Choosing the optimal HPV vaccine: The health impact and economic value of the nonavalent and bivalent HPV vaccines in 48 Gavi-eligible countries

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Abstract
The human papillomavirus (HPV) vaccines may provide some level of cross-protection against high-risk HPV genotypes not directly targeted by the vaccines. We evaluated the long-term health and economic impacts of routine HPV vaccination using either the nonavalent HPV vaccine or the bivalent HPV vaccine in the context of 48 Gavi-eligible countries. We used a multi-modeling approach to compare the bivalent with or without cross-protection and the nonavalent HPV vaccine. The optimal, that is, most cost-effective, vaccine was the vaccine with an incremental cost-effectiveness ratio below the per-capita gross domestic product (GDP) for each country. By 2100 and assuming 70% HPV vaccination coverage, a bivalent vaccine without cross-protection, a bivalent vaccine with favorable cross-protection and the nonavalent vaccine were projected to avert 14.9, 17.2 and 18.5 million cumulative cases of cervical cancer across all 48 Gavi-eligible countries, respectively. The relative value of the bivalent vaccine compared to the nonavalent vaccine increased assuming a bivalent vaccine conferred high cross-protection. For example, assuming a cost-effectiveness threshold of per-capita GDP, the nonavalent vaccine was optimal in 83% (n = 40) of countries if the bivalent vaccine did not confer cross-protection; however, the proportion of countries decreased to 63% (n = 30) if the bivalent vaccine conferred high cross-protection. For lower cost-effectiveness thresholds, the bivalent vaccine was optimal in a greater proportion of countries, under both cross-protection assumptions. Although the nonavalent vaccine is projected to avert more cases of cervical cancer, the bivalent vaccine with favorable cross-protection can prevent a considerable number of cases and would be considered a high-value vaccine for many Gavi-eligible countries.

KEYWORDS
cervical cancer, human papillomavirus, low- and middle-income countries, vaccines

Abbreviations: CIN, cervical intraepithelial neoplasia; DALY, disability-adjusted life years; GDP, gross domestic product; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; ICER, incremental cost-effectiveness ratio; LMIC, low- and middle-income countries; MAC, multi-age cohort; WHO, World Health Organization.

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1 | INTRODUCTION

Persistent infections with high-risk human papillomavirus (hrHPV), primarily HPV genotypes 16 and 18, cause nearly all cervical cancer cases worldwide.1 Globally, cervical cancer is the fourth most common cancer among women, but the burden lies disproportionately in low- and middle-income countries (LMICs), where nearly nine out of every 10 cervical cancer deaths occur.2 The World Health Organization (WHO) recommends two-dose prophylactic HPV vaccination for young girls aged 9 to 14 years, with completion prior to initiation of sexual activity.3

Three prophylactic HPV vaccines, targeting either two or seven hrHPV genotypes, are currently available. The bivalent and quadrivalent HPV vaccines target HPV-16 and HPV-18, which cause approximately 70% of cervical cancers worldwide, while the nonavalent vaccine targets seven high-risk HPV genotypes (HPV-16/18/31/33/45/52/58), which cause approximately 90% of cervical cancer cases worldwide.3 The quadrivalent and nonavalent HPV vaccines also protect against two low-risk HPV genotypes (HPV-6 and HPV-11), responsible for approximately 90% of genital warts. All three HPV vaccines confer high protection against vaccine-targeted HPV genotypes,5-9 but there is growing evidence from vaccine trials and postimplementation evaluations that suggest the bivalent and quadrivalent vaccines may provide some additional level of cross-protection against high-risk HPV genotypes not directly targeted by the vaccines. However, the level of cross-protection varies with vaccine type, HPV genotype and study.10-13 In particular, the bivalent vaccine has demonstrated greater cross-protection than the quadrivalent vaccine,10 primarily against HPV-31, HPV-33 and HPV-45, which account for approximately 13% of cervical cancer cases. In contrast, the five additional HPV genotypes directly protected by the nonavalent vaccine (HPV-31/33/45/52/58) account for approximately 18% of cervical cancers. The duration of cross-protective efficacy is uncertain,10 but has been documented up to six13 and seven years.12

Previous cost-effectiveness analyses, performed solely in high-income countries, have generally concluded that the nonavalent HPV vaccine confers enough additional benefit to warrant a higher price compared to the bivalent and quadrivalent HPV vaccines.14-16 However, these studies have not: (a) considered the most recent evidence on the bivalent cross-protection; (b) evaluated the cost-effectiveness in low-income countries eligible for funding from Gavi, the Vaccine Alliance; or (c) used Gavi-negotiated vaccine prices. Our objective was to evaluate the long-term health and economic impacts of routine HPV vaccination using either the nonavalent or the bivalent HPV vaccines with alternative cross-protective assumptions in the context of 48 Gavi-eligible countries.

