HPV Vaccination's Second Act: Promotion, Competition, and Compulsion

Developments regarding human papillomavirus (HPV) vaccines will transform HPV vaccination in the United States while simultaneously raising several new policy and ethical concerns.

Policymakers, vaccine manufacturers, and the public health community must now respond to the presence of competing vaccines that are similar but distinct, particularly with respect to genital wart prevention and the benefits of vaccinating males. This work arises in the shadow of the contentious introduction of the HPV vaccine Gardasil (Merck & Co, Inc, Whitehouse Station, NJ) in 2006, particularly the opposition to efforts in many states to require the vaccine for school attendance.

I review the current status of HPV vaccine policy in the United States and examine issues of public health ethics and policy central to ongoing and future HPV vaccination programs. (*Am J Public Health.* 2010;100:1841–1844. doi:10.2105/AJPH.2010.193060)

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RECENT DEVELOPMENTS regarding human papillomavirus (HPV) vaccines signal the beginning of a new era in cervical cancer prevention. The October 2009 licensure of a second vaccine, Cervarix (GlaxoSmithKline, Philadelphia, PA), for females and the expanded approval of the first vaccine, Gardasil (Merck & Co, Inc, Whitehouse Station, NJ), for use by both genders create new opportunities to further reduce the burden of cervical cancer and other HPV-related diseases. However, as the introduction of Gardasil in 2006 revealed, HPV vaccine policy can be extremely contentious, and vaccination overall remains a source of considerable controversy.

As this next phase of HPV vaccination efforts begins, policymakers, public health officials, and vaccine manufacturers have the opportunity to avoid repeating the mistakes that plagued the arrival of Gardasil while building on its successes. Doing so, and addressing the new ethical and policy challenges that result from having two similar yet distinct vaccines, will be critical to the long-term success of HPV vaccination programs in the United States and worldwide.

A NEW OPTION FOR CERVICAL CANCER PREVENTION

Until last fall, a single HPV vaccine, Merck's Gardasil, was available in the United States. Licensed by the Food and Drug Administration (FDA) in June 2006 for use by girls and young women, the quadrivalent vaccine provides protection against two types of the virus responsible for approximately 70% of cervical cancer cases in the United States and two additional HPV types that cause up to 90% of genital warts.[1] Expert advisors at the Centers for Disease Control and Prevention (CDC) voted to recommend routine HPV vaccination for girls aged 11 to 12 years and "catch-up" vaccination of young women up to age 26 years.[2] Clinical trial data suggested that the vaccine was highly safe and effective, and despite occasional unconfirmed reports of serious adverse events, four years of postlicensure surveillance support those assessments.

After several years of regulatory delays, a second HPV vaccine, GlaxoSmithKline's Cervarix, was licensed in the United States last October.[3] Cervarix, a bivalent vaccine, protects against the same two cervical cancer–causing HPV types (16 and 18) included in Gardasil and has a similar safety and efficacy profile. The new vaccine, however, lacks protection against genital warts. Before US approval, Cervarix had already been approved in more than 100 countries.

COMPETING VACCINES AND THE QUESTION OF PREFERENCE

With two HPV vaccines now available in the United States, public health officials and health care providers are faced with a decision regarding which vaccine to recommend to adolescent girls and young women. Both vaccines appear to be highly effective at preventing infections from the two HPV types associated with cervical cancer. Research is underway to assess whether one vaccine produces longer-lasting immunity or superior "cross-protection" against HPV strains not actually included in the vaccine.

Absent a large difference in price, the additional protection against genital warts provided by Gardasil may be a compelling factor in favor of the preferential use of that vaccine. Genital warts, which are overwhelmingly caused by HPV types 6 and 11, are not fatal but require medical evaluation and treatment. Commentators have noted the significant emotional impact on quality of life due to genital warts, which is a condition more common among adolescents and young adults.[4] The benefits of HPV vaccination in preventing genital warts and other less common conditions have largely been overwhelmed by attention to cervical cancer prevention. Many groups, including manufacturers and government agencies, have referred to HPV vaccines simply as "cervical cancer vaccines."

