Comprehensive Global Cervical Cancer Prevention

Costs and Benefits of Scaling up within a Decade

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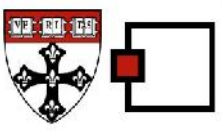

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Executive Summary

Introduction

Cervical cancer is the fourth most common cancer in women, resulting in an estimated 528,000 incident cases and 266,000 deaths worldwide in 2012 [1]. While organized and opportunistic screening programs have reduced cervical cancer incidence in high-income countries through early detection and treatment of precancerous lesions, the implementation of organized screening has not been effective in low-resource settings— where 85% of the global cervical cancer burden resides— due to the lack of health delivery infrastructure and limited financial resources.

Human papillomavirus (HPV) vaccines offer new opportunities to reduce future adverse health outcomes including deaths from cervical cancer. However, currently marketed vaccines are most effective when administered to young girls who have not yet been exposed to HPV, and, even then, only protect against the types of HPV responsible for 70% of cervical cancers. Thus, screening is still required for older cohorts, and over the lifetime of vaccinated cohorts. In 2013, Gavi, the Vaccine Alliance began providing support for HPV vaccines to eligible countries to increase access to vaccination where the disease burden is greatest [2], but few countries have achieved high coverage. Few non-Gavi middle income countries have implemented HPV vaccination at scale, in part due to high vaccine prices.

In 2015, there are nearly 50 million 10-year-old girls and more than 750 million women of screening age in low- and middle-income countries (LMIC). To provide information to those making immunization and screening policy recommendations— including the World Health Organization (WHO), financing coordination mechanisms (e.g., Gavi, the Vaccine Alliance; the Pan American Health Organization [PAHO] Revolving Fund), and potential donors— our objective was to estimate the economic and health impact of scaling up HPV vaccination and cervical cancer screening coverage for the total target population of women in low- and middle-income countries from 2015 to 2024.

Approach

We used a model-based approach to synthesize population, demographic, and epidemiological data from 102 low- and middle-income countries with populations over 1 million persons. Countries were classified into 5 income groups based derived from World Bank defined income ranges. The Excel-based CERVIVAC model, developed by the PAHO's ProVac Initiative, was used to project the costs and health impact of HPV-16/18 vaccination of young adolescent girls aged 10 years; screening of adult women aged 30 to 49 years; and cervical cancer treatment, by income tier, under various scenarios of vaccine price per dose, screening test, and screening frequency. 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 published and unpublished literature. Unit cost data were extrapolated from the original setting using an index of healthcare facility visit unit cost from WHO-CHOICE [1] to account for variation in country income. We estimated country-specific epidemiologic data inputs on burden of HPV, precancer, and cervical cancer using 1) multivariate regression models to predict country- and age-specific HPV prevalence; 2) Globocan 2012 to inform country- and age-specific cervical cancer incidence; and 3) a peer-reviewed individual-based microsimulation model that was previously calibrated to several low- and middle-income countries of interest [2-4] to predict country-specific prevalence of precancer. 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 [5-9]. CERVIVAC inputs pertaining to screening effectiveness were derived from a complex microsimulation model of cervical

cancer developed by researchers at Harvard T.H. Chan School of Public Health (HSPH) [2], 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 [10] in order to project cervical cancer treatment cost savings, as well as increased survival attributable to earlier detection, associated with each vaccination and screening scenario.

The analysis was conducted from a payer perspective. We present undiscounted costs as well as costs discounted at an annual rate of 3% in 2013 US dollars (US$). Health benefits are reported as cervical cancer cases averted, cervical cancer deaths averted, and disability-adjusted life years (DALYs) averted; DALYs have been discounted at an annual rate of 3%. We present incremental cost-effectiveness ratios (ICERs) separately for vaccination and screening (relative to no intervention). ICERs are presented as the net cost per DALY averted to account for cancer treatment offsets resulting from vaccination and screening. 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 the country's per capita gross domestic product (GDP) would be "very cost-effective" and less than three times per capita GDP would be "cost effective"[11].

Policy Alternatives

In all countries, we assumed 2-dose HPV vaccination, as recommended by the WHO [13], of girls aged 10 years. We modeled an ideally performing vaccination program in which all targeted girls are reached and accept vaccination, and there is no drop-out between doses.

Screening strategies were based on country income classification and WHO guidelines [14]. Three scenarios reflect levels of intensity (Table E1). The Minimal Intensity scenario involves screening once in a lifetime, with visual inspection with acetic acid (VIA) in the lower resource settings. The Moderate Intensity scenario assumes the same screening test according to income tier, but increases the screening frequency to every five years. The High Intensity scenario assumes screening takes place every five years, but with HPV testing in all but the Low Income (LI) countries. In the Minimal and Moderate Intensity scenarios, for countries in the lower-middle income 2 (LMI2) income tier and higher, strategies may vary by the presence of an existing cytology program if population surveys indicated more than 40% of women 15-49 had ever been screened [15, 16], to reflect the potential for continued use in countries where Pap testing is already established. In the Moderate and High intensity scenarios, we adjusted the prevalence of lesions for repeated screening. For women who screen positive, we assumed no loss-to-follow-up between visits for confirmatory diagnostic testing and/or treatment of precancer. In this way we represent a best case for program operations that would lead to upper bound health impact.

Pace of scale-up

For both vaccination and screening and preventive treatment, we considered a gradual 10-year roll-out scenario from 2015 to 2024 with steadily increasing coverage from 10% coverage in 2015 to 100% coverage of the target population in 2024. Our scenarios did not include any "catch-up" vaccination or screening. We assumed these scenarios irrespective of a country's existing program coverage, as existing levels were poorly documented and generally assumed to be very low.

Table E1. Screening strategies, by income tier.[a]

World Bank Income Tier	Income tier	Existing Cytology Program[b]	Minimal Intensity: Screening once in a lifetime	Moderate Intensity: Screening every 5 years	High Intensity: Screening every 5 years with HPV testing in MICs
Low income	Low income (LI) (< $1045)	No	VIA 1x	VIA *Q5*	VIA Q5
Lower middle income	Lower-middle income 1 (LMI1) ($1046 - $2585)	No	VIA 1x	VIA *Q5*	*HPV* Q5
	Lower-middle income 2 (LMI2) ($2586 - $4125)	No	VIA 1x	VIA *Q5*	*HPV* Q5
		Yes	PAP 1x	PAP *Q5*	*HPV* Q5
Upper middle income	Upper-middle income 1 (UMI1) ($4126 - $8435)	No	HPV 1x	HPV *Q5*	*HPV-VIA* Q5
		Yes	PAP 1x	PAP *Q5*	*HPV-VIA* Q5
	Upper-middle income 2 (UMI2) ($8436 - $12745)	No	HPV-VIA 1x	HPV-VIA *Q5*	HPV-VIA Q5
		Yes	PAP 1x	PAP *Q5*	*HPV-VIA* Q5

[a] HPV: human papillomavirus testing; HPV-VIA: HPV testing with visual inspection triage; PAP: Pap testing; VIA: visual inspection with acetic acid; 1x: Once in a lifetime at age 35 years; Q5: screening at 5 year intervals (at age 30, 35, 40, 45 years); $: 2013 US$. [b] Existing cytology programs with >40% coverage (includes Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, El Salvador, Hungary, Kazakhstan, Mexico, Paraguay, Peru, Ukraine) [15, 16]. Italics highlights what aspect of the program is different from the next least intense strategy.

Unit Costs

Vaccination unit costs were divided into two parts: vaccine doses and service delivery costs. Since the market price for HPV vaccine in non-Gavi countries is uncertain, we considered two vaccine pricing scenarios in which we varied the per-dose price of the vaccine by income tier (Table E2). We assumed Gavi-eligible countries would have access to the Gavi-negotiated prices in all years in both scenarios. Similarly, we assumed all Latin America and Caribbean (LAC) region countries and South Africa will access the PAHO Revolving Fund (RF) price in all years in both scenarios, since they currently have access to these prices. Prices for non-Gavi, non-LAC countries were based on country income tiers. Under each scenario we assumed that vaccine pricing would remain constant between 2015 and 2024, and that countries would remain in the same income tier. The base case (more favorable pricing) scenario is a two-tier scheme where all Gavi-eligible countries access Gavi price of US$4.55 per dose, all non-Gavi lower-middle income 1 (LMI1) countries access the Gavi price as well, and all non-Gavi countries in income tier LMI2 or higher access a price equal to the RF price of US$13.79 per dose. However, pricing for HPV vaccine in middle-income countries is not well established yet, as many countries are negotiating bilaterally with pharmaceutical companies. In the alternative scenario, prices for non-Gavi non-RF countries are assumed to be higher, with LMI2 countries paying 2 times the RF price (i.e., $27.58/dose) and upper-middle income (UMI) countries paying $40/dose (which is the best observed price for UMI countries in the recent Médecins Sans Frontières study of HPV vaccine cost in middle-income countries).

We identified data on HPV vaccination delivery cost per dose from the published literature and restricted estimates to economic costs, defined as the cost of all health sector resources required for service delivery regardless of payer [17-19]. All costs were converted to 2013 US$ using GDP deflators and exchange rates. We assumed that delivery costs did not vary with vaccine coverage. To extrapolate published estimates for HPV vaccine delivery costs from their original settings, accounting for variation in countries' income level, we adjusted unit costs using an index of primary healthcare visit costs from WHO-CHOICE [20].

Table E2. HPV vaccine price per dose scenarios, by income tier (2013 US$).[a]

Income tier	Base case (2 tier)	Alternative (4 tier)
Low income (LI) (< $1045)	4.55 Gavi	4.55 Gavi
Lower-middle income 1 (LMI1) ($1046 - $2585)	4.55 Gavi	13.79 PAHO RF
Lower-middle income 2 (LMI2) ($2586 - $4125)	13.79 PAHO RF	27.58 2 x PAHO RF
Upper-middle income 1 (UMI1) ($4126 - $8435)	13.79 PAHO RF	40 Best UMI price, MSF
Upper-middle income 2 (UMI2) ($8436 - $12745)	13.79 PAHO RF	40 Best UMI price, MSF

[a] Gavi: Gavi, the Vaccine Alliance; PAHO RF: Pan American Health Organization Revolving Fund; MSF: Médecins Sans Frontières; $: 2013 US$. We assumed Gavi-eligible countries would have access to the Gavi-negotiated prices in all years under all scenarios. Similarly, we assumed all Latin America and Caribbean (LAC) region countries and South Africa will access the PAHO Revolving Fund price in all years under all scenarios, because these countries have access to the PAHO Revolving Fund (though not all use it). Prices for non-Gavi, non-LAC countries were based on country income tiers.

For screening-related costs, we included direct medical costs associated with screening, diagnosis, and treatment of precancerous lesions. We assumed that screening costs were not dependent upon coverage level. To estimate the unit cost of each procedure, we identified available data from the published and unpublished literature [22-26], such that the following countries were represented by primary data: Ghana, El Salvador, India (n=3 studies), Kenya, Nicaragua, Peru, Uganda, South Africa, and Thailand. All unit costs were converted to 2013 US$ using GDP deflators and exchange rates [21]. We extrapolated costs from their original settings to other countries using the same method and WHO-CHOICE index applied to vaccine service delivery costs. Average unit costs are shown, by country income tier, in Table E3.

Table E3. Average procedure cost, by income tier (2013 US$). [a]

Income tier	VIA	Pap	HPV Test[b]	Cryotherapy	Colposcopy/biopsy	LEEP
LI[c]	1.60	NA	NA	11.39	22.74	47.72
LMI1	3.52	NA	8.52	24.99	49.87	101.64
LMI2	6.65	11.81	11.66	50.77	94.30	197.87
UMI1	11.92	21.17	16.94	84.72	169.07	354.76
UMI2[d]	19.46	34.12	24.11	137.83	285.17	565.75

[a] LI: Low Income; LMI1: Lower-middle income 1; LMI2: Lower-middle income 2; UMI1: Upper-middle income 1; UMI2: Upper-middle income 2; NA: Not applicable, as these strategies were not considered for the specified income tier. In countries for which the official exchange rate for 2013 was unavailable, we used the DEC alternative conversion rate [21]. Because 2013 GDP deflators were not available to convert WHO-CHOICE 2008 local currency unit costs to 2013 US$ in several countries, we used the 2012 GDP deflator [21].

[b] We assumed that the HPV test had a standardized tradable value of US$5, and did not apply the WHO-CHOICE facility ratios to this component of HPV screening costs.

[c] For Zimbabwe, we substituted cost data from Kenya as a proxy country, given the similarity in 2013 GNI per capita between Kenya and Zimbabwe. In Zambia in 2013, 1000 ZMK became equivalent to 1 ZMW, so we divided the official exchange rate by 1000.

[d] For Brazil, WHO-CHOICE data from 2008 suggested low procedure costs that did not fit the generally linear relationship with GNI per capita, so instead of using the average extrapolated value we used the maximum extrapolated value implied by the primary data.

In many LMICs, cancer treatment options are limited and not universally accessible. Policy scenarios did not include *expansion* of treatment programs for advanced cancer. However, we did include the treatment benefits and costs associated with currently available treatment so as to estimate health impacts and possible cost offsets to investment in prevention programs that reduce the need for spending on advanced cancer treatment. For cervical cancer treatment costs among the proportion of cases with access to cancer treatment in a given setting, we included direct medical costs associated with the stage-specific FIGO treatment protocols, assuming that cancer treatment costs were not dependent upon coverage level. We assumed that all cancer staging, treatment, palliative care, and follow-up took place at a tertiary facility. To estimate the unit cost of each procedure, we identified available data from the published literature and unpublished data from a preliminary economic analysis of Latin America such that the following countries were represented by primary data: Argentina [12], Brazil[12], Colombia [12], China [13], El Salvador [3], India [14, 15], Kenya [15], Mexico [12], Morocco [16], Peru [12, 15], South Africa [15], and Thailand [15, 17, 18]. All unit costs were converted to 2013 US$ using GDP deflators, exchange rates, and purchasing power parity conversion rates (when costs were reported in international dollars) [19]. We extrapolated costs from their original settings to other countries using the same method and WHO-CHOICE index applied to vaccine service delivery and screening costs, except that for the index we used the WHO-CHOICE average cost of a tertiary inpatient visit instead of a primary health outpatient visit. Average unit costs are shown, by country income tier, in Table E4. We assumed that cancer treatment costs only applied to the proportion of women with access to cancer treatment in a given setting; the remainder of women incurred no costs for cancer treatment.

Table E4. Average stage-specific cost for cancer treatment, by income tier (2013 US$). [a]

Income tier	Local cancer	Regional cancer	Distant cancer
LI[b]	628	887	601
LMI1	1,765	2,494	1,689
LMI2	3,780	5,369	3,636
UMI1	8,791	12,421	8,502
UMI2[c]	17,642	24,531	16,564

[a] LI: Low Income; LMI1: Lower-middle income 1; LMI2: Lower-middle income 2; UMI1: Upper-middle income 1; UMI2: Upper-middle income 2. Local cancer includes FIGO stages 1a-2a; regional cancer includes FIGO stages 2b-3b; and distant cancer includes FIGO stages 4a-4b. Because 2013 GDP deflators were not available to convert WHO-CHOICE 2008 local currency unit costs to 2013 US$ in several countries, we used the GDP deflator from the World Factbook [20].

[b] For Zimbabwe, we substituted WHO-CHOICE cost data from Kenya as a proxy country, given the similarity in 2013 GNI per capita between Kenya and Zimbabwe. In Zambia in 2013, 1000 ZMK became equivalent to 1 ZMW, so we divided the official exchange rate by 1000.

[c] For Brazil, WHO-CHOICE data from 2008 suggested low procedure costs that did not fit the generally linear relationship with GNI per capita, so instead of using the average extrapolated value we used the maximum extrapolated value implied by the primary data.

Health impact

Health outcomes included cervical cancer cases, cervical cancer deaths, and disability-adjusted life years (DALYs) averted due to HPV vaccination, screening and preventive treatment, and cancer treatment (assuming access to cancer treatment remains stable at current levels) over the lifetime of those receiving vaccine or screening in the decade 2015-2024. For HPV vaccination of 10 year old girls, we assumed health impact was equivalent to 100% coverage multiplied by 93% efficacy, with lifelong protection against 70% of cervical cancer cases (i.e., those attributable to HPV 16/18)[21]. Vaccine impact was then applied to age-specific cervical cancer incidence and mortality rates to project the number of cases, deaths, and DALYs averted. The individual-based microsimulation model of HPV infection and cervical cancer 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 test and interval considered. In the CERVIVAC model,

these incidence and mortality reductions were applied to age-specific cancer incidence and mortality rates to project the number of cervical cancer cases, deaths, and DALYs averted from each screening scenario. The microsimulation model was also used to estimate the stage distribution of cervical cancer (i.e., local, regional, or distant) associated with full coverage of each screening strategy. We estimated current access to cancer treatment in each country from the published literature [10], and among women with access to cancer treatment, we optimistically assumed 5-year survival by stage resembled 5-year relative survival rates from the U.S. Surveillance, Epidemiology, and End Results Program (92% for local, 57% for regional, and 17% for distant cancer) [22]; among women without access to treatment, 5-year survival was based on a linear regression of access and survival from registries in the IARC SurvCan database (65% local, 47% regional, and 16% distant) [23, 24]

Key Findings

This study finds that a steady effort to achieve full coverage by 2024 of a lower intensity comprehensive cervical cancer prevention program involving 2-dose HPV vaccination for all 10-year-old girls and once in a lifetime screening for older women in all low- and middle-income countries would cost US$13.6 billion over 10 years, if the favorable vaccine pricing scenario was realized. The annual outlays would increase from $232 million in 2015 to $2.6 billion in 2024 as the program reaches full scale. Of the total cost, US$8.6 billion would be for vaccination and US$5.1 billion for screening and preventive treatment, which includes primary screening tests, diagnostic testing, and treatment of precancerous lesions. (Table E5). Of the 10-year vaccination cost estimate, US$2.1 billion is for Gavi-eligible countries, and of that, US$1.4 billion is for purchase of vaccine. The discounted program cost would be $11.6 billion, and the discounted *net cost after accounting for cancer treatment cost savings* would be $7.3 billion. This investment would provide vaccine to 292 million girls (about 60% of 513 million eligible during the period) and one screening to 252 million 35-year old women. Combined, this program would prevent as many as 6.2 million cervical cancer cases and 4.3 million cervical cancer deaths over the lifetimes of the women who were reached during the decade of scale up.

The intensity of screening programs, both in terms of technology used and frequency of screening, is a major driver of screening and preventive treatment costs. The Moderate Intensity scenario which increases screening frequency to every 5 years (4 times per lifetime) increases the 10-year screening program cost from $5.0 billion to $18.1 billion. However, the High Intensity program which switches screening technology to HPV testing in all settings except the lowest income category *lowers* the 10-year cost of strategy 5-year screening interval to US$14.5 billion, primarily because of the increased use of VIA triage following a positive HPV test and the replacement of cytology with HPV-based screening. While using HPV testing instead of VIA has additional cost, using HPV testing instead of Pap saves money, so the net effect is a lower 10-year program cost for the High Intensity program that excludes the use of Pap, than for the Moderate Intensity scenario that includes Pap in 10 countries. Importantly, the high intensity screening strategy also results in greater health benefit, as HPV testing detects more precancer than VIA and Pap (Table E5).

Table E5. Total (10-year) program cost of scenarios for scaling up vaccination and screening and preventive treatment. The costs shown are undiscounted.

Program component	Scenario				Program Cost
	Description	Technology	Frequency	Target Age (Female only)	10-year Scale Up[b]
Vaccination	A (2 tier)	Gardasil or Cervarix	2 doses	10	$8.6 B
	B (4 tier)	Gardasil or Cervarix	2 doses	10	$13.1 B
Screening and preventive treatment	Minimal Intensity	VIA in LIC VIA (or PAP[a]) in LMI1,LMI2 HPV (or PAP[a]) in UMIC	1 screening per lifetime	35	$5.0 B
	Moderate Intensity	VIA in LIC, VIA (or PAP[a]) in LMIC HPV (or PAP[a]) in UMIC	Screening every 5 years	30, 35, 40, 45	$18.1 B
	High Intensity	VIA in LIC HPV or HPV-VIA in all MIC	Screening every 5 years	30, 35, 40, 45	$14.5 B

[a] HPV: human papillomavirus testing; HPV-VIA: HPV testing with visual inspection triage; LIC: low income countries; LMI: lower-middle income countries; PAP: Pap testing; UMIC: upper-middle income countries; VIA: visual inspection with acetic acid; 1x: Once in a lifetime at age 35 years; Q10: screening at 10 year intervals (at age 30, 40 years); Q5: screening at 5 year intervals (at age 30, 35, 40, 45 years); Q3: screening at 3 year intervals (at age 30, 33, 36, 39, 42, 45, 48 years); $: 2013 US$. [b] Existing cytology programs with >40% coverage (includes Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, El Salvador, Hungary, Kazakhstan, Mexico, Paraguay, Peru, Ukraine) [15, 16].

[b] Immediate roll-out is full coverage of target population in each calendar year from 2015-2024. The 10-year roll out is linearly increasing coverage from 10% in 2015 to 100% in 2024.

Vaccine price is a major driver of the overall cost of cervical cancer prevention. In our 10-year roll-out scenario, if non-Gavi LMI2 countries that were not able to participate in PAHO Revolving Fund had to pay double the PAHO RF price (i.e. 2 x 13.79 per dose), and UMI countries had to pay US$40 per dose (Vaccine Pricing Scenario B), the global price tag for vaccination would increase by over 50% for a total of US$13.1 billion over 10 years (vs. US$8.6 billion). Of course, over a longer time horizon, it is reasonable to expect vaccine prices to decline somewhat as negotiations continue, markets evolve, and more substantially as patents expire and generics enter the market. But these findings illustrate the importance of vaccine price negotiations in middle-income countries that are not Gavi-eligible.

In aggregate, across the set of 102 LMICs, both vaccination and screening provided very good value for money, as has been shown in numerous other studies. In our analysis, a vaccination program with the favorable baseline 2-tier pricing scenario will prevent 4.8 million cases and 3.3 million cervical cancer deaths over the lifetimes of the 292 million women vaccinated during the decade of program scale up (2015-2024). The program also has the benefit of averting costs associated with cervical cancer treatment. Indeed, averted treatment costs offset about 1/3 of the vaccination program cost. On average, the vaccination program would prevent a disability-adjusted life year (DALY) for a cost of $360, after accounting for the treatment cost savings (Table E5). This represented very good value – well under the benchmark of 0.5 to 1 times GDP per capita per DALY averted.

The Minimal and High Intensity screening scenarios also show good value. The Moderate Intensity program is dominated by the High Intensity program because it costs more and produces less benefit (Table E6). For this reason, the Moderate Intensity program, which included the use of Pap testing in some countries, was not

considered further, although this program also produced reasonable value when compared to no screening. As with vaccination, at least 1/3 of the cost of the program is offset by savings in treatment cost. With the Minimal Intensity program, 252 million women receive primary screening during the decade, resulting in 1.4 million cases and 968 thousand cervical cancer deaths prevented over these women's lifetimes. The cost per DALY averted is a very favorable $255. The High Intensity program's cost per DALY is $330 when compared to no screening. However, the *incremental* cost of the high intensity screening program to achieve the *incremental* benefit above and beyond the minimal screening program is $375 (ICER Calculation for High vs. Minimal: [$8.6b-$2.5b]/[26.1m-9.51m] = $375/DALY) indicating that even the intensive program in which HPV testing is used in all but low-income settings and screening is every 5 years between age 30 and 49 also appears to be very good value in comparison to GDP-based cost-effectiveness benchmarks.

