Monitoring HPV Vaccine Impact: Early Results and Ongoing Challenges

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(See the Major Article by Tabrizi et al, on pages 1645–51.)

In this issue of the Journal of Infectious Diseases, Tabrizi and colleagues present new data from Australia on genital human papillomavirus (HPV) infection prevalence in the periods immediately before and after HPV vaccine introduction [1]. Based on cross-sectional studies of women aged 18–24 years who received Papanicolaou screening in selected family planning clinics throughout the country, the authors report a 20% decrease in overall genital HPV prevalence and a more dramatic decrease of 77% in HPV types targeted by the quadrivalent vaccine (HPV types 6, 11, 16, and 18) from the 2 years before (2005–2007) to the 2 years after (2009–2010) the vaccine was widely implemented through a government-funded program. In addition to comparing HPV prevalence trends across periods, Tabrizi et al obtained HPV vaccination history from participants to more directly evaluate the effect of vaccination on HPV prevalence. Their results indicate significantly lower vaccine-type HPV prevalence among vaccinated women in the post-vaccine sample (5.0%) compared with both unvaccinated women from the same period (15.8%) and women from the prevaccine period (28.7%). Using the age-adjusted HPV prevalence ratio of vaccinated to unvaccinated women, the authors calculate a vaccine effectiveness of 73% against infection with any of the 4 vaccine types.

Because the major benefit of HPV vaccination—prevention of cervical and other less common HPV-associated cancers—will not be evident for decades, a spectrum of intermediate outcomes are being monitored to assess the early impact of HPV vaccines. Although considered to be the simplest and earliest indicator of vaccine impact, a reduction in HPV vaccine type prevalence may not be sufficient to guide vaccine policy and practices. Therefore, in addition to ongoing HPV type prevalence monitoring, cancer and precancer outcomes as well as HPV-associated genital warts are also included in the monitoring portfolios of most high-income and some middle- and low-income countries where quadrivalent vaccine is being used [2, 3].

Although this study is the first to report a reduction in HPV vaccine type prevalence in Australia, it is not the first to suggest population impact of quadrivalent HPV vaccine. In fact, Australia was the first country to show reductions in genital warts associated with HPV types 6 and 11, which are targeted by the quadrivalent vaccine [4, 5]. Genital warts develop soon after HPV infection and can be an early indicator of vaccine impact in countries where the quadrivalent vaccine is exclusively or predominantly used. Published in 2009, the study from Melbourne, Australia, demonstrated progressive and significant decreases in new genital warts diagnoses <3 years after vaccine introduction among young women in the age group targeted for vaccination [4]. The Australia data also showed significant decreases in young heterosexual men during the same period, suggesting possible herd immunity in the population. Since the publication of that study, a new analysis examining data through June 2011 suggests that genital warts have nearly disappeared in the same population of females and males <21 years of age [6]. More recently, ecologic data emerging from the United States suggest a decrease in rates of genital warts diagnoses in young women despite the lower vaccine coverage [7].

Another intermediate outcome, which can be used to monitor bivalent or quadrivalent vaccine, is high-grade cervical lesions that can develop into invasive cancer if not treated. These precancerous lesions were used as the primary endpoints in the vaccine clinical trials. Although cervical lesions can take years after infection to become clinically detectable, in 2010, a study co-authored by some authors on the present study reported a significant decrease in high-grade lesions among girls aged <18 years who were screened for cervical cancer in Victoria, Australia [8]. Because
precancerous cervical lesions can only be detected through cervical cancer screening, monitoring these outcomes is not feasible in countries that lack screening programs. In addition, because detection depends on screening, changes in guidelines and screening practices that are likely as vaccination coverage increases and new screening technologies are introduced will complicate estimation of vaccine impact on the lesions.

Australia’s ability to serve as a bellwether for HPV vaccine impact on disease is owed largely to a unique combination of factors: Australia was the first country to implement a universal government-funded HPV vaccination program in April 2007 for females aged 12–17 years, and for a limited time, the program included free catch-up vaccination in females aged ≤26 years; coverage with at least 1 dose of vaccine quickly reached and remained at about 80% in younger females aged 12–17 years [9] and >50% in the catch-up age group [10]; cervical screening recommendations in Australia are such that some girls may be screened before age 18 years whereas screening does not begin before age 21 years in other countries; and, Australia is one of very few countries with some regional population-based cervical cytology registries, such as the one in Victoria, which allow evaluation of trends in cervical lesions among women who are screened [11].

Compared with the earlier studies from Australia, this study has the advantage of using individual-level data to estimate vaccine effectiveness. The estimate of effectiveness is consistent with what might be expected since some women likely received vaccine after sexual debut and after infection with HPV vaccine types; however, reliance on self-reported history to determine HPV vaccination status could have led to reporting bias in this observational study. Given that HPV vaccines are most efficacious in those who are naïve to vaccine types at the time of vaccination, complete and accurate vaccination history can help refine estimates of effectiveness. Validating self-reported vaccination history with data from the Australia national vaccination registry could have provided a more accurate estimate of vaccine effectiveness. Additionally, more detailed information from the vaccine registry on number of doses received could have allowed evaluation of a question of current interest to HPV vaccine programs worldwide: the comparative effectiveness 3 versus <3 doses. National vaccination registries are a valuable resource that should not be underutilized in future vaccine effectiveness studies from Australia and other countries with such registries.

Since the current HPV vaccines protect against some but not all types capable of causing associated cancers, monitoring both positive and negative effects of these vaccines on other HPV types is a critical aspect of monitoring population impact. Post hoc analyses of clinical trial data suggest cross-protection of the quadrivalent vaccine against some related oncogenic types [12]. In this study, Tabrizi et al. found a nonsignificant decrease in the odds of infection with high-risk HPV types not included in the quadrivalent vaccine among vaccinated women in the postvaccine period compared with those in the pre-vaccine period. Although these preliminary findings seem to support possible cross-protective effects, further evaluation will be required to confirm these early results. The authors also report that unvaccinated women in the postvaccine period were significantly less likely to have vaccine types 6, 11, 16, or 18 compared with women in the prevaccine period, suggesting a herd immunity effect in this population. Although herd immunity is a plausible explanation given the high vaccination rates and previous findings for genital warts in Australia, the difference could be due to differences in sexual behavior between these groups, if unvaccinated young women were less likely to be sexually active (or have fewer sex partners) compared with all women in the prevaccination period. Although concerns related to potential type replacement due to selective elimination of HPV types creating an ecologic niche for other types were not directly addressed in this article, the lack of increase in prevalence of non-vaccine oncogenic types in the postvaccine period is reassuring.

Given the previous findings from Australia on early decreases in HPV-associated genital warts and high-grade cervical lesions after vaccine introduction, the results in the current report are not surprising, but they are nevertheless an important contribution to the emerging data on HPV vaccine impact. More importantly, monitoring HPV type distribution in Australia, where dramatic reductions in genital warts and to a lesser extent, cervical lesions, have already been demonstrated, and where vaccine coverage remains high, will be important to shed light on remaining questions about the indirect impacts of current and future HPV vaccines. Data on type-specific HPV distribution can provide the basis for evaluating additional benefits of vaccines such as cross-protection against non-vaccine types and herd immunity, but also to monitor unlikely adverse phenomena including type replacement. The population effectiveness of HPV vaccines is currently an active area of research but most evaluations are still underway. As more study results become available [13], additional findings will emerge that will require careful examination, given the implications for vaccine programs and policy.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

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