Impact and Cost-Effectiveness of Human Papillomavirus Vaccination Campaigns

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ABSTRACT

Background: Data to inform evidence-based policy of human papillomavirus (HPV) vaccine delivery strategies in low- and middle-income countries are limited. We examined the cost-effectiveness of campaign compared with routine delivery strategies of adolescent female HPV vaccination in Uganda.

Methods: We used a multiple modeling approach that captured HPV transmission, cervical carcinogenesis, and population demographics to project health and economic outcomes associated with HPV vaccination. Costs included vaccination and operational costs and cervical cancer costs over the lifetimes of the current female population in Uganda. Health outcomes included number of cervical cancer cases and disability-adjusted life years (DALY). Incremental cost-effectiveness ratios (i.e., cost per DALY averted) were calculated and compared against gross domestic product (GDP) per capita.

Results: Compared with routine HPV vaccination of 9-year-old girls at 70% coverage, campaign vaccination yielded greater health benefits if campaigns occurred frequently and targeted a wide age range. Campaign delivery strategies were both less costly and more effective than routine HPV vaccination. Campaign vaccination of 9- to 30-year-old girls/women at a 3-year frequency (40% coverage) was considered cost-effective compared with the GDP per capita threshold for Uganda ($674 in U.S. 2015 dollars).

Conclusions: We projected that campaign HPV vaccination would provide substantial population health benefits compared with routine vaccination. Expanding the target age range of campaign vaccination up to age 30 years may be an efficient strategy, depending on the achievable coverage level and campaign frequency.

Impact: In settings where routine health systems infrastructure may be limited, reaching adolescent populations with a campaign delivery strategy may be an efficient use of resources.

Introduction

Persistent human papillomavirus (HPV) infections are a necessary cause of cervical cancer and can lead to genital warts, other anogenital cancers, and cancers of the head and neck, with HPV types 16 and 18 causing 70% of all cases of cervical cancer (1, 2). More than 85% of the approximately 274,000 cervical cancer deaths each year occur in low- and middle-income countries (LMIC), where fewer than 5% of women have access to preventive screening (3, 4).

Prophylactic HPV vaccination has a direct, proximal effect on whether an individual contracts a high-risk HPV infection. Studies of currently licensed HPV vaccines have shown that they provide almost 100% protection against HPV-16 and -18 (5, 6). By the beginning of 2015, there were an estimated 80 national HPV vaccination programs and 37 pilot programs worldwide (7). As HPV vaccination is recommended to adolescents (typically ages 9–14 years), there are several different delivery strategies to administer vaccination, including school-based vaccination, facility-based vaccination, or vaccination combined with the provision of other health interventions [e.g., antenatal or human immunodeficiency virus (HIV) care].

A routine vaccination strategy is characterized by delivery at fixed sites and adhering to a consistent dosing schedule. This allows for consistent budgeting and allocation of health care workers. However, reaching a target group with limited health services may not be best achieved by a routine vaccination strategy. A campaign delivery strategy differs from routine delivery vaccination in that the scheduling is determined by disease burden and/or programmatic coverage needs. In LMICs, campaigns have typically been used to achieve specific global goals, such as measles elimination or polio eradication, often by the World Health Organization (WHO; e.g., Global Measles and Rubella Strategic Plan, Global Vaccine Action Plan; ref. 8). During a vaccination campaign, health workers and volunteers establish additional outreach service points or go door-to-door to offer vaccinations to all members of a target population, irrespective of previous vaccination status. Vaccination campaigns may be conducted nationwide or may target specific districts/regions (9–12).

Because vaccination campaigns require a level of "surge capacity" in terms of human and financial resources for vaccine delivery, there is less consistency in terms of budgeting and allocation of health care workers. In addition, although a routine strategy can provide flexibility to serve public demand, a campaign strategy only provides limited times during which the vaccine can be accessed. As the HPV vaccine is typically targeted to adolescents not often served by routine health services, characteristics and effectiveness of a potential campaign strategy in LMICs are highly uncertain.

The objective of this analysis was to estimate the health and economic outcomes of female HPV-16/18 vaccination delivered via

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Prior presentations: Earlier versions of this paper were presented at the 2018 International Papillomavirus Conference, 2018 Society for Medical Decision-Making Conference, and 2019 Institute for Disease Modeling Symposium, and we received valuable comments from conference participants.

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campaign strategy in Uganda. We examine a range of campaign delivery strategies, varying programmatic features (i.e., campaign coverage, frequency, target age range, cancer treatment costs, and delivery costs) as well as vaccine attributes (i.e., efficacy, duration of protection) to compare the health benefits, costs, and cost-effectiveness of routine and campaign vaccination delivery strategies.

Materials and Methods

Analytic overview

We used a multiple modeling approach to estimate the health and economic outcomes associated with various campaign HPV vaccination strategies compared with routine one-dose and two-dose vaccination strategies in Uganda. We linked a dynamic agent-based model of HPV transmission ("Harvard-HPV") to a static individual-based model of cervical cancer development ("Harvard-CC"), which enables us to capture the complex natural history of HPV-induced cervical cancer, the direct benefits of vaccination to vaccinated individuals, and the indirect benefits of vaccination to unvaccinated individuals due to herd immunity. We then used a population-based model ("Harvard-Scale Up") to project the health and economic impact for women in Uganda over time. This modeling approach has been previously described in Burger and colleagues (13), but we summarize it briefly here.

