancer mortality.
- The greatest gains in cancer prevention will be achieved if HPV vaccination and cervical cancer screening are increased among populations at greatest risk for cancer. Innovative programs are needed to reach these populations. Minority and underserved populations need to be educated about the importance of preventive services, and the barriers to vaccination and screening need to be addressed in targeted and creative ways.
- Many women from minority and underserved populations want health information and screening services but are often too intimidated to seek care at hospitals or other large health care delivery settings. Some of these women seek care at pop-up clinics, which often overcharge for their services and may not provide accurate information about screening. Dia de la Mujer Latina holds one-day "health fiestas" to provide access to health care services for Latina women; these events are well attended and the women who participate have expressed interest in the HPV vaccine.
- Researchers are working to find ways to address disparities in cervical cancer screening. A study was conducted in Mississippi regarding the use of self-collected cervical specimens for screening. Efforts through radio, TV, newspapers, and community outreach failed to recruit sufficient numbers of minority women for the study. However, these women were willing to participate and refer friends when researchers came to their homes. Programs will be more successful in engaging minorities if they have staff that speak the same language and understand the cultures of the target populations.
- Some minority populations have distrust for the medical establishment and/or may prefer to consult with members of their communities about health issues. For example, one participant reported consulting with a spiritualist when she was diagnosed with breast cancer. She and her family did not trust the medical system because her mother had been involuntarily sterilized by doctors when she was young.
- Individuals from minority and underserved populations are more likely to receive care if researchers and health care professionals commit to long-term engagement with these communities. This has been observed with efforts to reach out to indigenous populations in Australia.

- Patients being treated for cancer generally are more concerned about clinical outcomes than the costs of treatment. This is particularly true for patients with health insurance, who are often responsible for only a fraction of the total cost of their treatment.
- Health care would be more cost-effective if it were delivered in a coordinated way. One participant stated that a woman should be able to receive all of her screenings during a single visit.
- The Vaccines for Children (VFC) program provides vaccines at no cost to eligible children. This is an entitlement program that fully covers the cost of vaccines recommended by ACIP for routine use. Many VFC-eligible children do not receive their vaccinations because they do not have access to care, but the cost of the vaccine should not be a barrier for these children.
- NBCCEDP provides free breast and cervical cancer screenings to women without health insurance. The program has created quality metrics to ensure that partners are not funded if they do not follow guidelines about screening intervals and age. The demand for safety-net programs such as NBCCEDP may change with the implementation of the Affordable Care Act, but it is likely that such services will still be needed to some extent.
- Many foreign-born immigrants will not be covered by the Affordable Care Act. These populations are often at high risk for cervical cancer and less likely to undergo screening than those born in the United States.
- Modeling studies need to take into account the costs associated with efforts to increase vaccination and/or screening among at-risk populations. They also should integrate information related to noncervical HPV-associated cancers.
- When considering the cost savings associated with reductions in screening, it is important to realize that this savings represents a loss of revenue for providers.

PUBLIC COMMENT

- There was no comment from the public.

SESSION THREE: TOOLS AND RESOURCES NEEDED TO SUPPORT AN INTEGRATED HPV VACCINATION AND SCREENING PROGRAM

DR. MARCUS PLESCIA

TOOLS AND RESOURCES NEEDED TO SUPPORT AN INTEGRATED HPV VACCINATION AND SCREENING PROGRAM

BACKGROUND

Dr. Plescia is director of the CDC Division of Cancer Prevention and Control. He leads all scientific, policy, and programmatic activities related to the Colorectal Cancer Control Program, the National Breast and Cervical Cancer Early Detection Program, the National Comprehensive Cancer Control Program, and the National Program of Cancer Registries (NPCR). He oversees a well-developed research agenda, including the national Cancer Prevention and Control Research Network. Before coming to CDC in 2009, Dr. Plescia was Chronic Disease Director at the North Carolina Division of Public Health. He directed the program policy, planning, and evaluation efforts for 12 public health programs and the State Center for Health Statistics. Under his leadership, the North Carolina cancer screening programs were expanded to reach more underserved adults. Public-health-focused legislation on tobacco, cancer, and obesity was passed, including a state law banning smoking in all restaurants and bars. Dr. Plescia's research interests focus on community health and health disparities. His publications focus on the application or evaluation of public health programs, with an emphasis on primary prevention and policy. While on the family

