SUPPLEMENT ARTICLE

The health and economic impact of scaling cervical cancer prevention in 50 low- and lower-middle-income countries

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Abstract

Objective: To estimate the health impact, financial costs, and cost-effectiveness of scaling-up coverage of human papillomavirus (HPV) vaccination (young girls) and cervical cancer screening (women of screening age) for women in countries that will likely need donor assistance.

Methods: We used a model-based approach to synthesize population, demographic, and epidemiological data from 50 low- and lower-middle-income countries. Models were used to project the costs (US $), lifetime health impact (cervical cancer cases, deaths averted), and cost-effectiveness (US $ per disability adjusted life year [DALY] averted) of: (1) two-dose HPV-16/18 vaccination of girls aged 10 years; (2) once-in-a-lifetime screening, with treatment when needed, of women aged 35 years with either HPV DNA testing or visual inspection with acetic acid (VIA); and (3) cervical cancer treatment over a 10-year roll-out.

Results: We estimated that both HPV vaccination and screening would be very cost-effective, and a comprehensive program could avert 5.2 million cases, 3.7 million deaths, and 22.0 million DALYs over the lifetimes of the intervention cohorts for a total 10-year program cost of US $3.2 billion.

Conclusion: Investment in HPV vaccination of young girls and cervical cancer screen-and-treat programs in low- and lower-middle-income countries could avert a substantial burden of disease while providing good value for public health dollars.

KEYWORDS

Cancer screening; Cost-effectiveness analysis; HPV; HPV DNA tests; Uterine cervical neoplasms

1 | INTRODUCTION

Despite the availability of both primary and secondary prevention, an estimated 528 000 women worldwide developed cervical cancer in 2012, and 266 000 died from the disease.[1] Primary prevention is available in the form of effective prophylactic vaccines against the oncogenic human papillomavirus (HPV) genotypes that cause approximately 70% (bivalent and quadrivalent vaccines) to 90% (9-valent vaccine) of cervical cancers.[2–5] For women beyond the target age of adolescent vaccination, secondary prevention with screening can detect and treat precancerous lesions caused by oncogenic HPV before progression to invasive cancer. Yet these opportunities for prevention are not reaching women in poor countries, where 85% of the cervical cancer burden resides.

The WHO recommends HPV vaccination for girls aged 9–13 years, prior to initiation of sexual activity.[6] For screening, the WHO

recommends that cervical cancer screening programs should prioritize women aged 30–49 years, as the risk of cervical cancer rises after age 30 years. The WHO recommendations note that setting-specific screening intervals and frequency will depend upon availability of funds and infrastructure, and that screening even once in a lifetime—with treatment if needed—is beneficial. While organized screening with Papanicolaou (Pap) testing has reduced the incidence of and mortality attributable to cervical cancer in many high-income countries, Pap testing is logistically difficult in low-resource settings. It requires costly laboratory infrastructure and multiple visits for screening, diagnosis, and treatment. Thus, where sufficient resources are available, the WHO recommends screening with HPV testing to detect oncogenic infections, with prompt linkage to treatment for women who test positive. For settings with fewer resources, visual inspection with acetic acid (VIA)—a less sensitive but low-cost test that involves application of acetic acid (vinegar) to the cervix to detect abnormalities, yielding an immediate result—is recommended, and can be followed by same-day treatment with cryotherapy, to destroy precancerous lesions by freezing.

Due to high vaccine prices and the logistical challenges of delivering an adolescent vaccine, roll-out of HPV vaccination programs has been slow in the settings where it is needed most. In low- and lower-middle-income countries, where 56% of the global burden of cervical cancer resides, only 1.0% and 0.1%, respectively, of females aged 10–20 years had been vaccinated as of October 2014.[7] Momentum appears to be increasing as Gavi, The Vaccine Alliance—an international public–private partnership aiming to improve access to new and underused vaccines in 54 eligible countries[8]—began accepting applications for HPV vaccines support in 2012. Gavi has since negotiated a vaccine price of US $4.50 per dose for eligible countries,[9] and 27 countries have been approved for HPV vaccine demonstration projects.[10] In addition, the Gavi-eligible countries of Lesotho, Rwanda, and Uganda have initiated national HPV vaccination programs.[11]

Scale-up of cervical cancer screening programs in low- and lower-middle-income countries has not, to date, experienced the same forward momentum as vaccination. There is only a handful of HPV testing demonstration projects, and no fully scaled national programs in low-resource settings.[12] While more low- and lower-middle-income countries have introduced VIA pilot programs or include VIA in national guidelines, coverage remains low.[13]

To evaluate any policy intervention, decision makers require information on feasibility, acceptability, financing, and value for money. At this critical juncture for cervical cancer prevention efforts, we sought to provide information to those making immunization and screening policy recommendations, including the WHO, financing mechanisms, donors, and country governments. Our objective was to estimate, for countries that will likely need donor assistance, the financial costs and cost-effectiveness of scaling-up coverage of HPV vaccination for young girls and cervical cancer screening and treatment of precancerous lesions for women of screening age. We considered vaccination and screening separately (for eligible girls and women, respectively) during a 10-year intervention period between 2017 and 2026.