Simulation models

As previously described (13), Harvard-HPV is an agent-based dynamic model of partnership acquisition and HPV transmission, stratified by genotype (HPV-16, -18, -31, -33, -45, -52, -58). The model assigns sexual behavior characteristics to individual heterosexual men and women who form partnerships, such as partner concurrency, number of lifetime partners, and duration of current partnership(s). Individuals interact in the model to capture both HPV transmission and the benefits of a proposed HPV vaccination program, directly to the individual and indirectly to unvaccinated partners (i.e., herd immunity). Inputs for sexual behavior in Uganda predominantly varied by the number and duration of heterosexual partnerships and assortativeness by age and sexual activity category (Supplementary Fig. S1). We calibrated Harvard-HPV to reflect these sexual behavior inputs and used the model to estimate HPV incidence reductions over time according to genotype and age. HPV incidence reductions for alternative HPV vaccination strategies then served as inputs into Harvard-CC.

Harvard-CC is a static, individual-based (i.e., microsimulation) model that tracks women beginning at age of vaccination (e.g., 9 years) and as they age and transition through HPV-related health states until death, either due to cervical cancer or background mortality rates. The specific health states included are: no HPV infection, HPV infection, cervical intraepithelial neoplasia grades 2 and 3, cervical cancer, and death. Transitions occur on a monthly time step and depend on age, HPV genotype (HPV-16, -18, -31, -33, -45, -52, -58), duration of infection, and history of prior HPV infection. As previously described and published (14, 15), Harvard-CC relies on baseline parameters derived from large, empirical studies (16–19) and calibrated to fit epidemiologic outcomes in Uganda (20–22). Reductions in HPV-16/18 cervical cancer incidence from Harvard-CC then served as inputs into the population-based model, Harvard-Scale Up.

Harvard-Scale Up is a multicohort model used to scale the health and economic impacts to the population level (23). Harvard-Scale Up uses data on the age-specific incidence of cervical cancer (24), HPV-16/18 type distribution in cervical cancer (20), and population demographics at the country or region level over time. We applied the estimated age-specific cancer incidence reductions to the associated incidence rates in Uganda (24). The Excel-based model then outputs the estimated number of cervical cancer cases and deaths averted, disability-adjusted life years (DALY) averted, and total economic costs associated with the alternative HPV vaccination strategies.

Scenarios

We conducted analyses to evaluate the impact of campaign HPV vaccination strategies compared to a routine one-dose and two-dose HPV vaccination program. We explored a landscape of plausible strategies guided by other vaccine campaigns and consultation with experts. The following programmatic parameters were varied accordingly—campaign coverage (20%, 40%, or 60%), frequency (every 3, 4, 5, or 6 years), target age range (9- to 14-year-old girls, 9- to 18-year-old girls, 9- to 26-year-old girls, and 9- to 30-year-old girls in 2019), and delivery costs ($0.70–$1.70 recurrent costs per girl with one-time fixed introduction cost of $2.00 per girl in year one of the program)—to identify thresholds at which the campaign or routine delivery strategy becomes the optimal delivery strategy (**Table 1**). For the base case strategy, we assumed a campaign vaccination coverage level of 40% for 9- to 14-year-old girls every 4 years. We compared campaign HPV vaccination for these strategies to routine one-dose and two-dose HPV vaccination of 9-year-old girls, including temporary one-year vaccination of 10- to 14-year-old girls at 70% coverage in

Table 1. Analytic scenarios.

	Campaign base case	Routine strategies	Campaign strategies
Frequency	4 years	Annual	3, 4, 5, 6 years
Doses	1 dose	1 or 2 doses	1 dose
Target age(s)	9- to 14-year-old girls	9-year-old girls	9- to 14-, 9- to 18-, 9- to 26-, 9- to 30-year-old girls/women
Catch-up age(s)	Not applicable	10- to 14-year-old girls	Not applicable
Coverage	40%	70%	20%, 40%, 60%
Delivery costs	$1.00/girl	$1.70/girl	$0.70, $1.00, $1.20, $1.70/girl/woman

Note: We assume vaccination with two doses in the base case for routine vaccination. Individual campaigns deliver one dose, but individual girls can receive two doses if they remain in the target age range for a subsequent campaign. Campaign frequency ranges are based on prior childhood vaccination campaign strategies. Campaign target age ranges are based on current recommendations for multiage cohort and catch-up HPV vaccination programs. Campaign coverage levels are based on population-adjusted mean coverage levels of subnational childhood measles vaccination campaigns, with the decreased coverage levels applied to the national population in the HPV context to address delivery challenges with the adolescent target population. All delivery costs include a one-time fixed introduction cost of $2.00 per girl in year 1 of the program.

the year 2019 alone (i.e., "multiage cohort" vaccination). Cases and costs averted were calculated in relation to a strategy of no HPV vaccination.

