

EDITORIALS

Less Is More: A Step in the Right Direction for Human Papillomavirus (HPV) Vaccine Implementation

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Although immunization with two highly efficacious human papillomavirus (HPV) vaccines holds great promise for reducing the global burden of HPV-related cancers, the barriers to achieving this goal remain substantial. The cost of HPV vaccination still represents an important obstacle to implementation in many countries but there are several challenges beyond the high cost (1). It has proven difficult to achieve high levels of coverage with all three HPV vaccine doses even in countries with considerable resources. In the United States, where HPV vaccine delivery is principally by primary care physicians, the uptake of the complete three-dose series of HPV vaccine was recently estimated at 32% among 13- to 17-year-old girls (2). This low rate of series completion contrasts with the outstanding successes in Australia and the United Kingdom where school-based HPV vaccine programs have achieved much higher rates of coverage for the third HPV vaccine dose ($\geq 72\%$ and $\geq 84\%$, respectively) in the primary target population of 12- and 13-year-old girls (3,4). Functional and routine preventive health-care platforms are nearly nonexistent for adolescents worldwide, therefore school-based immunization programs, where feasible, can provide a solution to achieving high vaccine coverage. Beyond providing a venue for adolescent immunization, evidence from England (4) suggests that school-based HPV vaccine delivery can achieve equity in coverage of 12-year-old girls across deprivation levels of the areas where they live. In the United States, HPV vaccination rates have been strongly and inversely correlated with cervical cancer mortality rates and median income (5). Because cervical screening coverage is inversely associated with poverty and deprivation (6), ensuring equitable HPV vaccine delivery and high coverage in populations that are less likely to have opportunities for cervical screening as adults remains a priority.

In addition to problems associated with the cost and organizational challenges of HPV vaccine delivery, there has been little to no information available to examine potential alternative immunization schedules or the efficacy of HPV vaccination with less than the recommended full three-dose series. Sustained immunogenicity and immune memory has been demonstrated following administration of two doses of the hepatitis B vaccine (7), and preliminary data on HPV-specific antibody titers have suggested that two HPV vaccine doses may be equivalent to three (8). However, experts have speculated that a single dose of the HPV vaccine, like other recombinant subunit vaccines, is unlikely to be efficacious.

In this issue of the Journal, Kreimer et al. (9) present the first clinical evidence to support the efficacy of fewer than three doses of the bivalent HPV16/18 vaccine. The Costa Rica Vaccine Trial, in which this study was nested, was not specifically designed to measure

vaccine efficacy (VE) when less than the complete three-dose HPV vaccine series was delivered. Thus, the main reasons that participants in this analysis did not receive three doses were involuntary, including pregnancy and colposcopy referral; few participants refused vaccination. After a median follow-up time of 4.2 years, two doses of the bivalent HPV vaccine demonstrated high VE against incident HPV16 and HPV18 infections that persisted for at least 1 year (VE = 84.1%, 95% confidence interval [CI] = 50.2% to 96.3%), and even a single dose was highly efficacious (VE = 100%, 95% CI = 66.5% to 100%). The VE for two and three doses was essentially the same. Importantly, the VE estimates are supported by similar attack rates of incident HPV16 or HPV18 infections that persisted for 1 year among women who received one dose (5.3%), two doses (4.5%), or three doses (4.4%), indicating that they were at similar risk for acquiring HPV infections regardless of the number of doses.

Cross-protection against the composite endpoint of incident 1-year persistent infection by HPV31, HPV33, and HPV45 has been reported previously (10) for women who received the standard three-dose regimen of the bivalent HPV vaccine (VE = 41.3%, 95% CI = 18.9% to 57.9%). Kreimer et al. (9), however, show no evidence of vaccine cross-protection in women who received two doses of the HPV16/18 vaccine (VE = -25.9%, 95% CI = -334% to 61.1%), and although the data are limited, they do suggest that a full three-dose series may confer greater cross-protection against heterologous HPV types, as previously reported for HPV31, HPV33 and HPV45 (11,12). This finding is not surprising because cross-neutralizing antibodies are already induced by HPV vaccination at much lower levels than type-specific antibodies (13) and are probably generated against a limited number of neutralizing epitopes shared between vaccine and non-vaccine HPV types. Although overall HPV-specific antibody titers may appear nearly identical for two vs three doses of the bivalent HPV vaccine, the concentration, affinity, or avidity of antibody that is specific to any given neutralizing and cross-protective epitope within the overall HPV-specific antibody pool may not be equal for two vs three doses of the HPV16/18 vaccine. If, over the long term, clinically meaningful and durable cross-protection is achieved with a three-dose but not with a two-dose regimen of the bivalent HPV vaccine, the trade-offs will need to be considered in the context of cost-effectiveness and resource availability.

The finding of protection against persistent HPV16/18 infections following a single dose of the recombinant bivalent HPV vaccine is unexpected. This result must be viewed with caution given the small numbers of endpoint events, limited follow-up time, and potential previous HPV16 or HPV18 exposures in the Costa Rica

Vaccine Trial population, which was comprised largely of sexually active women aged 18–25 years. Also, as noted by the authors, these results from a trial of the bivalent HPV16/18 vaccine in Costa Rica may not apply to other HPV vaccine formulations or to other populations with lower overall immune health or greater comorbidities.

It is important to consider that the findings reported by Kreimer et al. (9) are limited to endpoints of persistent HPV infection. It remains unknown whether these observations will translate, over the long term, to the prevention of disease endpoints such as cervical intraepithelial neoplasia grade 3 and higher (CIN3+) and whether HPV vaccine protection, with fewer than three doses, will be sustainable even for homologous HPV vaccine types 16 and 18. Additional larger studies that are specifically designed to evaluate the efficacy of one-, two-, and three-dose regimens in young adolescent girls, with long-term follow-up and more stringent endpoints, could prove critical. Immunization of young adolescents not targeted by the Costa Rica Vaccine Trial may improve the potential for cross-protective immunity generated by two doses of the bivalent HPV vaccine because more robust immune responses have been observed in younger individuals than in older ones (14). Because it is expensive to conduct adequately sized clinical trials, phase IV effectiveness studies and population-based surveillance programs may become the means for addressing these unknowns. If it were possible to achieve high vaccine efficacy with fewer than three doses of HPV vaccine, more women could be vaccinated for the same cost, which could be particularly advantageous in low-resource settings. In this context, the age old adage of less is more may apply to HPV vaccination and if so, the report of Kreimer et al. (9) represents an important step on the road to more effective and sustainable cervical cancer prevention programs.

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