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Commentary

COMMENTARY

The Case for Conducting a Randomized Clinical Trial to Assess the Efficacy of a Single Dose of Prophylactic HPV Vaccines Among Adolescents

Aimée R. Kreimer, Mark E. Sherman, Vikrant V. Sahasrabuddhe, Mahboobeh Safaeian

Affiliations of authors: Division of Cancer Epidemiology and Genetics, Infections and Immunoepidemiology Branch (ARK, MS), Division of Cancer Prevention, Breast and Gynecologic Cancer Research Group (MES, VVS), Division of Cancer Epidemiology and Genetics, Human Genetics Program (MES), and Division of Cancer Epidemiology and Genetics, Hormonal and Reproductive Epidemiology Branch (VVS), National Cancer Institute, National Institutes of Health, Bethesda, MD; Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN (VVS).

Correspondence to: Aimée R. Kreimer, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, RM 6-E104, Bethesda, MD 20892 (e-mail: kreimera@mail.nih.gov).

Human papillomavirus (HPV) types 16 and 18 collectively cause approximately 70% of cervical cancers worldwide (1) and are linked to an even higher percentage of HPV-associated anogenital and oropharyngeal cancers (2). Three-dose regimens of prophylactic vaccines (the bivalent vaccine Cervarix, GlaxoSmithKline Biologicals; the quadrivalent vaccine Gardasil, Merck and Co, Inc.) provide nearly complete protection against HPV16 and -18 infections and related cervical lesions among individuals uninfected with these types at the time of vaccination (3,4). The structure of the HPV virus-like particles (VLPs), the key component of HPV prophylactic vaccines, present closely spaced, repetitive epitopes to the immune system that induce highly potent, protective antibody responses (14), which may reduce or eliminate the need for booster doses. Further, the immune-stimulatory effects of a toll-like receptor agonist adjuvant in the bivalent vaccine may also contribute to the magnitude and durability of the immune response to this vaccine.

Data suggest that two doses of either the bivalent or quadrivalent vaccines, especially if administered to adolescents six or twelve months apart, evoke immune responses comparable to that of three doses among adult women (5–9), for which efficacy has been demonstrated. These favorable results led multiple organizations, including the European Medicines Agency (EMA) (10), the Pan American Health Organization's (PAHO) Technical Advisory Group (TAG) (11), and the World Health Organization's (WHO's) Strategic Advisory Group of Experts (SAGE), to endorse a two-dose vaccination strategy (regardless of vaccine manufacturer) for young adolescents (12). However, in nations that experience the highest cervical cancer mortality rates (13), the resources needed to implement even a two-dose program may be lacking. Accordingly, establishing the protective effect of a single dose could potentially provide enormous benefit. The objective of this commentary is to discuss the need and current evidence supporting the conduct of a clinical trial assessing the efficacy of one-dose HPV vaccine regimens.

Post hoc analyses in the Costa Rica Vaccine Trial (CVT), a phase III efficacy trial that compared the bivalent vaccine with placebo among women age 18 to 25 years, showed that protection over four years against HPV16/18 infections among women initially uninfected with these types was uniformly high for recipients of one (100%, 95% confidence interval [CI] = 79% to 100%), two (81%, 95% CI = 53% to 94%), or three (84%, 95% CI = 77% to 89%) doses (5). Among women who received a single dose, HPV16 and HPV18 antibody titers (assessed by enzyme-linked immunosorbent assay, ELISA) were substantially higher than those among naturally infected women (approximately nine-fold higher for HPV16 and five-fold higher for HPV18);

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titers remained stably elevated from six to 48 months postvaccination, albeit at four- to five-fold lower levels than for two or three doses (6). Neutralizing antibody titers, the presumed mediators of protection, were highly correlated with levels measured by ELISA (15). At four years, the HPV16 VLP antibody avidity index among CVT recipients of one dose was greater than 70% than that of three-dose vaccinees (16). Similarly, an observational study conducted in Uganda among recipients, age 12 to 14 years, of the bivalent vaccine found that HPV16 and HPV18 antibody levels measured at more than 24 months were similar by dose to those measured in CVT (7).