Vaccine characteristics

In the base case, we assumed a single HPV vaccine dose conferred 80% protection against incident HPV-16 and -18 infections based on the lower-bound target efficacy for one-dose HPV vaccination in an ongoing randomized control trial (ClinicalTrials.gov Identifier: NCT 03180034). Given the unknown duration of one-dose vaccine protection, we assumed 15 years of full protection followed by waning protection at a constant rate over an additional 20 years. For any second doses given in campaign strategies, and for two-dose routine vaccination, we assumed 100% protection against HPV-16 and -18 infections over the lifetime in the base case. In a scenario analysis, we also considered 100% protection against HPV-16 and -18 infections for 15 years from the point of the second vaccination (i.e., a booster) followed by waning protection at a constant rate over an additional 20 years. To address the possibility that vaccine efficacy is lower at older ages, we also conducted a threshold analysis around vaccine efficacy for girls 19 years of age and older in which we examined one- and two-dose efficacies in 20% decrements from the base case for these ages, including: (i) 60% for one-dose, 80% for two-dose; (ii) 40% for one-dose, 60% for two-dose; (iii) 20% for one-dose, 40% for two-dose; and (iv) 0% for one-dose, 20% for two-dose.

Cost inputs

We assumed a base-case HPV vaccine cost of US$4.50 per dose (25) for both campaign and routine vaccination, and included costs for vaccine wastage at a rate of 5% for a single dose vial, liquid formulation (26). For the routine vaccination strategy, we assumed a base-case HPV vaccine delivery cost of US$1.70 per girl, including costs for personnel, training, social mobilization, disease surveillance, program management, and other recurrent costs; for the campaign vaccination strategy, we assumed a base-case HPV vaccine delivery cost of US$1.00 per girl. Relying on the Vaccine Introduction Grant and Operational Support for Campaigns Policy (Gavi, the Vaccine Alliance), we also examined three additional delivery cost scenarios for campaign vaccination: (i) decreased delivery cost of $0.70 per girl; (ii) increased delivery cost of $1.20 per girl; and (iii) delivery costs of $1.00 per girl for ages 9–14 and $1.70 per girl for ages 15 and above (i.e., we assume the same delivery costs as routine vaccination for older girls; refs. 27–29). The supplementary file outlines the assumptions for these delivery costs (Supplementary Fig. S2).

We assumed in the base case that all women with detected cervical cancer would have access to cervical cancer treatment and incur the relevant treatment costs. Cervical cancer treatment costs included direct medical costs at a tertiary facility associated with stage-specific International Federation of Gynecology and Obstetrics (FIGO) treatment protocols and assumed to be independent of vaccination coverage (30, 31). We assumed 20% of detected cancers to be local (i.e., stage I) and 80% to be late stage (i.e., stages II–IV). To estimate the unit cost of each procedure, we identified available data from the published literature (32–38) and unpublished data (39). All costs were converted to 2015 U.S. dollars using local consumer price index (CPI) deflators and exchange rates (World Bank 2019). To extrapolate published estimates for cervical cancer treatment costs from their original settings, accounting for variation in income level, we adjusted unit costs using an index of tertiary inpatient visit costs from WHO Cost-effectiveness and strategic planning (WHO-CHOICE) and World Bank world development indicators, resulting in $907 for stage I and $1,081 for stage II to IV in Uganda in 2015 U.S. dollars. In a scenario analysis, we assumed that cervical cancer treatment costs only applied to the estimated proportion of women with access to radiation therapy in a given setting (8.5%); the remainder of women incurred no costs for cancer treatment (40).

Outcomes

The cost outcomes included the lifetime costs of vaccination and/or cervical cancer treatment associated with alternative HPV vaccination strategies in 2015 U.S. dollars. Health outcomes included the number of cervical cancer cases and DALYs. We discounted both future costs and DALYs at a rate of 3% annually. By aggregating model outcomes over multiple cohorts, we captured the benefits of averted cancer cases and costs for women aged 9 to 100 years in the year 2019, as well as girls born between 2020 and 2118 (i.e., 99 additional incoming cohorts).

We calculated the incremental cost-effectiveness ratio (ICER) to measure cost-effectiveness. The ICER was defined as the additional cost of a particular strategy divided by the additional health benefits (i.e., DALYs averted), compared with the next less-costly strategy. Strategies that were more costly and less effective ("strongly dominated"), or having higher ICERs than more effective strategies ("weakly dominated"), than an alternative strategy were removed from further consideration. The estimated ICERs for the remaining strategies (i.e., the efficient strategies) were compared with a cost-effectiveness threshold of $674 (2015 U.S. dollars) per DALY averted, the gross domestic product (GDP) per capita in Uganda (World Bank), which represented the willingness of the health care system in Uganda to pay for care, to identify the optimal strategy.

Results

Health benefits

In the base case, campaign HPV vaccination assuming vaccination coverage of 40%, target age group of 9- to 14-year-old girls, and a frequency of 4 years averted approximately 500,000 cases of cervical cancer across 2019 to 2118 (i.e., a 15% reduction), compared with a strategy of no HPV vaccination (**Table 2**). Vaccinating at high frequency and targeting a wide age range increases the effective coverage for campaign compared with routine strategies, resulting in greater cervical cancer cases averted. These health benefits were comparable to routine two-dose vaccination with 70% coverage and a 1-year multiage vaccination program to age 14 years (**Fig. 1A**).

When we varied campaign frequency, the model projected greater benefits for a campaign frequency of 3 years compared with the routine two-dose vaccination delivery strategy. However, campaign vaccination at a frequency of 5 or 6 years yielded fewer health benefits than routine two-dose vaccination. When target age group was varied from the base case, campaign HPV vaccination frequency of 4 years for 9- to 18-, 9- to 26-, or 9- to 30-year-old girls yielded greater health benefits than routine two-dose vaccination (**Fig. 1B**). On average, the 19- to 26-year-old target age group contributed the largest percentage of cervical cancer cases averted, followed by 9 to 14 years old, 15 to 18 years old, and 27 to 30 years old. When varying vaccination coverage from the base case, campaign vaccination at a coverage level of 20% yielded fewer health benefits than routine two-dose vaccination, whereas campaign vaccination at a coverage level of 60% yielded greater health benefits.