2 | METHODS

2.1 | Analytic overview

We used a multiple modeling approach that captures HPV transmission, cervical carcinogenesis and population demographics to project long-term population health and economic outcomes associated with implementation of a WHO-recommended vaccination program with either the bivalent or the nonavalent HPV vaccines in 48 Gavi-eligible countries. Economic outcomes included the cost of a 100-year vaccine program (including dosage and delivery costs) and cervical cancer costs (2015 US Dollar [$]). Cancer costs reflect all costs related to treatment of cervical cancer, including women's time and transportation for receiving cancer treatment. Health outcomes included the number of cervical cancer cases and disability-adjusted life years (DALYs). Costs and DALYs were discounted at 3% per year. Model outcomes were aggregated over multiple birth cohorts to capture the lifetime costs and benefits of women born prior to 2120. HPV vaccination scenarios assumed routine vaccination of 9-year-old girls that continued indefinitely and a temporary 1-year multi-age cohort (MAC) program for girls aged 10 to 14 years. Model projections and cost-effectiveness results from the 48 Gavi-eligible countries were reported aggregately as well as for each country individually.

We calculated the incremental cost-effectiveness ratio (ICER) defined as the additional cost of a particular strategy divided by the additional health benefits (ie, DALYs averted). Strategies that were either more costly and less effective (dominated), or less costly and less cost-effective (extended dominated), than an alternative strategy was considered inefficient and removed from further consideration. Remaining strategies were identified as efficient, and those with an ICER below a cost-effectiveness threshold of per-capita gross domestic product (GDP; 2015$) for each country were considered cost-effective. To reflect the lack of consensus around a single cost-effectiveness threshold, we considered additional thresholds that were higher (ie, three times the per-capita GDP), lower (ie, 0.5 times the per-capita GDP) and very low (ie, the WHO’s universal “Best Buy” threshold of $100 per DALY averted).

2.2 | Simulation models

As previously described,17 our multiple modeling approaches involve the linkage of a dynamic transmission model of HPV
transmission (Harvard-HPV), an individual-based model of cervical carcinogenesis (Harvard-CC) and a companion multi-country population model (Harvard-Scale Up) to project the population health and economic consequences for alternative HPV vaccination scenarios over time. For the current analysis, we expanded our single-country analysis performed in Uganda\textsuperscript{17} to capture the potential vaccination impacts among women in all 48 LMICs eligible for Gavi funding in 2018. As both the Harvard-HPV and Harvard-CC models require highly-detailed data on sexual behavior and cervical cancer epidemiology that are limited in most Gavi-eligible countries, we relied on a mapping process to extend the existing, calibrated Harvard-HPV and Harvard-CC models to project the burden of cervical cancer under alternative HPV vaccination scenarios in each of the individual 48 Gavi-eligible countries (Supporting Information Section S1).

First, we adapted Harvard-HPV, an individual (ie, agent-based) model that includes seven independent hrHPV genotypes (HPV-16/18/31/33/45/52/58) to reflect two distinct sexual mixing behavior patterns. Inputs for each setting generally varied by the number and duration of heterosexual partnerships, and assortativeness by age and sexual activity category (Supporting Information Section S1a). For each sexual mixing behavior profile, we projected reductions in HPV incidence (including herd protection) by genotype and age over time associated with the HPV vaccination scenarios, which served as inputs into Harvard-CC.