Although tangible evidence for single-dose efficacy is strongest for the bivalent vaccine, this result may also be attained for the quadrivalent vaccine, if the protection afforded by one dose is primarily attributable to the structure of the VLPs. Furthermore, Gardasil 9, a nonavalent HPV vaccine (Merck and Co, Inc.) covering carcinogenic types HPV 16, 18, 31, 33, 45, 52, and 58 plus the condyloma viruses HPV 6 and 11 (17) that was recently licensed by the U.S. Food and Drug Administration (FDA), is formulated similarly to the quadrivalent vaccine and may also provide protection with a single dose. While higher immunogenicity was demonstrated for three doses of the bivalent compared with the quadrivalent vaccine (18), the impact of these differences on efficacy is unknown.

Postmarket, surveillance studies of the quadrivalent vaccine have evaluated the relative efficacy of fewer than three doses, albeit based on imperfect study designs, and yielded mixed results (19–21). Specifically, analysis of registry data in which women are categorized by total number of doses received (as a time-independent variable) may suffer from biases between vaccine-dose groups. It has been reported that fewer-than-three–dose recipients were older at vaccination and younger at first cervical cancer screen (suggesting earlier sexual debut) than those fully vaccinated (19,20). Therefore, one- and two-dose recipients may be more likely to harbor missed prevalent infections at enrollment (22). Such infections would manifest as apparent "vaccine failures," because these vaccines do not eliminate preexisting infections (23). Without detailed individual-level data (eg, prevaccination cervical HPV DNA or serologic status, screening history, or sexual behavior), it is impossible to statistically adjust for potential differences by dose group in the prevalence of HPV infections at first vaccination.

Evaluating efficacy of fewer than three doses in surveillance studies by relating "apparent" vaccine failures to person-time may also be misleading. Because HPV status at the time of vaccination is unknown, women with preexisting HPV infections are most likely to contribute "endpoints" at their earliest follow-up visits, prior to receipt of all three doses, giving the false impression that one and two doses are less protective than the three-dose regimen. Furthermore, the cumulative person-time for the one- and two-dose groups is comparatively limited, which reduces the power of potentially important subgroup analyses, such as efficacy among the youngest participants (ie, the group that is least likely to have prevalent infections at the time of vaccination). Despite limited power, data suggest that younger individuals achieve similar levels of protection irrespective of number of doses received (19). Importantly, providing even a single dose provides considerable protection compared with not vaccinating at all (19). Future observational analyses triggered when more person-time accrues among girls vaccinated before sexual debut may enable robust analyses, which could provide a more unbiased estimate of the effectiveness of one and two doses. Such registry-based observational studies, particularly for Gardasil 9, will take several more years, if not decades, and could therefore be confounded by temporal changes in vaccine formulations and receipt of multiple different vaccines. Finally, assessing the durability of protection will be critically important for all levels of dosing (24,25).

Scientific evidence and public health imperatives provide strong impetus for conducting prospective studies, ideally noninferiority randomized trials, to evaluate the efficacy of single-dose strategies of HPV prophylactic vaccines among young girls. To ensure study validity, such a trial should be performed in a setting where adherence to long-term follow-up is likely, effective cervical cancer screening is performed (for participant safety), and widespread vaccination is unavailable. Targeting young girls reduces safety concerns because additional doses can be administered to participants if one dose proves less efficacious, most incident infections will clear spontaneously, and development of cancers can be prevented by screening; it also minimizes the problem of misclassifying prevalent HPV infections as intervention failures. Analysis of patterns of serial serological titers in randomized controlled trials (RCTs) could support efficacy equivalence, identify thresholds of antibody concentrations that are protective, and provide an early alert about possible declines in efficacy.