2 | METHODS

2.2 | Analytic overview

We used a model-based approach to synthesize population, demographic, and epidemiological data from 50 low- and lower-middle-income (LI and LMI) countries with populations over 1 million persons and gross national income (GNI) per capita less than or equal to US $2585 (Supplementary material Tables S1 and S2); this represents the midpoint GNI per capita of the World Bank LMI country income tier,[14] and henceforth we refer to LMI countries with a GNI per capita below this midpoint as "LMI1." The Excel-based CERVIVAC model described in the next section was used to project the costs and lifetime health impact of: (1) two-dose HPV-16/18 vaccination of girls aged 10 years; (2) once-in-a-lifetime screening (with treatment if needed) of women aged 35 years with either HPV testing or VIA; and (3) cervical cancer treatment. We estimated country-specific unit cost inputs for the CERVIVAC model (including vaccine doses and service delivery; direct medical costs of screening, diagnosis, and treatment of precancer; and direct medical costs of cervical cancer treatment by stage) from the literature, using previously described methods.[15] We estimated country-specific epidemiologic data inputs on burden of HPV, precancer, and cervical cancer by applying previously described methods,[15] using: (1) multivariate regression models to predict country- and age-specific HPV prevalence (Supplementary material Table S3)[15]; (2) a peer-reviewed individual-based microsimulation model that was previously calibrated to four separate low- and lower-middle-income countries (El Salvador, India, Nicaragua, and Uganda)[16–18] to predict country-specific prevalence of precancer[15]; and (3) GLOBOCAN 2012 to inform country- and age-specific cervical cancer incidence and mortality (Supplementary material Tables S4 and S5).[1] To estimate the effectiveness of HPV-16/18 vaccination, we relied on vaccine trial data and epidemiologic data on the proportion of cervical cancers attributed to HPV-16/18.[5,19–21] CERVIVAC inputs pertaining to screening and treatment effectiveness were derived from the microsimulation model, which was used to estimate the reduction in age-specific cervical cancer incidence and mortality, as well as shifts in stage distribution of detected cervical cancer, associated with each screening strategy. We estimated current access to cancer treatment in each country using published literature to project cervical cancer treatment cost savings associated with each vaccination and screening scenario.[22]

The analysis was conducted from a payer perspective. The time horizon was the lifetime of birth cohorts who received either vaccination or screening based on age during the 10-year intervention period (2017–2026). Because girls aged 10 years would not be subsequently eligible for screening during the intervention period, we did not examine the impact of screening in vaccinated women. We present both undiscounted costs and future costs discounted at an annual rate of 3% in 2013 US $. Health benefits are reported as cervical cancer cases, deaths, and disability-adjusted life years (DALYs) averted; DALYs have been discounted at an annual rate of 3%. We present incremental cost-effectiveness ratios (ICERs)—as the net cost per DALY averted to account for cancer treatment offsets—separately for vaccination and
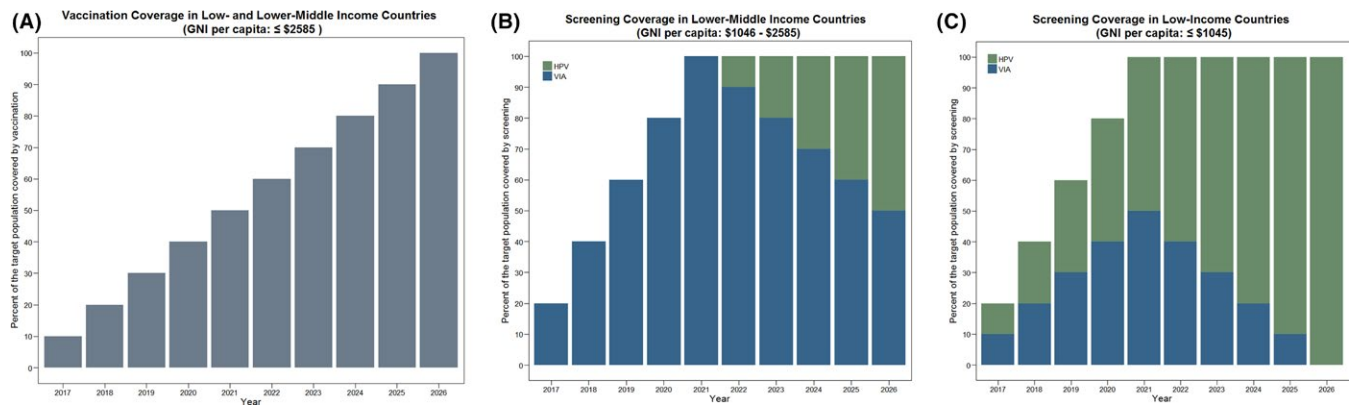
FIGURE 1 Scale-up scenarios for HPV-16/18 vaccination of young girls, aged 10 years, and once-in-a-lifetime screening of women, aged 35 years. (A) In both low- and lower-middle-income countries (with Gross National Income [GNI] per capita less than or equal to US $2585), we assumed that HPV vaccination coverage would roll out with linear increases of 10% per year during the 10-year intervention period, beginning at 10% coverage in 2017 and reaching full coverage (100%) in 2026. (B) In lower-middle-income countries (with Gross National Income [GNI] per capita between US $1046 and US $2585), we assumed that screening with both visual inspection with acetic acid (VIA) and HPV testing would roll out with linear increases of 10% per year for each test, beginning at 20% total screening coverage in 2017 and reaching full coverage (100%) in 2021. We then assumed a gradual replacement with HPV-based screening, which replaced VIA in 10% of the population in 2022 and increased linearly to cover 100% of the screening-eligible population by 2026. (C) In low-income countries (with Gross National Income [GNI] per capita less than or equal to US $1045), we assumed that screening with visual inspection with acetic acid (VIA) would roll out with linear increases of 20% per year, beginning at 20% coverage in 2017 and reaching full coverage (100%) in 2021. We then assumed a gradual replacement with HPV-based screening, which replaced VIA in 10% of the population in 2022 and increased linearly to cover 50% of the screening-eligible population by 2026. [Colour figure can be viewed at wileyonlinelibrary.com]

