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HPV Vaccines—Prophylactic, Not Therapeutic

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Two human papillomavirus (HPV) L1 viruslike particle (VLP) vaccines have been developed against HPV types 16 and 18—the 2 HPV types that account for about 70% of cervical cancers worldwide. Both vaccines have been found to have high prophylactic efficacy in large clinical trials.

In this issue of JAMA, Hildesheim and colleagues report the effect of vaccination with one of these vaccines, the bivalent HPV-16/18 vaccine, on viral clearance. These results are from an ongoing community-based trial of more than 7000 18- to 25-year-old women in Costa Rica. The main analysis of the ongoing trial, as for other recently published trials of HPV vaccines, will focus on vaccine efficacy among women not infected with the specific HPV vaccine types at the time of enrollment. In contrast, the analysis by Hildesheim et al addresses the question of whether the vaccine can clear HPV type 16/18 infection present at the time of vaccination. The results demonstrate no effect of the vaccine on viral clearance. Among women who had HPV-16 or HPV-18 infection at enrollment, defined as HPV DNA detected in a cervical specimen, vaccine efficacy for preventing persistent infection with HPV-16, HPV-18, or both at 6 months was 2.5% (95% confidence interval [CI], −9.8% to 13.5%) and at 12 months was −2.0% (95% CI, −24.3% to 16.3%).

These findings are consistent with data from trials of the quadrivalent HPV-6/11/16/18 vaccine. That vaccine has not been found to provide protection against progression to cervical intraepithelial neoplasia (CIN) from HPV vaccine types present at the time of vaccination. In one trial, among women who were DNA positive but seronegative for HPV-16 or HPV-18, the efficacy against HPV-16/18–related CIN grade 2 or 3 was 10.6% (95% CI, <0%-46%). For those who were DNA positive and seropositive for HPV-16/18, the efficacy against HPV-16/18–related CIN 2/3 was 1.2% (95% CI, <0%-35%).

Data from recently published HPV vaccine trials have consistently shown high efficacy in evaluations among women who had no evidence of infection with the vaccine HPV type for which efficacy was being evaluated. However, vaccine efficacy in the overall populations has been lower, reflecting prevalence of infection with HPV types at enrollment and lack of efficacy against progression to disease among women already infected. Although these analyses show lower efficacy in the overall study populations, efficacy increases over time as new infections occur in the control group but not in the vaccine group.

What are the implications of these data and how do they bear on recommendations? The lack of therapeutic efficacy of the quadrivalent HPV vaccine was considered in deliberations by the Advisory Committee on Immunization Practices (ACIP). These data, along with data demonstrating the high likelihood of acquiring HPV infection soon after onset of sexual activity and data on sexual behavior in the United States, all contributed to recommendations for routine immunization at 11 to 12 years of age. Because the vaccine has no therapeutic efficacy, the greatest effect will be realized if the vaccine is administered before sexual debut, prior to exposure to HPV. In making the recommendation for this age group, the ACIP also considered safety and immunogenicity data and programmatic issues. While there are safety and immunogenicity data in this age group through 18 months, as well as studies indicating good protection through 5 years after vaccination among older women, as for other new vaccines, data on long-term efficacy are limited. Data on longer-term efficacy will be important, particularly when targeting vaccination of 11- to 12-year-olds. Postlicensure safety monitoring, as done for all vaccines, will also be important.

The quadrivalent HPV vaccine has also been recommended for catch-up vaccination of 13- to 26-year-old US females. Ideally, females should be vaccinated before sexual debut, because those who are sexually active may benefit less from vaccination as they could already be infected with one of the HPV vaccine types. Although the benefit of vaccination may be less in women who are already sexually active, models evaluating the potential impact of HPV vaccination programs in the United States suggest that routine vaccination of 12-year-old girls is cost-effective, as is including catch-up through age 24 years. Importantly, with catch-up vaccination programs, models indicate that the time to effect of the vaccination program on CIN lesions and cer-
vical cancer is shorter compared with programs that focus on vaccination of only 12-year-old girls.\textsuperscript{13,14}

The report by Hildesheim et al\textsuperscript{7} also provides data on the magnitude of prevalent HPV infection in this community-based trial of 18- to 25-year-old women. Among the sexually experienced women enrolled in the trial (excluding a small number with high-grade CIN), 41.3\% were positive for any HPV DNA. Of note, this prevalence is similar to the recently reported prevalence of any HPV DNA detected among a representative sample of similar-aged US women (44.8\% among 20- to 24-year-olds).\textsuperscript{10} However, the percentage of women who tested positive for HPV-16 and/or HPV-18 DNA was higher in Costa Rica than in the United States or in other HPV vaccine trials.\textsuperscript{3,5} Because high baseline prevalence may reduce vaccine efficacy in the overall trial population, efficacy in this overall trial population might be less than in other published studies. Variations in the population prevalence of specific HPV types could affect vaccine recommendations in different settings.

In the coming months and years, additional data will become available for both the quadrivalent HPV-6/11/16/18 and the bivalent HPV-16/18 vaccines. Data will also be available from epidemiologic studies of HPV. Advisory groups making vaccine recommendations will need to consider all of these data. The bivalent and quadrivalent HPV vaccines appear to be equally effective in preventing HPV-16/18-related precancerous lesions\textsuperscript{16} and neither vaccine has a therapeutic effect. Even though both are L1 VLP vaccines, they differ in their adjuvant, the manufacturing, and the HPV types included. The quadrivalent vaccine also provides protection against HPV-6 and HPV-11 and has high efficacy against genital warts. Recurrent respiratory papillomatosis is also caused by HPV-6 and HPV-11. Both vaccines are being evaluated in women older than 26 years. If the vaccines are licensed for use in older women, recommendations will need to consider the epidemiology of HPV in older age groups and cost-effectiveness.

Current data and models suggest that the public health benefit of HPV vaccines diminishes with increasing age at vaccination because most infections are acquired at younger ages.\textsuperscript{14} The quadrivalent HPV vaccine is also being evaluated in males, although these data will not be available for several years. Recommendations for HPV vaccination and cervical cancer screening may vary in different countries depending on local conditions, epidemiology, and infrastructure. The majority of the burden of cervical cancer is in developing countries and efforts should be made to assist in developing recommendations for those countries and to overcome challenges to introduction of HPV vaccine.\textsuperscript{17}

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REFERENCES