medicine faculty at Carolinas Healthcare System, he received a grant from CDC to implement a community-oriented primary care project that addressed racial and ethnic disparities. Dr. Plescia received his medical, master's, and bachelor's degrees from the University of North Carolina (UNC) at Chapel Hill. He trained in family medicine at the Montefiore Residency Program in Social Medicine in the Bronx, New York, and started practice in a federally qualified health center there, where he also led a team providing care to the homeless. Dr. Plescia practices family medicine through the Indian Health Service and holds an academic appointment as associate professor in the UNC Department of Family Medicine.

KEY POINTS

- The CDC Division of Cancer Prevention and Control has been considering how increased HPV vaccination should affect cervical cancer screening programs. The following quote from a publication by Phil Castle summarizes the need to balance vaccination and screening: "Maintaining screening at the same intensity and simply adding on the expense of vaccination would result in redundancy of prevention efforts at enormously increased cost without necessarily further reducing cervical cancer mortality."
- Decisions about changes to screening programs in response to HPV vaccination uptake should be informed by various types of surveillance data. Information is needed regarding who is and is not being fully vaccinated, as well as whether there are any adverse reactions to the vaccine. Information on HPV infection rates and the distribution of HPV types observed in vaccinated patients also is needed to facilitate risk assessment. Other types of surveillance are needed to monitor changes in incidence rates of precancerous lesions and cancers, as well as changes in cervical cancer mortality rates. It is important that surveillance data be collected in a way that allows for analysis of differences in vaccination benefit among demographic groups.
- The United States has a very robust cancer surveillance system that covers 100 percent of the population. Cancer registries are operated by the CDC NPCR and the NCI SEER program. SEER has been collecting data for approximately 40 years, and NPCR has been collecting data for about 20 years. These databases collect information on the type, extent, location, stage, and treatment of each cancer case. Data are used to assess the incidence of different cancers, inform prevention efforts, and address health disparities. Cancer reporting has been added as an optional capability for achieving Meaningful Use of EHR, which may help make cancer registries more complete.
- Cancer registry data can be linked to other data sources such as state and national vital statistics, hospital discharge records, and the Indian Health Service.
- Most U.S. cancer registries do not collect data on precancerous lesions, but four registry sites are currently collecting these data as part of a pilot project. The primary study objectives are to evaluate the feasibility of routine surveillance of precancerous lesions and to estimate the incidence rates for precancerous cervical lesions in the study population overall and by relevant demographic characteristics. So far, the pilot has confirmed the feasibility of collecting high-quality preinvasive cervical lesion data using existing registry infrastructure. To date, 5,720 cases of precervical lesions have been submitted for 2009. Much of these data have been collected through access to pathology lab data via electronic reporting. Based on these results, it would be useful to support efforts in sentinel states to monitor preinvasive cervical lesions. Although it would be optimal to collect these data in all registries, valuable insights could be gained using a sentinel state approach, which would be more economically feasible.
- Surveillance efforts would benefit from expanded electronic reporting (e.g., e-pathology, Meaningful Use uptake for cancer reporting, development of Meaningful Use standards for cancer screening). Electronic reporting allows collection of significant data with minimal financial investment.
- The potential benefits of screening registries to surveillance efforts should be discussed.

- The NCI Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) study is evaluating the comparative effectiveness of current and emerging screening processes in community practice; assessing the balance of benefits and harms across recognized cancer risk profiles; conducing preliminary studies to inform future research to optimize screening processes and outcomes; and actively sharing data and findings in order to foster research. The results of these and similar efforts will provide valuable data for future work related to HPV vaccination and cervical cancer screening.