Table 2. Cervical cancer cases averted compared with no vaccination over 2019 to 2118 by vaccine delivery strategy.

Strategy	Cervical cancer cases averted	Percent reduction compared with no vaccination
6 years, 9 to 14 years old	274,000 (128,000–413,000)	8% (4%–12%)
5 years, 9 to 14 years old	364,000 (167,000–581,000)	11% (5%–17%)
Routine one dose	421,000	12%
4 years, 9 to 14 years old	504,000 (222,000–837,000)	15% (6%–24%)
Routine two doses	562,000	16%
6 years, 9 to 18 years old	593,000 (261,000–997,000)	17% (8%–29%)
3 years, 9 to 14 years old	732,000 (318,000–1,259,000)	21% (9%–37%)
5 years, 9 to 18 years old	747,000 (323,000–1,274,000)	22% (9%–37%)
4 years, 9 to 18 years old	981,000 (427,000–1,599,000)	29% (12%–47%)
6 years, 9 to 26 years old	1,202,000 (529,000–1,887,000)	35% (15%–55%)
3 years, 9 to 18 years old	1,352,000 (604,000–1,965,000)	39% (18%–57%)
5 years, 9 to 26 years old	1,450,000 (656,000–2,048,000)	42% (19%–60%)
6 years, 9 to 30 years old	1,468,000 (669,000–2,076,000)	43% (20%–61%)
5 years, 9 to 30 years old	1,729,000 (818,000–2,151,000)	50% (24%–63%)
4 years, 9 to 26 years old	1,768,000 (843,000–2,142,000)	52% (25%–63%)
4 years, 9 to 30 years old	1,994,000 (1,039,000–2,190,000)	58% (30%–64%)
3 years, 9 to 26 years old	2,052,000 (1,141,000–2,187,000)	60% (33%–64%)
3 years, 9 to 30 years old	2,141,000 (1,380,000–2,218,000)	63% (40%–65%)

Note: Cervical cancer cases averted are aggregated over 2019 to 2118 for females currently alive in 2019 plus those women born between 2020 and 2118 and rounded to the nearest thousand. Campaign delivery strategies are presented for 40% coverage, with 20% and 60% coverage in parentheses. Routine strategies assume 70% vaccination coverage, including 1-year multiage vaccination of 10- to 14-year-old girls. In the base case, for HPV-16/18 infections, we assumed 80% efficacy and 15-year duration of protection followed by waning over 20 years with one dose and 100% efficacy and lifelong duration of protection with two doses.

When we assumed that the second dose boosted the duration of protection by 15 years from the point of the second vaccination rather than provide lifelong protection, the routine two-dose strategy averted more cases of cervical cancer than any campaign frequency at 40% coverage of 9- to 14-year-olds (Supplementary Fig. S3A). However, assuming a campaign frequency of 4 years and campaign vaccination coverage of 40%, campaign HPV vaccination of 9- to 18-, 9- to 26-, or 9- to 30-year-old girls continued to yield greater health benefits than routine two-dose vaccination (Supplementary Fig. S3B). Examining the threshold analysis around vaccine efficacy for girls 19 years of age and older, we found that campaign vaccination at 40% coverage of 9 to 26 years old at a 4-year frequency yielded greater health benefits than routine two-dose vaccination as long as the vaccine efficacy was at least 20% for one dose and 40% for two doses (**Fig. 2**). This pattern also held for 40% coverage of 9 to 30 years old at a 4-year frequency.

Economic outcomes

All HPV vaccination strategies (i.e., campaign and routine with one dose or two doses) were associated with substantial upfront costs related to vaccine procurement and delivery, but resulted in long-term cost offsets from future averted cervical cancer cases. For example, the total vaccine-related cost associated with routine two-dose vaccination with 70% coverage and a 1-year catch-up program to age 14 years exceeded $308 million between 2019 and 2118, whereas the base case campaign vaccination strategy, assuming 4-year frequency, 40% vaccination coverage, and a target age group of 9- to 14-year-old girls, cost approximately $124 million (**Fig. 3**). Compared with no HPV vaccination, the total disease-specific costs were lower under all vaccination programs due to averted cancer cases, which accrued over time. Of note, a vaccination campaign targeting a 9- to 30-year-old age group (assuming 40% coverage and 4-year frequency) was associated with more than three times the initial investment of a vaccination campaign targeting 9- to 14-year-old girls ($395 million compared with $124 million). However, by the same token, the cost offsets due to cervical cancer prevention were 2.5 times higher ($266 million compared with $76 million).