Table E6. Costs, outcomes, and cost-effectiveness of each variation of vaccination and screening program component.

		Program Component Alternatives				
		Vaccination Pricing		Screening Intensity		
		2-tier	4-tier	Minimal	Moderate	High
Costs (Billions)						
Program Cost	D	$7.30	$13.60	$4.30	$15.90	$12.70
Cancer Treatment Costs AVERTED	D	$2.30	$2.30	$1.90	$4.60	$4.10
Net Cost	D	$4.90	$11.30	$2.40	$11.30	$8.60
Treatment Savings as Percentage of Program Costs	D	32%	17%	44%	29%	32%
Health Outcomes (Thousands)						
Cases Averted	U	4793	4793	1430	3292	3849
Deaths Prevented	U	3338	3338	968	2260	2605
DALYs Averted	D	13663	13663	9513	22538	26071
Cost-effectiveness						
Program Cost per Death Averted	D/U	$2,173	$4,070	$4,473	$7,023	$4,880
Net Cost per DALY Averted	D	$360	$825	$255	$500	$330[b]

[a] U = undiscounted, D = discounted. DALY = disability adjusted life year. CS = cost-saving. Net cost represents the Program Cost minus Cancer Treatment Costs Averted. Net Cost per DALY Averted is compared to no intervention. [b] Note: the ICER for High Intensity program *vs. Minimal Intensity* program is $375 per DALY averted.

Our scenarios assume ideally functioning programs in terms of precision in reaching the target population and avoiding drop-out along the care cascade. Therefore the health benefits represent a best case. It is possible that the costs to achieve best case results would be higher than we assumed. However, even if programs were 25-50% less efficient, they would still be quite good value.

Because of the gradual pace of scale-up, yearly program costs would start low in 2015, but grow to a level of about US$2.5 billion per year by 2024. This can be viewed as a rough estimate of the recurring cost of the comprehensive vaccination and screening program at full scale (not accounting for cancer treatment cost offsets which occur over the lifetimes of women reached by the program). We did not model the costs or benefits of continuing the prevention program beyond 2024, but it is likely to continue to have a similarly favorable cost-effectiveness for many years beyond 2024.

Conclusion

We found that HPV vaccination of young girls and cervical cancer screening for women aged 35 years can be provided for an average annual cost of US$2.5 billion at scale. A 10-year roll-out of HPV vaccination from 2015 to 2024 would avert as many as 4.8 million cases and 3.3 million deaths from cervical cancer over the lifetimes of vaccinated girls; a similar roll-out of a one-time cervical cancer screening for women aged 35 years would avert 1.4 million cases and 968,000 deaths from cervical cancer. Both HPV vaccination and cervical cancer screening provide very good value for public health dollars; importantly, while the health impact of screening can be observed immediately, 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 health care systems and reduce cancer disparities. We hope this study will catalyze the current policy dialogue to expediently secure necessary resources and facilitate country-level discourse on implementation of healthcare delivery strategies to rapidly scale up HPV vaccination and cervical cancer screening.

Introduction

Cervical cancer is the fourth most common cancer in women, resulting in an estimated 528,000 incident cases and 266,000 deaths worldwide in 2012 [1]. While organized and opportunistic screening programs have reduced cervical cancer incidence in high-income countries through early detection and treatment of precancerous lesions, the implementation of organized screening has not been effective in low-resource settings due to the lack of health delivery infrastructure and limited financial resources. Approximately 85% of cases and deaths occur in low- and middle-income countries (LMIC) [1], often affecting mid-adult women who are critical to social and economic stability.

New opportunities to reduce future adverse health outcomes including deaths from cervical cancer stem from two human papillomavirus (HPV) vaccines— both with high efficacy against HPV types 16 and 18 (HPV-16/18), which cause approximately 70% of cervical cancers— and point-of-care HPV-based testing designed for low-resource settings [25, 27, 28]. In 2013, Gavi, the Vaccine Alliance began providing support for HPV-16/18 vaccines to eligible countries to increase access to vaccination where the disease burden is greatest [2]. Due to reduced vaccine effectiveness in older birth cohorts who have already been exposed to HPV and the presence of oncogenic HPV types not covered by current vaccines, secondary prevention will be necessary for decades to come in order to reduce deaths attributable to cervical cancer [29]. Screening with HPV testing and visual inspection with acetic acid (VIA) have been demonstrated to be effective [30-32] and potentially cost-effective [22] in low-resource settings, allowing for fewer follow-up visits (e.g., screen-and-treat approaches) and, in the case of HPV testing, automated processing of laboratory specimens that reduces resource and quality control requirements. Moreover, the World Health Organization (WHO) has recently recommended the use of HPV testing or VIA for cervical cancer screening in those regions and countries that have not already established an effective, high-coverage Pap test based program [14].

There are nearly 50 million 10-year-old girls and more than 750 million women of screening age in LMICs today. To design and coordinate HPV vaccination and cervical cancer screening programs, decision makers must consider many attributes and outcomes associated with available prevention strategies, including: 1) feasibility, related to human resources, infrastructure, and financial capacity; 2) the likelihood of acceptability and political support; 3) health and economic impact; and 4) short- and long-term affordability.

Motivated by the need for information on financial cost requirements by those making immunization and screening policy recommendations— including the WHO, financing coordination mechanisms (e.g., Gavi, the Vaccine Alliance; the Pan American Health Organization [PAHO] Revolving Fund), and potential donors— our objective was to estimate the cost of scaling up coverage of HPV vaccination and cervical cancer screening and preventive treatment for women in low- and middle-income countries from 2015 to 2024.

Methods

Analytic overview

We used a model-based approach to synthesize population, demographic, and epidemiological data from 102 low- and middle-income countries with populations over 1 million persons. The Excel-based CERVIVAC model was used to project the costs and health impact of HPV-16/18 vaccination of young adolescent girls aged 10 years; screening of adult women aged 30 to 49 years; and cervical cancer treatment, by income tier and World Bank region, under various scenarios of vaccine price per dose, screening test, and screening frequency. 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 published and unpublished literature. Unit cost data were extrapolated from the original setting using an index of healthcare facility visits from WHO-CHOICE [1] to account for variation in country income. We estimated country-specific epidemiologic data inputs on burden of HPV, precancer, and cervical cancer using 1) multivariate regression models to predict country- and age-specific HPV prevalence;

2) Globocan 2012 to inform country- and age-specific cervical cancer incidence; and 3) a peer-reviewed individual-based microsimulation model that was previously calibrated to several low- and middle-income countries of interest [2-4] to predict country-specific prevalence of precancer. 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 [5-9]. CERVIVAC inputs pertaining to screening 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 [10] in order to project cervical cancer treatment cost savings, as well as increased survival attributable to earlier detection, associated with each vaccination and screening scenario.

The analysis was conducted from a payer perspective. We present both undiscounted costs and future costs discounted at an annual rate of 3% in 2013 US dollars (US$). Health benefits are reported as cervical cancer cases averted, cervical cancer deaths averted, and disability-adjusted life years (DALYs) averted; DALYs have been discounted at an annual rate of 3%. We present incremental cost-effectiveness ratios (ICERs) separately for vaccination and screening (relative to no intervention); ICERs are presented as the net cost per DALY averted to account for cancer treatment offsets. 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 the country's per capita gross domestic product (GDP) would be "very cost-effective" and less than three times per capita GDP would be "cost effective"[11].

We included LMIC with population size greater than 1 million persons. We excluded countries that were missing basic data (e.g., United Nations population data, gross national income [GNI] per capita, WHO CHOICE facility visit cost estimates). A list of the 102 included countries, stratified by income tier according to GNI per capita (Atlas method, 2013 US$)[19], is shown in Table S1; Lower Middle Income (LMI) and Upper Middle Income (UMI) countries have been further stratified at the midpoint GNI per capita into LMI1 and LMI2 and UMI1 and UMI2, respectively. Country stratification by world region is displayed in Table S2. The countries included in the analysis contain over 90% of the world's total LMIC population.

CERVIVAC Model

The CERVIVAC model was developed for the PAHO'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 preventive treatment, and cervical cancer treatment. The model, programmed using Microsoft© Excel and Visual Basic for Applications 2007 (Microsoft Corporation, Redmond, WA), tracks multiple birth cohorts starting at a target age (e.g., 10 years for HPV vaccination; 30 years for screening), projecting cost outcomes associated with HPV vaccination, screening and preventive treatment, and cervical cancer treatment by counting events that involve resource utilization and multiplying these events by a country-specific unit cost.

The HPV vaccination module counts the cost of vaccine products as well as service delivery costs. The screening module counts the costs of screening visits, follow-up visits in triage strategies, cryotherapy, diagnostic confirmation with colposcopy for cytology (i.e., Pap)-based strategies and for women who are not eligible for screen-and-treat cryotherapy, and loop electrosurgical excision procedures (LEEP). Resource utilization associated with screening is driven by screening test characteristics (i.e., sensitivity and specificity), HPV prevalence, and the prevalence of precancerous lesions. The cancer treatment module counts stage-specific treatment costs for local (FIGO stages 1a1 to 2a), regional (FIGO stages 2b to 3b), and distant (FIGO stages 4a and 4b) cancer.

Health outcomes are cervical cancer cases, cervical cancer deaths and disability-adjusted life years (DALYs) associated with HPV vaccination and screening and preventive treatment (relative to no vaccination or screening). For these analyses, we assumed cancer treatment access remains at current levels. None of the strategies involved scaling up of local, regional or distant cancer treatment, although this is technically possible with the CERVIVAC model.

Population and epidemiologic input data

The number of females alive in each of the 102 countries, in each single year of age, was based on the 2012 United Nations World Population Prospects [25]. Each birth cohort was then tracked over its lifetime to capture relevant health service utilization and burden of disease and the long-term impact associated with cervical cancer control programs delivering prevention services between 2015 and 2024.

To estimate HPV prevalence in countries without epidemiologic survey data, we constructed multivariate regression models using previously published methods [26]. We included the following variables in the regression models to predict HPV prevalence in countries with available data: country income classification (low, lower middle, upper middle) [19]; geographic region (Central and South America, Eastern Europe, Asia, North Africa, and sub-Saharan Africa) [19]; and age-specific cervical cancer incidence in ten-year age groups (age 25 to 34 years; age 35 to 44 years; age 45 to 54 years, age 55 to 64 years) from registry data in *Cancer in Five Continents Volume X* when available (N=99) [27]; else from Globocan 2012 (N=16) [28]). The model was restricted to LMIC to control for the impact of screening. Generalized linear modeling for proportions with binomial family and log link was employed to assess the relationship between HPV prevalence and predictor variables. Four models were created (for women age 30 to 34 years; 35 to 39 years; 40 to 44 years; and 45 to 49 years). The models were then used to predict age-specific HPV prevalence for countries without prevalence survey data. Models were examined for goodness of fit, leverage, and normality.

We adjusted countries with unusually high or low predicted HPV prevalence (relative to cancer burden) in the following manner. We calculated the regional HPV prevalence from countries with available data, as well as regional cancer incidence from registries and Globocan; if the difference between the model-predicted HPV prevalence and the regional HPV prevalence was more than 10%, we examined cervical cancer incidence. If country-specific cervical cancer incidence was substantially different than regional cancer incidence (e.g., the model predicted higher HPV prevalence because the country's cervical cancer incidence was higher than regional estimates), we used model estimates. Otherwise, we substituted for the model-predicted HPV prevalence either 1) the regional HPV prevalence (if cancer incidence in the country in question was similar to regional cancer incidence); or 2) HPV prevalence survey data from a neighboring country (if cancer incidence in the country in question was similar to cancer incidence in a neighboring country). Neighboring country substitutions were made for Malawi (substitution: Mozambique) and Rwanda and Uganda (substitution: Kenya). HPV prevalence inputs are presented in Table S3.

To estimate prevalence of precancerous lesions, we utilized an existing microsimulation model [2]of cervical carcinogenesis to discern the typical relationship (i.e., age-specific ratio) between cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) prevalence and detected cancer incidence in the absence of screening and preventive treatment. We selected this relationship given the association of CIN2/3 with cervical cancer incidence, for which we have empirical data in many countries. The model was used to derive the prevalence of CIN2/3 as described below. The prevalence of CIN1 is ignored in the version of CERVIVAC we used for this analysis[1]; rather, we assume clinical procedures are applied to women based on test performance characteristics for CIN2+ and the underlying prevalence of HPV and CIN2+ in each country considered.

To determine the relationship between CIN2/3 prevalence and cancer incidence, we used output from four variants of the model, calibrated to specific countries (El Salvador, India, Nicaragua, Uganda) to determine the median age-specific ratio of CIN2/3 prevalence to detected cancer incidence for women aged 30 to 49 years in LMICs. We applied this ratio to age-specific cancer incidence in 5-year intervals from Globocan 2012 [28] (Table S4) to estimate age-specific CIN2/3 prevalence in each country in the analysis. The ratios applied to cancer incidence rate per woman for each age group were as follows:

[1] In our initial analysis and report, we used a version of the previously described microsimulation model that had been calibrated to epidemiologic data from the following 20 LMIC to derive prevalence of CIN1 and CIN2/3: Argentina, Brazil, China, Colombia, Costa Rica, Haiti, India, Kenya, Lebanon, Mexico, Mozambique, Nigeria, Peru, South Africa, Tanzania, Thailand, Turkey, Uganda, Vietnam, Zimbabwe [29-38]. Since that time, we developed an updated version of the microsimulation model, and applied this newer version in the analyses described in this report. The updated model has been modified to reflect the time-dependent progression of HPV infection to precancer and cancer. This updated model does not include a separate health state for CIN1, which is interpreted as a microscopic manifestation of acute HPV infection and is therefore incorporated into the HPV-infected state; CIN2 and CIN3 are modeled as nonsequential precancerous health states with distinct probabilities of progression to cancer. The choice of model version does not have large impacts on the overall findings of the analysis.

121.2 (age 30 to 34); 78.4 (age 35 to 39); 58.4 (age 40 to 44); and 49.9 (age 45 to 49). Applying these ratios to Globocan 2012 cancer incidence rates led to CIN2/3 prevalence estimates of 2-3% on average across countries. This is consistent with estimates of CIN2/3 prevalence in the literature [39-46].

Vaccination strategy

We assumed 2-dose HPV vaccination, as recommended by the WHO [47], of girls aged 10 years. Coverage of the program in LMICs was scaled up linearly (stepwise) over 10 years as follows: 10% coverage in 2015, 20% coverage in 2016, 30% coverage in 2017, 40% coverage in 2018, 50% coverage in 2019, 60% coverage in 2020, 70% coverage in 2021, 80% coverage in 2022, 90% coverage in 2023, and 100% coverage of the target population in 2024. To date, very few LMICs have implemented HPV vaccination at scale.

We assumed these scenarios irrespective of a country's existing immunization program coverage. We also assumed no "catch-up" vaccination of older age cohorts. In reality, it is not likely that all LMICs would simultaneously and synchronously scale up their HPV programs, as we have modeled. However, since the country order and timing of HPV vaccine adoption is unknown, we model the aggregate scale up as described to give a reasonable approximation of the cost and health benefits associated with all LMIC reaching full coverage over 10 years.

Health impact of vaccination is calculated based on a proportionate reduction in age-specific cancer incidence over the lifetime of the vaccinated cohorts, assuming 93% vaccine efficacy against the 70% of cervical cancers attributable to HPV-16/18 [5-9, 21], lifelong protection, no serotype replacement, and no "herd immunity" effect. Girls vaccinated at age 10 during the time period 2015-2024 would not eligible for screening until after 2024, so we did not apply our screening strategies to the vaccinated cohorts.

Screening strategies

Screening strategies were based on country income classification and WHO guidelines [48], and did not depend on existing screening modality or coverage level in a given country. Three scenarios— Minimal Intensity, Moderate Intensity, and High Intensity—vary screening frequency and screening technology (Table 1). For countries in the LMI2 income tier and higher, strategies may vary by the presence of an existing cytology (Pap) testing program, to reflect the potential for continued use in countries where Pap testing is already established. We defined countries with existing cytology programs of sufficient scale as those which reported at least 40% of women of reproductive age (15-49) had been screened at least once [21, 49].

As with vaccination, screening was scaled up linearly (stepwise) over 10 years from 10% coverage in 2015 to 100% coverage of the target population in 2024. Screening was assumed to take place at exact ages. In the once-per-lifetime Minimal Intensity scenario, the screening age is 35 years. In the Moderate and High Intensity scenarios where screening frequency was every 5 years, women were screened at ages 30, 35, 40, and 45 years. Because screening roll-out was assumed to take place over a 10-year intervention period, women could only incur costs and receive health benefits based on their age at screening throughout the 10-year period and the designated screening frequency; thus, women could receive at most 2 screening episodes between 2015 and 2024. "Full coverage" therefore, describes a situation in which 100% of women *of the designated screening ages* receive screening. In actual screening programs, there would undoubtedly be more variation than we have modeled in the distribution of screening ages and intervals.

We assumed no loss-to-follow-up of screen-positive women between visits for confirmatory diagnostic testing and/or treatment of precancer. Because management algorithms for screen-positive women vary by setting, we made the following simplifying assumptions across all countries: 1) visual inspection with acetic acid (VIA) and HPV testing are followed by cryotherapy for eligible screen-positive women (i.e., a screen-and-treat approach); 2) HPV testing followed by VIA triage for HPV-positive women (HPV-VIA) is followed by cryotherapy for eligible women who screen positive on VIA (i.e., a screen-and-treat approach); 3) a proportion of women who screen positive with HPV and/or VIA testing are deemed ineligible for immediate treatment (5% of women with no lesion and 25% of women with CIN2/3) and require a colposcopy/biopsy; 5) Pap testing is followed by colposcopy/biopsy for all screen-positive women; 6) women with histologically confirmed CIN2/3 receive LEEP.

Screening test performance parameters are displayed in Table S5. To capture costs associated with screening, diagnosis, and treatment of precancer, CERVIVAC estimates the number of true positives (women with CIN2/3 that screen positive) and the number of false positives (women with no lesion that screen positive) based on screening test performance and the prevalence of oncogenic HPV and CIN2/3. To establish the number of women who screen positive and thus may accrue further diagnostic and/or treatment costs, we input test sensitivity values for CIN2/3 based on the literature. To capture the health impact of screening, diagnosis, and treatment of precancer, we simulated screening with VIA, Pap, HPV, and HPV-VIA (with test performance parameters in Table S5) in our updated microsimulation model for the 4 calibrated countries. Because we assumed screening took place at exact ages, we simulated screening at each possible age combination at which a woman could be screened for a given scenario during the 10-year roll-out, in order to account for fewer screening opportunities in older women. We used the average reduction in age-specific cancer incidence and mortality (in 5-year age groups from age 20 to age 84 years) from the 4 calibrated simulation models as inputs to the CERVIVAC model (Tables S6, S7, S8, S9, and S10) to generate the reduction in cancer cases and deaths attributable to each screening modality and frequency, thus capturing the future benefits of screening through age 84 years for all women screened between 2015 and 2024.

Due to limited data and variation in colposcopy performance by setting, we have assumed perfect colposcopy (i.e., 100% sensitivity and specificity at the CIN2+ threshold) in each country. We assumed cryotherapy was 90% effective at treating HPV infections and underlying precancer, while treatment with either cryotherapy or LEEP following histologic verification of CIN2+ was 100% effective.

To avoid overestimating effectiveness, we account for reduced lesion prevalence in scenarios with repeated screening, by deriving "attenuation factors" for HPV infections (for HPV testing) and CIN2/3 lesions (for all screening strategies). We simulated VIA, Pap, HPV, and HPV-VIA in the calibrated microsimulation models at 100% coverage of the target group of women (aged 30 to 49 years), for each screening frequency considered. From model output we calculated the average percent reduction in CIN2/3 lesions immediately prior to the second screening. The average percent reduction in CIN2/3 lesions was subtracted from one to generate the "attenuation factor," or reduction in lesion prevalence associated with each equally spaced screening, associated with a given screening modality. Attenuation factors are displayed in Table S11.

Cancer treatment

There are limited data on cancer stage at diagnosis in the poorest countries, where many cancers remain unstaged. To estimate stage distribution in the absence of any organized screening program, we relied on the updated microsimulation model, which was calibrated to data on stage distribution from the published literature [50, 51]. In the absence of screening (i.e., LI and LMI countries), the microsimulation model estimated that 19%, 73%, and 8% of cases would present with local, regional, and distant cancers, respectively. In countries with existing screening programs and greater access to healthcare (i.e., UMI countries), the microsimulation model estimated that 50%, 40%, and 10% of cases would present with local, regional, and distant cancers, respectively. Although direct comparisons between FIGO stages and SEER stages (i.e., local, regional, and distant cancer) are not possible, we examined the validity of our microsimulation model's natural history projections by comparing these to data in the FIGO report (Figure S1).

To account for the stage shift observed with the presence of an organized screening program, we derived the stage distribution associated with each screening test at each screening age and frequency from the updated microsimulation model, taking the average proportion of women in each stage across the India, Nicaragua, and Uganda models to represent the stage shift with screening in LI and LMI countries, and from the El Salvador model to represent the stage shift in UMI countries where some screening is already in place. We input these values (Table S12) into the CERVIVAC model to capture potential health benefits attributable to earlier cancer detection.

Assumptions regarding stage-specific treatment of cancer were based on FIGO guidelines [52]. The CERVIVAC model distinguishes local (FIGO stages 1a-2a), regional (FIGO stages 2b-3b), and distant (FIGO stages 4a-4b) stages of cancer, so we mapped FIGO stages accordingly and derived the proportion of women presenting with each sub-stage from a FIGO report that gathered data from 27 country registries, including 12 LMIC [53]; because the report did not distinguish stages

2a1 and 2a2, we assumed an equal distribution of these substages within stage 2a. We restricted follow-up to the year following primary treatment.

All women with access to cancer treatment were assumed to be staged to determine the course of treatment, and to receive palliative care regardless of stage at presentation. For women presenting with local cancer in FIGO stage 1a1, we assumed surgical treatment with conization (2.9% of local cancers[54]) or simple hysterectomy (9.8% of local cancers[54]); for women presenting with FIGO stage 1a2, 1b1, or 2a1 (62.3% of local cancers), we assumed surgical treatment consisting of radical hysterectomy with pelvic lymphadenopathy. Post-surgical follow-up included 2 Pap tests with vaginal and rectal exams in the year following surgery. For women presenting with local cancer in FIGO stages 1b2 or 2a2 (25% of local cancers), we assumed treatment with radiotherapy, brachytherapy, and chemotherapy; follow-up included 4 vaginal and rectal exams in the year following treatment. Following treatment for local cancer, we assumed 11.6% of women would receive radiotherapy for subsequent recurrence [54].

For women presenting with regional cancer, we assumed treatment with radiotherapy, brachytherapy, and chemotherapy; follow-up included 4 vaginal and rectal exams in the year following treatment. Following treatment for regional cancer, we assumed 30% of women would receive radiotherapy for subsequent recurrence [54].

For women presenting with distant cancer in FIGO stage 4a, we assumed treatment with radiotherapy, brachytherapy, and chemotherapy (54% of distant cancers[53]) and follow-up with 4 vaginal and rectal exams in the year following treatment. For women presenting with FIGO stage 4b, we assumed treatment with palliative radiation (45.7% of distant cancers[53]). Following treatment of distant cancer, we assumed 13% would receive radiation for subsequent recurrence.