DR. LAURI MARKOWITZ

TOOLS AND RESOURCES NEEDED TO SUPPORT AN INTEGRATED HPV VACCINATION AND SCREENING PROGRAM

BACKGROUND

Dr. Markowitz received her medical degree from Albert Einstein College of Medicine and completed her residency training in internal medicine at the University of Pennsylvania. She currently works at the Centers for Disease Control and Prevention where she is the team lead for epidemiology research in the Division of STD Prevention. Over the past 25 years, Dr. Markowitz has worked on a variety of vaccine-preventable diseases as well as sexually transmitted infections. Since 2005, she has coordinated the HPV Vaccine Working Group of the 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.

KEY POINTS

- Through its participating organizations, the United States monitors the impact of HPV vaccination to assess whether programs are working, determine if changes are needed in vaccination policy (e.g., number of doses, duration of protection, type replacement, cross-protection), and determine if changes should/can be made to cervical cancer screening recommendations.
- There are several challenges associated with monitoring the impact of HPV vaccination. There are no systems in place for measuring outcomes other than cancers, so special studies and/or monitoring efforts are needed. There is no national Pap test registry; in fact, only one state has a Pap registry. There is no national vaccine registry, and state vaccine registries are incomplete, particularly with respect to adolescent vaccines. Many outcomes for HPV vaccination must be studied over years and/or decades, which requires sustained investment in monitoring and evaluation.
- Monitoring the biologic impact of HPV vaccination in the United States involves assessment of early, mid, and late outcomes. Early outcomes include type-specific HPV prevalence and genital warts; mid outcomes include cervical precancers; and late outcomes include HPV-associated cancers.
- To assess prevalence of HPV types, the National Health and Nutrition Examination Survey (NHANES) incorporated self-collected vaginal swabs in 2003. Among 14- to 19-year-olds, the only age group expected to be impacted by HPV vaccination to date, the collective prevalence of HPV 6, 11, 16, and 18 was over 11 percent in the time period between 2003 and 2006, compared with approximately 5 percent in the same age group in 2007 to 2010. No changes were observed in other age groups.
- Analysis of MarketScan® Database data revealed a decrease in prevalence of anogenital warts among females 15 to 19 years of age between 2006 and 2009, but decreases were not observed in other female age groups. Rates of anogenital warts increased among 15- to 19-year-old males over this

same timeframe. These data suggest that HPV vaccination has had an impact on the prevalence of anogenital warts.

- The impact of HPV vaccination on cervical precancers is being monitored via two approaches. The first is the previously discussed pilot project being conducted by four cancer registries. The second is the HPV vaccine monitoring project (HPV IMPACT) being supported by the CDC Emerging Infection Program. This project includes five sites that are collecting information on CIN2, CIN3, and adenocarcinoma *in situ*, as well as HPV types. HPV IMPACT collects data on vaccination history through a variety of sources, including registries, medical charts, and patient interviews; collection of these data should become easier as vaccine registries are improved and expanded.
- HPV IMPACT data indicate that the prevalence of oncogenic HPV types in CIN2 and CIN3 lesions differs between non-Hispanic white and non-Hispanic black women, with black women exhibiting lower rates of HPV 16 infection than white women.
- Among HPV IMPACT participants with CIN2/3, the prevalence of HPV 16 or 18 is 56 percent among nonvaccinated women and 39.6 percent among women who were vaccinated at least 24 months prior to their abnormal Pap test. This suggests that the vaccine is reducing the number of HPV 16/18-associated cervical lesions.
- It is possible to monitor CIN using existing infrastructure, but additional resources are required to collect meaningful data.

MS. THERESE HOYLE

IMMUNIZATION INFORMATION SYSTEMS: SHARING HPV VACCINE DATA

BACKGROUND

Ms. Hoyle has been working in the field of immunization information systems (IIS) for the past 16 years. She currently works with the Michigan Department of Community Health providing project management assistance for the technical team for the immunization information system (Michigan Care Improvement Registry); Harvard University developing an HL7 interface specifications document for health plans to share data with immunization information systems; and the Public Health Informatics Institute as a consultant on the IIS Enhanced Technical Assistance Project, IIS requirements project, Public Health Informatics Academy. She is designing a public health informatics course for the University of North Carolina at Chapel Hill. Ms. Hoyle is secretary of the Every Child By Two (ECBT) Board of Directors. ECBT was founded by former First Lady Rosalynn Carter and former First Lady of Arkansas Betty Bumpers in 1991 as a result of the measles epidemic that killed over 120 people, many of them children. The goals of ECBT are to raise awareness of the critical need for timely immunizations and to foster a systematic way to immunize all of America's children by age 2. Ms. Hoyle is treasurer of the American Immunization Registry Association (AIRA) Board of Directors. AIRA is a membership organization that promotes the development and implementation of immunization information systems as an important tool in preventing and controlling vaccine-preventable diseases.