Despite Gardasil's added protection against genital warts and no clear differences between it and Cervarix in cervical cancer prevention, an expert advisory

committee at the CDC declined at its October 2009 meeting to express a preference between the two vaccines.[5] Instead, its published recommendations state that either HPV vaccine is recommended for adolescent girls, one for the prevention of cervical cancer–related lesions and the other for that purpose as well as for the prevention of genital warts.[6] No guidance is provided as to how health care providers should decide which vaccine to administer or what circumstances might warrant choosing against the additional genital wart protection provided by Gardasil.

Such a decision by the CDC Advisory Committee on Immunization Practices (ACIP) is not uncommon when similar vaccines are available against the same disease. The committee has adopted comparable positions regarding competing rotavirus and influenza vaccines, although the differences between the quadrivalent Gardasil and bivalent Cervarix are more significant than in the rotavirus and influenza examples.

During the ACIP discussion in this case, the majority view emphasized that the primary goal of HPV vaccination was cervical cancer prevention. That objective was believed to be best served by ensuring that two vaccines are available. The implicit concern was that a preferential recommendation for Gardasil could so imperil the market for Cervarix that the vaccine might cease to be a worthwhile investment for its manufacturer, leaving the public reliant on only one HPV vaccine. When only a single vaccine is available against a disease, as is unfortunately common in the United States, supply disruptions are frequent and highly problematic for vaccination efforts. The availability of multiple vaccines provides insulation against shortages and protection if safety problems, confirmed or alleged, emerge for one vaccine.

The CDC advisors placed the benefits of ensuring the long-term availability of two vaccines against cervical cancer ahead of emphasizing the additional physical and emotional burdens of genital warts. Given the stark difference in the potential fatality of each condition, such a policy is defensible as a matter of ethics and public health, even if the likelihood of Cervarix ceasing to be available seems remote. However, the current policy would seem to impede any genital wart prevention efforts by the CDC and its partners because it would amount to promotion of Gardasil at the expense of Cervarix in the zero-sum world of HPV vaccination.

In the future, additional data about the relative safety and effectiveness of HPV vaccines may render the current policy of nonpreference moot, with one vaccine emerging as a clearly superior product independent of genital wart protection. Until then, the decision regarding which vaccine to use may be made on less justifiable grounds, such as third-party payers choosing to cover only one vaccine simply on the basis of price. Because the vaccines share a similar FDA indication and CDC recommendation, this scenario seems likely, analogous to what occurs with many classes of pharmaceuticals.

THE IMMINENT VACCINE WARS

The lack of guidance from the CDC on the relative merits of HPV vaccines adds to the incentive for their manufacturers, Merck and GlaxoSmithKline, to attempt to influence attitudes of health care providers and the public. An advertising war is about to begin, as each company competes for control of the limited HPV vaccine market. This market, approximately two million 11- to 12-year-old girls annually plus those adolescents and young adults still unvaccinated, is far smaller than that of most highly profitable drugs, however. Accordingly, the financial stakes for HPV vaccine manufacturers are extremely high.

Beginning this year, Merck and GlaxoSmithKline will aggressively promote their HPV vaccines, making claims of superiority accompanied by the slogans, jingles, and other techniques present throughout contemporary drug marketing. Complementary efforts will be directed toward pediatricians and the many other types of health care providers who offer vaccinations.

Direct-to-consumer advertising is a deeply flawed method of educating the public about the risks and benefits of medical interventions.[7,8] The prospect of each HPV vaccine manufacturer simultaneously conducting multimedia ad campaigns that tout its own product while disparaging the competition is worrisome. The risk exists that the value of both HPV vaccines as part of a comprehensive cervical cancer prevention strategy will be lost amid the flurry of claims and counterclaims.