screening (relative to no intervention). While there is no universal criterion that defines a threshold cost-effectiveness ratio, we consider the heuristic that an intervention with an ICER less than GDP per capita is estimated to be "very cost-effective" and less than three times GDP per capita is estimated to be "cost-effective".[23]

2.2 | CERVIVAC model

The CERVIVAC model was developed for the Pan American Health Organization's ProVac Initiative (provac-toolkit.com) as a tool to enable Latin America and Caribbean country teams to conduct local cost-effectiveness analysis of cervical cancer prevention. CERVIVAC contains separate modules for evaluating the costs and effectiveness associated with HPV vaccination, screening and treatment of precancerous lesions, and cervical cancer treatment. The model, programmed using Microsoft Excel and Visual Basic for Applications 2007 (Microsoft Corporation, Redmond, WA, USA), tracks multiple birth cohorts starting at a target age (i.e. 10 years for HPV vaccination; 35 years for screening), projecting cost outcomes by counting resource utilization events and multiplying these by a country-specific unit cost.

The HPV vaccination module counts the cost of vaccine doses and service delivery costs. The screening module counts the costs of screening visits, treatment with cryotherapy, and—for women ineligible for cryotherapy—colposcopy and loop electrosurgical excision procedures (LEEP); resource utilization is driven by screening test sensitivity and specificity, HPV prevalence, and the prevalence of precancer. The cancer treatment module counts stage-specific treatment costs for local, regional, and distant cancers.

The number of females alive in each of the 50 countries, in each single year of age, was based on the 2015 United Nations World Population

Prospects.[24] Each birth cohort was tracked over its lifetime to capture health service utilization, burden of disease, and long-term health impact of vaccination and screening during the intervention period.

2.3 | HPV vaccination and cervical cancer screening strategies

Scale-up assumptions for vaccination and screening are displayed in Figure 1A–C. The health impact of vaccination was calculated based on a proportionate reduction in age-specific cancer incidence over the lifetime of the vaccinated cohorts, assuming 93% lifelong vaccine efficacy against the 70% of cervical cancers attributable to HPV-16/18,[5,19–21] with no serotype replacement and no herd immunity benefit.

The health impact of screening was based on the screening test and its performance characteristics (Supplementary material Table S6). We made the following simplifying assumptions across all countries: (1) VIA and HPV testing were followed by cryotherapy for all eligible women, which was 90% effective at treating HPV infections and underlying precancer; (2) a proportion of women who screened positive were deemed ineligible for immediate cryotherapy (5% of women with no lesion and 25% of women with cervical intraepithelial neoplasia (CIN) 2/3) and required a colposcopy and biopsy; (3) colposcopy and biopsy had 100% sensitivity and specificity at the CIN 2+ threshold; (4) women with histologically confirmed CIN 2/3 received LEEP, which was 100% effective. To capture costs associated with screening, diagnosis, and treatment of precancer, CERVIVAC estimated the number of true positives (women with CIN 2/3 that screened positive) and the number of false positives (women with no lesion that screened positive) based on screening test performance and the prevalence of oncogenic HPV and CIN 2/3.