KEY POINTS

- If children born in the United States receive all recommended vaccines, including an annual flu shot, they will receive 25 vaccines by the time they are age 2 and 50 by the time they are 18.
- Immunization information systems provide operational support to immunization programs, providers, patients, and parents by producing real-time data.
- Funding through the Health Information Technology for Economic and Clinical Health (HITECH) Act and the Prevention and Public Health Fund (PPHF) has improved U.S. immunization information

systems. With the exception of New Hampshire, which does not yet have an immunization registry, all states can send messages electronically from their immunization registries to doctors' offices through EHR systems.

- Across the United States, 84 percent of children under 6 years of age have a record in an immunization registry. In many states, more than 95 percent of children under 6 are included in the registries. Coverage is lower for adolescents—only 60 percent of 11- to 17-year-olds are included in an immunization registry nationwide, although some states have very high coverage of adolescents.
- In Michigan, 66.4 percent of 11- to 12-year-olds and 75.7 percent of 13- to 17-year-olds have received at least one dose of the Tdap (tetanus-diphtheria-pertussis) vaccine; 65.3 percent of 11- to 12-year-olds and 74.9 percent of 13- to 17-year-olds have received at least one dose of the meningococcal vaccine; and 84.3 percent of 11- to 12-year olds and 73.6 percent of 13- to 17-year-olds have received at least two doses of the varicella vaccine. These high vaccination rates illustrate the value of vaccination requirements for school entry. The rates for HPV vaccination are considerably lower. Only 5.76 percent of 11- to 12-year-old girls and 25.7 percent of 13- to 17-year-old girls have received all three doses of the HPV vaccine. Rates among males are even lower—less than 1 percent of 11- to 12-year-old boys and less than 2 percent of 13- to 17-year-old boys have received three doses of the HPV vaccine.
- It is easy to generate summary vaccine coverage data using immunization information systems like the one in Michigan. These summaries can be sent to providers on a regular basis to let them know how well their practices are adhering to vaccination guidelines.
- Data from Michigan's immunization registry have been shared with the Michigan cancer registry to facilitate analysis of cervical cancer rates among vaccinated and unvaccinated women. The data can be linked because records in both databases use the same unique birth record identifier for each person.
- It is technologically feasible to link data from different databases, although policy and other changes may be needed to facilitate these linkages.

SESSION THREE MODERATED DISCUSSION

KEY POINTS

- In the United States, 83 percent of immunization registries include individuals across their lifespan and, thus, should include information on adult vaccinations. Other registries are expanding to include data on adults. In Michigan, individuals not born in the state are added to the immunization registry by their physicians when they receive their first vaccinations.
- There are currently gaps in coverage for adolescents in immunization information systems, which have hindered efforts to monitor HPV vaccination. In some states, participation in immunization registries is voluntary for both providers and patients, which results in lower rates of coverage. However, approximately 79 percent of states mandate data entry into the immunization database, and other states are trying to implement mandates.
- Coverage of adolescent immunization is increasing, in part because of increasing adoption of EHRs. Also, registries can be accessed in most or all places that immunizations are administered, including pharmacies, emergency rooms, schools, and health centers, which helps to capture vaccinations received by adolescents.
- All immunization registries have recall functionality, although not all registries utilize this functionality. Results of an ongoing study by researchers at the University of Michigan suggest that recall systems are more efficient if public health offices rather than providers send recall notices to patients.