Country-specific data on current access to cancer treatment in LMIC are very limited, so we used 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. We relied on a published analysis that used the International Atomic Energy Agency – Directory of Radiotherapy Centres (IAEA-DIRAC) database to estimate access to radiotherapy in 84 LMIC [23]; for countries with no data in the IAEA-DIRAC database, we assumed no current access to cancer treatment at any stage (Table S13).

We assumed that the proportion of women with access to cancer treatment received the stage-specific standard of care based on FIGO guidelines, as described above, while the remaining proportion had no access to cancer care. Health impact was determined by separate 5-year survival rates for women with and without access to cancer treatment. For women with access to the FIGO standard of care, we assumed 5-year survival would resemble 5-year relative survival rates from the U.S. Surveillance, Epidemiology, and End Results Program (92% for local, 57% for regional, and 17% for distant cancer)[22]. For women with no access to treatment, we examined 5-year absolute survival rates from the IARC SurvCan database. Because countries with data on stage-specific survival tend to have sufficient resources for registries and for some cancer staging, survival rates in this database are not likely representative of settings with no access to treatment, so we constructed a linear regression model to predict 5-year survival for each stage based on access to radiation therapy [10]. We used the regression models to predict 5-year survival given no access to radiation therapy, and input these values into CERVIVAC for application to women without access to cancer treatment (65% for local, 37% for regional, 16% for distant cancer).

Costs

Vaccination

For vaccination, we included HPV vaccination delivery costs and the price of the vaccine under two vaccine pricing scenarios in which we varied the per-dose price of the vaccine by income tier. Sources of HPV vaccine price information included Gavi, the Vaccine Alliance, PAHO Revolving Fund (RF), and a report from Médecins Sans Frontières (Table 2). We assumed Gavi-eligible countries would have access to the Gavi-negotiated prices in all years under all scenarios. Similarly, we assumed all Latin America and Caribbean (LAC) region countries and South Africa will access the PAHO Revolving Fund price in all years under all scenarios, because these countries have access to the PAHO Revolving Fund (though not all use it). Prices for non-Gavi, non-LAC countries were based on country income tiers. In both scenarios, we assumed that vaccine

pricing would remain constant between 2015 and 2024, and that countries would remain in the same income tier. The base case (more favorable) scenario is a two-tier scheme where all Gavi countries access Gavi price of US$4.55 per dose, all non-Gavi LMI1 countries access the Gavi price as well, and all non-Gavi countries in income tier LMI2 or higher access a price equal to the RF price of US$13.79 per dose. In the alternative scenario, there are four price tiers and prices for non-Gavi non-RF countries are assumed to be as high as $40 per dose.

We identified data on HPV vaccination delivery cost per dose from the published literature and restricted estimates to economic costs, defined as the cost of all health sector resources required for service delivery, regardless of payer [55-57]; unlike financial costs, economic costs include the salaries of health personnel which have already been paid for prior to initiation of an HPV vaccination program, but still represent an opportunity cost. When possible, we excluded start-up costs which would only be relevant within the initial years of a program. We considered all delivery mechanisms, including school-based, health center-based, and integrated outreach. All costs were converted to 2013 US$ using GDP deflators and exchange rates (Table S14). We assumed that delivery costs did not vary with vaccine coverage.

To extrapolate published estimates for HPV vaccine delivery costs to all countries, we obtained the cost of the average primary health center visit in each country from the WHO-CHOICE costing tool [1]. The latest available local currency unit estimates from 2008 were converted into 2013 US$. We took the ratio of the WHO-CHOICE facility cost in Country X to the WHO-CHOICE facility cost in a country with published data. We multiplied this ratio by the HPV vaccine delivery cost in the published data setting to obtain an estimate of the vaccine delivery cost in Country X. We repeated this calculation for each published estimate, and then took the average of extrapolated values to use in analysis. By incorporating WHO-CHOICE data, these extrapolated values explicitly take into account the high correlation between a country's GDP per capita and health care costs. Results for the average HPV vaccine delivery cost per dose, by income tier and Gavi eligibility, are shown in Table S15.

Screening and treatment of precancerous lesions

For screening-related costs, we included direct medical costs associated with screening, diagnosis (if relevant), and treatment of precancerous lesions. We assumed that screening costs were not dependent upon coverage level. Procedures and assumed location of service delivery are presented in Table S16. To estimate the unit cost of each procedure, we identified available data from the published literature [15, 58], unpublished data from PATH's START-UP demonstration projects [59, 60], and data from El Salvador [3], such that the following countries were represented by primary data: Ghana, El Salvador, India (n=3 studies), Kenya, Nicaragua, Peru, Uganda, South Africa, and Thailand. All unit costs were converted to 2013 US$ using GDP deflators and exchange rates [19]; we assumed the HPV test was a tradable good (i.e., a good that can be sold in a location other than where it was produced) (Table S17).

To extrapolate primary data estimates for each procedure to all countries, we used the same procedure described above for vaccination delivery cost. However, we assumed that the HPV test was a tradable good with a standardized value of US$5 across all settings, and thus did not apply WHO-CHOICE facility unit cost ratios to this value to obtain HPV screening costs; rather, we applied WHO-CHOICE ratios to the other direct medical cost components of HPV testing (e.g., staff time, laboratory processing, other supplies) and added US$5 afterward. We performed a sensitivity analysis in which we assumed the cost of the HPV test was US$2.50, to estimate the potential impact of bulk purchasing of HPV tests or economies of scale in the laboratory processing of samples. Results for the average unit costs by procedure for each income tier are shown in Table S18. Unit costs for each procedure are plotted against 2013 GNI per capita in Figure S2.

Cancer treatment

We included direct medical costs associated with the stage-specific cancer treatment protocols described above, assuming that cancer treatment costs were not dependent upon coverage level. We assumed that all cancer staging, treatment, palliative care, and follow-up took place at a tertiary facility. To estimate the unit cost of each procedure, we identified available data from the published literature and unpublished data from a preliminary economic analysis of Latin America such that the following countries were represented by primary data: Argentina [12], Brazil[12], Colombia [12], China [13], El Salvador [3], India [14, 15], Kenya [15], Mexico [12], Morocco [16], Peru [12, 15], South Africa [15], and Thailand [15, 17,

18]. All unit costs were converted to 2013 US$ using GDP deflators, exchange rates, and purchasing power parity conversion rates (when costs were reported in international dollars) [19] (Table S19).

Again, we extrapolate primary data estimates for each procedure to all countries, using the WHO-CHOICE unit cost ratios as described above for vaccination delivery cost. However, for treatment costs we used the ratio of tertiary hospital day (as opposed to clinic visit or outpatient visit costs) from WHO-CHOICE to reflect the likely care setting for cancer treatment. Assuming the stage-specific treatment protocols and distribution of FIGO stages within local, regional, and distant cancers described above, we added the weighted relevant country-specific extrapolated unit costs to establish the cost of treating local, regional, and distant cancers (respectively) in each country. By incorporating WHO-CHOICE data, these extrapolated values explicitly take into account the high correlation between a country's GDP per capita and health care costs. Stage-specific costs for cancer treatment, by income tier, are presented in Table S20.

Results

Vaccination

We found that an HPV vaccination program from 2015 to 2024 would cost from US$8.6 billion to US$13.1 billion (Table 3a), depending on vaccine price. The 10-year roll-out would reach 286 million girls (of 513 million eligible) and would avert 4.8 million cases and 3.3 million deaths from cervical cancer. This is about $30 per vaccinated girl. About 58% of this cost was for the vaccine product itself. In the years after 2024, the full scale program would cost approximately $1.5 billion annually. With a less favorable four-tier pricing model, the 10-year roll out of the vaccination program between 2015 and 2024 cost would rise from $8.6 to $16.2 billion (Table 3b). The additional cost would be concentrated in UMI countries.

In Gavi-eligible countries, the cost of vaccination would be US$2.2 billion, of which about 33% ($0.7 billion) would be for vaccine itself, assuming current prices remain stable over the roll-out period. In Gavi-eligible countries, an HPV vaccination program would cost about US$16 per vaccinated girl and could avert 3.0 million cases and 2.2 million deaths from cervical cancer.

The vaccination program would also avert costs associated with cervical cancer treatment (relative to no vaccination), offseting nearly one-third of the vaccination program cost. When including cervical cancer treatment cost offsets based on current access to cancer treatment, the *net* cost would be US$330 per DALY averted under a 2-tiered vaccine pricing scenario, and US$830 per DALY averted under a 4-tiered vaccine pricing scenario. Under both scenarios, HPV vaccination of 10-year-old girls would be very cost-effective in each income tier, using a benchmark cost-effectiveness threshold equal to GDP per capita.

Screening

The total cost of cervical cancer screening, diagnostic testing, and treatment of precancerous lesions from 2015 to 2024 by income tier and World Bank region, for each screening scenario, is presented in Table 4a-c. Under the Minimal Intensity scenario (once in a lifetime screening), yearly costs of 10-year roll-out rose from US$83 million in 2015 to US$982 million in 2024. Over the 10-year period the total cost was $4.95 billion, and 252 million women were screened, for an average cost per women reached of $19.60 (Table 4a). This per woman cost was as low as $3.60 in LI settings and as high as $59.00 in the UMI2 settings, primarily due to the higher cost of labor. The Moderate Intensity scenario in which screening frequency is increased to every 5 years, was approximately 4 times higher— costing $18.1 billion over 10 years— since about 4 times more women received at least one screen, and a fraction of these women received a second screen during the interval 2015 to 2024, though a lower proportion of screening episodes led to follow up diagnosis and treatment as a result of reduced precancer prevalence at subsequent screening encounters.

The total cost of screening and preventive treatment over the intervention period was US$14.5 billion in High Intensity Scenario where HPV-VIA is used in UMI1 countries, and cytology based screening is replaced with HPV-based screening. The High Intensity scenario dominated the Moderate Intensity scenario since it detected more cases and cost less.

For the Moderate and High Intensity screening scenarios, we did not compute a program cost per woman reached by the program, since our model is a cohort model that does not track individuals. However, for the High Intensity scenario with more frequent, and mostly HPV test-based, screening, the cost per primary screen was $15.26, including any follow-up diagnosis and precancer treatment. Under this scenario, some women received 2 primary screens— five years apart— between 2015 and 2024. Note, however, that over a lifetime, assuming the screening program continued, a woman under 30 at the start of the program can be expected to have 4 primary screenings over her lifetime, for an undiscounted cost of $61 ($15.26 * 4).

The Minimal Intensity scenario, in which women receive a one-time screening at age 35, could avert 1.4 million cases and 968,000 deaths from cervical cancer, while High Intensity screening at 5-year age intervals could avert 3.8 million cases and 2.6 million deaths over the lifetime of women screened.

For one-time screening, the cost in LI and LMI1 countries that may be dependent on foreign aid to finance screening would range from US$0.7 billion to US$3.6 billion, averting 757,000 cases and 540,000 deaths from cervical cancer.

As with vaccination, a substantial portion of program costs— between 32% and 44%— were offset by savings in cancer treatment costs. Considering cervical cancer treatment cost offsets based on current access to cancer treatment, the *net* cost per DALY averted would range from US$255 (Minimal Intensity scenario, relative to no screening) to US$380 (High Intensity scenario, relative to Minimal Intensity scenario). Thus, cervical cancer screening would be considered very cost-effective, using a benchmark cost-effectiveness threshold of GDP per capita.

Distribution of Screening Program Costs

The relative distribution of screening, diagnostic, and treatment costs is displayed in Figure 1. In the Minimal Intensity screening scenario, 43% of total costs were attributable to screening procedures. Because HPV-VIA was offered only in UMI2 countries without existing Pap programs, triage tests accounted for <1% of total costs. The reliance on Pap screening in the countries with existing programs resulted in 7% of total costs being spent on colposcopy. Cryotherapy accounted for 47% of costs, and LEEP for 3%. The shift to screening every 5 years, and shifting to HPV-based testing in all but LI countries under the High Intensity scenario raised the relative contribution of screening costs to 70%. The proportional cost of triage tests increased slightly to 4%, as HPV-VIA was adopted in all UMI countries, while the reduced reliance on Pap testing led to a reduced contribution of colposcopy to total costs (3%). Cryotherapy and LEEP accounted for 19% and 3%, respectively, of total costs, as the number of women treated decreased as a result of HPV-VIA triage testing.

We performed a sensitivity analysis in which the assumed cost of the HPV test was reduced from US$5 to US$2.50 in the High Intensity scenario (HPV-based screening in all but LI countries). Program costs were reduced about 12%. Overall, the unit cost of the test is a significant, but not overwhelming share of the cost. However, the HPV tests are a relatively greater share of the program cost in low-income settings where labor costs and other non-tradeable input are less costly.

Timing of Health Impacts

HPV-16/18 vaccination of 10-year old girls between 2015 and 2024 in 102 LMIC ultimately averted 3.3 million cervical cancer deaths over the lifetime of the vaccinated girls. Screening just once in a lifetime with the Minimal Intensity scenario ultimately averted 968,000 cervical cancer deaths over the lifetime of women screened during 2015 - 2024. The High Intensity screening scenario, with HPV testing every 5 years in all but LI countries, would ultimately avert 2.6 million deaths over the lifetime of women screened during 2015-2024.

Although screening averts fewer total deaths, its impact is realized sooner, since the target population is older and closer to the age of highest cervical cancer risk. To illustrate this, Figure 2 displays the timing of deaths averted with a vaccination program as compared to a Minimal Intensity screening program in India. In India, screening just once in a lifetime with VIA

would reap immediate health benefits, with averted cervical cancer mortality steadily rising until 2041, when women who were not eligible for screening during the intervention period begin to face heightened cervical cancer risk. The impact would be even greater using HPV testing as the screening technology, as it is a more sensitive test than VIA. The vaccination program, on the other hand, averts few deaths until the vaccinated cohorts reach older ages. Even by 2050, the cumulative number of deaths averted from screening once with VIA are 2.7-fold higher than deaths averted from HPV vaccination. Our model calculates but does not record deaths averted by calendar year beyond 2050. However, the reported cumulative deaths averted over the populations entire lifetime are greater for vaccination than any screening strategy we examined, indicating that a large share of the deaths prevented by vaccination would have occurred after 2050.

Discussion

This study provides the first comprehensive estimate of the cost and health impact of cervical cancer prevention in LMIC, including HPV vaccination of young girls and screening and preventive treatment of women aged 30 to 49 years. We considered multiple policy scenarios— 2 vaccine pricing scenarios and 3 screening test and frequency assumptions— to capture the range of potential costs. Other studies have examined the cost-effectiveness of HPV vaccination in Gavi-eligible countries and LMIC [37, 61]. Our findings that HPV-16/18 vaccination is very cost-effective in the aggregate, with a cost per DALY less than the GDP per capita in each income tier, are consistent with these published studies that found HPV vaccination of young adolescents to be a very cost-effective intervention, although the price of the vaccine is a key driver of cost-effectiveness. While we are not aware of other studies that have estimated the aggregate health and economic impact of cervical cancer screening in LMIC, a modelling 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) [62]. Country-contextualized analyses have found a two-visit screen-and-treat approach, with careHPV testing, to be very cost-effective [3, 4], yielding greater health benefits and a better value for public health dollars than VIA or Pap [4].

There are several limitations to this analysis, including limitations pertaining to epidemiologic data and assumptions. Due to limited information on future disease trends, we assumed Globocan projections of cancer incidence and mortality were stable over the lifetimes of 10-year old girls and women of screening age during the intervention period. In the absence of country-specific epidemiologic data in many settings, we relied upon model-based extrapolation techniques, including the prediction of HPV prevalence based on cancer incidence using a multivariate regression and the prediction of lesion prevalence using a microsimulation model calibrated to 4 LMIC. We examined extrapolated HPV prevalence estimates and made the described adjustments for outliers accordingly. For estimates of lesion prevalence, we believe that considering microsimulation models from 4 settings with different epidemiologic profiles provided a reasonable approximation of the relationships between CIN2/3 and cancer incidence. We also used the microsimulation models to generate estimates of screening effectiveness, in terms of cancer incidence and mortality reduction and shifts in stage distribution. While we averaged the estimates of screening effectiveness across the 4 microsimulation models, we note that, given comparable assumptions of coverage, test performance, compliance, and precancer treatment efficacy, the percent reduction in incidence and mortality was stable across the calibrated models. However, there remains uncertainty in these estimates due to potential issues with the microsimulation model structure and quality of epidemiologic data to which the models were calibrated, including limitations in cancer registry data, cancer survival data, and the high proportion of unstaged cancers in low-resource settings.

We did not explicitly consider HIV burden in this analysis. WHO treatment guidelines recommend more frequent screening in women with HIV or women of unknown HIV status in areas with high endemic HIV infection [14]. In areas with a high burden of HIV, the recommendation is to rescreen women who screen negative with VIA, Pap, or HPV testing within 3 years. At this time, the background risk of HIV that warrants increased screening intervals has not been established in guidelines. Our analysis did not consider HPV testing more frequently than every 5 years, and our existing models are not calibrated to predict the health impact of cervical screening among women living with HIV. We expect both the cost and benefits of targeted high frequency screening among women with known HIV infection could be substantial in a few hyper-endemic

settings (such as South Africa, Zambia, Botswana, Namibia, or Swaziland). However, a policy of frequent screening among HIV-infected women who are identified and in HIV care is not expected to add substantially to the global cost estimates we have calculated, despite the moderate increased risk of cervical cancer associated with HIV, because the fraction of women in LMICs who are HIV-infected is small.

We focused upon screening and triage algorithms recommended by WHO guidelines [14]. Therefore, in countries with enough resources to provide a sequence of tests (i.e., UMI1 and UMI2 countries), we considered an HPV-based screening strategy with VIA triage for HPV-positive women. For countries with existing Pap programs that meet quality indicators, the WHO guidelines recommend either continued Pap testing or an HPV test followed by colposcopy. We examined scenarios in which the countries where Pap coverage was greater than 40% either continued with Pap or switched to HPV testing (followed by either cryotherapy or a VIA triage test). However, we did not consider a scenario where HPV-positive women were triaged based on Pap testing, although this is a possible path UMI countries might consider. Relative to HPV testing with VIA triage, where triage tests comprise only ~4% of total costs in UMI countries, the total cost of HPV testing with Pap triage in countries with existing high-coverage Pap screening programs might increase only slightly due to the higher cost of Pap relative to VIA, assuming similarities in test sensitivity. Furthermore, the impact on total cost of global cervical cancer prevention would probably be modest due to the small number of countries with sufficient cytology programs to expand.

The HPV vaccine delivery costs we considered were primarily from demonstration projects, and may overestimate the costs of delivery with national scale-up. We note, however, that extrapolated HPV vaccine delivery costs in this analysis appear comparable to recent estimates of the average delivery costs associated with the traditional EPI vaccines (forthcoming EPIC Immunization Costing Study). Because published and primary cost data on HPV vaccine delivery and cervical cancer screening and preventive treatment are limited to a handful of settings, we extrapolated these cost data by using the WHO-CHOICE tool to leverage the relationship between healthcare costs and GDP per capita across settings [20]. Due to inconsistencies in cost reporting across the literature, we cannot be certain that the published and primary data cost estimates we used contain comparable components. We attempted to address this by considering all available data that was described in adequate detail, and we used the average of extrapolated values to account for variability and uncertainty.

HPV vaccination costs may be lower than we assumed here if, in the latter years of the time horizon, HPV vaccine patents expire, if competition from one or more second-generation vaccines reduces first generation HPV vaccine price, or if developing country vaccine manufacturers can obtain licensing agreements to produce low-cost second generation vaccines [44]. The impact of the U.S. Food and Drug Administration's recent approval of a HPV 9-valent vaccine on the price of first generation vaccines and prospects for generic manufacturing or voluntary licensing deals is unclear [45]. Nonetheless, the latest PAHO Revolving Fund price for bivalent HPV vaccine of $8.50 per dose is encouraging.

This study provides much-needed estimates of the costs and health benefits associated with HPV vaccination and cervical cancer screening, yet important questions remain. We did not account for the programmatic investment costs that may be necessary to achieve high coverage levels of screening and vaccination such as infrastructure improvements to supply chain, training health workers, and social mobilization, nor did we account for potential economies of scale. Current data are insufficient to establish the point at which economies of scale may be counterbalanced by increasing programmatic costs of achieving high coverage.

While we considered the cost-effectiveness of screening at the aggregate level for 102 LMIC and found screening to be very cost-effective, the present analysis does not consider the cost-effectiveness of screening at the country level. Analyses will need to be contextualized to a given setting— considering local burden of disease, infrastructure, costs, and competing health priorities— in order to inform local decision-making. We did not assess the relative cost-effectiveness of all possible screening tests and intervals, even at the aggregate level, so results should not be used to identify the optimal test or screening frequency. While we found that HPV testing with VIA triage of HPV-positive women may lead to lower total costs than HPV testing alone, due to fewer women being referred to treatment, data on performance of HPV-VIA triage suggests a low sensitivity for CIN2+ [42, 46][63], which may compromise health gains associated with screening and treatment,

particularly in settings where screening opportunities are limited. We note that as UMI1 countries shifted from HPV testing alone (Moderate Intensity scenario) to HPV with VIA triage (High Intensity scenario), the number of DALYs averted declined. Further data are needed on the effectiveness of HPV with VIA triage, and whether the reduced costs outweigh the potential reduction in health benefits. For countries interested in maintaining Pap-based screening programs, data on the comparative effectiveness of more frequent Pap-based screening relative to less frequent HPV-based screening should also be considered; we only considered screening at a minimum of 5-year intervals.

New technologies on the horizon may alter the landscape of cervical cancer screening and preventive treatment. Current screen-and-treat approaches rely on gas-based cryotherapy, which in turn relies on consistent resupply of gas that is expensive to transport and not always available in low-resource settings. However, new non-gas ablative technologies that are smaller and more portable than conventional cryotherapy equipment are currently undergoing testing. Thermocoagulation has been used as part of a screen-and-treat program in Malawi [64] and for treatment of HIV-infected women in India [65], with interim cure rates comparable to cryotherapy [66]. These treatment technologies may improve management of screen-positive women by improving access to ablative therapy. For countries considering diagnostic technologies to improve management of screen-positive women, early assessments of high-resolution microendoscopy find this point-of-care diagnostic test to be a potentially low-cost and accurate method of diagnosing precancer without the need for biopsy [67].

Conclusion

In 2015, US$36.4 billion in development assistance for health was disbursed [68]. Of this, US$10.8 billion was allocated for HIV/AIDS, US$6.5 billion for child and newborn health, and US$3.6 billion for maternal health. While development assistance for health has increased markedly since 2000 [68], cancer prevention and treatment in LMIC has been underfunded, resulting in an estimated 5% of global cancer resources spent in countries hosting 80% of the global cancer burden [69]. We found that HPV vaccination of young girls and cervical cancer screening for women aged 35 years can be provided for an average annual cost of US$2.4 billion at scale. A 10-year roll-out of HPV vaccination from 2015 to 2024 would avert 4.8 million cases and 3.3 million deaths from cervical cancer over the lifetimes of vaccinated girls; a similar roll-out of cervical cancer screening for women aged 35 years would avert 1.4 million cases and 968,000 deaths from cervical cancer. Both HPV vaccination and cervical cancer screening provide very good value for public health dollars; importantly, while the health impact of screening can be observed immediately, 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 health care systems and reduce cancer disparities. We hope this study will catalyze the current policy dialogue to expediently secure necessary resources and facilitate country-level discourse on implementation of healthcare delivery strategies to rapidly scale up HPV vaccination and cervical cancer screening.