For each screening test, we used the microsimulation model to estimate percent reductions in age-specific cervical cancer incidence and mortality (in 5-year age groups from age 20 to age 84 years) attributable to a screening program with the features described above (e.g. treatment effectiveness, eligibility for cryotherapy, etc). Descriptions of this microsimulation model and the parameterization process (including model calibration to epidemiologic data for the development of four country-specific models reflecting the natural history of cervical cancer in El Salvador, India, Nicaragua, and Uganda) have been previously published.[16–18] In brief, we estimated baseline "prior" input values for natural history transitions using longitudinal data.[25–28] To reflect heterogeneity in age- and type-specific HPV incidence between settings, as well as natural immunity following initial infection and uncertainty in progression and regression of precancer, we set plausible ranges around these input values. We then performed repeated model simulations in the absence of any intervention, selecting a single random value from the plausible range for each uncertain parameter thereby creating a unique natural history input parameter set. For each unique parameter set, we computed a goodness-of-fit score by summing the log-likelihood of model-projected outcomes to represent the quality of fit to country-specific epidemiologic data (e.g. age-specific prevalence of oncogenic HPV; age-specific cervical cancer incidence). For the present analysis, we selected 10 input parameter sets that produced good fit to the epidemiologic data from each country to use as a form of probabilistic sensitivity analysis (Supplemental material Figures S1–S8). We averaged the percent reduction in cancer incidence and mortality across the 10 parameter sets to arrive at average values for each of the four country models. Because test performance and programmatic assumptions were identical across model simulations, there were only modest differences between countries in the percent reductions in cancer incidence and mortality attributable to screening. Thus, we assumed that the percent reductions would not be likely to vary substantially across settings with different disease burdens, so long as screening program characteristics were held constant. We averaged the percent reductions across the four calibrated microsimulation models and used these values as inputs into the CERVIVAC model. These reductions were applied to cervical cancer incidence and mortality rates and population inputs to generate the reduction in cancer cases and deaths, as well as shifts in cancer stage distribution, attributable to screening during the intervention period (Figure 2A,B; Supplementary material Tables S7 and S8).

The health impact of cervical cancer treatment was used for DALY calculations. We used country-specific access to radiation therapy infrastructure as a proxy for access to treatment at any stage, given that most women with cervical cancer present with regional cancer in the absence of organized screening.[22] For countries with no data on radiation therapy infrastructure, we assumed no current access to cancer treatment at any stage (Supplementary material Table S9). We assumed that the proportion of women with access to treatment in a country received the stage-specific standard of care based on the International Federation of Gynecology and Obstetrics (FIGO) guidelines and accordingly had 5-year relative survival rates resembling the US Surveillance, Epidemiology, and End Results Program: 92% for local, 57% for regional, and 17% for distant cancer.[28] We assumed that the proportion of women who had no access to cancer treatment had 5-year absolute survival rates based on a linear regression of survival in the IARC SurvCan database and access to radiation therapy[22,29] (65% for local, 37% for regional, and 16% for distant cancers). In a sensitivity analysis, we assumed all women with cancer had access to treatment based on the FIGO guidelines.

2.4 | Costs

All costs were converted to 2013 US $, and we assumed that intervention costs did not vary with coverage level. For vaccination, we assumed the price of $4.50 per dose for Gavi-eligible countries and the PAHO Revolving Fund Price of $8.50 per dose for the four remaining countries (Bolivia, Honduras, Republic of Moldova, and Uzbekistan). We estimated the country-specific HPV vaccine delivery cost per dose as previously described (Supplementary material Tables S10 and S11).[15] For screening-related costs, we included the country-specific direct medical costs associated with screening, diagnosis (if relevant), and treatment of precancer, as previously described (Supplementary material Tables S12–S14).[15]

Cancer treatment costs were similarly derived for each country, assuming stage-specific treatment protocols based on FIGO guidelines (Supplementary material Tables S15 and S16).

3 | RESULTS

3.1 | Health impact

The aggregated health impact of HPV vaccination of 10-year-old girls and cervical cancer screening of women aged 35 years over a 10-year