Campaign HPV vaccination strategies were both less costly and more effective than routine one-dose and two-dose HPV vaccination at 20%, 40%, or 60% coverage (Supplementary Table S1). Compared with no vaccination, campaign vaccination of 9- to 30-year-old girls at a 3-year frequency and 40% coverage in the base case was the most effective strategy with an ICER below the willingness-to-pay threshold of the GDP per capita for Uganda ($674 in 2015 U.S. dollars according to the World Bank; **Fig. 4**). At the same threshold, this strategy was optimal at 20% coverage, but was no longer optimal at 60% coverage. Compared with Uganda's GDP per capita, campaign vaccination of 9- to 30-year-old girls at a 5-year frequency was optimal at 60% coverage. For a lower cost-effectiveness threshold of 50% GDP per capita ($337), campaign vaccination of 9- to 30-year-old girls at a 4-year frequency was considered the most cost-effective vaccination delivery approach assuming 40% coverage in the base case. Compared with no vaccination, campaign vaccination of 9- to 30-year-old girls at a 3-year frequency or 4-year frequency (at either 20% or 60% campaign coverage) was considered efficient (Supplementary Table S1).

In scenario analyses, when we assumed a 15-year boost to the duration of protection rather than lifelong protection with two doses, campaign HPV vaccination strategies were still less costly and more effective than routine one-dose and two-dose HPV vaccination at 20%, 40%, or 60% coverage (Supplementary Table S2). When we varied the delivery costs, assuming either a lower ($0.70) or higher ($1.20) per girl recurrent HPV vaccine campaign delivery cost rather than the base case assumption of $1.00 per girl, the ICERs changed slightly, but the strategies on the efficiency frontier and their rankings remained unchanged (Supplementary Tables S3 and S4). In addition, even when we assumed $1.70 per girl for recurrent HPV vaccine delivery cost among those 15 years of age and older, the strategies on the efficiency frontier and their rankings remained the same, with one exception: when we assumed 60% and lifelong duration of protection, the efficiency frontier included a campaign strategy involving 3-year frequency, targeting 9- to 14-year-old girls rather than a campaign strategy

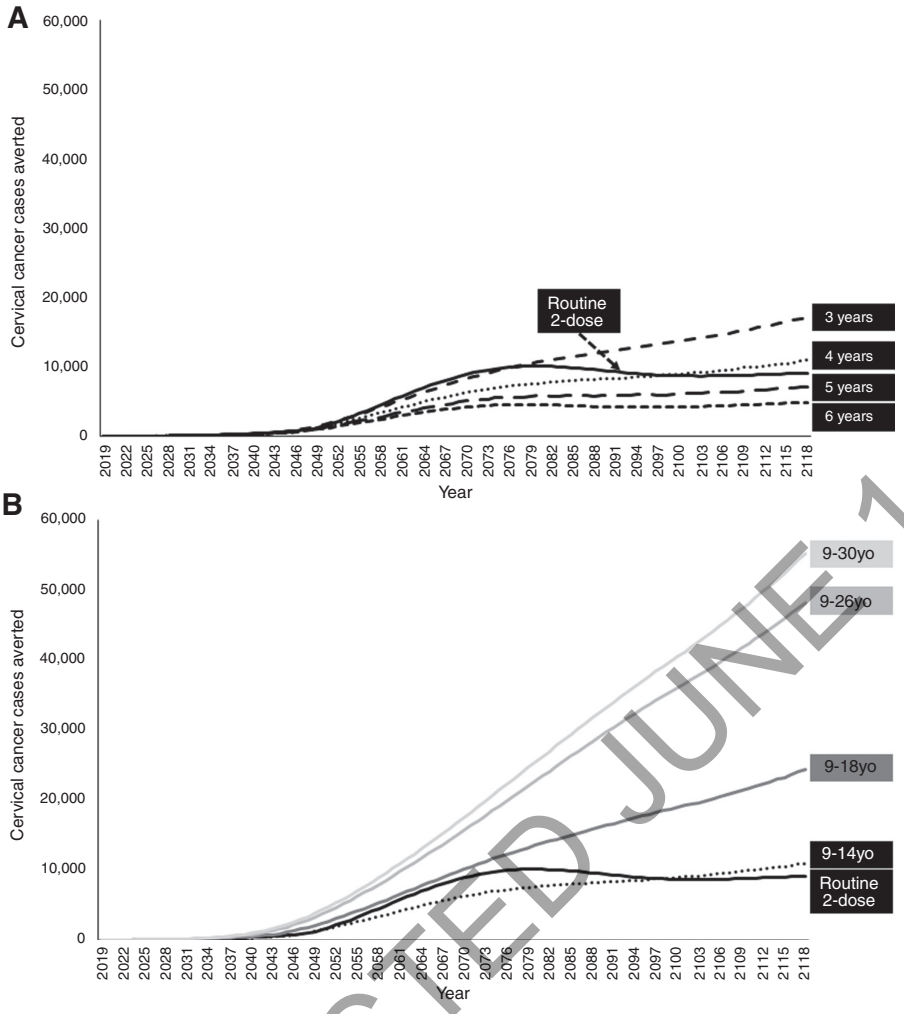

Figure 1.
Annual number of cervical cancer cases averted: varying campaign frequency (**A**) and varying target age group (**B**). Note: Campaign strategies represent 40% vaccination coverage. Campaign strategies that vary frequency assume vaccination of 9- to 14-year-old girls (i.e., 9–14 yo); campaign strategies that vary target age group strategies assume 4-year frequency. Routine strategies assume 70% vaccination coverage, including a 1-year multiage program of 10- to 14-year-old girls.

involving 5-year frequency, targeting 9- to 18-year-old girls (Supplementary Table S5). When we adjusted cancer treatment costs to reflect imperfect level of treatment access, campaign strategies with a 5-year frequency targeting 9 to 30 years old became more attractive at very low coverage levels (i.e., 20%); optimal strategies remained the same at 40% and 60% coverage (Supplementary Table S6).