To avoid this, vaccine manufacturers and the public health community must emphasize the importance of both vaccination and regular Papanicolau (Pap) screening as essential tools for preventing cervical cancer and other HPV-related conditions. Such efforts can call attention to areas where unacceptable health disparities persist, as is the case for cervical cancer, a disease disproportionately common and deadly among African American women.[9] The availability of two preventive vaccines and a heightened awareness of the importance of regular Pap screening can help those groups most severely impacted by cervical cancer.

Many hope that competition may lead to reductions in the price of HPV vaccines, because the current prices severely strain public and private sources of vaccine financing. It is unclear at present how significant a role competitive pricing will play in the business strategies of the two HPV vaccine manufacturers. The ongoing experience with rotavirus vaccines may serve as a useful analog, however. Two rotavirus vaccines with a similar indication—from the same manufacturers of the competing HPV vaccines—were licensed in the United States in the past four years, one vaccine being licensed two years after the other.[10] Competition has not led to reductions in the prices of rotavirus vaccine in either the public or private sectors. Instead, the prices of both vaccines have increased modestly each year since their licensure.[11]

VACCINATING MALES

After the arrival of the first HPV vaccine in 2006, discussion about policy options was limited to its use by females, the only group for which Gardasil was approved. However, in fall 2009, on the same day that Cervarix was approved for females, the FDA expanded the licensed indication for Gardasil to include administration to boys and young men (between the ages of 9 and 26 years) for the prevention of genital warts.[12]

After FDA approval, the same CDC advisory panel discussed

previously was charged with developing a recommendation regarding Gardasil for men and boys. Although the term recommendation may imply a modest suggestion of best practices for disease prevention, a recommendation from the ACIP is tremendously important to the success of a vaccination program. A vaccine with a routine recommendation, that is, an endorsement of its use in the full population at a specific age, is much more likely to be included in insurance plans, to be more actively promoted by physicians and to be more widely adopted by government-supported vaccination programs. Vaccines with broad recommendations typically succeed in gaining high uptake and reducing disease rates, whereas those with a more limited recommendation do not.[13–16]

Arguments in favor of the broad use of Gardasil among males can be made in terms of direct and indirect benefits. The clearest direct benefit involves genital wart protection, for which the vaccine appears to be highly effective. However, the high cost of the vaccine and the nonfatal nature of genital warts lead to highly unfavorable cost-effectiveness analyses when modeling large-scale vaccination of males for this purpose.[17]

A second class of direct benefits to males involves protection against several anogenital cancers and a respiratory condition caused by the HPV types included in the vaccine.[18,19] Whereas these benefits are widely believed to exist, the FDA approval of Gardasil for males does not include these indications. Obtaining data sufficient to do so will be difficult, because the conditions are relatively rare and lack the "precursor lesions" of cervical cancer that facilitated approval of the vaccines for females. Including these additional presumed benefits results in cost-effectiveness figures generally accepted as representing a worthwhile investment of health care resources.[17]

The indirect benefit of male HPV vaccination is the additional reduction in cervical cancer incidence that would result from targeting a reservoir for the virus. Once again, economic modeling of male vaccination efforts for this additional objective remains unfavorable, suggesting that concentrated attention to vaccinating females is a superior strategy for cervical cancer prevention.[17] However, encouraging both genders to receive the vaccine not only appeals to fairness but also simplifies promotional efforts made by the medical community. It would also symbolize the shared responsibility of men and women in the prevention of cervical cancer and other sexually transmitted infections.

In October 2009, the ACIP opted against a routine recommendation for male HPV vaccination. As explained in their published guidance, this decision was based on cost-effectiveness data considering only the licensed indication for genital wart prevention.[20] The committee instead adopted a "permissive use" statement that says little beyond acknowledging that the vaccine is available for those who want it.[5] This decision and its consequences for vaccine availability and affordability likely mean that male HPV vaccination will be a rarity for the foreseeable future.