FIGURE 2 Model-based approach to quantifying the health and economic impact of HPV vaccination (young girls aged 10 years) and cervical cancer screening (women aged 35 years). (A) To estimate the health and economic impact of HPV vaccination, we used the CERVIVAC vaccination module. CERVIVAC is an Excel-based population model that integrates disease burden and population statistics; the vaccination module estimates the impact of HPV vaccination based on country-specific vaccination costs, cancer costs, vaccine efficacy, type distribution of HPV-16/18 in cancer, and cancer incidence and mortality. (B) To estimate the health and economic impact of cervical cancer screening, we used an individual-based microsimulation model of HPV infection and cervical carcinogenesis calibrated to four low- and lower-middle-income country settings. The microsimulation model reflects transitions between health states based on HPV genotype, age, duration of HPV infection and precancer, and history of prior infection. Outputs of the microsimulation model include cancer incidence and mortality reduction by age and cancer stage distribution at detection. We used these outputs to inform the CERVIVAC screening module, which estimates the impact of screening based on country-specific screening and treatment costs, cancer costs, screening test performance, prevalence of HPV and precancer, and cancer incidence and mortality. [Colour figure can be viewed at wileyonlinelibrary.com]

(A)

CERVIVAC Model: Vaccination Module

List below is a lookup so do not change

Total scenarios included in batch: 50

Inputs:
- Vaccine efficacy
- Proportion of cervical cancer attributable to HPV-16/18

Space to organise country groupings		Country scenario included in batch:		
Country group	Country name	Country name	Vaccine cov	Target age
Low-income	Afghanistan	Bolivia (Plurinational State of)	50%	10
Low-income	Bangladesh	Cameroon	50%	10
Low-income	Benin	Côte d'Ivoire	50%	10
Low-income	Burkina Faso	Ghana	50%	10
Low-income	Burundi	Honduras	50%	10
Low-income	Cambodia	India	50%	10
Low-income	Central African Republic	Lao People's Democratic Republic	50%	10
Low-income	Chad	Lesotho	50%	10
Low-income	Democratic Republic of the Congo	Mauritania	50%	10
Low-income	Eritrea	Nicaragua	50%	10
Low-income	Ethiopia	Pakistan	50%	10
Low-income	Gambia	Papua New Guinea	50%	10
Low-income	Guinea	Republic of Moldova	50%	10
Low-income	Guinea-Bissau	Senegal	50%	10
Low-income	Haiti	Sudan	50%	10
Low-income	Kenya	Uzbekistan	50%	10

– Population-based.
– Scales up vaccination impact to demographic projections.
– Integrates disease burden and population statistics.
– Outputs include country-specific cancer costs, cases, deaths, and DALYs.

(B)

Microsimulation Model

Cervical Cancer

CIN 2   CIN 3

HPV Infection

No HPV Infection
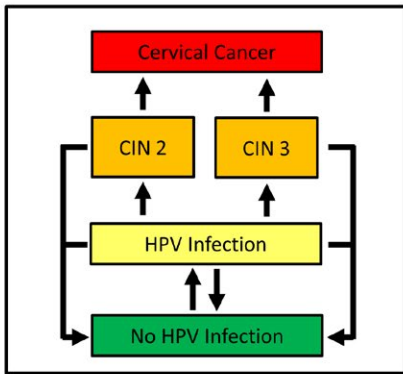
Inputs:
- Cancer reduction by age
- Cancer stage distribution

CERVIVAC Model: Screening/Cancer Treatment Modules

– Individual-based.
– Simulates HPV progression to precancer and invasive cancer.
– Calibrated to reflect country-specific HPV and cervical cancer in India, El Salvador, Nicaragua, Uganda.
– Transitions between health states based on HPV type, age, duration of HPV infection and precancer, and history of prior infection.
– Outputs health benefits associated with screening.

– Population-based.
– Scales up screening impact to demographic projections.
– Integrates disease burden and population statistics.
– Outputs include country-specific costs, cancer cases, deaths, and DALYs.

TABLE 1 Costs, health outcomes, and cost-effectiveness of HPV vaccination of 10-year-old girls and cervical cancer screening for women aged 35 years (2017–2026) in 50 low- and lower-middle-income countries.[a]

Income tier	Number eligible (millions)	Number reached (millions)	Program cost (millions) U	Program cost (millions) D	CCTx cost averted (millions) D	CCTx cost as % of program cost	Net cost (program -CCTx averted) (millions)	Cases averted (thousands) U	Deaths averted (thousands) U	DALYs averted (millions) D	Program cost per woman reached U	Program cost per case averted U	Program cost per death averted U	Program Cost per DALY Averted D	Net Cost per DALY Averted D
Vaccine															
LI	112	63	$768	$643	$15	2%	$628	1732	1318	5.0	$12.14	$443	$583	$129	$126
LMI1	181	100	$1538	$1291	$222	17%	$1069	1563	1099	4.5	$15.42	$984	$1399	$287	$238
Total	293	163	$2306	$1934	$237	12%	$1697	3295	2417	9.5	$14.15	$700	$954	$204	$179
Screening															
LI	61	50	$247	$207	$15	7%	$192	551	446	3.9	$4.95	$448	$553	$52	$49
LMI1	148	120	$1265	$1072	$466	43%	$606	1312	880	8.6	$10.51	$964	$1437	$124	$70
Total	209	170	$1512	$1279	$481	38%	$799	1863	1326	12.6	$8.88	$811	$1140	$102	$64
Combined															
LI	173	113	$1014	$850	$29	3%	$821	2283	1764	8.9	$8.97	$444	$575	$95	$92
LMI1	329	220	$2803	$2363	$688	29%	$1675	2875	1979	13.1	$12.74	$975	$1416	$180	$128
Total	502	333	$3817	$3213	$717	22%	$2496	5158	3743	22.0	$11.46	$740	$1020	$146	$113