References

1. *World Health Organization Statistical Information System: CHOICE (CHOosing Interventions that are Cost Effective)*. October 17, 2007]; Available from: http://www.who.int/choice/en/. .
2. Campos, N.G., et al., *An updated natural history model of cervical cancer: derivation of model parameters.* Am J Epidemiol, 2014. 180(5): p. 545-55.
3. Campos, N.G., et al., *The comparative and cost-effectiveness of HPV-based cervical cancer screening algorithms in El Salvador.* Int J Cancer, 2015.
4. Campos, N.G., Tsu, V., Jeronimo, J., Mvundura, M., Lee, K., Kim, J.J., *When and how often to screen for cervical cancer in three low- and middle-income countries: A cost-effectiveness analysis.* Papillomavirus Research, 2015.
5. Paavonen, J., et al., *Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women.* Lancet, 2009. 374(9686): p. 301-14.
6. De Carvalho, N., et al., *Sustained efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women.* Vaccine, 2010. 28(38): p. 6247-55.
7. Herrero, R., et al., *Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica.* Cancer Discov, 2011. 1(5): p. 408-19.
8. Romanowski, B., et al., *Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study.* Hum Vaccin, 2011. 7(12): p. 1374-86.
9. Brown, D.R., et al., *The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years.* J Infect Dis, 2009. 199(7): p. 926-35.
10. Datta, N.R., M. Samiei, and S. Bodis, *Radiation therapy infrastructure and human resources in low- and middle-income countries: present status and projections for 2020. In reply to Sharma et al.* Int J Radiat Oncol Biol Phys, 2014. 90(4): p. 971-2.
11. WHO, *Macroeconomics and health: Investing in health for economic development: Report of the Commission on Macroeconomics and Health*, 2001, World Health Organization: Geneva.
12. Constenla, D., Goldie, S.J., Alvis, N., O'Shea, M., Sweet, S., Valenzuela, M., Cavada, G., de la Hoz, F., Koumans, E., Labbo, M.N., Koss, C., Posso, H., *Health and Economic Outcomes of Human Papillomavirus (HPV) Vaccination in Selected Countries in Latin America: A Preliminary Economic Analysis.* 2008.
13. Shi, J.F., et al., *Estimation of the costs of cervical cancer screening, diagnosis and treatment in rural Shanxi Province, China: a micro-costing study.* BMC Health Serv Res, 2012. 12: p. 123.
14. Ranson, M.K. and K.R. John, *Quality of hysterectomy care in rural Gujarat: the role of community-based health insurance.* Reprod Health Matters, 2002. 10(20): p. 70-81.
15. Goldie, S.J., et al., *Cost-effectiveness of cervical-cancer screening in five developing countries.* N Engl J Med, 2005. 353(20): p. 2158-68.
16. Berraho, M., et al., *Direct costs of cervical cancer management in Morocco.* Asian Pac J Cancer Prev, 2012. 13(7): p. 3159-63.
17. Termrungruanglert, W., et al., *Cost and effectiveness evaluation of prophylactic HPV vaccine in developing countries.* Value Health, 2012. 15(1 Suppl): p. S29-34.
18. Katanyoo, K., et al., *Cost-utility analysis of treatments for stage IB cervical cancer.* J Gynecol Oncol, 2014. 25(2): p. 97-104.
19. *World Development Indicators*, 2013, World Bank.
20. Agency., U.S.C.I., *The World Factbook.*
21. ICO, *HPV Information Centre*, 2014.
22. Surveillance, E., and End Results (SEER) Program, *SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases Nov 2011 Sub (1973-2009 varying) – Linked to County Attributes – Total U.S., 1969-2010 Counties*.

23. Datta, N.R., M. Samiei, and S. Bodis, *Radiation therapy infrastructure and human resources in low- and middle-income countries: present status and projections for 2020.* Int J Radiat Oncol Biol Phys, 2014. 89(3): p. 448-57.
24. Cancer., I.A.f.R.o., *Cancer survival in Africa, Asia, the Caribbean and Central America.*
25. United Nations, D.o.E.a.S.A., Population Division, *World Population Prospects, The 2012 Revision*, 2013: Geneva.
26. Sharma, M., et al., *Using HPV prevalence to predict cervical cancer incidence.* Int J Cancer, 2013. 132(8): p. 1895-900.
27. Forman, D., Bray, F., Brewster, D.H., Gombe Mbalawa, C., Kohler, B., Piñeros, M., Steliarova-Foucher, E., Swaminathan, R., Ferlay, J. (eds) *Cancer Incidence in Five Continents, Vol. X*, 2013, IARC: Lyon, France.
28. Ferlay, J., et al., *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]*, 2013, International Agency for Research on Cancer: Lyon, France.
29. Campos, N.G., et al., *Health and economic impact of HPV 16/18 vaccination and cervical cancer screening in Eastern Africa.* Int J Cancer, 2012. 130(11): p. 2672-84.
30. Kim, J.J., et al., *Exploring the cost-effectiveness of HPV vaccination in Vietnam: insights for evidence-based cervical cancer prevention policy.* Vaccine, 2008. 26(32): p. 4015-24.
31. Goldie, S.J., et al., *Cost-effectiveness of HPV 16, 18 vaccination in Brazil.* Vaccine, 2007. 25(33): p. 6257-70.
32. Diaz, M., et al., *Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India.* Br J Cancer, 2008. 99(2): p. 230-8.
33. Kim, J.J., et al., *Model-based impact and cost-effectiveness of cervical cancer prevention in sub-saharan Africa.* Vaccine, 2013. 31 Suppl 5: p. F60-72.
34. Sharma, M., et al., *Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in Thailand.* BJOG, 2012. 119(2): p. 166-76.
35. Kim, J.J., et al., *Model-based impact and cost-effectiveness of cervical cancer prevention in the Extended Middle East and North Africa (EMENA).* Vaccine, 2013. 31 Suppl 6: p. G65-77.
36. Goldie, S.J., et al., *Health and economic impact of human papillomavirus 16 and 18 vaccination of preadolescent girls and cervical cancer screening of adult women in Peru.* Rev Panam Salud Publica, 2012. 32(6): p. 426-34.
37. Goldie, S.J., et al., *Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries.* Vaccine, 2008. 26(32): p. 4080-93.
38. Kim, J.J., et al., *Multiparameter calibration of a natural history model of cervical cancer.* Am J Epidemiol, 2007. 166(2): p. 137-50.
39. Qiao, Y.L., et al., *A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China.* Lancet Oncol, 2008. 9(10): p. 929-36.
40. Sankaranarayanan, R., et al., *HPV screening for cervical cancer in rural India.* N Engl J Med, 2009. 360(14): p. 1385-94.
41. Deodhar, K., et al., *Accuracy of concurrent visual and cytology screening in detecting cervical cancer precursors in rural India.* Int J Cancer, 2012. 131(6): p. E954-62.
42. Cremer, M., et al., *Adequacy of visual inspection with acetic acid in women of advancing age.* Int J Gynaecol Obstet, 2011. 113(1): p. 68-71.
43. Denny, L., et al., *Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial.* JAMA, 2005. 294(17): p. 2173-81.
44. Gage, J.C., et al., *Effectiveness of a simple rapid human papillomavirus DNA test in rural Nigeria.* Int J Cancer, 2012. 131(12): p. 2903-9.
45. Muwonge, R., et al., *Visual screening for early detection of cervical neoplasia in Angola.* Int J Gynaecol Obstet, 2010. 111(1): p. 68-72.
46. Ngoma, T., et al., *Evaluation of cervical visual inspection screening in Dar es Salaam, Tanzania.* Int J Gynaecol Obstet, 2010. 109(2): p. 100-4.
47. *Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 -- conclusions and recommendations.* Wkly Epidemiol Rec, 2014. 89(21): p. 221-36.
48. Organization, W.H., in *WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention*2013: Geneva.
49. Gakidou, E., S. Nordhagen, and Z. Obermeyer, *Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities.* PLoS Med, 2008. 5(6): p. e132.

50. Sankaranarayanan, R., et al., *Cancer survival in Africa, Asia, and Central America: a population-based study.* Lancet Oncol, 2010. 11(2): p. 165-73.
51. Wabinga, H., et al., *Cancer survival in Kampala, Uganda, 1993-1997.* IARC Sci Publ, 2011(162): p. 243-7.
52. Wiebe, E., L. Denny, and G. Thomas, *Cancer of the cervix uteri.* Int J Gynaecol Obstet, 2012. 119 Suppl 2: p. S100-9.
53. Quinn, M.A., et al., *Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer.* Int J Gynaecol Obstet, 2006. 95 Suppl 1: p. S43-103.
54. Ginsberg, G.M., et al., *Screening, prevention and treatment of cervical cancer -- a global and regional generalized cost-effectiveness analysis.* Vaccine, 2009. 27(43): p. 6060-79.
55. Hutubessy, R., et al., *A case study using the United Republic of Tanzania: costing nationwide HPV vaccine delivery using the WHO Cervical Cancer Prevention and Control Costing Tool.* BMC Med, 2012. 10: p. 136.
56. Levin, C.E., et al., *Delivery cost of human papillomavirus vaccination of young adolescent girls in Peru, Uganda and Viet Nam.* Bull World Health Organ, 2013. 91(8): p. 585-92.
57. Quentin, W., et al., *Costs of delivering human papillomavirus vaccination to schoolgirls in Mwanza Region, Tanzania.* BMC Med, 2012. 10: p. 137.
58. Countries, P.f.R.a.C.B.i.S.a.R.H.a.H.i.D., *Costs of cervical cancer screening in Ghana*, 2010, UK Department for International Development: London.
59. Jeronimo, J., et al., *A multicountry evaluation of careHPV testing, visual inspection with acetic acid, and papanicolaou testing for the detection of cervical cancer.* Int J Gynecol Cancer, 2014. 24(3): p. 576-85.
60. Mvundura, M. and V. Tsu, *Estimating the costs of cervical cancer screening in high-burden Sub-Saharan African countries.* Int J Gynaecol Obstet, 2014. 126(2): p. 151-5.
61. Jit, M., et al., *Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study.* Lancet Glob Health. 2(7): p. e406-14.
62. Ginsberg, G.M., et al., *Cost effectiveness of strategies to combat breast, cervical, and colorectal cancer in sub-Saharan Africa and South East Asia: mathematical modelling study.* BMJ. 344: p. e614.
63. Tebeu, P.M., et al., *Effectiveness of a two-stage strategy with HPV testing followed by visual inspection with acetic acid for cervical cancer screening in a low-income setting.* Int J Cancer, 2015. 136(6): p. E743-50.
64. Campbell, C., et al., *Use of thermo-coagulation as an alternative treatment modality in a 'screen and treat' programme of cervical screening in rural Malawi.* Int J Cancer, 2016.
65. Joshi, S., et al., *Screening of cervical neoplasia in HIV-infected women in India.* AIDS, 2013. 27(4): p. 607-15.
66. Sauvaget, C., R. Muwonge, and R. Sankaranarayanan, *Meta-analysis of the effectiveness of cryotherapy in the treatment of cervical intraepithelial neoplasia.* Int J Gynaecol Obstet, 2013. 120(3): p. 218-23.
67. Grant, B.D., et al., *High-resolution microendoscopy: a point-of-care diagnostic for cervical dysplasia in low-resource settings.* Eur J Cancer Prev.
68. Dieleman, J.L., et al., *Development assistance for health: past trends, associations, and the future of international financial flows for health.* Lancet, 2016.
69. Farmer, P., et al., *Expansion of cancer care and control in countries of low and middle income: a call to action.* Lancet, 2010. 376(9747): p. 1186-93.

Table 1. Screening strategies, by income tier.[a]

Income tier	Existing Cytology Program[b]	Minimal Intensity: Screening once in a lifetime	Moderate Intensity: Screening every 5 years	High Intensity: Screening every 5 years with HPV testing in middle-income countries
Low income (LI) (< $1045)	No	VIA 1x	VIA *Q5*	VIA Q5
Lower-middle income 1 (LMI1) ($1046 - $2585)	No	VIA 1x	VIA *Q5*	*HPV* Q5
Lower-middle income 2 (LMI2) ($2586 - $4125)	No	VIA 1x	VIA *Q5*	*HPV* Q5
	Yes	PAP 1x	PAP *Q5*	*HPV* Q5
Upper-middle income 1 (UMI1) ($4126 - $8435)	No	HPV 1x	HPV *Q5*	*HPV-VIA* Q5
	Yes	PAP 1x	PAP *Q5*	*HPV-VIA* Q5
Upper-middle income 2 (UMI2) ($8436 - $12745)	No	HPV-VIA 1x	HPV-VIA *Q5*	HPV-VIA Q5
	Yes	PAP 1x	PAP *Q5*	*HPV-VIA* Q5

[a] HPV: human papillomavirus testing; HPV-VIA: HPV testing with visual inspection triage; PAP: Pap testing; VIA: visual inspection with acetic acid; 1x: Once in a lifetime at age 35 years; Q10: screening at 10 year intervals (at age 30, 40 years); Q5: screening at 5 year intervals (at age 30, 35, 40, 45 years); $: 2013 US$.

[b] Existing cytology programs with >40% coverage (includes Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, El Salvador, Hungary, Kazakhstan, Mexico, Paraguay, Peru, Ukraine) [15, 16].

Table 2. HPV vaccine price per dose scenarios, by income tier.[a]

Income tier	Base case Scenario (favorable 2 tiers)	Alternative Scenario (more costly 4 tiers)
Low income (LI) (< $1045)	4.55 Gavi	4.55 Gavi
Lower-middle income 1 (LMI1) ($1046 - $2585)	4.55 Gavi	13.79 PAHO RF
Lower-middle income 2 (LMI2) ($2586 - $4125)	13.79 PAHO RF	27.58 2 x PAHO RF
Upper-middle income 1 (UMI1) ($4126 - $8435)	13.79 PAHO RF	40 Best UMI price, MSF
Upper-middle income 2 (UMI2) ($8436 - $12745)	13.79 PAHO RF	40 Best UMI price, MSF

[a] Gavi: Gavi, the Vaccine Alliance; PAHO RF: Pan American Health Organization Revolving Fund; MSF: Médecins Sans Frontières; UMI: Upper Middle Income; $: 2013 US$. We assumed Gavi-eligible countries would have access to the Gavi-negotiated prices in all years under all scenarios. Similarly, we assumed all Latin America and Caribbean (LAC) region countries and South Africa will access the PAHO Revolving Fund price in all years under all scenarios, because these countries have access to the PAHO Revolving Fund (though not all use it). Prices for non-Gavi, non-LAC countries were based on country income tiers.

Table 3a. HPV vaccination program costs, health outcomes, and cost-effectiveness: 10-year roll-out of a 2-dose vaccination program for 10-year old girls with no catch-up, 2-tier vaccine pricing.

10-year scale up [b] *2-tier pricing*	Costs (Billions)					Health Outcomes (Thousands)				Cost-effectiveness		
	Vaccination Cost		Cancer Treatment Costs AVERTED	Net Cost	Treatment Savings as Percentage of Program Costs	Vaccin-ations (Millions)	Cases Averted	Deaths Averted	DALYs Averted	Program Cost per Vaccinated Girl	Program Cost per Death Averted	Net Cost per DALY Averted
	U	D	D	D	D	U	U	U	D	U	D/U	D
TOTAL	$8.7	$7.3	$2.3	$4.9	32%	292	4793	3338	13663	$30	$2,173	$361
Income Tier[a]												
LI	$0.75	$0.63	$0.01	$0.61	2%	61	1637	1256	5045	$12	$500	$122
LMI1	$1.52	$1.27	$0.23	$1.04	18%	99	1543	1099	4678	$15	$1,158	$222
LMI2	$1.91	$1.60	$0.13	$1.47	8%	47	641	397	1636	$41	$4,018	$896
UMI1	$2.98	$2.50	$0.59	$1.91	24%	59	561	377	1419	$50	$6,635	$1,345
UMI2	$1.50	$1.26	$1.33	-$0.07	105%	25	416	213	899	$59	$5,897	CS
Other Categories[a]												
SSA	$1.71	$1.43	$0.23	$1.20	16%	76	2048	1515	5960	$22	$944	$202
Gavi-eligible[c]	$2.22	$1.86	$0.23	$1.63	13%	143	3003	2228	9186	$16	$837	$177
HBC	$0.95	$0.80	$0.03	$0.76	4%	40	1162	843	4554	$24	$945	$168
India	$0.97	$0.81	$0.18	$0.63	22%	64	1077	781	3379	$15	$1,041	$187

[a] CS: cost-saving; D: discounted; DALY: disability-adjusted life-year; HBC: high burden country; LI: Low Income; LMI1: Lower-middle income tier 1; LMI2: Lower-middle income tier 2; UMI1: Upper-middle income tier 1; UMI2: Upper-middle income tier 2; SSA: Sub-Saharan Africa; U: undiscounted. This vaccination program is using the base case 2-tier vaccine pricing assumption that all countries with GDP per capita under $2585 (LI and LMI1 countries) will access the vaccine at $4.55 per dose and all countries with higher GDP per capita will access the vaccine at the $13.79 price that is available currently only to a subset of these countries in the LAC region who participate in the PAHO Revolving Fund. Negative net cost indicates the averted treatment costs fully offset the cost of the vaccination program. This occurs in UMI2 setting and the LAC region.

[b] Gradual roll-out: 10% coverage in 2015, 20% coverage in 2016, 30% coverage in 2017, 40% coverage in 2018, 50% coverage in 2019, 60% coverage in 2020, 70% coverage in 2021, 80% coverage in 2022, 90% coverage in 2023, and 100% coverage of the target population in 2024.

[c] Gavi-eligible in 2014. See Table S1 for listing of 43 countries.

Table 3b. HPV vaccination program costs, health outcomes, and cost-effectiveness: 10-year roll-out of a 2-dose vaccination program for 10-year old girls with no catch-up, 4-tier vaccine pricing.

10-year scale up [b] *4-tier pricing*	Costs (Billions)					Health Outcomes (Thousands)				Cost-effectiveness		
	Program Cost		Cancer Treatment Costs AVERTED	Net Cost	Treatment Savings as Percentage of Program Costs	Vaccin-ations (millions)	Cases Averted	Deaths Averted	DALYs Averted	Program Cost to Vaccinate a Girl with 2 doses	Program Cost per Death Averted	Net Cost per DALY Averted
	U	D	D	D	D	U	U	U	D	U	D/U	D
TOTAL	$13.1	$11.0	$2.32	$8.69	$0.21	292	4793	3338	13,663	$45	$3,299	$636
Income Tiers												
LI	$0.75	$0.63	$0.01	$0.61	$0.02	61	1637	1256	5045	$12	$500	$122
LMI1	$1.56	$1.31	$0.23	$1.08	$0.18	99	1543	1099	4678	$16	$1,195	$231
LMI2	$3.14	$2.63	$0.13	$2.50	$0.05	47	641	397	1636	$68	$6,617	$1,528
UMI1	$5.82	$4.87	$0.59	$4.28	$0.12	59	561	377	1419	$98	$12,943	$3,018
UMI2	$1.87	$1.57	$1.33	$0.24	$0.85	25	416	213	899	$74	$7,343	$267
Other Categories												
SSA	$2.44	$2.04	$0.23	$1.81	11%	76	2048	1515	5960	$31.94	$1,346	$304
Gavi-eligible	$2.22	$1.86	$0.23	$1.63	13%	143	3003	2228	9186	$15.51	$837	$177
HBC	$1.37	$1.15	$0.03	$1.11	3%	40	1162	843	4554	$34.22	$1,360	$245
India	$0.97	$0.81	$0.18	$0.63	22%	64	1077	781	3379	$15.00	$1,041	$187

[a] CS: cost-saving; D: discounted; DALY: disability-adjusted life-year; HBC: high burden country; LMIC: low- and middle-income countries; LI: Low Income; LMI1: Lower-middle income tier 1; LMI2: Lower-middle income tier 2; UMI1: Upper-middle income tier 1; UMI2: Upper-middle income tier 2; SSA: Sub-Saharan Africa; U: undiscounted. This vaccination program is using the alternative 4-tier vaccine pricing assumption. Negative net cost indicates the averted treatment costs fully offset the cost of the vaccination program. This occurs in UMI2 setting and the LAC region.

[b] Gradual roll-out: 10% coverage in 2015, 20% coverage in 2016, 30% coverage in 2017, 40% coverage in 2018, 50% coverage in 2019, 60% coverage in 2020, 70% coverage in 2021, 80% coverage in 2022, 90% coverage in 2023, and 100% coverage of the target population in 2024.

[c] Gavi eligible in 2014. See Table S1 for listing of 43 countries.

Table 4a. Screening program costs, health outcomes, and cost-effectiveness: 10-year roll-out of Minimal Intensity screening.

Minimal Intensity: Once in a lifetime 10-year scale up[b]	Costs (Billions)					Health Outcomes (Thousands)				Cost-effectiveness		
	Screening and Lesion Treatment Cost		Cancer Treatment Costs AVERTED	Net Cost	Treatment Savings (% Program Costs)	Primary Screenings (Millions)	Cases Averted	Deaths Averted	DALYs Averted	Cost per Woman Reached	Program Cost per Death Averted	Net Cost per DALY Averted
	U	D	D	D	D	U	U	U	D	U	D / U	D
TOTAL	$5.0	$4.3	$1.9	$2.4	44%	252	1430	968	9513	$19.63	$4,473	$253
Income Tier												
LI : VIA 1X	$0.12	$0.10	$0.01	$0.10	7%	33	284	223	2159	$3.63	$470	$45
LMI1 : VIA 1X	$0.55	$0.48	$0.17	$0.31	36%	81	473	317	3326	$6.75	$1,507	$93
LMI2 : VIA 1X[c]	$0.54	$0.47	$0.08	$0.39	18%	33	152	92	943	$16.51	$5,125	$413
UMI1 : HPV 1x[c]	$2.21	$1.92	$0.83	$1.10	43%	79	409	273	2409	$27.85	$7,042	$455
UMI2 : HPVVIA 1x[c]	$1.54	$1.35	$0.82	$0.53	61%	26	113	62	675	$58.93	$21,679	$780
Other Categories												
SSA	$0.36	$0.31	$0.22	$0.09	70%	37	357	271	2512	$9.73	$1,145	$37
Gavi-eligible	$0.59	$0.52	$0.17	$0.35	33%	103	722	516	5230	$5.75	$1,009	$67
HBC	$0.15	$0.13	$0.01	$0.12	10%	18	175	132	1236	$8.35	$1,013	$98
India	$0.37	$0.33	$0.14	$0.19	43%	57	372	249	2627	$6.54	$1,317	$71

[a] 1x: once in a lifetime screening at age 35; D: discounted; DALY: disability-adjusted life-year; HBC: high burden country; HPV: HPV testing; HPVVIA: HPV testing followed by visual triage; LMIC: low- and middle-income countries; LI: Low Income; LMI1: Lower-middle income tier 1; LMI2: Lower-middle income tier 2; UMI1: Upper-middle income tier 1; UMI2: Upper-middle income tier 2; SSA: Sub-Saharan Africa; U: undiscounted; VIA: visual inspection with acetic acid. Minimal intensity screening involves screening once in a lifetime at age 35 years, with the specified screening test.

[b] Gradual roll-out: 10% coverage in 2015, 20% coverage in 2016, 30% coverage in 2017, 40% coverage in 2018, 50% coverage in 2019, 60% coverage in 2020, 70% coverage in 2021, 80% coverage in 2022, 90% coverage in 2023, and 100% coverage of the target population in 2024.

[c] Cost per woman reached is defined as the cost divided by the number of primary screenings.

[d] Countries with existing cytology programs to scale up cytology instead of HPV testing or VIA. Existing cytology programs with >40% coverage (includes Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, El Salvador, Hungary, Kazakhstan, Mexico, Paraguay, Peru, Ukraine) [15, 16].