Similar to Harvard-HPV, we adapted Harvard-CC,\textsuperscript{17,18} an individual-based model that tracks women from age 9 years as they transition through cervical cancer-related health states until death, to reflect four different LMIC cervical cancer epidemiological profiles (Supporting Information Section S1b).\textsuperscript{19–23} Using trends in age- and genotype-specific HPV prevalence, we mapped the two sexual mixing behavior settings to one of the four epidemiological profiles. The four epidemiological profiles primarily varied by HPV incidence, the duration of high-grade precancerous lesions (defined as cervical intraepithelial neoplasia grade 2 [CIN2] and grade 3 [CIN3]), the degree of HPV natural immunity, the history of prior HPV infection(s) and cervical cancer incidence. For each epidemiologic profile, we projected reductions in cervical cancer incidence by age over time for each of the HPV vaccination scenarios, which served as inputs into Harvard-Scale Up.

Finally, Harvard-Scale Up, a multi-cohort Excel-based companion model that accounts for changes in demographics (eg, population size) over time, captures important country- and region-specific variations in each of the 48 Gavi-eligible countries. Harvard-Scale Up reflects baseline cervical cancer cases from Globocan 2012 that are adjusted for the proportion of HPV-16/18 genotype distribution by geographic region\textsuperscript{24} or HPV-16/18/31/33/45/52/58 genotype distribution (ie, 90%), as well as population growth over time using the 2017 United Nations population projections.\textsuperscript{25} Using trends in age-specific cervical cancer incidence, we mapped each Gavi-eligible country to one of the four epidemiological profiles reflected in Harvard-CC (Supporting Information Section S1c). Subsequently, we applied the age-specific cancer incidence reductions over time for each of the HPV vaccination scenarios to the baseline age-specific cancer incidence rates in Harvard-Scale Up.

### 2.3 Strategies and parameter inputs

We evaluated the impact of three HPV vaccination scenarios on the comparative and cost-effectiveness of the bivalent and nonavalent HPV vaccines. In scenario 1 (bivalent with no cross-protections), we assumed 100% vaccine efficacy against vaccine-targeted HPV genotypes HPV-16 and HPV-18 with zero cross-protection against other hrHPV types, consistent with per-protocol cohorts in clinical trials.\textsuperscript{26} In Scenario 2 (bivalent with high cross-protection), we assumed favorable cross-protective efficacy against HPV-31 (93.8%), HPV-33 (79.1%) and HPV-45 (82.6%) based on data recently reported from Scotland.\textsuperscript{12} In Scenario 3 (nonavalent vaccine), we assumed 100% vaccine efficacy against HPV-16 and HPV-18 and 96% vaccine efficacy against the five additional vaccine-targeted HPV genotypes (HPV-31/33/45/52/58), consistent with the phase III study.\textsuperscript{27} According to WHO recommendations, we assumed all vaccine recipients received two doses, which was assumed to protect over the lifetime. All vaccine analyses assumed 70% coverage for a routine vaccination program of all girls aged 9 years, and a temporary 1-year MAC program for girls aged 10 to 14 years.

DALYs were calculated assuming a stage-weighted disability weight of 0.303 for invasive cancer\textsuperscript{28} based on the Global Burden of Disease study. Based on Gavi’s negotiated vaccine prices reported in the detailed product profiles,\textsuperscript{29} we assumed an HPV vaccine price per dose of $4.60 and $6.90 plus 5% wastage for the bivalent and nonavalent vaccines, respectively. In addition, we assumed a vaccine delivery cost of $3.70 per fully vaccinated girl in year one of the HPV vaccination program followed by a lower delivery cost of $1.70 per fully vaccinated girl for years 2+. Cancer costs (2015 US$) included the direct (eg, treatment) and indirect medical (eg, transportation) costs, as well as women’s time costs associated with treating invasive cervical cancer in each country. 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 (Supporting Information Section S1d).

### 3 RESULTS

#### 3.1 Cervical cancer cases

Among the 48 Gavi-eligible countries and assuming 70% HPV vaccination coverage, the nonavalent HPV vaccine averted more cervical cancer cases than the bivalent HPV vaccine regardless of the cross-protection assumption (Figure 1A). A bivalent HPV vaccine that provides only direct protection against HPV-16 and HPV-18 infections was projected to cumulatively avert over 14.9 million cases of cervical cancer compared to no HPV vaccination by the year 2100, while a bivalent HPV vaccine that provides favorable, lifelong cross-protection
against three additional HPV genotypes (HPV-31/33/45) was projected to avert an additional 2.3 million cases (ie, 17.2 million cumulative cases of cervical cancer averted compared to no HPV vaccination; Figure 1B). The nonavalent vaccine, assuming high protection against seven high-risk HPV genotypes, was projected to avert over 18.5 million cases of cervical cancer compared to no HPV vaccination.