When assuming decreased vaccine efficacy for girls 19 years of age and older, we found that the campaign strategy involving a 3-year frequency targeting 9- to 30-year-old girls was not efficient if the efficacy of one dose was 40% or less and the two-dose efficacy was 60% or less (Supplementary Tables S7–S10). At these lower efficacy levels, routine two-dose vaccination became an attractive strategy when campaign coverage was low (i.e., 20%). When a single dose of vaccine was assumed to confer no protection but two doses were 20% efficacious, vaccinating women ages 19 years and over was not efficient.

Discussion

Using a model-based approach that incorporates HPV transmission dynamics, cervical cancer disease natural history, and population demographics, we projected that campaign HPV vaccination assuming 80% efficacy for one dose against HPV-16/18 infections would provide substantial population health benefits compared with routine one-dose or two-dose vaccination. In settings where routine health systems infrastructure may be limited, reaching adolescent populations with a campaign delivery strategy may be feasible. Assuming up to 60% coverage, we found that campaign HPV vaccination can be cost-effective compared to a routine two-dose vaccination program if campaigns occur frequently and target a wide age range (**Fig. 4**). This result also held for 20% and 40% campaign vaccination coverage (Supplementary Table S1). Even without targeting a wide age range, these results indicate that a campaign strategy might still be more attractive than a routine strategy for many 9- to 14-year-old or 9- to 18-year-old target age scenarios. To our knowledge, our study is the first to assess the value of a campaign delivery strategy for HPV vaccination, under scenarios of coverage, frequency, target age range, and delivery costs.

There are several limitations to this analysis. We were restricted in modeling assumptions due to limited data. First, the natural history of HPV infection in older women is highly uncertain and vaccine efficacy has been shown to be lower among individuals with prevalent HPV

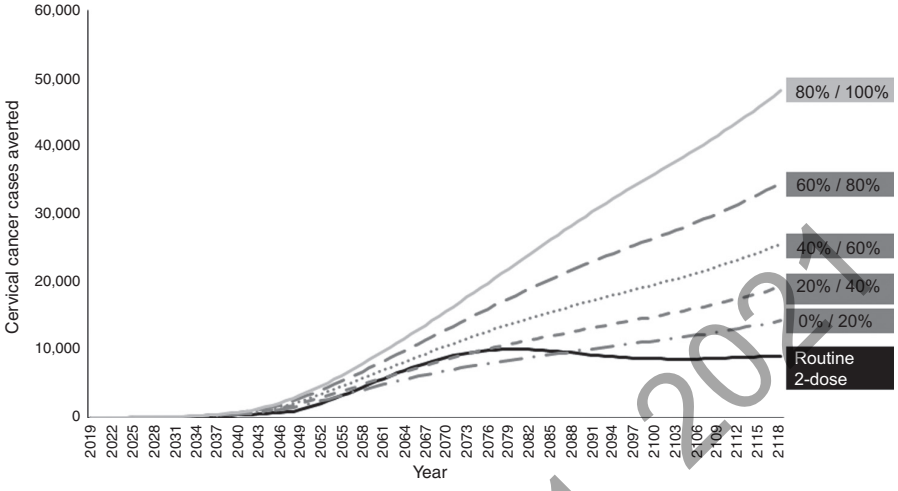

Figure 2.
Annual number of cervical cancer cases averted: varying one- and two-dose vaccine efficacy among 19- to 26-year-old women. Note: Percentages represent one- and two-dose efficacies, respectively, for 19- to 26-year-old women. For girls under age 19 years, we assumed 80% vaccine efficacy for one dose and 100% vaccine efficacy for two doses. Campaign strategies assume 40% vaccination coverage, 4-year frequency, and 9- to 26-year-old target age group. Routine strategies assume 70% coverage, including a 1-year multiage program of 10- to 14-year-old girls.

infections, which might impact the effectiveness of vaccination at older ages (41–43). To address this uncertainty, we conducted a threshold analysis of vaccine efficacy for women 19 to 30 years old, and found that strategies to vaccinate women in this age group were no longer efficient at a two-dose efficacy of 20%. We found that, on average, the 19- to 26-year-old target age group contributed the largest percentage of cervical cancer reductions, but this is likely due to the sheer number of women included in this larger age group bucket and does not mean that we would not see diminishing returns by age.

Second, as a campaign delivery strategy has not yet been implemented for HPV vaccination, empirical data to support modeling assumptions are lacking. We relied on information from an alternate childhood vaccination program (i.e., measles; ref. 44). National multiage cohort measles campaigns had an estimated mean coverage of 70% [population-adjusted national coverage; standard deviation (SD): 30%]. Alternatively, when we estimated national coverage from subnational (rather than national) multiage cohort measles campaign coverage, we found a mean coverage of 40% (SD: 20%). We chose the coverage levels derived from subnational campaign levels to represent what might be feasible for an HPV vaccination campaign, given older target ages outside of routine infant vaccination. The most common age range targeted by the measles campaign data we reviewed is 9 months to 14 or 15 years of age, which indicates that the wide target age ranges examined in this analysis might be reached by a campaign delivery strategy. To counteract the uncertainty of these assumptions, we included scenario analyses aimed at addressing this limitation by presenting a plausible landscape for HPV vaccination campaigns (i.e., coverage, target ages, frequency, and delivery costs).