Prominent voices in the public health and vaccination communities have expressed their disappointment with the panel's recommendation.[21] Public attention to the disparate messages regarding male and female HPV vaccination should cause this important question of ethics and public health to be reopened and discussed far more broadly than it has been thus far.

Amid limited health care resources, concerns over the total costs of broad HPV vaccination programs are well-founded. As our ability to model the financial and medical impact of health policy options grows, so too does the influence of such analyses among policymakers and third-party payers. Among the questions worthy of discussion on this topic is how well even the most sophisticated economic modeling can reflect the values and priorities of communities in improving public health.

REVISITING VACCINE MANDATES

Nothing was more damaging to early efforts to promote the first HPV vaccine in 2006 and 2007 than the rush to include it among those mandated for school attendance.[22] Regardless of whether those efforts were motivated by well-meaning legislators or by more nefarious inducements involving lobbying and political donations by Merck, as some alleged, even many public health experts generally supportive of vaccination requirements believed it was too soon to consider mandating HPV vaccination.[23]

There is broad agreement that vaccine requirements should be considered only after a new vaccine is well established and widespread support exists for it. This includes creating stable financing and supply arrangements, collecting evidence of long-term safety, and conducting successful educational initiatives for both parents and health care providers.[24] These activities are critical to the long-term success of any vaccination program. For other vaccines receiving broad recommendations in the recent past, at least five years have been spent on these areas before introducing state mandates.[25,26]

With Gardasil now approved for use by males, discussions of HPV vaccine school mandates will be further complicated by debates regarding fairness between the genders. No vaccine has been mandated for only a single gender, and previous efforts to require Gardasil only for school-age girls were justified by its limited FDA approval at the time. Future attempts to mandate the vaccine only for girls will face new opposition on these grounds, whereas requiring it for both genders would be an unprecedented action for a vaccine lacking a CDC recommendation for males. Although some argue that HPV vaccines should never be mandated for school attendance, the temptation for policymakers to revisit this ethical and policy debate must be resisted until HPV vaccination has successfully become a routine, trusted component of adolescent medical care.

THE POTENTIAL OF VACCINATION IN THE DEVELOPING WORLD

When giving close attention to the opportunities, challenges, and questions regarding HPV vaccine policy and ethics in the United States, we risk losing sight of the very different profile of cervical cancer globally. In the United States, advances in screening and treatment have resulted in encouraging trends in cervical cancer incidence and mortality long before the arrival of HPV vaccines. Here, an estimated 12 000 cases of

cervical cancer occur each year, with approximately 4000 deaths.[27]

Worldwide, the impact of cervical cancer is staggering. An estimated 493 000 cases and 274 000 deaths occur globally each year, with more than 80% in developing countries.[28] There, HPV vaccines, Pap screening, and necessary infrastructure and medical expertise are largely unaffordable or unavailable. The prospect of multimillion dollar advertising campaigns for competing HPV vaccines in the United States is especially unseemly in light of the transformative potential of these vaccines globally and the obstacles, financial and otherwise, likely to hinder their success.

HPV vaccination efforts are underway in the developing world, largely removed from the idiosyncratic policy debates and controversies regarding vaccination in the United States. However, sustained attention by wealthy countries to the remarkable value of HPV vaccines globally and corresponding support from public and private groups will be essential to successful vaccination programs in the developing world in the years ahead.

Vaccines are central and essential components of public health preparedness and prevention strategies against a growing array of disease targets. Preserving widespread public support for vaccine policy is imperative, particularly in the face of vocal criticism. The furor surrounding the initial arrival of HPV vaccines in 2006 jeopardized the confidence in vaccination necessary to ensure that its benefits are available to individuals and communities. A thoughtful, robust public dialogue on the policy and ethical questions raised by recent developments in HPV vaccines is important not only for HPV prevention efforts but also for the overall continued success of vaccination as one of public health's most valuable weapons. ■

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