Abbreviations: CCTx, Cervical cancer treatment; D, Discounted at a rate of 3% per year; DALY, disability adjusted life year; LI, low-income countries (Gross National Income [GNI] per capita <$1045); LMI1, lower-middle income countries tier 1 (GNI per capita $1046–$2585)[14]; U, undiscounted.

[a]Screening includes treatment of any women with precancerous lesions eligible for cryotherapy or loop electrosurgical excision surgery.

Total Program Cost, by Technology Type (Undiscounted)
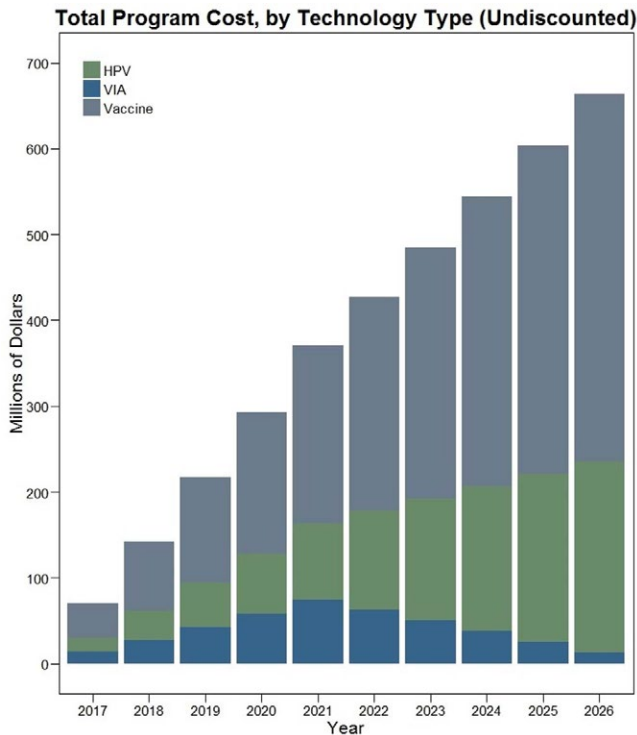
FIGURE 3 Total program costs for HPV vaccination of young girls aged 10 years and once-in-a-lifetime screening of women aged 35 years, 2017–2026. [Colour figure can be viewed at wileyonlinelibrary.com]

intervention period (2017–2026) is presented in Table 1 for all 50 countries considered; results are also presented separately for India in Supplemental material Table S17. An HPV vaccination targeting young girls and scaling up at a rate of 10% per year would reach an estimated 163 million girls in low-income and lower-middle-income tier 1 countries. HPV vaccination during a 10-year intervention period would avert an estimated 3.3 million cervical cancer cases, 2.4 million deaths, and 9.5 million DALYs over the lifetimes of the vaccinated cohorts.

A screening program reaching full scale within the first 5 years of the intervention period would reach an estimated 170 million women. Screening efforts during a 10-year intervention period would avert an estimated 1.9 million cervical cancer cases, 1.3 million deaths, and 12.6 million DALYs over the lifetimes of the screened cohorts.

3.2 | Cost and cost-effectiveness

Total costs for the HPV vaccination program and cervical cancer screening program, by year, are displayed in Figure 3. The total cost of the HPV vaccination program rolling out coverage at a rate of 10% per year was an estimated US $1.93 billion (discounted) over the intervention period. Due to the limited availability of cancer treatment, particularly in low-income countries, cervical cancer treatment offsets were relatively small, particularly in low-income countries; US $237 million in cervical cancer treatment costs were averted. As a result, the net

cost of an HPV vaccination program remained high at US $1.70 billion. The program cost per vaccinated girl was US $14.15 (undiscounted), while the net cost per DALY averted was US $179 (discounted).

The total cost of a screening program for women aged 35 years, reaching full coverage during the first 5 years of the intervention period, was US $1.28 billion (discounted). Cancer treatment offsets were approximately 38% of total program costs; the net cost of the screening program was US $799 million. The program cost per woman reached was US $8.88, and the net cost per DALY averted was US $64.

While we report the aggregated results across all countries in each income tier, the ICER for HPV vaccination was below country per capita GDP in all but one country, and the ICER for screening was below country per capita GDP in all countries. Thus, both HPV vaccination of young girls and cervical cancer screen-and-treat programs for women aged 35 years were estimated to be very cost-effective.