- Each immunization registry uses its own unique birth identifier. There is not a national record identifier. If data are shared between states, they cannot be linked by birth identifiers; rather, they need to be linked using name and birth date or other data fields.
- It would be more straightforward to monitor HPV vaccination if the vaccine were administered to young children rather than adolescents. It may be possible to lower the age of vaccination if future data indicate that the vaccine continues to confer protection over many years. Research is being conducted in this area.
- It may be informative to link immunization registry data with other databases, such as those maintained by health maintenance organizations or other groups. The NCI Cancer Research Network may be one mechanism to support this type of work. Some of these linkages already are being made; for example, immunization registries are being linked to health plan databases to study vaccine safety.
- HPV vaccine monitoring for research purposes can be done with data from sentinel sites rather than comprehensive, population-based data, in part because HPV infection is relatively common. Sentinel sites have been used to evaluate other vaccines (e.g., pneumococcol, meningococcal). These sites were not necessarily selected to be representative of the country, but the data from these sites have been well received. The number of sentinel sites needed depends on the question being asked. However, if different screening guidelines are developed based on vaccine status, it will be necessary to create a population-based system so that patients and providers can access data for individuals.
- NCI has supported the Breast Cancer Surveillance Consortium, a screening registry, for more than 15 years. PROSPR is a screening registry that also conducts research to better understand screening in U.S. clinical practice.
- The District of Columbia and Virginia have implemented mandates for HPV vaccination, but both have liberal opt-out provisions. HPV vaccination rates in both areas are lower than for other mandated adolescent vaccines. Mandates will not be an effective way to increase vaccination rates if it there are few barriers to opting out. However, it may be politically difficult to put mandates in place if opt-out provisions are not included.
- The 50 percent reduction in prevalence among 14- to 19-year-olds of the HPV types targeted by current vaccines is more than what would be expected given current vaccination rates. It is unclear what other factors may have contributed to this trend. Only modest decreases were observed in nonvaccine HPV types, suggesting that there was not a global decrease in HPV infection, and no differences in sexual behavior were observed between the two time periods studied.
- The incidence of condyloma provides an earlier indication of HPV vaccine impact than does cancer incidence. It may be beneficial to make condyloma a reportable condition. A reduction in condyloma cases will help save health care resources.
- Surveillance can be done in different settings, depending on the question being asked. For some studies, it is appropriate to focus on populations within managed care organizations. However, population-based studies are also important, because they capture more variability in practice and behavior.
- A majority of pathology labs use electronic reporting and should be able to share data on precancerous cervical lesions, which could be used to analyze HPV vaccine impact. One option would be to require labs to share these data with CDC so that such analyses could be done.
- Registries should be designed to collect data that will allow researchers to analyze the processes surrounding vaccination and screening in order to identify ways to improve processes by intervening at specific points.
- Although some participants had suggested dentists' offices as a potential location for HPV vaccination, other cautioned that vaccination has not been in dentists' purview. However, as they have for smoking behavior, dentists could assess vaccination status and refer patients to their primary

care physicians for vaccination. Pharmacists also may be a viable option for increasing vaccine uptake. However, it is important to ensure that care does not become fractionated if many types of providers are involved. EHRs can help coordinate care among providers (.e.g., allow dentist to see that a patient has not received a recommended vaccine).

- Some participants expressed concern that misconduct by pharmaceutical companies leads to mistrust among the public, particularly minority and underserved populations. General mistrust for companies makes it difficult to convince people that they should be vaccinated and/or screened. Community health workers and *promotoras* can help communicate with the public and dispel myths.
- Self-reported data on cervical cancer screening are evaluated as part of *Healthy People 2020*. Data should be expanded to include information on new screening technologies and HPV vaccination status to aid interpretation of screening data.
- The role of HPV in oropharyngeal cancer is included in dental school curricula.

SESSION FOUR: IDENTIFYING PARTICIPANT PRIORITIES

Key themes that emerged during the workshop were identified, including strategies for monitoring and integrating HPV vaccination and cervical cancer screening. Invited participants discussed which strategies and activities should be given priority. Priorities recommended by the invited participants will be considered by the Panel as it develops recommendations for its annual report.