### 3.2 | Cost-effectiveness analysis

Assuming a cost-effectiveness threshold of per-capita GDP and a bivalent vaccine that provides only direct protection against HPV-16 and HPV-18 infections, we found that the nonavalent vaccine was optimal (ie, ICER below the cost-effectiveness threshold) in 83%
(n = 40) of the Gavi-eligible countries, while the bivalent vaccine was optimal in the remaining 17% (n = 8) of countries (Figure 2A; Supporting Information Section S2). When we assumed the bivalent vaccine provided favorable, lifelong cross-protection, the value of bivalent vaccine increased; subsequently, the nonavalent was considered the optimal vaccine in fewer (ie, 63%, n = 30) Gavi-eligible countries, while the bivalent vaccine was optimal in the remaining 38% (n = 18) of the Gavi-eligible countries (Figures 2B; Supporting Information Section S2).

Compared to a per-capita GDP threshold, at a very high cost-effectiveness threshold assumption of three times per-capita GDP, we found that the nonavalent vaccine was considered good-value-for-money in nearly all 48 Gavi-eligible countries, regardless of assumptions about bivalent cross-protection (Figure 3; Supporting Information Section S2). When we assumed the bivalent vaccine did not provide cross-protection at low (0.5 times per-capita GDP) and very-low (universal “Best Buy” threshold of $100 per DALY averted) cost-effectiveness thresholds, the nonavalent was optimal in 71% (n = 34) and 52% (n = 25) of the Gavi-eligible countries, respectively (Figure 3A). At the very-low universal threshold, there were seven Gavi-eligible countries where introducing an HPV vaccination program with either vaccine was not cost-effective, as the ICERs of the bivalent and nonavalent vaccines exceeded the “Best Buy” threshold. The cost-effectiveness threshold had a bigger effect when we assumed the bivalent vaccine had high cross-protection (Figure 3B). For example, at a very low universal “Best Buy” threshold of $100 per DALY averted and assuming favorable cross-protection of the bivalent vaccine, the bivalent vaccine was optimal in 75% (n = 36) of the Gavi-eligible countries and the nonavalent vaccine remained optimal in only 10% (n = 5) of the Gavi-eligible countries.

4 | DISCUSSION

Using a model-based approach that incorporates HPV transmission dynamics, cervical cancer disease natural history and population
demographics, we found that HPV vaccination with a bivalent vaccine assuming favorable cross-protection would prevent nearly 2.3 million additional cases of cervical cancer over 80 years in 48 Gavi-eligible countries compared to a bivalent vaccine without cross-protection. The relative cost-effectiveness of the HPV vaccines was highly dependent on whether the bivalent HPV vaccine provided long-standing cross-protection and the choice of cost-effectiveness threshold. Without cross-protection for the bivalent vaccine, it was very cost-effective for nearly all Gavi-eligible countries to opt for the nonavalent vaccine, but with favorable cross-protection, the bivalent vaccine was optimal in 38% (n = 18) of the Gavi-eligible countries, assuming the per-capita GDP threshold. At lower cost-effectiveness thresholds, the bivalent vaccine was optimal in a greater number of countries. Notably, if the cost-effectiveness threshold increased to three times per-capita gross domestic product (GDP), one times per-capita GDP, 0.5 times per-capita GDP and a universal “Best Buy” $100 per disability-adjusted life year (DALY) averted.

To the best of our knowledge, this is the first analysis to project the health and economic tradeoffs associated with using either the nonavalent HPV vaccine or the bivalent HPV vaccine that accounts for alternative cross-protective assumptions in the context of the 48 Gavi-eligible countries and includes Gavi-negotiated vaccine prices. We used the most recent analysis of vaccine protection reported for the bivalent HPV vaccine against nonvaccine targeted HPV types in Scotland.12 Although the vaccine efficacy trials9 and studies in both the Netherlands and Scotland have shown a cross-
protective effectiveness that is sustained for 6 or 7 years, a considerable uncertainty around the duration of cross-protective efficacy remains; therefore, we opted to evaluate the lower and upper bounds of the impact of cross-protection (ie, no cross-protection vs long-lasting cross-protection). As additional postimplementation studies become available, future analyses can continue to explore the potential impact of the duration of cross-protection. We did not explicitly evaluate the marginally less costly quadrivalent vaccine ($4.50 vs $4.60 per dose); however, we expect that the projected benefits and costs of a quadrivalent vaccine would be comparable to Scenario 1 (bivalent vaccine with no cross-protection), and slightly less effective than Scenario 2 (bivalent vaccine with high cross-protection), due to the lower cross-protection reported for the quadrivalent vaccine.  