Third, we did not include program costs for reaching older target age groups and increasing coverage. As a result, the findings should be interpreted with caution, particularly if the delivery costs associated with expanding the vaccination program increase with higher coverage. However, we did include a scenario in which we assumed increased delivery costs ($1.70 per girl) for girls ages 15 and older to

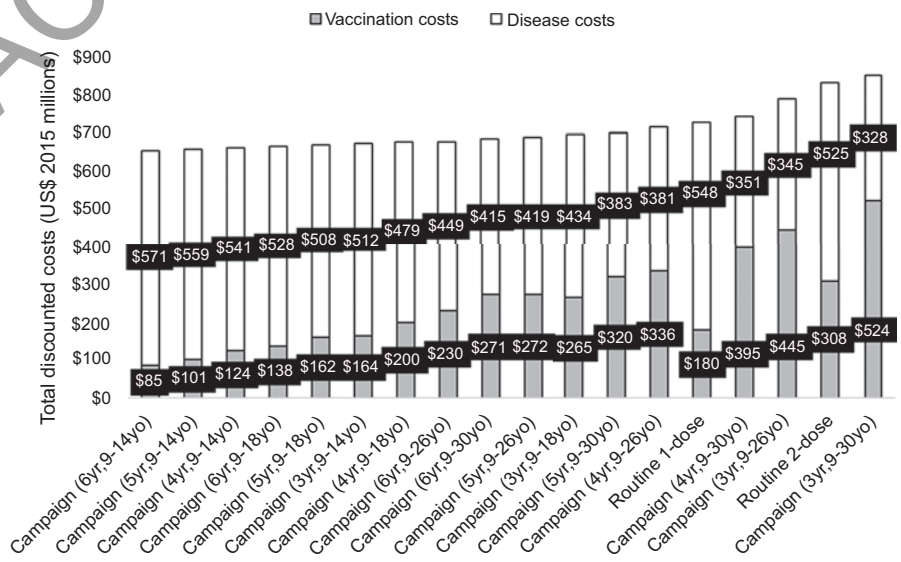

Figure 3.
Total discounted costs in 2015 U.S. dollars associated with campaign and routine vaccination strategies. Note: Campaign strategies assume 40% vaccination coverage. Each strategy is labeled with the campaign frequency and target age range in parentheses; for example, "Campaign (6 yr, 9–14yo)" on the far left refers to a campaign strategy with 6-year frequency and 9- to 14-year-old target age group. Vaccine program costs (gray bars) reflect 100 cohorts of 9-year-old girls from years 2019 to 2118. Disease costs (white bars) capture disease offsets over the lifetimes of women alive in year 2019 as well as girls born between 2020 and 2118 (i.e., 99 additional incoming cohorts).