The results from the sensitivity analysis in which we assumed full access to cancer treatment are presented in Supplementary material Table S18. As more cancer treatment costs were averted, the net cost per DALY averted from HPV vaccination became more attractive. The net cost associated with screening became negative, as the screening program costs were lower than the cancer treatment costs averted. As a result, the net cost per DALY averted from a screening program was cost saving.

4 | DISCUSSION

To our knowledge, this study provides the first comprehensive estimate of the cost and health impact of cervical cancer prevention in low- and lower-middle-income countries, including HPV vaccination of young girls and once-in-a-lifetime screening and treatment of pre-cancer for women of screening age. We found that both HPV vaccination and screening once in a lifetime were very cost-effective, and a comprehensive program could avert 5.2 million cases, 3.7 million deaths, and 22.0 million DALYs over the lifetimes of the intervention cohorts for a total 10-year program cost of US $3.2 billion (discounted). We note that the program cost per woman reached was higher for vaccination than for screening because the cost of two vaccine doses and the delivery cost per dose tended to be higher than the cost of screening with either VIA or HPV testing. While vaccination averted more cervical cancer cases and deaths than screening over the lifetime of the intervention cohorts (despite a slower roll-out for vaccination), DALYs averted were higher with screening owing to stage shifts in cancer detection that lead to fewer years lived with disability (YLD).

Other studies have examined the cost-effectiveness of HPV vaccination in Gavi-eligible countries and low- and middle-income countries (LMICs).[30,31] Our estimate that HPV-16/18 vaccination is very cost-effective, with a cost per DALY less than GDP per capita, is consistent with the published literature. Analyses will need to be contextualized to individual countries—with setting-specific costs, screening algorithms, and roll-out scenarios—for local decision making. While we are not aware of other studies that have estimated the health and

economic impact of cervical cancer screening aggregated across countries in LMICs, a modeling study found Pap testing and VIA to be very cost-effective in the WHO sub-regions of Sub-Saharan Africa (AfrE) and South East Asia (SearD).[32] Country-contextualized analyses have found a two-visit screen-and-treat approach, with *care*HPV testing (Qiagen, Gaithersburg, MD, USA; a lower-cost HPV DNA test), to be very cost-effective, yielding greater health benefits and a better value for public health dollars than VIA or Pap.[17,18]

There are several limitations to this analysis. In the absence of data on future disease trends, we assumed GLOBOCAN estimates of cervical cancer incidence and mortality were stable over the lifetimes of girls aged 10 years and women aged 35 years during the intervention period. We relied upon extrapolation techniques to estimate country-specific epidemiologic and cost data. The country-specific unit costs were extrapolated from primary data, and it was not always possible to parse the financial versus the opportunity costs from the multiple primary data sources used; we assumed these generally represented financial costs. We assumed the four countries that were not eligible for support from Gavi would be able to procure the HPV vaccine at a price similar to that of the PAHO Revolving Fund, which may not be true for the two that are not PAHO member states. We also did not explicitly consider HIV burden in this analysis. Our estimates of vaccine impact do not account for indirect protection due to herd immunity among unvaccinated girls, and thus may underestimate the health benefits of HPV vaccination. To account for herd immunity benefits, HPV transmission models informed by sexual behavior data are needed. We have not explored the impact of varying coverage, vaccine efficacy, screening test performance, or visit compliance here, but have described elsewhere the importance of these parameters in estimating the cost-effectiveness of cervical cancer prevention.[33,34]

While our assumption of scale-up to 100% coverage of the target populations and perfect compliance with vaccination or screening are not realistic, we believe the estimates of cost and health impact represent an upper bound on the required financial outlays (from a payer's perspective) for cervical cancer prevention in LMICs. A societal perspective would be needed to capture all costs regardless of payer, including women's costs for time and transportation, which can be substantial in low-resource settings.[35] Due to lack of data, we have not included programmatic costs for infrastructural improvements, which may be substantial. By not including these important societal costs, we are likely underestimating the economic costs of cervical cancer prevention. On the other hand, because we assumed cancer treatment was based on estimated current access to cancer care in each country—which is low in nearly all of the countries considered—we underestimated cancer treatment offsets in the base case; in sensitivity analysis, ICERs decreased (i.e. became more attractive) when we assumed all women with cancer had access to the standard of care. Furthermore, household and productivity losses attributable to cervical cancer are likely sizable but very difficult to quantify. Finally, we did not assess the relative cost-effectiveness of all possible screening tests, so results cannot be used to identify the optimal test.