Table 4b. Screening program costs, health outcomes, and cost-effectiveness: 10-year roll-out of Moderate Intensity screening

Moderate Intensity: Every 5 years 10-year scale up[b]	Costs (Billions)					Health Outcomes (Thousands)				Cost-effectiveness	
	Screening and Lesion Treatment Cost (Billions)		Cancer Treatment Costs AVERTED (Billions)	Net Cost (Billions)	Treatment Savings as Percentage of Program Costs	Screenings (Millions)	Cases Averted (Thousands)	Deaths Averted (Thousands)	DALYs Averted (Thousands)	Program Cost per Death Averted	Net Cost per DALY Averted
	U	D	D	D	D	U	U	U	D	D / U	D
TOTAL	$18.1	$15.9	$4.6	$11.3	29%	940	3292	2260	22538	$7,023	$502
Income Tier											
LI : VIA Q5	$0.42	$0.36	$0.02	$0.35	5%	121	695	543	5332	$671	$65
LMI1 : VIA Q5	$1.96	$1.72	$0.45	$1.27	26%	302	1182	799	8447	$2,148	$150
LMI2 : VIA Q5 [c]	$1.95	$1.71	$0.22	$1.49	13%	124	397	244	2511	$7,019	$592
UMI1 : HPV Q5 [c]	$8.08	$7.13	$1.57	$5.56	22%	291	730	514	4581	$13,870	$1,214
UMI2 : HPVVIA Q5 [c]	$5.64	$4.95	$2.22	$2.73	45%	101	303	170	1828	$29,143	$1,493
Other Categories											
SSA	$1.28	$1.12	$0.44	$0.68	39%	134	831	627	5908	$1,780	$115
GAVI	$2.12	$1.86	$0.45	$1.40	24%	384	1793	1281	13150	$1,449	$107
HBC	$0.54	$0.47	$0.03	$0.44	7%	67	432	320	3036	$1,468	$144
India	$1.35	$1.18	$0.37	$0.81	31%	215	936	628	6697	$1,879	$121

[a] D: discounted; DALY: disability-adjusted life-year; HBC: high burden country; HPV: HPV testing; HPVVIA: HPV testing followed by visual triage; LMIC: low- and middle-income countries; LI: Low Income; LMI1: Lower-middle income tier 1; LMI2: Lower-middle income tier 2; Q5: 5-year screening intervals; UMI1: Upper-middle income tier 1; UMI2: Upper-middle income tier 2; SSA: Sub-Saharan Africa; U: undiscounted; VIA: visual inspection with acetic acid. Moderate Intensity screening involves screening at 5-year intervals at ages 30, 35, 40, and 45 years with the specified screening test, which is the same as in the Minimal Intensity screening scenario. During the 10-years of the program, women who were covered by the program received screening at ages 30, 35, 40, or 45, so, at most, women received 2 screens during the intervention period. Over a lifetime, however, a woman currently under 30 who is covered by the program will receive 4 screenings at 5 year intervals.

[b] Gradual roll-out: 10% coverage in 2015, 20% coverage in 2016, 30% coverage in 2017, 40% coverage in 2018, 50% coverage in 2019, 60% coverage in 2020, 70% coverage in 2021, 80% coverage in 2022, 90% coverage in 2023, and 100% coverage of the target population in 2024.

[c] Countries with existing cytology programs to scale up cytology instead of HPV testing or VIA. Existing cytology programs with >40% coverage (includes Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, El Salvador, Hungary, Kazakhstan, Mexico, Paraguay, Peru, Ukraine) [15, 16].

Table 4c. Screening program costs, health outcomes, and cost-effectiveness: 10-year roll-out of High Intensity screening

High Intensity: *Every 5 years, with HPV testing in middle-income countries* 10-year scale up[b]	Costs (Billions)					Health Outcomes (Thousands)				Cost-effectiveness	
	Screening and Lesion Treatment Cost (Billions)		Cancer Treatment Costs AVERTED (Billions)	Net Cost (Billions)	Treatment Savings as Percentage of Program Costs	Screenings (Millions)	Cases Averted (Thousands)	Deaths Averted (Thousands)	DALYs Averted (Thousands)	Program Cost per Death Averted	Net Cost per DALY Averted
	U	D	D	D	D	U	U	U	D	D /U	D
TOTAL	$14.5	$12.7	$4.1	$8.6	32%	940	3849	2605	26071	$4,880	$331
By Income Tier											
LI : VIA Q5	$0.42	$0.36	$0.02	$0.35	5%	121	695	543	5332	$671	$65
LMI1 : HPV Q5	$3.20	$2.81	$0.64	$2.16	23%	302	1744	1183	11899	$2,373	$182
LMI2 : HPV Q5	$2.57	$2.26	$0.33	$1.93	14%	124	594	364	3568	$6,200	$541
UMI1 : HPVVIA Q5	$5.63	$4.95	$1.07	$3.88	22%	291	458	312	3109	$15,855	$1,248
UMI2 : HPVVIA Q5	$2.66	$2.34	$2.17	$0.16	93%	101	294	166	1797	$14,047	$91
By Other Categories											
SSA	$1.38	$1.20	$0.29	$0.91	24%	134	905	672	6290	$1,792	$145
GAVI	$3.13	$2.74	$0.67	$2.08	24%	384	2334	1642	16419	$1,670	$127
HBC	$0.77	$0.68	$0.05	$0.63	8%	67	511	371	3434	$1,825	$182
India	$2.14	$1.88	$0.53	$1.35	28%	215	1370	924	9373	$2,035	$144

[a] D: discounted; DALY: disability-adjusted life-year; HBC: high burden country; HPV: HPV testing; HPVVIA: HPV testing followed by visual triage; LMIC: low- and middle-income countries; LI: Low Income; LMI1: Lower-middle income tier 1; LMI2: Lower-middle income tier 2; Q5: 5-year screening intervals; UMI1: Upper-middle income tier 1; UMI2: Upper-middle income tier 2; SSA: Sub-Saharan Africa; U: undiscounted; VIA: visual inspection with acetic acid. Moderate Intensity screening involves screening at 5-year intervals at ages 30, 35, 40, and 45 years with the specified screening test, which is the same as in the Minimal Intensity screening scenario. During the 10-years of the program, women who were covered by the program received screening at ages 30, 35, 40, or 45, so, at most, women received 2 screens during the intervention period. Over a lifetime, however, a woman currently under 30 who is covered by the program will receive 4 screenings at 5 year intervals.

[b] Gradual roll-out: 10% coverage in 2015, 20% coverage in 2016, 30% coverage in 2017, 40% coverage in 2018, 50% coverage in 2019, 60% coverage in 2020, 70% coverage in 2021, 80% coverage in 2022, 90% coverage in 2023, and 100% coverage of the target population in 2024.

[c] Countries with existing cytology programs to scale up cytology instead of HPV testing or VIA. Existing cytology programs with >40% coverage (includes Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, El Salvador, Hungary, Kazakhstan, Mexico, Paraguay, Peru, Ukraine) [15, 16].

Figure 1. Distribution of cervical cancer screening, diagnostic, and preventive treatment costs for three scenarios.

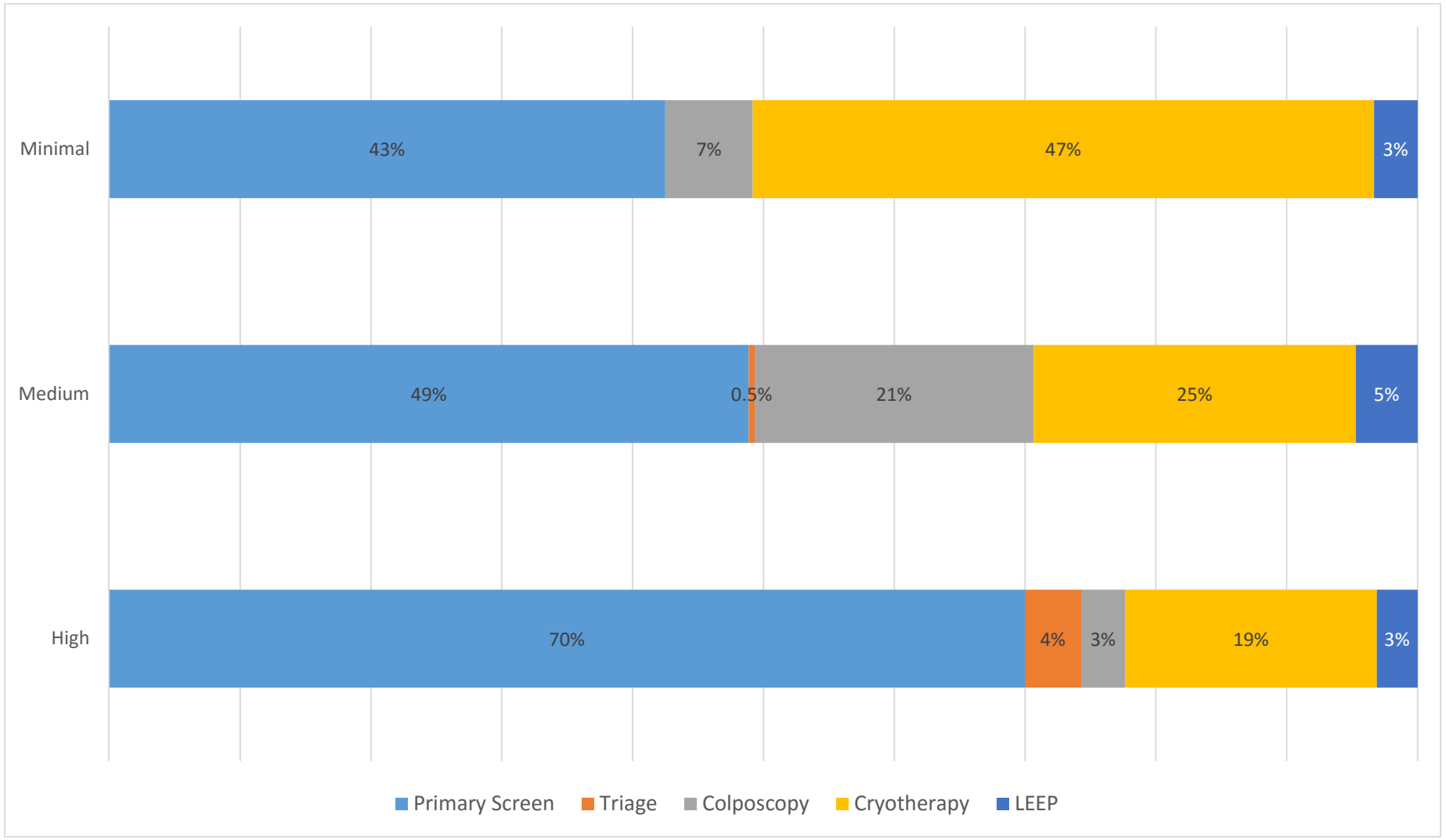
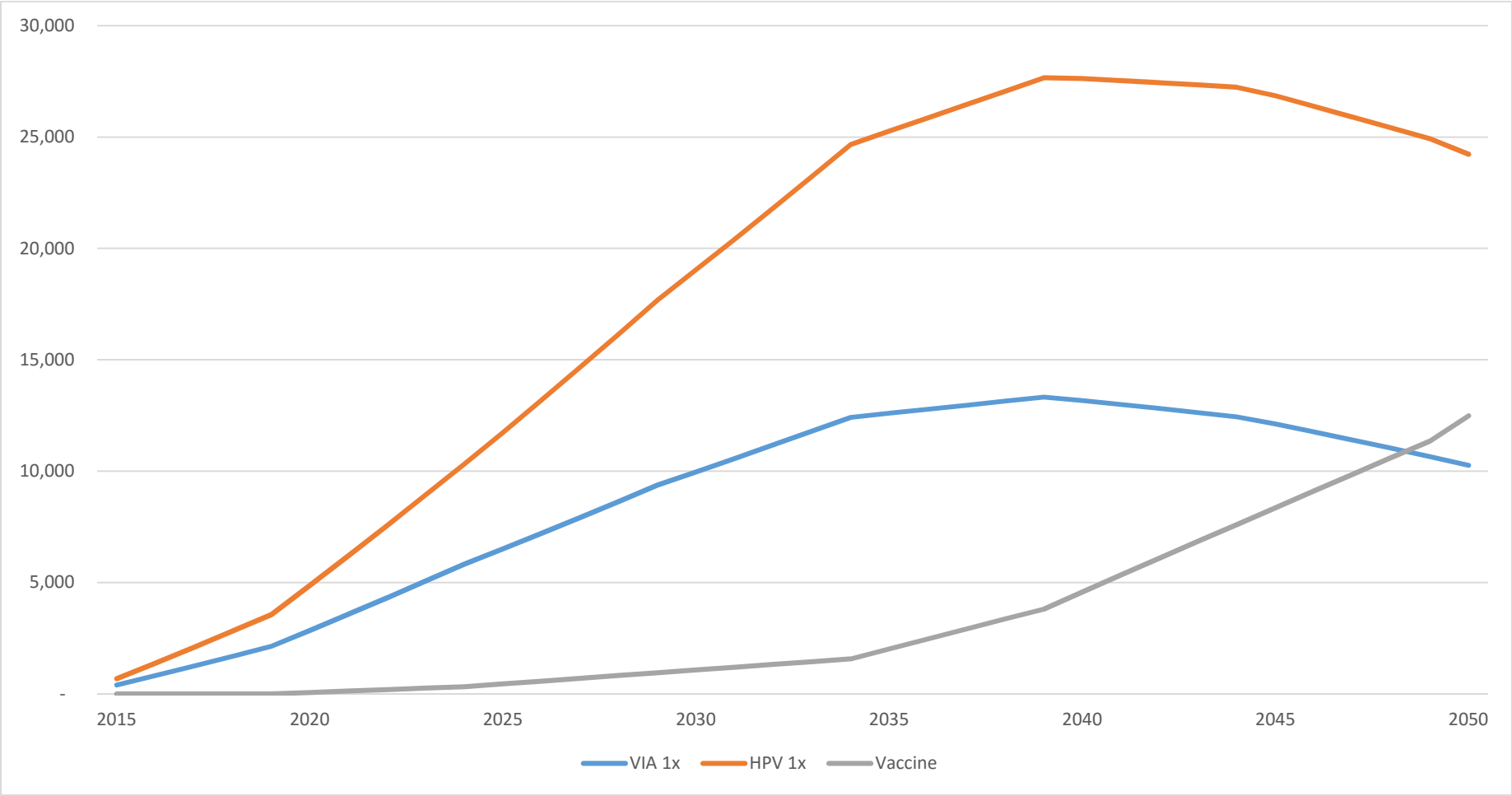


Figure 2. Deaths Averted in each calendar year 2015-2050 due to prevention activities operating at full scale in India during 2015-2024.



Annex 1. Policy Scenario for Cervical Cancer Action

Cervical Cancer Action (CCA) is a coalition of several organizations dedicated to working collaboratively to eliminate cervical cancer through strategic advocacy, information sharing, human and resource mobilization, and collaborative partnerships. (http://www.cervicalcanceraction.org). It's five-year initiative, "Taking Cervical Cancer Prevention to Scale: Protecting All Women and Girls" aims to build momentum for action on global cervical cancer prevention over the next five years. To support this effort, we applied the cost and impact modeling framework described in this report to a custom scenario tailored to CCA priorities.

CCA Scenario Specification

The CCA scenario covers a lower-income subset of the countries included in our main analysis. Specifically, it focuses on the LI and LMI1 categories, that is those countries with GDP per capita under $2585. The vaccination strategy was the same as in the main analysis—a linear scale up reaching full scale in 10 years, of 2 dose vaccination for 10-year-old girls with no catch-up vaccination outside these cohorts. However, the screening strategy was unique. We considered a more rapid scaling up of screening, to reach full scale (100% coverage of target population) in 5 years. Additionally, the screening strategy includes a transition over time, from VIA to HPV testing (Figure A1-1). The shift to HPV is most accelerated in the LMI1 countries, reaching 100% HPV-based screening by 2024 vs. 50% replacement of VIA with HPV-based screening in LI countries by 2024.

Results

Cost

The CCA strategy costs $3.64 billion *over 10 years* (Table A1-1). The annual costs grow over time as the programs scale up from about $60 million in 2015 to $550 million in 2024 (Figure A1-2). The cost per girl reached with vaccination is $14.13 In all countries, the vaccine cost was assumed to be the Gavi price of $4.55 per dose. Cost per girl for vaccination is modestly higher in the less poor LMI1 countries due to higher service delivery cost. The cost per woman reached with screening is $8.36. Screening costs are about double in LMI1 compared to LI countries due to both higher service delivery costs and more use of HPV testing. Overall, VIA is 31% of the total screening program costs.

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Impact and Cost-Effectiveness

Vaccination will prevent 2.36 million cervical cancer deaths over the lifetimes of the 160 million girls in the vaccinated cohorts. Screening will prevent 1.23 million cervical cancer deaths over the lifetimes of the 164 million women screened during the intervention decade (Table A1-1).

Approximately 11% of the program costs are offset by averted cancer treatment costs in low-income settings. In low-middle income settings up to GDP 2585 per capita, where access to cancer treatment is higher, approximately 26% of the program costs are offset. The *net* cost per disability-adjusted life year (DALY) averted is $170 for vaccination and $70 for screening (Table A1-1).

Menu of Options

In addition to the CCA scenario for comprehensive cervical cancer control, we also estimated the cost and impact of several specific policy actions which are reported in Table A1-2. Impact is shown both in terms of cancer deaths averted as well as disability adjusted life years (DALYs) averted.

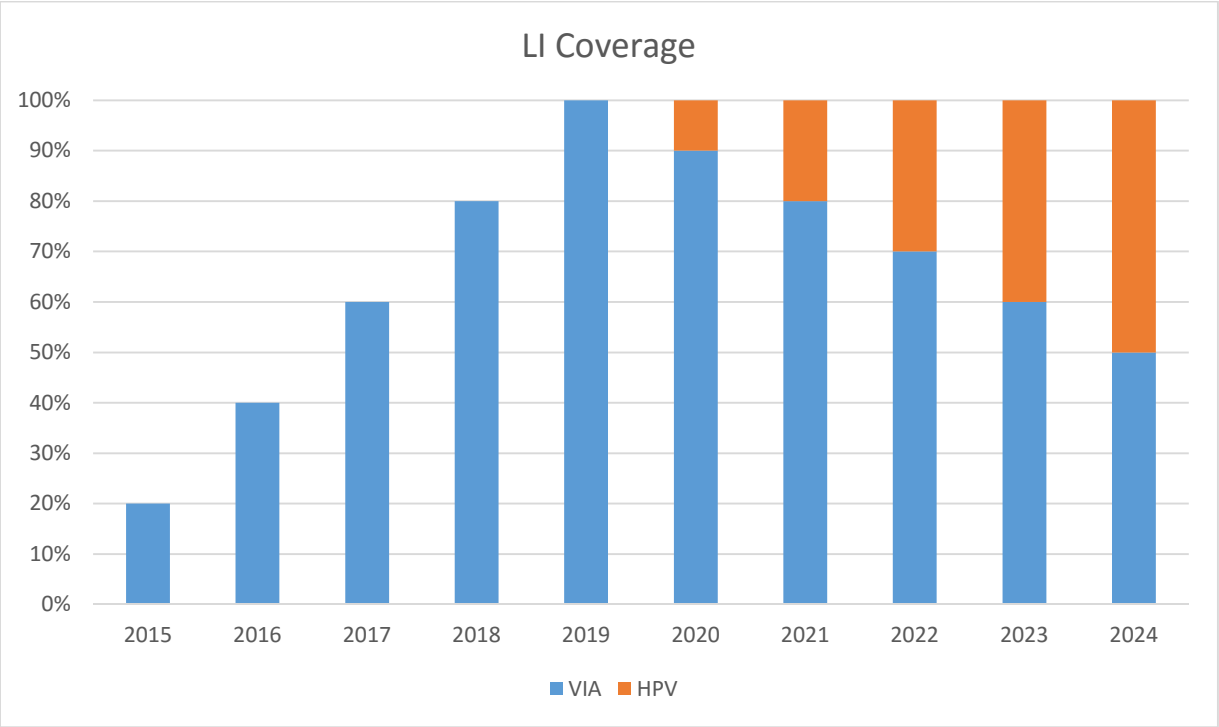
Table A1-1. Cost, outcomes, and cost effectiveness of the CCA policy scenario.

	Program Cost (millions) U	Program Cost (millions) D	Number Reached (millions) U	Deaths Averted (thousands) U	DALYs Averted (millions) D	CCTx Cost Averted (millions) D	Net Cost (millions) D	CCTx Cost as Share of Program Cost D	Program Cost per Woman Reached U	Program Cost Per Death Averted U	Net Cost per DALY Averted D
Vaccine											
LI	$751	$629	61	1,256	5.0	$23	$605	4%	$12.25	$598	$122
LMI1	$1,516	$1,272	99	1,099	4.7	$183	$1,089	14%	$15.29	$1,379	$222
Total Screening	$2,267	$1,901	160	2,355	9.7	$207	$1,694	11%	$14.13	$962	$170
LI	$420	$369	74	395	3.9	$83	$286	23%	$5.71	$1,063	$66
LMI1	$953	$792	91	836	8.1	$363	$429	46%	$10.52	$1,139	$71
Total Combined	$1,372	$1,161	164	1231	12.0	$446	$715	38%	$8.36	$1,115	$70
LI	$1,171	$997	135	1651	8.9	$107	$891	11%	$8.68	$709	$100
LMI1	$2,468	$2,064	190	1935	12.8	$546	$1,518	26%	$13.01	$1,276	$119
Total	$3,639	$3,062	325	3586	21.7	$653	$2,409	21%	$11.21	$1,015	$111

Low income (LI) (GNI pc < $1045) ; Lower-middle income 1 (LMI1) (GNI pc $1046 - $2585)

The CCA strategy costs $3.64 billion *over 10 years*. The annual costs grow over time as the programs scale up. The cost per woman reached with screening is $8.36. The cost per girl reached with vaccination is $14.13. Approximately 11% of the program costs are offset by averted cancer treatment costs in low-income settings. In low-middle income settings up to GDP 2585 per capita, where access to cancer treatment is higher, approximately 26% of the program costs are offset. Vaccination will prevent 2.36 million cervical cancer deaths over the lifetimes of the 160 million girls in the vaccinated cohorts. Screening will prevent 1.23 million cervical cancer deaths over the lifetimes of the 164 million women screened during the intervention decade. The net cost per disability-adjusted life year (DALY) averted is $170 for vaccination and $70 for screening.

Figure A1-1. Coverage of CCA screening policy scenario by technology type, stratified by country income tier.