Innovative approaches for developing a noninferiority trial of one and two doses are needed (Table 1). Studying unvaccinated individuals of the same birth cohorts and geographic location as trial participants will allow for the estimation of absolute efficacy as well as relative efficacy by dose. In the event that HPV detection postvaccination proves vanishingly rare, noninferiority comparisons of one- and two-dose regimens will lack statistical power; comparisons with this representative, unvaccinated "control" group will become pivotal. Demonstrating a reduction in HPV infections (26) among recipients of one dose compared with an unvaccinated population could justify a public health strategy, which aims to deliver a single dose to as many girls as possible, with careful postimplementation surveillance to assess the need for revaccination. Revaccination of study participants would be required if vaccine failures develop as a function of reduced dosing. In addition, girls from the unvaccinated control group should be offered vaccination at study completion.

If RCTs to evaluate efficacy of a single dose are successful, public health officials may have strong evidence to endorse universal single-dose coverage, with deferral of a second dose contingent upon evidence of breakthrough infections. Even if a single dose yields somewhat inferior efficacy to two doses, high single-dose coverage in a population may result in herd immunity, thereby extending protection to individuals who have not been fully protected by vaccination or remain unvaccinated. Achieving 20 years of vaccine protection with fewer doses should result in considerable reductions in cervical cancer incidence, even if immunity wanes in later years. Undoubtedly, the large RCTs required to test a one-dose approach will be expensive; however, the potential long-term cost savings and reductions in cancer incidence would justify the investment. If a single dose is effective, it could enable wider implementation of vaccines in poorer nations without effective screening, reducing costs, suffering, and mortality secondary to cervical cancer, and eliminate costs of cancer care; partial effectiveness could prompt a cost-benefit analysis that addresses conditions in a country. If a single dose proves ineffective, the results will provide strong impetus to carefully monitor vaccine coverage and outcomes in nations with existing programs using state-of-the-science approaches (such as the New Mexico HPV Pap Registry; 27) and to argue for investments to identify and complete vaccination

Table 1. Design of a noninferiority trial comparing one vs two doses of prophylactic HPV vaccines: challenges and potential solutions

Study design element	Challenge	Approach for mitigating challenge
Setting the noninferiority margin	Setting minimum level of noninferiority is subjective.	Develop value-based noninferiority threshold reflecting locally available cervical cancer control strategies local contextual realities (ie, no vaccination, public acceptance, logistics, per capita healthcare spending, etc.) and consensus views of public officials and program staff.
Choice of HPV endpoint	One-time HPV detection among girls and younger women largely represents a transient infection (or viral deposition) destined to spontaneously regress; persistence with progression to a cancer precursor is rare.	Persistent HPV infection represents a better surrogate endpoint of clinical disease; longer-duration persistence suggests lower probability of clearance. However, the use of persistent HPV detection as an endpoint requires a larger sample size, an a *priori* definition, and standardized specimen collection and HPV genotyping methods.
Lack of placebo group	Given anticipated high efficacy of even one dose, a large study is required to ensure precision based on rare study endpoints.	Greater efforts to engage communities/organizations for trial participation.
Estimation of rare endpoints	Power calculations are limited by uncertainty in estimating the occurrence of rare events (eg, persistent HPV infection), compounded by limited preliminary data.	Conduct pre-hoc sensitivity analysis to estimate best- and worst-case scenarios to arrive at optimal and realistic choices about the number of expected endpoints and needed sample sizes. Inclusion of a concurrently conducted population-based HPV DNA prevalence survey will support conclusions if endpoints are limited.
Vaccine failures	Observed higher rate of vaccine failures in the experimental (one-dose) arm than expected.	Although risk of cervical cancer precursors is low at young age, those with persistent infections will need adequate monitoring. However, a second dose can be offered to all in the one-dose arm of the trial.
Herd immunity	Artificial inflation of observed vaccine efficacy secondary to herd immunity.	Conduct study in a country/locale with low preexisting vaccine coverage.
Assessing durability of protection	Infrastructure for long-term surveillance needed.	Establish postsurveillance registry, including mechanisms required for random periodic testing of vaccine recipients.

among one-dose recipients, who represent a significant proportion (around 20%) of teenagers in the United States (28).

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