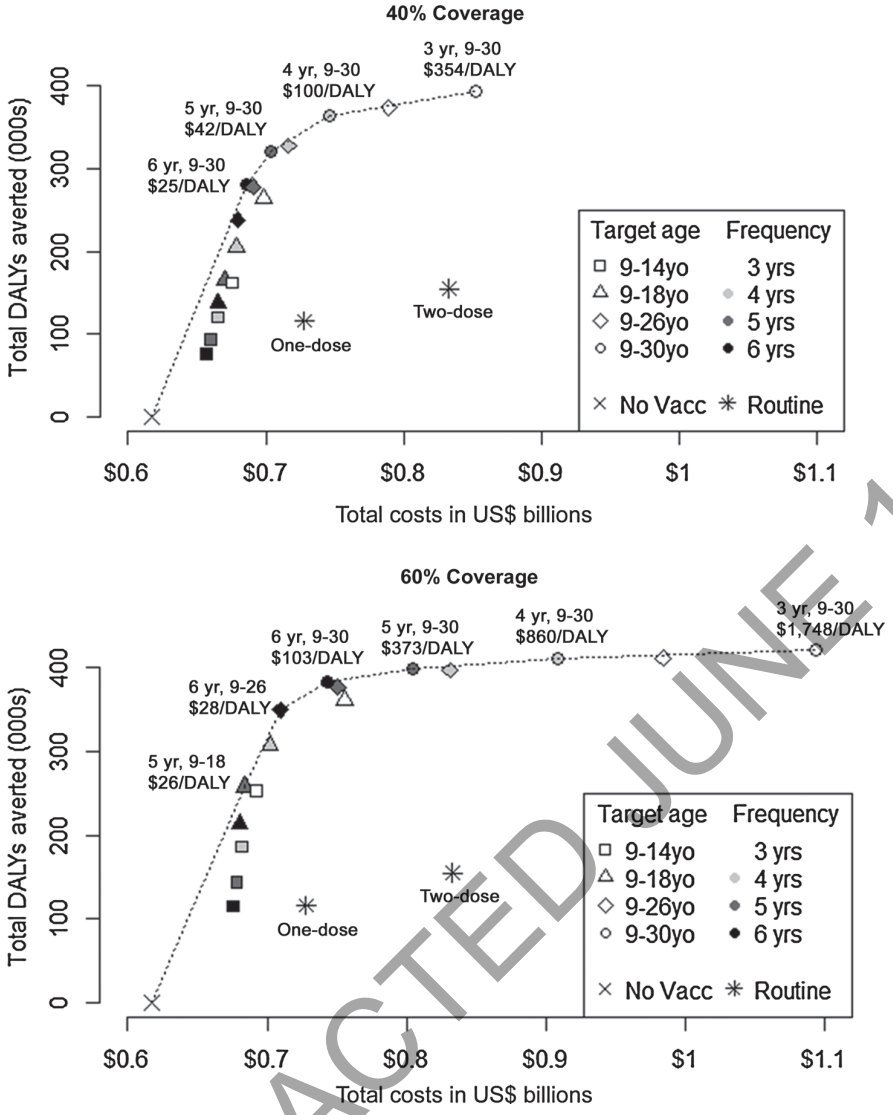

Figure 4.
Discounted incremental cost in 2015 U.S. dollars per disability-adjusted life year (DALY) averted. Note: The base case strategy involved 4-year frequency and a 9- to 14-year-old target age group, assuming one-dose efficacy of 80%, two-dose efficacy of 100%, 15-year duration of protection followed by waning over 20 years with one dose, lifelong duration of protection with two doses, full cancer treatment costs, $1.00 per girl recurrent vaccine delivery cost for campaign vaccination, and $1.70 per girl recurrent vaccine delivery cost for routine vaccination (both campaign and routine vaccination assumed $2.00 per girl introduction cost in year 1). Costs and DALYs were discounted at 3% per year. The incremental cost-effectiveness ratio can be compared with a threshold of the GDP per capita in Uganda ($674) or 0.5 times the GDP per capita ($337). yo, years old; yr(s), year(s).

address how costs might increase when targeting older ages. It is important to note that while campaign vaccination of 9- to 30-year-old girls was identified as efficient in the cost-effectiveness analysis, the number of additional cervical cancer cases averted was relatively small in this age group. For example, at the level of 40% campaign coverage, vaccinating girls ages 27 to 30 years old contributed less than or equal to 18% of the cervical cancer cases averted at all campaign frequencies. Moreover, these strategies were only identified as efficient when vaccine efficacy was assumed to be similar to that of younger girls, such that the strategy involving a 3-year frequency targeting 9- to 30-year-old was not efficient when vaccine efficacy associated with one dose was less than or equal to 40% and vaccine efficacy associated with two doses was less than or equal to 60% (Supplementary Tables S7–S10). We also did not assume economies of scale for increasing the target age range or increasing the coverage level, which might offset the lack of programmatic costs and even result in more cost-effective results for campaign strategies.

In addition, this analysis captured the costs of the vaccination program over 100 years including the disease costs and health benefits over the lifetimes of women alive up to age 100 years in 2019. We assumed that cervical cancer incidence rates were stable over this time period. Vaccine efficacy against high-risk HPV types other than HPV-16/18 (i.e., cross-protection) was not included. This assumption and the assumption of 80% vaccine efficacy for a single HPV dose suggest that our results are conservative regarding the impact of HPV campaign vaccination.

This analysis did not consider the likely changes to the incidence of cervical cancer and efficacy of HPV vaccination among individuals with HIV infection. Studies show that HIV may impact the immunogenicity of vaccines (45–49). Therefore, including women ages 19 years and older in an HIV-endemic setting may not yield as much benefit.

We did not examine cervical cancer screening programs in this analysis and assumed that any ongoing screening programs did not change as HPV vaccination introduction and delivery changed. We

also did not incorporate an examination of the budgetary impact of HPV campaign vaccination. Finally, given limited data on the burden of other HPV-related diseases in LMICs, we did not evaluate the impact HPV vaccination may have on non–cervical cancers in women and men, which likely increases the value of all HPV vaccination strategies.

This analysis does not address the integration of a routine and campaign delivery program within the same health system, which may affect the overall impact of vaccination campaigns. We also do not address the normative discussion of whether a campaign strategy should be implemented for HPV vaccination. There are conflicting views regarding the impact of "vertical" delivery of specific health interventions on the "horizontal" delivery of primary and preventive services in the health system, and the broader benefits and disadvantages of a campaign delivery strategy for public health interventions. Previous work examining the impact of measles vaccination delivered by a campaign vaccination strategy on the broader health system have ranged from positive to negative associations with system functioning (50–56). Furthermore, others have proposed that campaign efforts should focus specifically on strengthening the routine vaccination program, integrating vaccination with other health services, and encouraging donor support of primary health care (57). These are important considerations for the decision-making process regarding HPV vaccine delivery, particularly if the goals of an HPV campaign vaccination strategy include combination with other interventions or programs.

Nonetheless, our analysis enables us to draw several key insights. There is great potential for a campaign strategy of HPV vaccination to be cost-effective in LMIC settings, such as Uganda. Even under conservative assumptions regarding coverage level, frequency, target age range, and delivery costs, our analysis shows a campaign strategy has the potential to not only provide greater health benefits but also be cost-effective compared with routine one-dose or two-dose vaccination. The health and economic impact increases with greater campaign frequency and/or wider target age range. Although the effectiveness of vaccinating older women remains uncertain, we show that even lower vaccine efficacy or shorter duration of protection results in campaign strategies that are effective and cost-effective. This analysis can help to inform HPV vaccine introduction strategies in LMICs, and can serve to elucidate the potential impact of campaign delivery.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funder of the study had no role in study design, or data collection, analysis, or interpretation. The funders were given the opportunity to review this paper prior to publication, but the final decision on the content of the publication was taken by the authors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Portnoy
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