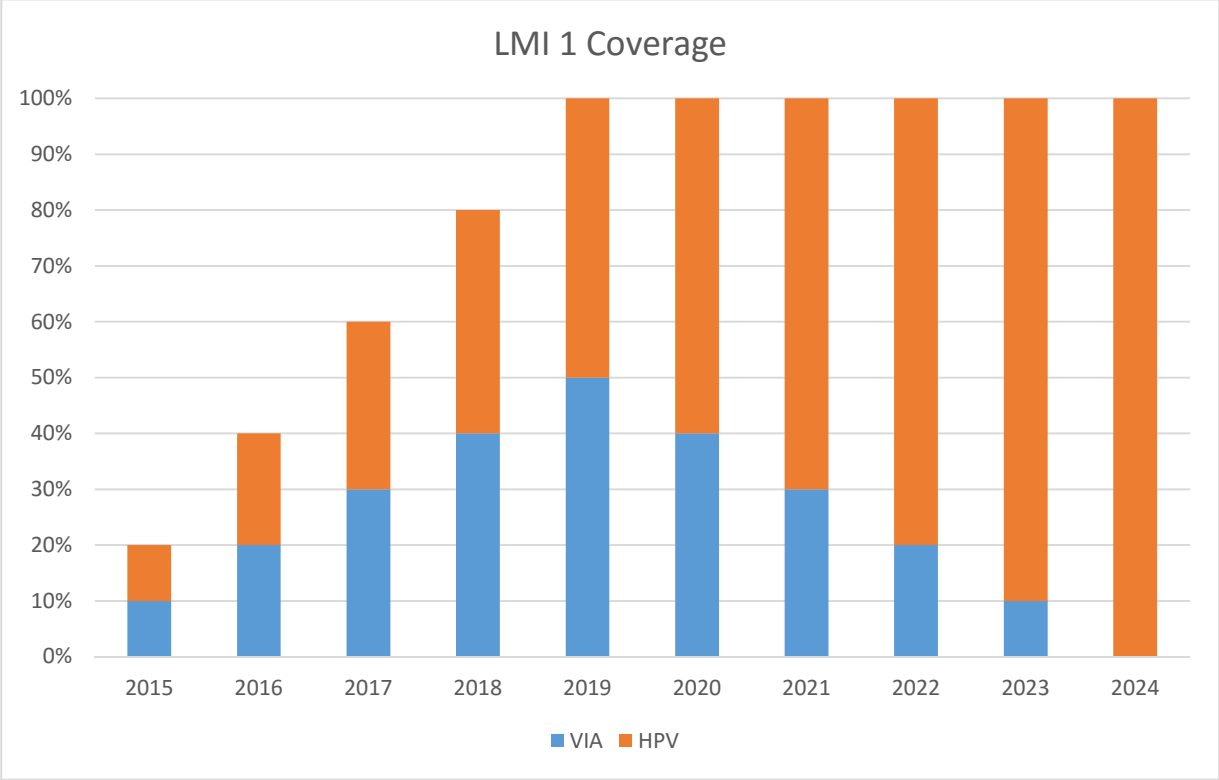


Figure A1-2. Total cost, by technology type.

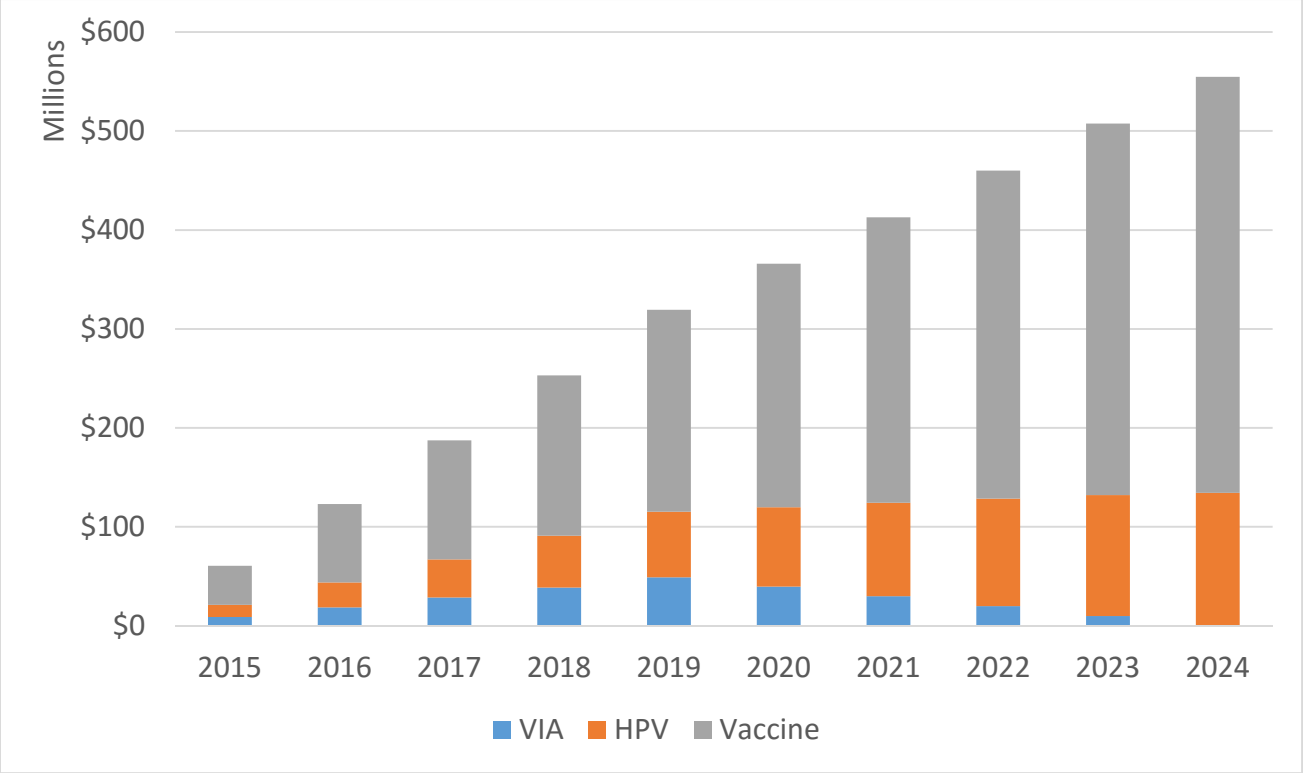


Table A1-2. Menu of Policy Options for Cervical Cancer Action.

HPV Vaccination	**Cost (USD)[a]**	**Deaths prevented[b]**	**DALYs averted[c]**
Service delivery costs for vaccinating one million young adolescent girls in a country receiving HPV vaccine from Gavi (two-dose regimen, service delivery costs only, no GAVI co-pay included)	$5m	NA	NA
Purchase vaccine doses for one million young adolescent girls in a middle-income country (two-dose regimen, vaccine only)	$27m	NA	NA
Vaccinate all young adolescent girls in the five highest-burden low- and lower-middle-income countries (Gavi countries, two-dose regimen, vaccine + service delivery)	$24m/year	66,000	355,000
Vaccinate all young adolescent girls in the 21 highest-burden countries in Africa (two-dose regimen, vaccine + service delivery, 19 Gavi countries, 2 non-Gavi countries)	$167m/year	148,000	798,000
Screening and Preventive Treatment	**Cost (USD)[a]**	**Deaths prevented[b]**	**DALYs averted[c]**
Screen and treat one million women aged 30–49 years in a sub-Saharan African country using VIA and cryotherapy	$9.2m	6800	64,000
Screen and treat one million women aged 30–49 years in India using HPV DNA testing and cryotherapy	$11m	9500	93,500
Screen and treat one million women aged 30–49 years in a sub-Saharan African country using HPV DNA testing and cryotherapy	$16.8m	15,100	132,000
Screen and treat one million women aged 30–49 years in a Latin American country using HPV DNA testing and cryotherapy	$33m	7500	69,750
Screen and treat one million women aged 30–49 years in the 21 highest-burden African countries using HPV DNA testing and cryotherapy in one year.	$16.6m	15,900	138,800

[a] undiscounted *program* costs do not account for cancer treatment costs averted by prevention. [b] over the lifetime of women reached by prevention program. [c] over the lifetime of women reached by prevention program, discounted at 3% per annum.

Annex 2. Data Appendix

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

Count	Low Income (LI) ≤$1045	Lower-middle income 1 (LMI1) $1046-$2585	Lower-middle income 2 (LMI2) $2586-$4125	Upper-middle income 1 (UMI1) $4126-$8435	Upper-middle income 2 (UMI2) $8436-12745
1	Afghanistan[b]	Bolivia	Armenia	Albania	Argentina[a]
2	Bangladesh[b]	Cameroon[b]	Congo, Rep.	Algeria	Brazil
3	Benin[b]	Cote d'Ivoire[b]	Egypt	Angola	Costa Rica
4	Burkina Faso[b]	Ghana[b]	El Salvador	Azerbaijan	Gabon
5	Burundi[b]	Honduras	Georgia	Belarus	Hungary
6	Cambodia[b]	India[b]	Guatemala	Bosnia and Herzegovina	Kazakhstan
7	Central African Republic[b]	Kyrgyz Republic[b]	Indonesia	Botswana	Lebanon
8	Chad[b]	Lao PDR[b]	Mongolia	Bulgaria	Malaysia
9	Congo, Dem. Rep.[b]	Lesotho[b]	Morocco	China	Mauritius
10	Eritrea[b]	Mauritania[b]	Nigeria	Colombia	Mexico
11	Ethiopia[b]	Moldova	Paraguay	Dominican Republic	Panama
12	Gambia, The[b]	Nicaragua	Philippines	Ecuador	Romania
13	Guinea[b]	Pakistan[b]	Sri Lanka	Jamaica	Turkey
14	Guinea-Bissau[b]	Papua N. Guinea	Swaziland	Jordan	Venezuela
15	Haiti[b]	Senegal[b]	Timor-Leste	Macedonia, FYR	
16	Kenya[b]	Sudan[b]	Ukraine	Namibia	
17	Liberia[b]	Uzbekistan		Peru	
18	Madagascar[b]	Vietnam[b]		Serbia	
19	Malawi[b]	Yemen, Rep.[b]		South Africa	
20	Mali[b]	Zambia[b]		Thailand	
21	Mozambique[b]			Tunisia	
22	Nepal[b]			Turkmenistan	
23	Niger[b]				
24	Rwanda[b]				
25	Sierra Leone[b]				
26	Tajikistan[b]				
27	Tanzania[b]				
28	Togo[b]				
29	Uganda[b]				
30	Zimbabwe[b]				

[a] Argentina was classified as UMI2, although no GNI per capita data is available.
[b] Eligible for GAVI assistance.

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

	Sub-Saharan Africa	East Asia & Pacific	Europe & Central Asia	Latin America & Caribbean	Middle East & North Africa	South Asia
1	Angola	Cambodia	Albania	Argentina	Algeria	Afghanistan
2	Benin	China	Armenia	Bolivia	Egypt	Bangladesh
3	Botswana	Indonesia	Azerbaijan	Brazil	Jordan	India
4	Burkina Faso	Lao PDR	Belarus	Colombia	Lebanon	Nepal
5	Burundi	Malaysia	Bosnia and Herzegovina	Costa Rica	Morocco	Pakistan
6	Cameroon	Mongolia	Bulgaria	Dominican Republic	Tunisia	Sri Lanka
7	Central African Republic	Papua N. Guinea	Georgia	Ecuador	Yemen, Rep.	
8	Chad	Philippines	Hungary	El Salvador		
9	Congo, Dem. Rep.	Thailand	Kazakhstan	Guatemala		
10	Congo, Rep.	Timor-Leste	Kyrgyz Republic	Haiti		
11	Côte d'Ivoire	Vietnam	Macedonia, FYR	Honduras		
12	Eritrea		Moldova	Jamaica		
13	Ethiopia		Romania	Mexico		
14	Gabon		Serbia	Nicaragua		
15	Gambia, The		Tajikistan	Panama		
16	Ghana		Turkey	Paraguay		
17	Guinea		Turkmenistan	Peru		
18	Guinea-Bissau		Ukraine	Venezuela		
19	Kenya		Uzbekistan			
20	Lesotho					
21	Liberia					
22	Madagascar					
23	Malawi					
24	Mali					
25	Mauritania					
26	Mauritius					
27	Mozambique					
28	Namibia					
29	Niger					
30	Nigeria					
31	Rwanda					
32	Senegal					
33	Sierra Leone					
34	South Africa					
35	Sudan					
36	Swaziland					
37	Tanzania					
38	Togo					
39	Uganda					
40	Zambia					
41	Zimbabwe					

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

Country	Age 30-34	Age 35-39	Age 40-44	Age 45-49
Afghanistan	0.188 [b]	0.229 [b]	0.155 [b]	0.385 [b]
Albania	0.248 [b]	0.239 [c]	0.168 [c]	0.105 [b]
Algeria	0.250 [a]	0.000 [a]	0.111 [a]	0.333 [a]
Angola	0.383 [b]	0.104 [b]	0.177 [b]	0.269 [b]
Argentina	0.172 [a]	0.140 [a]	0.143 [a]	0.118 [a]
Armenia	0.269 [c]	0.239 [c]	0.168 [c]	0.127 [c]
Azerbaijan	0.236 [b]	0.223 [b]	0.162 [b]	0.093 [b]
Bangladesh	0.140 [b]	0.127 [b]	0.143 [b]	0.174 [b]
Belarus	0.245 [b]	0.189 [b]	0.160 [b]	0.101 [b]
Benin	0.129 [b]	0.265 [b]	0.136 [b]	0.132 [b]
Bolivia	0.105 [b]	0.148 [b]	0.141 [b]	0.118 [b]
Bosnia and Herzegovina	0.345 [b]	0.203 [b]	0.182 [b]	0.196 [b]
Botswana	0.316 [b]	0.186 [b]	0.153 [b]	0.231 [b]
Brazil	0.142 [a]	0.118 [a]	0.100 [a]	0.114 [a]
Bulgaria	0.385 [b]	0.181 [b]	0.204 [b]	0.191 [b]
Burkina Faso	0.397 [b]	0.240 [b]	0.273 [b]	0.364 [b]
Burundi	0.312 [b]	0.140 [b]	0.206 [b]	0.358 [b]
Cambodia	0.099 [b]	0.112 [b]	0.111 [b]	0.142 [b]
Cameroon	0.300 [c]	0.282 [c]	0.245 [c]	0.198 [c]
Central African Republic	0.341 [b]	0.419 [b]	0.294 [b]	0.252 [b]
Chad	0.300 [c]	0.282 [c]	0.245 [c]	0.198 [c]
China	0.098 [a]	0.144 [a]	0.161 [a]	0.162 [a]
Colombia	0.148 [a]	0.098 [a]	0.093 [a]	0.077 [a]
Congo, Dem. Rep.	0.333 [b]	0.281 [b]	0.288 [b]	0.241 [b]
Congo, Rep.	0.216 [b]	0.282 [c]	0.289 [b]	0.079 [b]
Costa Rica	0.129 [b]	0.086 [b]	0.100 [b]	0.118 [b]
Cote d'Ivoire	0.385 [a]	0.385 [a]	0.273 [a]	0.182 [a]
Dominican Republic	0.090 [b]	0.042 [b]	0.076 [b]	0.082 [b]
Ecuador	0.076 [b]	0.055 [b]	0.045 [b]	0.202 [b]
Egypt	0.037 [a]	0.281 [a]	0.103 [a]	0.067 [a]
El Salvador	0.170 [c]	0.152 [c]	0.149 [c]	0.155 [c]
Eritrea	0.343 [b]	0.277 [b]	0.276 [b]	0.260 [b]
Ethiopia	0.377 [b]	0.229 [b]	0.288 [b]	0.297 [b]
Gabon	0.224 [c]	0.212 [b]	0.256 [b]	0.236 [c]
Gambia, The	0.300 [c]	0.282 [c]	0.245 [c]	0.069 [b]
Georgia	0.269 [c]	0.239 [c]	0.168 [c]	0.127 [c]
Ghana	0.300 [c]	0.282 [c]	0.245 [c]	0.198 [c]
Guatemala	0.344 [a]	0.286 [a]	0.313 [a]	0.273 [a]
Guinea	0.300 [c]	0.272 [b]	0.245 [c]	0.198 [c]
Guinea-Bissau	0.177 [b]	0.224 [b]	0.160 [b]	0.183 [b]

Table S3 (ctnd.) HPV prevalence inputs, by country and age group.

Country	Age 30-34	Age 35-39	Age 40-44	Age 45-49
Haiti	0.170 [c]	0.152 [c]	0.149 [c]	0.155 [c]
Honduras	0.361 [a]	0.351 [a]	0.342 [a]	0.393 [a]
Hungary	0.350 [b]	0.191 [b]	0.196 [b]	0.158 [b]
India	0.127 [a]	0.135 [a]	0.120 [a]	0.126 [a]
Indonesia	0.227 [a]	0.316 [a]	0.324 [a]	0.178 [a]
Jamaica	0.178 [b]	0.062 [b]	0.112 [b]	0.172 [b]
Jordan	0.150 [b]	0.094 [b]	0.086 [b]	0.253 [b]
Kazakhstan	0.319 [b]	0.255 [b]	0.192 [b]	0.121 [b]
Kenya	0.345 [a]	0.477 [a]	0.274 [a]	0.348 [a]
Kyrgyz Republic	0.313 [b]	0.537 [b]	0.290 [b]	0.169 [b]
Lao PDR	0.146 [b]	0.229 [b]	0.173 [b]	0.118 [b]
Lebanon	0.138 [b]	0.086 [b]	0.080 [b]	0.239 [b]
Lesotho	0.301 [b]	0.192 [b]	0.247 [b]	0.195 [b]
Liberia	0.177 [b]	0.306 [b]	0.177 [b]	0.156 [b]
Macedonia, FYR	0.264 [b]	0.167 [b]	0.161 [b]	0.125 [b]
Madagascar	0.311 [b]	0.304 [b]	0.251 [b]	0.247 [b]
Malawi	0.414 [d]	0.263 [d]	0.333 [d]	0.200 [d]
Malaysia	0.100 [b]	0.069 [b]	0.078 [b]	0.086 [b]
Mali	0.381 [b]	0.160 [b]	0.264 [b]	0.363 [b]
Mauritania	0.228 [b]	0.257 [b]	0.209 [b]	0.165 [b]
Mauritius	0.273 [b]	0.196 [b]	0.152 [b]	0.176 [b]
Mexico	0.044 [a]	0.060 [a]	0.044 [a]	0.095 [a]
Moldova	0.285 [b]	0.239 [c]	0.295 [b]	0.114 [b]
Mongolia	0.257 [a]	0.250 [a]	0.213 [a]	0.202 [a]
Morocco	0.094 [a]	0.226 [a]	0.154 [a]	0.227 [a]
Mozambique	0.414 [a]	0.263 [a]	0.333 [a]	0.200 [a]
Namibia	0.300 [b]	0.178 [c]	0.202 [c]	0.285 [c]
Nepal	0.187 [b]	0.139 [b]	0.175 [b]	0.215 [b]
Nicaragua	0.245 [b]	0.241 [b]	0.245 [b]	0.213 [b]
Niger	0.300 [c]	0.282 [c]	0.245 [c]	0.292 [b]
Nigeria	0.224 [a]	0.258 [a]	0.254 [a]	0.236 [a]
Pakistan	0.192 [b]	0.199 [b]	0.172 [b]	0.304 [b]
Panama	0.152 [b]	0.090 [b]	0.107 [b]	0.143 [b]
Papua N. Guinea	0.253 [b]	0.198 [b]	0.205 [b]	0.256 [b]
Paraguay	0.182 [a]	0.176 [a]	0.167 [a]	0.167 [a]
Peru	0.048 [a]	0.054 [a]	0.086 [a]	0.085 [a]
Philippines	0.075 [a]	0.143 [a]	0.094 [a]	0.071 [a]
Romania	0.385 [b]	0.235 [b]	0.202 [b]	0.225 [b]
Rwanda	0.345 [d]	0.477 [d]	0.274 [d]	0.348 [d]

Senegal	0.111 [a]	0.113 [a]	0.139 [a]	0.092 [a]

Table S3 (ctnd.) HPV prevalence inputs, by country and age group.

Country	Age 30-34	Age 35-39	Age 40-44	Age 45-49
Serbia	0.410 [b]	0.210 [b]	0.213 [b]	0.215 [b]
Sierra Leone	0.185 [b]	0.324 [b]	0.184 [b]	0.161 [b]
South Africa	0.322 [a]	0.195 [a]	0.199 [a]	0.130 [a]
Sri Lanka	0.097 [b]	0.187 [b]	0.128 [b]	0.096 [b]
Sudan	0.355 [b]	0.388 [b]	0.312 [b]	0.197 [b]
Swaziland	0.288 [b]	0.282 [c]	0.245 [c]	0.261 [b]
Tajikistan	0.278 [b]	0.239 [c]	0.168 [c]	0.127 [c]
Tanzania	0.300 [a]	0.282 [a]	0.245 [a]	0.203 [a]
Thailand	0.118 [b]	0.060 [b]	0.049 [b]	0.056 [b]
Timor-Leste	0.089 [b]	0.153 [b]	0.118 [b]	0.089 [b]
Togo	0.237 [b]	0.303 [b]	0.207 [b]	0.207 [b]
Tunisia	0.167 [a]	0.105 [a]	0.074 [a]	0.333 [a]
Turkey	0.147 [b]	0.096 [b]	0.084 [b]	0.254 [b]
Turkmenistan	0.203 [b]	0.162 [b]	0.140 [b]	0.082 [b]
Uganda	0.345 [d]	0.228 [b]	0.318 [b]	0.348 [d]
Ukraine	0.269 [c]	0.239 [c]	0.168 [c]	0.127 [c]
Uzbekistan	0.281 [b]	0.478 [b]	0.296 [b]	0.112 [b]
Venezuela	0.216 [b]	0.089 [b]	0.133 [b]	0.176 [b]
Vietnam	0.045 [a]	0.049 [a]	0.034 [a]	0.019 [a]
Yemen, Rep.	0.136 [b]	0.218 [b]	0.142 [b]	0.229 [b]
Zambia	0.300 [c]	0.282 [c]	0.245 [c]	0.198 [c]
Zimbabwe	0.300 [c]	0.282 [c]	0.245 [c]	0.198 [c]

[a] Prevalence estimate from survey data.
[b] Prevalence estimate from predictive model. R^2 values: 0.64 (Age 30-34); 0.70 (Age 35-39); 0.59 (Age 40-44); 0.42 (Age 45-49).
[c] Prevalence estimate from regional survey data.
[d] Prevalence estimate from neighboring country with similar cancer incidence (Malawi: used Mozambique prevalence estimates; Rwanda: used Kenya prevalence estimates; Uganda: used Kenya prevalence estimates).

Table S4. Cervical cancer incidence inputs, by country and age group [1].

Country	Age 30-34	Age 35-39	Age 40-44	Age 45-49
Afghanistan	9.3	15.3	21.9	27.0
Albania	5.9	12.5	15.3	9.8
Algeria	1.0	4.0	9.9	18.4
Angola	28.5	44.0	61.3	78.8
Argentina	26.7	37.4	44.2	46.3
Armenia	28.2	42.5	47.0	40.0
Azerbaijan	13.7	18.5	21.5	23.2
Bangladesh	9.6	20.4	35.9	54.9
Belarus	16.2	22.2	27.3	30.2
Benin	15.2	25.5	37.4	48.2
Bolivia	43.1	65.9	87.9	104.8
Bosnia and Herzegovina	14.4	29.1	33.3	40.2
Botswana	30.7	47.0	55.4	60.5
Brazil	15.4	21.8	27.1	31.6
Bulgaria	30.0	43.3	55.4	60.4
Burkina Faso	13.1	24.4	39.9	57.1
Burundi	29.3	53.4	83.9	115.9
Cambodia	13.2	25.5	41.4	61.2
Cameroon	17.7	38.6	65.5	81.0
Central African Republic	6.9	16.7	31.7	44.9
Chad	9.0	18.6	32.2	43.7
China	10.4	14.3	17.5	18.2
Colombia	18.9	27.6	33.6	35.3
Congo, Dem. Rep.	11.5	25.7	45.7	74.5
Congo, Rep.	1.3	8.0	21.2	40.3
Costa Rica	15.3	20.8	23.9	25.6
Cote d'Ivoire	12.5	21.5	32.1	43.0
Dominican Republic	31.9	41.7	51.0	59.9
Ecuador	22.3	36.3	52.0	60.8
Egypt	1.0	1.8	3.3	5.2
El Salvador	47.6	62.1	63.7	57.0
Eritrea	6.8	13.0	22.3	38.6
Ethiopia	11.4	22.1	37.4	63.2
Gabon	14.3	25.5	38.1	48.5
Gambia, The	11.8	21.6	25.1	37.7
Georgia	19.5	31.6	38.7	40.6
Ghana	20.7	34.2	49.4	62.7
Guatemala	38.7	53.8	62.2	60.3
Guinea	18.5	33.8	52.1	68.3
Guinea-Bissau	13.7	26.8	42.2	60.5

Table S4 (ctnd.) Cervical cancer incidence inputs, by country and age group [1].