KEY POINTS

- States should be encouraged to adopt school mandates for HPV vaccination.
- Special emphasis should be given to increasing HPV vaccination rates in states with high incidence of cervical cancer.
- Efforts should be made to raise awareness of HPV-associated cancers as a group (i.e., "branding" them as a group) rather than focusing only on individual cancer sites.
- Integrated educational messages that include information about both HPV vaccination and cervical cancer screening should be developed, tested, and disseminated. These messages should target both providers and patients. Adolescents should be the target of some efforts to promote vaccination. Social media may be a good way to reach this population.
- Innovative programs are needed to promote HPV vaccination within underserved populations, specifically populations with low rates of HPV vaccination and cervical cancer screening. These programs should include education and empowerment components. Community health workers and *promotoras* could be utilized to promote HPV vaccination, particularly among populations less likely to begin or complete the vaccine series. A standard curriculum should be developed to ensure that community health workers and *promotoras* are delivering accurate and consistent messages. It was noted earlier in the workshop that populations that are characterized by low initiation rates for HPV vaccination may be different from populations with low completion rates.
- Social media platforms (e.g., Facebook, Instagram, Twitter) should be used to convey information and promote health-related behavior change.
- A national population-based registry of cervical cancer screening that includes early, mid, and late outcomes should be established to facilitate research on the impact of the HPV vaccine. Early outcomes include type-specific HPV prevalence and genital warts; mid outcomes include cervical precancers; and late outcomes include HPV-associated cancers.
- Efforts should be made to monitor how screening and vaccination are being incorporated into clinical practice and the effects on outcomes. These efforts could include expansion of the NCI PROSPR

program and/or linkage of existing systems that track vaccination, screening, cancer diagnosis, and clinical outcomes.

- Research should be conducted to inform future changes in cervical cancer screening guidelines (e.g., based on uptake of the HPV vaccine). This research should include linkages between cervical cancer screening and cancer outcomes data.
- Performance measures related to HPV vaccination and cervical cancer screening should be developed for accountable care organizations. For screening, these measures must be based on adherence to guidelines rather than the percentage of the patient population screened so that incentives for over-screening are not created.
- Policy changes and system-level interventions are needed to incentivize providers to adhere to guidelines calling for less screening (i.e., longer intervals). These disincentives for over-screening should be combined with decision support tools for providers.
- Centralized screening registries (i.e., not limited to a single institution) should be created to make it easier for providers to determine patients' screening histories. EHRs and call/recall systems need to be strengthened to ensure that women are not lost to follow-up as recommended screening intervals are lengthened.
- Support should be provided for comparative modeling efforts in cervical cancer. These models should be used to predict the effects of increased HPV vaccination and changes in screening guidelines on the demand for certain types of providers (e.g., gynecologic oncologists).
- Research is needed to identify the most appropriate screening tools for the post-HPV-vaccine era. Demonstration projects should be conducted to evaluate how well primary HPV testing works in the clinical setting. New screening tools may be needed (in addition to or instead of cytology and HPV testing).
- Medical homes (e.g., primary care, pediatricians) should expand their current focus on chronic disease management to include disease prevention.
- The HPV vaccine should be made available through a broader array of providers (e.g., dentists, pharmacists) to make it easier to reach target populations.
- The Federal Government should negotiate with HPV vaccine manufacturers to reduce the price of the vaccine in the United States.
- There should be universal coverage for the HPV vaccine.
- Providers should be reimbursed for the cost of storing and administering the HPV vaccine.
- The costs of HPV testing and Pap screening should be reduced.
- Efforts should be made to create an HPV vaccine that is effective with a single dose.

PUBLIC COMMENT

- Participants were congratulated for engaging in productive discussions. Efforts related to vaccination and screening will help eradicate cervical cancer.

CLOSING REMARKS

Panel members and co-chairs thanked the participants for their enthusiastic and productive discussions. Dr. Rimer asked participants to submit any additional input via email.

CERTIFICATION OF MEETING SUMMARY

I certify that this summary of the President's Cancer Panel meeting, *Creating an Integrated HPV Vaccination and Screening Program*, held November 16, 2012, is accurate and complete.

Certified by: _____ Date: February 8, 2013

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