Three Important Findings From a Study on HPV "Real World" Effectiveness

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Early clinical trials of the human papillomavirus (HPV) vaccine demonstrated high vaccine efficacy against persistent infection with the vaccine-specific HPV subtypes, indicating that there will be significant reductions in the prevalence of HPV-related cancers and diseases with widespread vaccination.[1] Now that the vaccine has been available for public consumption for more than a decade, researchers are shifting their focus to the vaccine's effectiveness, that is, how the vaccine performs in real-world situations rather than in the highly controlled clinical trial environment. Several studies have been done in this regard in a variety of countries, indicating that the vaccine is performing well, as expected.[2] However, given the range of factors that can affect vaccine uptake and effectiveness, many more studies with this focus are needed to truly understand the vaccine's expected public health potential.

The study by Spinner et al[3] in this issue of *Pediatrics* adds significantly to this growing body of literature. In this study, researchers recruited 4 cross-sectional cohorts (ie, study "waves") of adolescent and young adult women (ages 13–26 years) from 2 clinical sites over a period of 11 years. The primary outcome assessed was HPV infection status, and analyses were stratified by whether the women had been vaccinated against HPV. HPV infection outcomes were divided into a group corresponding to the 4 types covered by the quadrivalent vaccine (HPV-6, HPV-11, HPV-16, and HPV-18) and an additional 5 HPV types covered in the 9-valent vaccine (HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58). The study started in 2006, when HPV vaccines were first licensed in the United States, and ended in 2017, corresponding to the time shortly after the transition from the quadrivalent to the 9-valent vaccine in the US market. The 1580 participants were at high risk for HPV infection because all were sexually active, >80% had at least 2 lifetime sex partners, and more than half had experienced a previous sexually transmitted infection. Rigorous statistical methods were used to account for differences over time in the prevalence of factors or behaviors that could have affected the different cohorts' HPV infection prevalence.

There were 3 important results from the study. First, as expected from other efficacy and effectiveness studies, vaccine effectiveness among women who were vaccinated was high for the 4 HPV types in the quadrivalent vaccine, estimated at 80.1% to 90.6% depending on the wave. Although these results may not be surprising at face value, a deeper look into the data reveals an important nuance. In this study, being categorized as vaccinated required receiving "1 or more doses" of the vaccine. Although not reported on specifically, this definition suggests that some, or maybe even many, women in the cohort had not received the 3 doses recommended for full protection. This (combined with the fact that because of their sexual

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activity, many women in the study cohorts were likely already infected with at least some types of HPV) makes the high vaccine effectiveness reported actually quite remarkable and adds further evidence that this vaccine is highly protective.

A second important finding is related to evidence of cross protection. Specifically, although the majority of women in the sample who were vaccinated (82%) had received the quadrivalent vaccine, they had a significantly reduced risk of being infected with the 5 additional HPV types included only in the 9-valent vaccine. The adjusted odds of being infected with these 5 additional HPV types ranged from 0.22 to 0.48 across the 4 waves of the study (an effect that was not seen in the unvaccinated cohort). Evidence of cross protection is important with the recent transition to the 9-valent vaccine in the United States because many women question whether there is a benefit to being revaccinated with the 9-valent vaccine after having completed the full course of the quadrivalent vaccine when they were younger. However, there is no specific recommendation from the Advisory Committee on Immunization Practices to do so.[4] The growing body of evidence suggesting that there is cross protection with the quadrivalent vaccine to the 5 additional types in the 9-valent vaccine[5] is an important consideration for women evaluating their vaccination status.

The third important finding from the study was the indication of herd immunity for the quadrivalent HPV types. That is, as more and more women in the population were vaccinated and were thus protected from infection, the likelihood of an individual who was unvaccinated being infected was also reduced. Evidence of herd immunity was based on data revealing a reduction over time in the prevalence of HPV-6, HPV-11, HPV-16, and HPV-18 infection among women who were unvaccinated from 32.4% to 19.4%. However, it is important to note that reductions were not consistent across all 4 waves of the study, nor were they statistically significant in the majority of the adjusted analyses, so these conclusions could be considered somewhat less solid than the others reported. This variability could be explained by the relatively small sample size of the study, leading to high variance in outcomes. However, several other studies with much larger populations support herd immunity for these 4 HPV types after implementation of the quadrivalent vaccine.[6,7]

There is 1 additional study finding that is intriguing in the context of the study's other results. The authors of the study provide evidence that the quadrivalent HPV vaccine has been used at sufficiently high levels to induce herd immunity for HPV-6, HPV-11, HPV-16, and HPV-18 and that the quadrivalent vaccine also can induce cross protection against 5 additional HPV types. So, would it not be expected that there would also be herd immunity for the additional 5 HPV types? Data did not support this conclusion and, in fact, suggested the opposite effect. Over time, women who were unvaccinated had higher odds of infection with the 5 additional HPV types than women who were vaccinated. The explanation provided by the authors for these seemingly counterintuitive results was that there were significant differences in the sexual behaviors of women who were vaccinated versus unvaccinated, which increased their risk of infection with these 5 HPV types. Although this may be the cause, it raises the question of whether there is some type of threshold effect in cross protection needed for inducing herd immunity. Said another way, is there a certain strength of cross protection required at the individual level necessary for inducing meaningful herd immunity in the broader population? If so, this could explain why herd immunity was found for the original 4 HPV types but not the additional 5. Future research will be needed to elucidate the answers to this interesting scientific question.

ABBREVIATION

HPV: human papillomavirus

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