Country	Age 30-34	Age 35-39	Age 40-44	Age 45-49
Haiti	26.3	36.4	38.1	37.9
Honduras	47.7	65.3	73.1	72.6
Hungary	24.9	34.5	42.2	44.6
India	12.7	25.0	41.9	60.4
Indonesia	7.2	16.5	30.4	43.9
Jamaica	33.0	45.4	55.2	64.5
Jordan	1.3	3.0	5.0	8.7
Kazakhstan	49.9	63.0	64.1	59.6
Kenya	21.5	41.5	63.5	84.0
Kyrgyz Republic	38.3	51.4	57.0	56.0
Lao PDR	11.2	18.3	26.9	33.3
Lebanon	3.3	5.3	7.6	10.5
Lesotho	38.6	40.4	67.0	92.6
Liberia	15.5	27.3	42.3	55.3
Macedonia, FYR	10.0	17.3	26.2	34.9
Madagascar	38.5	59.5	71.5	90.9
Malawi	84.3	128.8	171.7	189.2
Malaysia	9.6	16.8	25.9	35.4
Mali	20.4	41.1	72.5	107.2
Mauritania	13.2	25.4	40.8	58.7
Mauritius	7.4	13.6	20.7	26.0
Mexico	26.8	38.5	46.7	51.1
Moldova	24.8	34.4	42.0	45.2
Mongolia	17.8	32.1	47.5	62.3
Morocco	7.3	14.7	23.3	33.4
Mozambique	71.4	90.1	108.2	132.5
Namibia	11.8	18.5	27.6	33.8
Nepal	8.5	22.9	36.6	53.3
Nicaragua	46.8	66.7	78.7	85.4
Niger	7.2	11.7	17.1	18.1
Nigeria	8.9	21.2	39.7	61.3
Pakistan	4.8	9.2	15.0	23.4
Panama	27.9	36.7	41.9	42.3
Papua N. Guinea	37.5	59.5	80.1	87.8
Paraguay	49.0	66.1	75.7	76.7
Peru	26.6	44.9	63.3	74.5
Philippines	19.0	28.0	36.5	40.1
Romania	25.2	40.2	56.0	72.1
Rwanda	22.3	42.0	68.1	104.9
Senegal	20.3	38.2	61.9	88.0

Table S4 (ctnd.) Cervical cancer incidence inputs, by country and age group [1].

Country	Age 30-34	Age 35-39	Age 40-44	Age 45-49
Serbia	32.0	45.8	56.8	63.1
Sierra Leone	15.3	27.5	42.0	55.4
South Africa	37.6	53.1	63.4	68.3
Sri Lanka	0.0	11.2	22.5	33.2
Sudan	2.1	3.7	6.7	13.5
Swaziland	59.8	61.8	101.2	124.1
Tajikistan	13.8	21.5	28.8	30.4
Tanzania	27.5	51.4	80.3	116.5
Thailand	15.0	24.7	36.3	44.5
Timor-Leste	21.3	8.8	18.2	35.3
Togo	10.6	19.2	30.3	42.5
Tunisia	1.5	3.1	5.9	9.6
Turkey	3.5	6.1	8.4	10.5
Turkmenistan	14.1	19.4	24.8	29.8
Uganda	30.8	55.2	87.3	115.5
Ukraine	23.6	31.6	37.8	39.2
Uzbekistan	17.6	24.8	30.7	34.6
Venezuela	52.0	66.7	71.5	70.2
Vietnam	9.4	14.5	20.5	26.7
Yemen, Rep.	0.6	2.1	4.3	7.6
Zambia	60.3	88.1	110.4	127.0
Zimbabwe	19.9	41.4	71.2	105.8

Table S5. Screening test performance inputs.

Screening test (references)	True positive rate (sensitivity)	False positive rate (1-specificity)[a]
VIA [2,]	CIN2+: 60%	16%
HPV [4-8]	CIN2/3: 90%	
Pap [2,]	CIN2+: 58%	12%
HPV-VIA[b] [5-10]	CIN2/3: 54%	

[a] For VIA and Pap, test specificity was used to derive the false positive rate associated with each screening test for purposes of establishing the number of women with no lesion who screen positive and thus may accrue further diagnostic and/or treatment costs. For HPV testing, the mechanics of the test are based on the presence or absence of HPV, and we assumed the test detected oncogenic HPV infections with perfect accuracy; we considered a false positive result to occur among women with HPV infection but no CIN. Because we assumed 90% of CIN2/3 were attributable to oncogenic HPV [5-8], we multiplied the prevalence of CIN2/3 in a given country by 90% and subtracted these values from the prevalence of oncogenic HPV in that country to generate the proportion of women with HPV who screen positive but have no lesion. Thus, the false positive rate varies by country.

[b] Limited data on the performance of HPV testing with VIA triage suggests that sensitivity is similar to VIA alone [9, 10]. We again assumed the primary HPV test detected oncogenic HPV infections with perfect accuracy and that 90% of CIN2+ are attributable to oncogenic HPV; furthermore, we assumed that VIA triage of HPV-positive women performed similarly as in the general population (i.e., with 60% sensitivity for CIN2+). While the specificity of the VIA triage test was the same as the specificity of VIA alone, the false positive rate of the HPV-VIA testing system varied by a country's HPV prevalence, as described above.

Table S6. Reduction in age-specific cervical cancer incidence and mortality (%), by screening test and age at screening, for once in a lifetime strategies (1x).

Cancer Incidence					
Age (years)	VIA 1X at age 30	VIA 1X at age 35	Pap 1X at age 35	HPV 1X at age30	HPV 1X at age 35
20-24	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0
30-34	16.6	0.0	0.0	32.4	0.0
35-39	46.3	13.5	13.3	89.3	22.5
40-44	41.9	48.6	49.3	85.5	90.2
45-49	33.7	42.7	41.3	74.2	86.6
50-54	27.6	35.5	33.9	64.3	76.6
55-59	23.5	30.6	28.2	55.1	68.1
60-64	18.7	24.3	22.7	46.4	58.2
65-69	14.9	19.3	17.1	39.1	49.7
70-74	10.3	14.0	12.4	29.5	38.0
75-79	4.6	7.8	6.0	15.4	25.0
80-84	1.6	3.6	2.6	5.3	13.8
Cancer Mortality					
Age (years)	VIA 1X at age 30	VIA 1X at age 35	Pap 1X at age 35	HPV 1X at age 30	HPV 1X at age 35
20-24	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0
30-34	43.0	0.0	0.0	72.8	0.0
35-39	44.6	34.5	37.2	82.0	57.6
40-44	41.0	40.9	42.2	82.0	75.3
45-49	36.8	41.7	40.9	76.3	80.0
50-54	31.6	38.0	36.4	70.0	77.8
55-59	27.5	34.7	32.6	62.2	72.9
60-64	22.5	28.2	26.8	53.8	64.7
65-69	18.5	23.5	22.2	45.8	56.3
70-74	14.4	18.1	16.8	37.2	47.0
75-79	9.8	14.1	12.0	26.2	35.3
80-84	6.2	9.3	7.5	17.2	25.9

Table S7. Reduction in age-specific cervical cancer incidence and mortality (%), by age at screening, for VIA at a frequency of every 3 years (Q3).

Cancer Incidence													
Age (years)	VIA Q3 (at ages 30, 33)	VIA Q3 (at ages 30, 33, 36)	VIA Q3 (at ages 30, 33, 36, 39)	VIA Q3 (at ages 33, 36, 39)	VIA Q3 (at ages 33, 36, 39, 42)	VIA Q3 (at ages 36, 39)	VIA Q3 (at ages 36, 39, 42)	VIA Q3 (at ages 36, 39, 42, 45)	VIA Q3 (at ages 39, 42, 45)	VIA Q3 (at ages 39, 42, 45, 48)	VIA Q3 (at ages 42, 45, 48)	VIA Q3 (at ages 45, 48)	VIA Q3 (at age 48)
20-24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30-34	4.8	4.8	4.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
35-39	73.7	75.3	69.4	43.7	43.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
40-44	66.8	81.5	90.5	86.5	84.9	76.8	73.8	73.7	47.4	47.1	0.0	0.0	0.0
45-49	56.3	72.3	83.0	79.1	88.6	69.4	84.2	86.8	77.6	74.5	51.1	0.0	0.0
50-54	46.8	61.6	72.5	69.6	80.4	60.5	76.0	86.0	82.0	90.5	86.1	75.4	52.4
55-59	40.1	52.8	62.8	60.9	71.2	54.3	68.7	78.6	75.4	84.4	80.6	71.4	49.7
60-64	31.8	43.1	52.8	50.6	61.3	44.9	57.9	68.2	65.3	75.3	72.0	63.2	44.7
65-69	26.2	35.9	44.2	41.5	50.3	36.8	48.4	57.9	55.4	65.0	61.9	54.2	37.4
70-74	18.5	26.3	33.1	31.9	38.8	27.1	36.8	45.8	42.9	52.3	50.1	43.8	31.2
75-79	8.7	13.6	19.5	19.0	24.7	17.7	24.2	30.9	30.5	37.4	36.4	32.9	23.2
80-84	4.3	7.4	10.9	10.7	15.1	9.0	14.5	20.5	20.3	26.9	26.0	22.9	15.8
Cancer Mortality													
Age (years)	VIA Q3 (at ages 30, 33)	VIA Q3 (at ages 30, 33, 36)	VIA Q3 (at ages 30, 33, 36, 39)	VIA Q3 (at ages 33, 36, 39)	VIA Q3 (at ages 33, 36, 39, 42)	VIA Q3 (at ages 36, 39)	VIA Q3 (at ages 36, 39, 42)	VIA Q3 (at ages 36, 39, 42, 45)	VIA Q3 (at ages 39, 42, 45)	VIA Q3 (at ages 39, 42, 45, 48)	VIA Q3 (at ages 42, 45, 48)	VIA Q3 (at ages 45, 48)	VIA Q3 (at age 48)
20-24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30-34	50.8	50.8	50.8	15.7	15.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
35-39	65.7	71.9	72.9	55.3	55.3	28.7	28.7	28.7	4.5	4.5	0.0	0.0	0.0
40-44	62.3	75.1	81.3	71.3	73.5	57.3	61.9	61.9	40.5	40.5	15.8	0.0	0.0
45-49	59.0	72.7	81.2	74.3	80.6	61.6	72.2	76.5	66.4	67.8	51.4	31.2	8.1
50-54	52.1	66.0	76.5	71.0	80.0	60.4	73.1	80.5	72.9	78.3	68.1	54.6	33.5
55-59	45.2	58.4	68.7	64.1	74.3	56.6	69.2	78.4	72.8	79.8	72.9	61.9	41.4
60-64	38.4	50.3	60.4	56.9	67.2	49.7	62.8	72.7	68.1	76.7	71.2	61.1	41.3
65-69	32.2	42.8	51.5	49.0	58.6	42.9	55.2	64.4	60.5	69.2	65.9	57.0	38.4
70-74	24.9	33.9	42.3	39.5	48.2	33.4	44.2	53.7	50.3	59.7	56.3	48.7	33.5
75-79	17.4	24.7	32.0	29.8	36.8	27.2	35.1	43.0	40.5	48.5	46.0	40.6	28.2
80-84	11.0	16.5	21.8	20.1	25.9	17.6	24.9	31.5	29.4	36.1	35.2	29.0	20.6

Table S8. . Reduction in age-specific cervical cancer incidence and mortality (%), by age at screening, for VIA at a frequency of every 5 years (Q5).

Cancer Incidence					
Age (years)	VIA Q5 (at ages 30)	VIA Q5 (at ages 30, 35)	VIA Q5 (at ages 35, 40)	VIA Q5 (at ages 40, 45)	VIA Q5 (at ages 45)
20-24	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0
30-34	16.9	16.9	0.0	0.0	0.0
35-39	47.3	54.4	14.0	0.0	0.0
40-44	41.8	69.2	55.9	11.3	0.0
45-49	33.5	59.3	70.0	55.2	9.1
50-54	27.4	49.6	61.5	71.0	50.4
55-59	23.3	43.1	55.0	65.2	46.5
60-64	18.5	34.5	45.9	56.4	40.9
65-69	14.8	28.5	37.5	47.2	33.9
70-74	10.2	20.3	27.8	37.1	27.0
75-79	4.4	10.6	18.0	25.6	19.7
80-84	1.5	5.2	9.9	16.6	12.3
Cancer Mortality					
Age (years)	VIA Q5 (at ages 30)	VIA Q5 (at ages 30, 35)	VIA Q5 (at ages 35, 40)	VIA Q5 (at ages 40, 45)	VIA Q5 (at ages 45)
20-24	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0
30-34	44.1	44.1	0.0	0.0	0.0
35-39	45.0	63.3	34.6	0.0	0.0
40-44	41.0	62.6	56.2	30.1	0.0
45-49	36.8	61.1	62.3	53.6	27.5
50-54	31.6	54.4	61.1	60.7	38.9
55-59	27.4	47.6	57.2	62.6	42.4
60-64	22.4	40.7	50.3	58.2	40.5
65-69	18.4	34.5	43.6	52.2	36.2
70-74	14.3	27.0	34.3	42.7	30.4
75-79	9.7	19.3	27.1	35.4	25.3
80-84	6.1	12.2	18.3	25.0	16.8

Table S9. . Reduction in age-specific cervical cancer incidence and mortality (%), by age at screening, for Pap at a frequency of every 5 years (Q5).

Cancer Incidence					
Age (years)	Pap Q5 (at ages 30)	Pap Q5 (at ages 30, 35)	Pap Q5 (at ages 35, 40)	Pap Q5 (at ages 40, 45)	Pap Q5 (at ages 45)
20-24	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0
30-34	16.9	16.9	0.0	0.0	0.0
35-39	47.2	54.8	13.7	0.0	0.0
40-44	39.7	67.2	56.8	11.4	0.0
45-49	31.4	55.8	69.2	57.0	9.1
50-54	24.9	45.2	58.5	70.5	51.7
55-59	21.0	38.1	50.4	62.2	46.0
60-64	16.1	30.0	41.5	53.0	40.3
65-69	12.1	23.3	33.0	43.7	32.6
70-74	8.0	16.1	23.6	33.1	25.9
75-79	2.9	7.5	13.5	21.6	17.1
80-84	0.8	2.6	6.6	13.2	10.7
Cancer Mortality					
Age (years)	Pap Q5 (at ages 30)	Pap Q5 (at ages 30, 35)	Pap Q5 (at ages 35, 40)	Pap Q5 (at ages 40, 45)	Pap Q5 (at ages 45)
20-24	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0
30-34	43.8	43.8	0.0	0.0	0.0
35-39	45.3	64.3	37.2	0.0	0.0
40-44	39.9	62.0	57.7	31.9	0.0
45-49	35.1	58.3	62.0	55.1	28.8
50-54	29.1	50.7	59.1	60.9	39.9
55-59	24.8	43.7	53.8	61.3	42.7
60-64	20.0	36.0	46.3	55.8	40.1
65-69	16.0	29.7	39.8	49.4	35.9
70-74	12.4	22.8	30.6	39.5	29.6
75-79	7.5	15.2	22.6	31.3	23.3
80-84	4.7	9.4	14.8	21.4	15.2

Table S10. Reduction in age-specific cervical cancer incidence and mortality (%), by age at screening, for HPV testing at a frequency of every 5 years (Q5).

Cancer Incidence				
Age (years)	HPV Q5(at ages 30,35)	HPV Q5(at ages 35,40)	HPV Q5(at ages 40,45)	HPV Q5(at age 45)
20-24	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0
30-34	32.0	0.0	0.0	0.0
35-39	92.2	22.5	0.0	0.0
40-44	98.1	92.4	19.6	0.0
45-49	93.5	98.2	92.4	15.9
50-54	82.4	94.1	98.3	90.7
55-59	73.3	85.0	95.2	88.2
60-64	63.0	76.7	86.8	79.9
65-69	53.3	64.9	77.3	72.1
70-74	40.9	51.2	64.0	59.8
75-79	26.4	34.6	48.1	45.5
80-84	14.4	22.2	34.3	32.6
Cancer Mortality				
Age (years)	HPV Q5(at ages 30,35)	HPV Q5(at ages 35,40)	HPV Q5(at ages 40,45)	HPV Q5(at age 45)
20-24	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0
30-34	72.8	0.1	0.0	0.0
35-39	87.8	57.6	0.0	0.0
40-44	92.2	80.0	51.3	0.0
45-49	91.7	88.2	75.4	45.6
50-54	86.6	91.0	86.1	68.7
55-59	79.5	87.5	89.6	76.7
60-64	71.1	81.8	87.5	77.2
65-69	61.9	72.2	80.8	73.1
70-74	51.4	61.5	70.8	64.6
75-79	38.9	48.5	59.6	54.6
80-84	28.2	37.0	46.9	42.1

Table S11. Reduction in age-specific cervical cancer incidence and mortality (%), by age at screening, for HPV testing with VIA triage (HPV-VIA) at a frequency of every 5 years (Q5).

Cancer Incidence						
Age (years)	HPV-VIA Q5 (at age 30)	HPV-VIA Q5 (at age 35)	HPV-VIA Q5 (at age 30,35)	HPV-VIA Q5 (at age 35,40)	HPV-VIA Q5 (at age 40,45)	HPV-VIA Q5 (at age 45)
20-24	0.0	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0	0.0
30-34	15.4	0.0	14.8	0.0	0.0	0.0
35-39	43.9	11.5	50.0	11.5	0.0	0.0
40-44	36.5	45.4	63.2	61.5	8.7	0.0
45-49	29.3	38.7	52.9	66.2	62.8	6.4
50-54	23.4	31.5	43.1	56.0	67.7	48.7
55-59	19.6	41.0	35.9	41.4	58.3	42.9
60-64	15.2	21.4	28.9	38.8	50.4	36.7
65-69	11.2	16.2	22.0	30.7	41.2	29.6
70-74	14.7	11.2	15.9	22.2	31.4	23.9
75-79	2.7	5.8	7.0	12.6	20.4	15.6
80-84	0.6	2.3	2.4	6.5	11.8	10.2
Cancer Mortality						
Age (years)	HPV-VIA Q5 (at age 30)	HPV-VIA Q5 (at age 35)	HPV-VIA Q5 (at age 30,35)	HPV-VIA Q5 (at age 35,40)	HPV-VIA Q5 (at age 40,45)	HPV-VIA Q5 (at age 45)
20-24	0.0	0.0	0.0	0.0	0.0	0.0
25-29	0.0	0.0	0.0	0.0	0.0	0.0
30-34	40.8	0.0	40.4	0.0	0.0	0.0
35-39	41.6	36.1	60.0	36.1	0.0	0.0
40-44	37.7	39.3	60.5	62.9	30.8	0.0
45-49	31.7	37.8	54.7	60.0	58.7	28.1
50-54	28.4	35.3	49.4	57.8	59.8	37.7
55-59	22.8	40.7	41.7	51.3	57.9	39.7
60-64	19.0	25.5	34.9	44.1	52.7	37.4
65-69	15.1	21.2	28.2	37.4	46.5	32.4
70-74	11.3	15.5	22.1	28.9	38.3	27.2
75-79	6.7	10.8	14.9	21.3	29.3	21.3
80-84	4.1	7.2	8.9	13.8	19.8	14.8

Table S12. Attenuation factors to capture reduction in CIN1 and CIN2/3 prevalence associated with repeated screening, by screening modality and frequency.[a]

Strategy	HPV Attenuation Factor	CIN2/3 Attenuation Factor
VIA Q5	NA	0.67
VIA Q3	NA	0.6
Pap Q5	NA	0.69
HPV Q5	0.79	0.29
HPV-VIA Q5	0.95	0.78

[a] Q5: screening at 5 year intervals (at age 30, 35, 40, 45 years); Q3: screening at 3 year intervals (at age 30, 33, 36, 39, 42, 45, 48 years).

Table S13. Cancer stage distribution at detection, by screening strategy.

Strategy	Local (%)	Regional (%)	Distant (%)
	LI and LMI countries		
No screening	18.6	72.9	8.5
VIA 1x at 30	20.7	70.9	8.3
VIA 1x at 35	21.9	70.0	8.1
Pap 1x at 35	22.1	69.8	8.1
HPV 1x at 30	23.9	68.2	7.9
HPV 1x at 35	27.4	65.1	7.5
HPV-VIA 1x at 35	22.2	69.7	8.1
VIA Q3 at 30,33	23.0	69.0	8.1
VIA Q3 at 30,33,36	24.9	67.2	7.8
VIA Q3 at 30,33,36,39	26.9	65.5	7.6
VIA Q3 at 33,36,39	26.7	65.8	7.6
VIA Q3 at 33,36,39,42	28.9	63.8	7.3
VIA Q3 at 36,39	25.5	66.7	7.8
VIA Q3 at 36,39,42	28.2	64.4	7.4
VIA Q3 at 36,39,42,45	30.6	62.3	7.1
VIA Q3 at 39,42,45	29.3	63.4	7.3
VIA Q3 at 39,42,45,48	31.6	61.3	7.1
VIA Q3 at 42,45,48	29.9	62.9	7.2
VIA Q3 at 45,48	27.4	65.0	7.6
VIA Q3 at 48	23.7	68.3	8.0
VIA Q5 at 30	20.7	71.0	8.3
VIA Q5 at 30,35	23.4	68.5	8.1
VIA Q5 at 35,40	25.4	66.8	7.7
VIA Q5 at 40,45	27.0	65.4	7.6
VIA Q5 at 45	23.7	68.3	8.0
Pap Q5 at 30	20.7	71.0	8.3
Pap Q5 at 30,35	23.4	68.6	8.0
Pap Q5 at 35,40	25.6	66.8	7.6
Pap Q5 at 40,45	27.2	65.3	7.5
Pap Q5 at 45	24.1	68.0	7.9
HPV Q5 at 30,35	27.2	65.3	8.0
HPV Q5 at 35,40	31.7	65.3	7.0
HPV Q5 at 40,45	34.0	61.3	6.8
HPV Q5 at 45	30.5	62.3	7.2
HPV-VIA Q5 at 30	20.8	70.9	8.3
HPV-VIA Q5 at 35	22.2	69.7	8.1
HPV-VIA Q5 at 30,35	23.5	68.6	8.0
HPV-VIA Q5 at 35,40	25.8	66.5	7.7
HPV-VIA Q5 at 40,45	27.6	64.9	7.5
HPV-VIA Q5 at 45	24.1	68.0	7.8
	UMI countries		
Background screening	50.0	39.6	10.4
VIA 1x at 30	51.0	38.9	10.2
VIA 1x at 35	51.7	38.5	9.9
Pap 1x at 35	51.8	38.4	9.7

HPV 1x at 30	52.1	38.3	9.6
HPV 1x at 35	53.9	36.9	9.1
HPV-VIA 1x at 35	51.7	38.4	9.8
VIA Q3 at 30,33	52.1	38.3	9.6
VIA Q3 at 30,33,36	53.1	37.5	9.5
VIA Q3 at 30,33,36,39	53.8	37.0	9.2
VIA Q3 at 33,36,39	54.1	36.5	9.4
VIA Q3 at 33,36,39,42	54.8	36.1	9.1
VIA Q3 at 36,39	53.2	37.5	9.3
VIA Q3 at 36,39,42	54.2	36.8	9.0
VIA Q3 at 36,39,42,45	55.0	36.4	8.7
VIA Q3 at 39,42,45	53.9	37.2	8.9
VIA Q3 at 39,42,45,48	54.2	37.0	8.7
VIA Q3 at 42,45,48	53.9	37.2	8.9
VIA Q3 at 45,48	53.0	37.6	9.4
VIA Q3 at 48	51.9	38.2	9.8
VIA Q5 at 30	51.0	38.9	10.2
VIA Q5 at 30,35	52.2	38.2	9.6
VIA Q5 at 35,40	53.3	37.4	9.3
VIA Q5 at 40,45	53.2	37.6	9.2
VIA Q5 at 45	51.9	38.4	9.8
Pap Q5 at 30	51.2	38.7	10.1
Pap Q5 at 30,35	52.3	38.1	9.6
Pap Q5 at 35,40	53.3	37.5	9.2
Pap Q5 at 40,45	53.1	37.7	9.2
Pap Q5 at 45	51.8	38.4	9.8
HPV Q5 at 30,35	54.0	37.0	9.8
HPV Q5 at 35,40	55.8	37.0	8.6
HPV Q5 at 40,45	55.9	35.7	8.5
HPV Q5 at 45	54.1	36.9	9.0
HPV-VIA Q5 at 30	50.8	39.1	10.1
HPV-VIA Q5 at 30,35	52.4	38.0	9.6
HPV-VIA Q5 at 35,40	53.2	37.7	9.1
HPV-VIA Q5 at 40,45	53.0	37.7	9.3
HPV-VIA Q5 at 45	51.7	38.4	10.0

Table S14. Country-specific access to cancer treatment [11].