Similarly, we did not evaluate reduced, single-dose HPV vaccination schedules. Although the degree and duration of vaccine protection are still unknown, we would expect our findings comparing the incremental benefits and costs of the vaccines to remain consistent—that is—assuming that reduced doses would have similar impact on the bivalent and nonavalent vaccines.

We used four alternative benchmarks for a cost-effective intervention (an estimate of the economic value of a year of healthy life), including the per-capita GDP threshold proposed by the World Health Organization's Commission on Macroeconomics in Health.30 Other benchmarks have been suggested on the grounds that the per-capita GDP threshold is too high and would lead to inefficient allocation of resources.31-33 Decision makers need to consider other policy attributes in addition to context-specific cost-effectiveness, such as affordability, feasibility and equity.

Our analysis involves several important simplifying assumptions and limitations. As data sufficient for model development exist only in a few countries of the world, we relied on a global mapping approach to extend findings from one setting (with data) to another (without data). To the extent that sexual behaviors and cervical cancer natural histories are different across settings, the projected herd protection benefits (from Harvard-HPV) and cervical cancer incidence reductions (from Harvard-CC) may not be generalizable to all 48 Gavi-eligible countries. However, each Gavi-eligible country generally showed reasonable fit to each of our epidemiological profiles (Supporting Information Section S1). We elected to include some measure of herd protection even though it required data from different settings, as initial explorations indicate that the error introduced by not including any herd protection was greater than when including herd protection under various scenarios of sexual mixing (data not shown). Exploring the implications of these assumptions is a priority for ongoing work.

The incremental benefits of the vaccines are dependent on assumptions regarding the proportion of HPV-16/18 genotypes, the genotypes additionally reached by cross-protection, and the genotypes directly targeted by the nonavalent vaccine. We assumed the contribution of HPV-16/18 genotypes in cancer were region-specific,24 but that the contribution of HPV-16/18/31/33/45/52/58 genotypes was 90% globally, regardless of geographic location. HPV genotype contributions likely vary by geographic location, but we were not able to account for greater precision due to limited data availability. In addition, we assumed that the three-dose cross-protection estimated in the Scottish registry would yield comparable protection under a reduced, extended two-dose schedule. Although uncertain, a recent Costa Rica Vaccine Trial analysis found that a one-dose regimen yielded comparable cross-protective benefits against HPV-31/33/45 as the recommended three-dose regimen for the same age group.34 We assumed that cervical cancer incidence rates were stable over the time period of the analysis, which may have under-estimated cervical cancer burden in the absence of HPV vaccination.35 We also assumed women with cervical cancer had 100% access to cancer treatment; consequently, the cost offsets from preventing cancer (and the value of preventing the cancer through vaccination) may be greater in our analysis than in practice. Finally, we evaluated the impact of the nonavalent vaccine in the context of cervical cancer. Including the incremental benefits of averting noncervical cancers may yield a marginally more attractive cost-effectiveness profile for the nonavalent vaccine. However, relative to cervical cancer, HPV-16/18 infections contribute to a greater proportion of noncervical cancers, which are protected by both vaccines. Finally, genital warts may also affect the relative value of nonavalent vaccine, as HPV-6/11 types are not included in the bivalent vaccine.

5 | CONCLUSION

Although the nonavalent HPV vaccine is projected to avert more cases of cervical cancer, the bivalent vaccine, if cross-protective efficacy is high and long-lasting, can prevent a considerable number of cases and would be considered a cost-effective vaccine for nearly half of Gavi-eligible countries. Ultimately, the type of HPV vaccine a country selects will depend on availability, feasibility, acceptability, affordability and value for money.

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CONFLICT OF INTEREST

All authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Supporting Information contained in Supplementary Material provides details on microsimulation model inputs, calibration to epidemiologic
data and calibration approach in line with good modeling practice. Access to the raw results data will be made available upon reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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