In 2015, US $36.4 billion in development assistance for health was disbursed.[36] Of this, US $10.8 billion was for HIV/AIDS, US $6.5 billion was for child and newborn health, and US $3.6 billion was for maternal health. While development assistance for health has increased markedly since 2000,[36] cancer prevention and treatment in LMICs has been underfunded, resulting in an estimated 5% of global cancer resources spent in countries hosting 80% of the global cancer burden.[37] We estimate that HPV vaccination of young girls and once-in-a-lifetime screening of women aged 35 years will cost approximately US $664 million per year at full scale in 50 low- and lower-middle-income countries. Both HPV vaccination and cervical cancer screening with treatment when needed provide very good value for public health dollars. Importantly, while HPV vaccination may avert more cases and deaths than screening at comparable coverage levels, the benefits of vaccination will not be realized for decades to come. Comprehensive cervical cancer prevention will require both HPV vaccination *and* screening for the foreseeable future. These interventions provide opportunities to improve primary healthcare systems and reduce cancer disparities. In presenting estimates of the costs and health benefits associated with HPV vaccination and cervical cancer screening in the countries with the highest burden and the least access to prevention opportunities, we aim to provide decision makers with information to address health disparities and efficiently allocate resources.

AUTHOR CONTRIBUTIONS

NC contributed to the design, planning, and conduct of the study; analyzed data; and drafted the manuscript. MS contributed to study design, data analysis, and manuscript revisions. AC contributed to data analysis, programming of the CERVIVAC model, and manuscript revisions. KL contributed to planning of the study, data analysis, and manuscript revisions. FG analyzed data and contributed to manuscript revisions. CR analyzed data and contributed to manuscript revisions. JK contributed to the design and planning of the study, and manuscript revisions. SR contributed to the design, planning, and conduct of the study; analyzed data; and drafted the manuscript.

CONFLICTS OF INTERESTS

NC, MS, AC, KL, FG, CR, JK, and SR declare support from the American Cancer Society for the submitted work. The CERVIVAC model was developed in collaboration with the Pan American Health Organization ProVac Initiative, and inquiries regarding the model can be made to ProVac. Cost projections for individual countries are not

available, but rather are aggregated by region or income tier as documented in the text.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1. Selected model output compared with empirical data (i.e. calibration targets) on age-specific prevalence of high-risk HPV in El Salvador [15].

Figure S2. Selected model output compared with empirical data (i.e. calibration targets) on age-specific prevalence of high-risk HPV in India [29].

Figure S3. Selected model output compared with empirical data (i.e. calibration targets) on age-specific prevalence of high-risk HPV in Nicaragua [29].

Figure S4. Selected model output compared with empirical data (i.e. calibration targets) on age-specific prevalence of high-risk HPV in Uganda [29].

Figure S5. Selected model output compared with empirical data (i.e. calibration targets) on age-specific cancer incidence in El Salvador [15].

Figure S6. Selected model output compared with empirical data (i.e. calibration targets) on age-specific cancer incidence in India [29].

Figure S7. Selected model output compared with empirical data (i.e. calibration targets) on age-specific cancer incidence in Nicaragua [15].

Figure S8. Selected model output compared with empirical data (i.e. calibration targets) on age-specific cancer incidence in Uganda [29].

Table S1. Countries included in the study, by income tier [1].

Table S2. Countries included in the study, by region.

Table S3. HPV prevalence inputs, by country and age group [2].

Table S4. Cervical cancer incidence inputs, by country and age group [3].

Table S5. Cervical cancer mortality inputs, by country and age group [3].

Table S6. Screening test performance inputs.

Table S7. Reduction in age-specific cervical cancer incidence and mortality (%), by screening test and age at screening, for once-in-a-lifetime strategies (1x).

Table S8. Cancer stage distribution at detection, by screening strategy.[a]

Table S9. Country-specific access to cancer treatment [11].

Table S10. Published HPV vaccine delivery cost per dose estimates (2013 US $).[a]

Table S11. Average HPV vaccine delivery cost per dose, by income tier (2013 US $).[a]

Table S12. Screening, diagnosis, and treatment of cervical intraepithelial neoplasia: Procedures and location of service delivery.

Table S13. Primary data costs, by procedure, for screening and treatment of precancer (2013 US $).

Table S14. Average procedure cost for screening and treatment of precancer, by income tier (2013 US $).[a]

Table S15. Primary data costs, by procedure, for cancer treatment (2013 US $).

Table S16. Average stage-specific cost for cancer treatment, by income tier (2013 US $).[a]

Table S17. Costs, health outcomes, and cost-effectiveness of HPV vaccination of 10-year-old girls and cervical cancer screening for women aged 35 years (2017–2026) in India.

Table S18. Sensitivity analysis: Costs, health outcomes, and cost-effectiveness of HPV vaccination of 10-year-old girls and cervical cancer screening for women aged 35 years (2017–2026), with 100% access to cancer treatment.