Country	Access to radiation therapy, % (proxy for cancer treatment)
Afghanistan	0
Albania	50.4
Algeria	32.3
Angola	21
Argentina	71.3
Armenia	33.1
Azerbaijan	31
Bangladesh	11.2
Belarus	60
Benin	0
Bolivia	38.3
Bosnia and Herzegovina	87.2
Botswana	44
Brazil	57.6
Bulgaria	33.7
Burkina Faso	0
Burundi	0
Cambodia	4.7
Cameroon	5.2
Central African Republic	0
Chad	0
China	36.1
Colombia	69.5
Congo, Dem. Rep.	0
Congo, Rep.	0
Costa Rica	72.4
Cote d'Ivoire	0
Dominican Republic	54
Ecuador	52.4
Egypt	37.8
El Salvador	39.9
Eritrea	0
Ethiopia	2.4
Gabon	0
Gambia, The	0
Georgia	35
Ghana	13.7
Guatemala	54.3
Guinea	0
Guinea-Bissau	0

Table S14 (ctnd.) Country-specific access to cancer treatment.

Country	Access to radiation therapy, % (proxy for cancer treatment)
Haiti	0
Honduras	77.5
Hungary	57.1
India	36.3
Indonesia	8.7
Jamaica	37.2
Jordan	100
Kazakhstan	71.3
Kenya	10.5
Kyrgyz Republic	37.2
Lao PDR	0
Lebanon	100
Lesotho	0
Liberia	0
Macedonia, FYR	29.5
Madagascar	4
Malawi	0
Malaysia	78.9
Mali	0
Mauritania	39.1
Mauritius	82.4
Mexico	61.3
Moldova	29.1
Mongolia	35.5
Morocco	61.7
Mozambique	0
Namibia	53.7
Nepal	23
Nicaragua	28.1
Niger	0
Nigeria	9.2
Pakistan	21.4
Panama	66.5
Papua N. Guinea	19.6
Paraguay	44.2
Peru	57.1
Philippines	26.4

Romania	28.3
Rwanda	0
Senegal	10.6

Table S14 (ctnd.) Country-specific access to cancer treatment.

Country	Access to radiation therapy, % (proxy for cancer treatment)
Serbia	25.6
Sierra Leone	0
South Africa	69.7
Sri Lanka	39.6
Sudan	35.4
Swaziland	39
Tajikistan	39
Tanzania	6.4
Thailand	39.6
Timor-Leste	88.6
Togo	0
Tunisia	88.6
Turkey	98.8
Turkmenistan	0
Uganda	2.5
Ukraine	54.6
Uzbekistan	57.3
Venezuela	100
Vietnam	21.3
Yemen, Rep.	12.7
Zambia	13.6
Zimbabwe	13.9

Table S15. Published HPV vaccine delivery cost per dose estimates (2013 US$).[a]

Country and vaccine delivery strategy	HPV vaccine delivery cost per dose
Tanzania (school-based) [12]	3.68
Peru (school-based) [b] [13]	2.68
Uganda (school-based) [b] [13]	2.44
Uganda (integrated outreach) [b] [13]	0.95
Vietnam (school-based) [b] [13]	0.98
Vietnam (health center) [b] [13]	0.85
Tanzania (school-based)[14]	3.19

[a] Costs represent economic costs of HPV vaccine delivery, excluding the price of the vaccine.

[b] Recurrent costs only; start-up costs have been excluded.

Table S16. Average HPV vaccine delivery cost per dose, by income tier and GAVI eligibility status (2013 US$).[a]

Income tier	HPV vaccine delivery cost per dose
LI [b]	1.60
LMI1	3.51
LMI2	6.64
UMI1	11.90
UMI2[c]	19.43
GAVI-eligible	
Yes [b]	2.14
No [c]	11.80

[a] Costs represent economic costs of HPV vaccine delivery, excluding the price of the vaccine. LI: Low Income; LMI1: Lower-middle income 1; LMI2: Lower-middle income 2; UMI1: Upper-middle income 1; UMI2: Upper-middle income 2.
In countries for which the official exchange rate for 2013 was unavailable, we used the DEC alternative conversion rate [15]. Because 2013 GDP deflators were not available to convert WHO-CHOICE 2008 local currency unit costs to 2013 US$ in several countries, we used the 2012 GDP deflator [15].

[b] For Zimbabwe, we substituted cost data from Kenya as a proxy country, given the similarity in 2013 GNI per capita between Kenya and Zimbabwe. In Zambia in 2013, 1000 ZMK became equivalent to 1 ZMW, so we divided the official exchange rate by 1000.

[c] For Brazil, WHO-CHOICE data from 2008 suggested low procedure costs that did not fit the generally linear relationship with GNI per capita, so instead of using the average extrapolated value we used the maximum extrapolated value implied by the primary data.

Table S17. Screening, diagnosis, and treatment of CIN: Procedures and location of service delivery.

Procedure	Location of Service Delivery
VIA test	Primary outpatient clinic
Cytology test	Primary outpatient clinic
HPV test	Primary outpatient clinic
Colposcopy/biopsy	Secondary outpatient hospital
Cryotherapy	Primary outpatient clinic
LEEP	Secondary outpatient hospital

Table S18. Primary data costs, by procedure, for screening and treatment of precancer (2013 US$).

Country	VIA	Pap	HPV Test[a]	Cryotherapy	Colposcopy/biopsy	LEEP
El Salvador [16]	1.95	4.31	6.90	22.60	86.64	45.07
Ghana [17]	8.06			37.37		
India [18]	0.68	1.49	6.92	5.34	13.46	35.73
India (Hyderabad) [2, 19][b]	1.07	4.66	6.27	13.13	9.60	
India (New Delhi) [2, 19][b]	1.43	6.38	6.74	18.12	15.22	
Kenya [18]	1.32	2.81	8.98	14.20	15.83	127.02
Nicaragua [2, 19][b]	4.04	5.94	9.57	14.60	19.25	66.15
Peru [18]	3.03	4.72	10.72	8.62	7.65	163.18
South Africa [18]	9.77	13.51	15.92	61.11	74.18	260.39
Thailand [18]	1.09	2.17	8.07	21.20	42.39	169.56
Uganda [2, 19][b]	1.29	5.36	6.84	5.92	16.13	79.37

[a] In converting primary data costs to 2013 US$, we assumed the HPV test has a standardized tradable value of $5 (2013 US$).
[b] Unpublished data from the PATH START-UP demonstration projects.

Table S19. Average procedure cost for screening and treatment of precancer, by income tier (2013 US$). [a]

Income tier	VIA	Pap	HPV Test[b]	Cryotherapy	Colposcopy/biopsy	LEEP
LI[c]	1.60	NA	6.61	11.39	22.74	47.72
LMI1	3.52	NA	8.52	24.99	49.87	101.64
LMI2	6.65	11.81	11.66	50.77	94.30	197.87
UMI1	11.92	21.17	16.94	84.72	169.07	354.76
UMI2[d]	19.46	34.12	24.11	137.83	285.17	565.75

[a] LI: Low Income; LMI1: Lower-middle income 1; LMI2: Lower-middle income 2; UMI1: Upper-middle income 1; UMI2: Upper-middle income 2; NA: Not applicable, as these strategies were not considered for Low Income countries. In countries for which the official exchange rate for 2013 was unavailable, we used the DEC alternative conversion rate [15]. Because 2013 GDP deflators were not available to convert WHO-CHOICE 2008 local currency unit costs to 2013 US$ in several countries, we used the 2012 GDP deflator [15].

[b] We assumed that the HPV test had a standardized tradable value of US$5, and did not apply the WHO-CHOICE facility ratios to this component of HPV screening costs.

[c] For Zimbabwe, we substituted WHO-CHOICE cost data from Kenya as a proxy country, given the similarity in 2013 GNI per capita between Kenya and Zimbabwe. In Zambia in 2013, 1000 ZMK became equivalent to 1 ZMW, so we divided the official exchange rate by 1000.

[d] For Brazil, WHO-CHOICE data from 2008 suggested low procedure costs that did not fit the generally linear relationship with GNI per capita, so instead of using the average extrapolated value we used the maximum extrapolated value implied by the primary data.

Table S20. Primary data costs, by procedure, for cancer treatment (2013 US$).

Country	Staging	Conization	Simple hysterectomy	Radical hysterectomy with pelvic lymphadenectomy	Surgical follow-up [a]	Radiotherapy + Chemotherapy + Brachytherapy [b]	Radiotherapy + Chemotherapy + Brachytherapy, follow-up [c]	Radiotherapy alone [b]	Palliative Radiotherapy [d]	Palliative Care [e]
Argentina [20]	912.69	625.85	1551.54	2552.20	1047.54	5962.99	3317.96			180.69
Brazil [20]	529.04	1870.47	2137.70	4223.84	55.40	2412.31	106.84		726.22	780.85
Colombia [20]	836.80	989.06	1932.26	3172.12	62.91	3291.59	110.48		792.23	116.94
China [21]			548.41	737.65						
El Salvador [16]				3505.56		3319.26				
India [22]			180.12							
India [18]	67.74	79.03	112.89	384.97				466.50		
Kenya [18]	97.83	168.38	347.29	621.46				595.64		
Mexico [20]	2071.97	560.89	1308.22	2832.47	230.09	3722.99	494.00		1182.59	46.91
Morocco [23]		96.04	955.54						2041.42	
Peru [20]	936.00	578.01	1180.54	2470.01	158.45	2985.62	470.28		590.64	303.35
Peru [18]	106.76	290.64	393.48	2020.73				1606.85		
South Africa [18]	383.11	319.38	1102.52	2735.22				1277.83		
Thailand [18]	92.23	131.75	263.51	541.43				572.06		
Thailand [24]		1224.57	1443.23	3688.69				1904.48		2395.94
Thailand [25]				2298.42		4497.09				5234.44

[a] Follow-up for surgery included 2 Pap tests with vaginal and rectal exams within the year after surgery.
[b] We only included cost estimates from studies that reported costs for radiotherapy, chemotherapy, and brachytherapy, assuming that costing data considered the synergies of providing these treatments together. We excluded studies that reported only the costs for one of these therapies in isolation, although we did extract the costs of radiotherapy alone from several studies to isolate the cost of radiotherapy for patients requiring this treatment following cancer recurrence.
[c] Follow-up for radiotherapy, chemotherapy, and brachytherapy included 4 vaginal and rectal exams within the year after initial treatment.
[d] Palliative radiotherapy costs were reported as such from the literature, and we did not include reported costs of radiotherapy that was not distinguished as palliative radiotherapy.
[e] Components of palliative care were not typically identified or distinguished by stage in the literature, so we assumed the same palliative care costs for all stages.

Table S21. Average stage-specific cost for cancer treatment, by income tier (2013 US$). [a]

Income tier	Local	Regional	Distant
LI[b]	627.72	886.97	600.72
LMI1	1,764.90	2,493.82	1,688.99
LMI2	3,799.68	5,368.97	3,636.24
UMI1	8,790.61	12,421.20	8,501.86
UMI2[c]	17,642.35	24,530.60	16,563.98

[a] LI: Low Income; LMI1: Lower-middle income 1; LMI2: Lower-middle income 2; UMI1: Upper-middle income 1; UMI2: Upper-middle income 2. Because 2013 GDP deflators were not available to convert WHO-CHOICE 2008 local currency unit costs to 2013 US$ in several countries, we used the GDP deflator from the World Factbook [26].

[b] For Zimbabwe, we substituted WHO-CHOICE cost data from Kenya as a proxy country, given the similarity in 2013 GNI per capita between Kenya and Zimbabwe. In Zambia in 2013, 1000 ZMK became equivalent to 1 ZMW, so we divided the official exchange rate by 1000.

[c] For Brazil, WHO-CHOICE data from 2008 suggested low procedure costs that did not fit the generally linear relationship with GNI per capita, so instead of using the average extrapolated value we used the maximum extrapolated value implied by the primary data.

Figure S1. FIGO stage distribution of cervical cancer used for validation of microsimulation model projections [27].

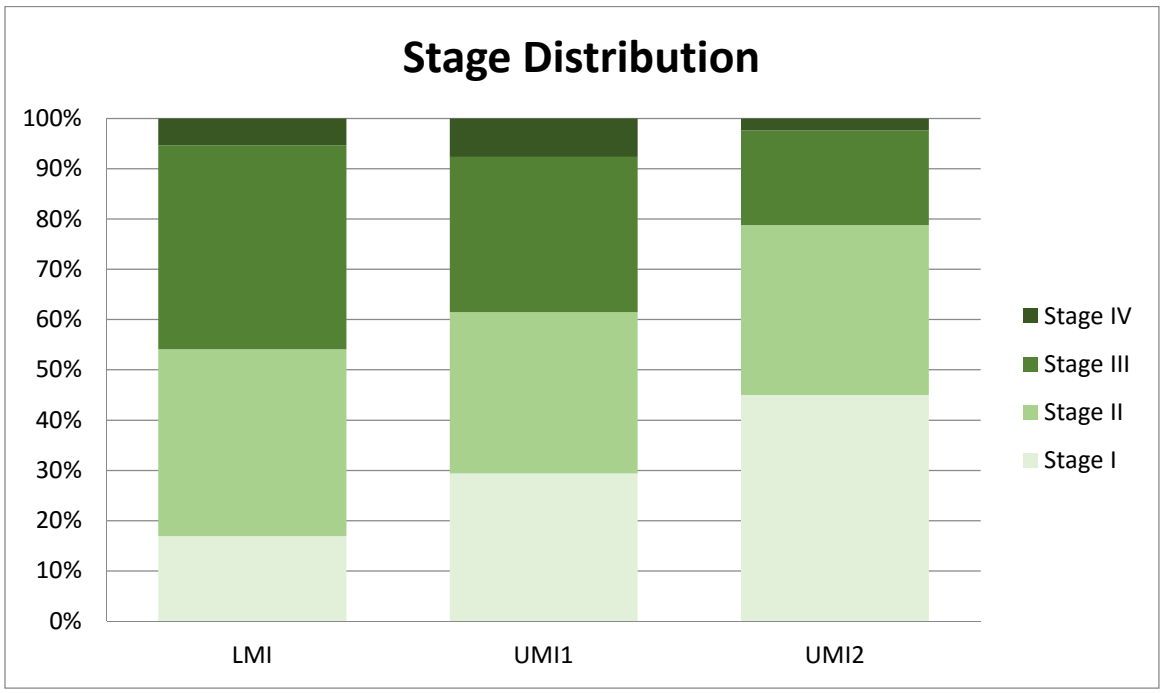
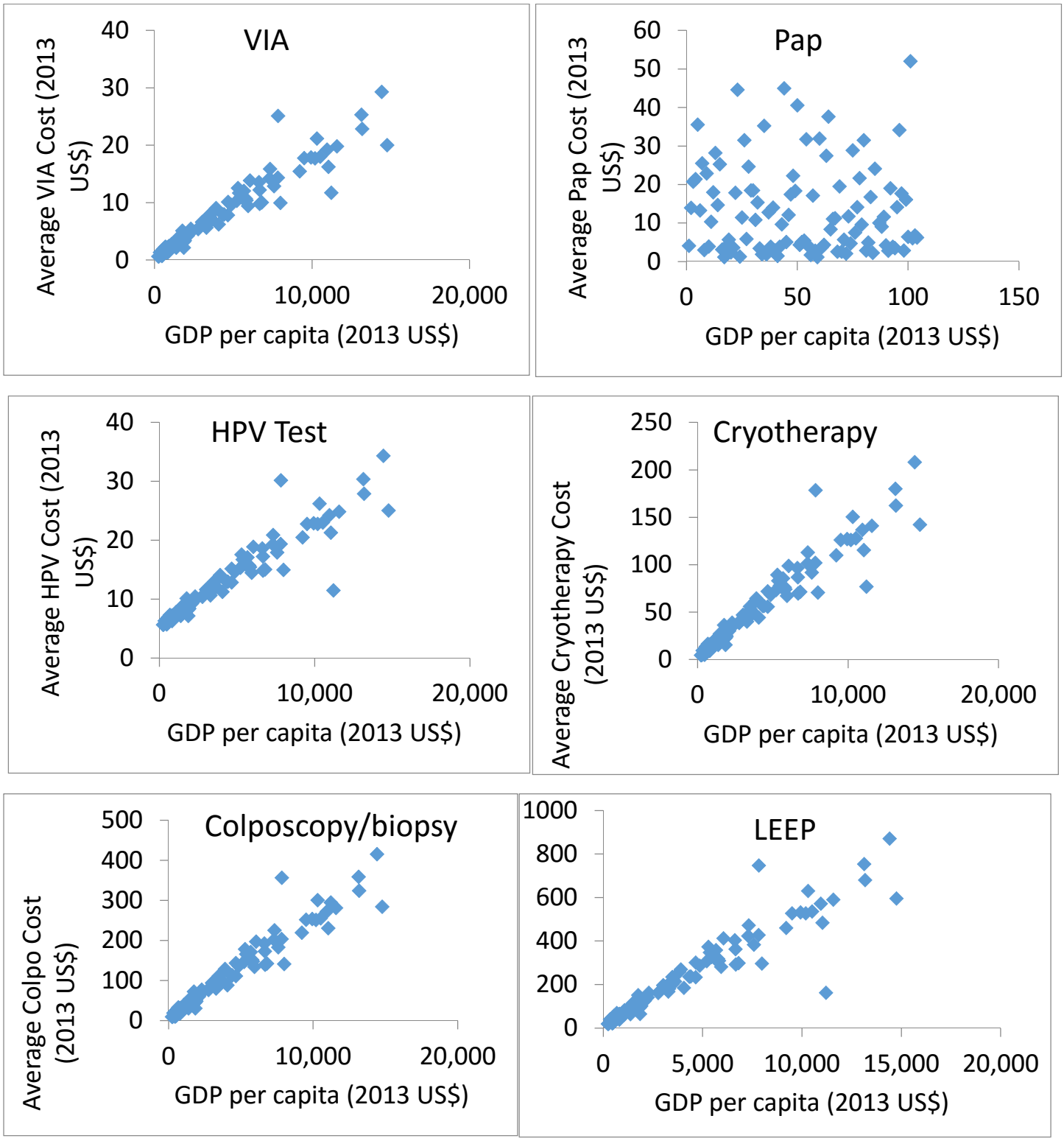


Figure S2. Unit costs by procedure in included countries, relative to GNI per capita (2013 US$).



References

1. Ferlay J, Soerjomataram I, Ervik M, et al. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]*, 2013, International Agency for Research on Cancer: Lyon, France.
2. Jeronimo J, Bansil P, Lim J, et al. A multicountry evaluation of careHPV testing, visual inspection with acetic acid, and papanicolaou testing for the detection of cervical cancer. *Int J Gynecol Cancer* 2014;24(3):576-585.
3. Arbyn M, Sankaranarayanan R, Muwonge R, et al. Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer* 2008;123(1):153-160.
4. Arbyn M, Verdoodt F, Snijders PJ, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* 2014;15(2):172-183.
5. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 2008;9(10):929-936.
6. ICO. *HPV Information Centre*, 2014.
7. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *Int J Cancer* 2012;131(10):2349-2359.
8. Zhang R, Velicer C, Chen W, et al. Human papillomavirus genotype distribution in cervical intraepithelial neoplasia grades 1 or worse among 4215 Chinese women in a population-based study. *Cancer Epidemiol* 2013;37(6):939-945.
9. Muwonge R, Wesley RS, Nene BM, et al. Evaluation of cytology and visual triage of human papillomavirus-positive women in cervical cancer prevention in India. *Int J Cancer* 2014;134(12):2902-2909.
10. Qiao YL, Jeronimo J, Zhao FH, et al. Lower cost strategies for triage of human papillomavirus DNA-positive women. *Int J Cancer* 2014;134(12):2891-2901.
11. Datta NR, Samiei M, and Bodis S. Radiation therapy infrastructure and human resources in low- and middle-income countries: present status and projections for 2020. *Int J Radiat Oncol Biol Phys* 2014;89(3):448-457.
12. Hutubessy R, Levin A, Wang S, et al. A case study using the United Republic of Tanzania: costing nationwide HPV vaccine delivery using the WHO Cervical Cancer Prevention and Control Costing Tool. *BMC Med* 2012;10:136.
13. Levin CE, Van Minh H, Odaga J, et al. Delivery cost of human papillomavirus vaccination of young adolescent girls in Peru, Uganda and Viet Nam. *Bull World Health Organ* 2013;91(8):585-592.
14. Quentin W, Terris-Prestholt F, Changalucha J, et al. Costs of delivering human papillomavirus vaccination to schoolgirls in Mwanza Region, Tanzania. *BMC Med* 2012;10:137.
15. *World Development Indicators*, 2013, World Bank.
16. Campos NG, Maza M, Alfaro K, et al. The comparative and cost-effectiveness of HPV-based cervical cancer screening algorithms in El Salvador. *Int J Cancer* 2015.
17. Countries PfRaCBiSaRHaHiD. *Costs of cervical cancer screening in Ghana*, 2010, UK Department for International Development: London.
18. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al. Cost-effectiveness of cervical-cancer screening in five developing countries. *N Engl J Med* 2005;353(20):2158-2168.
19. Mvundura M and Tsu V. Estimating the costs of cervical cancer screening in high-burden Sub-Saharan African countries. *Int J Gynaecol Obstet* 2014;126(2):151-155.
20. Constenla D, Goldie, S.J., Alvis, N., O'Shea, M., Sweet, S., Valenzuela, M., Cavada, G., de la Hoz, F., Koumans, E., Labbo, M.N., Koss, C., Posso, H. Health and Economic Outcomes of Human Papillomavirus (HPV) Vaccination in Selected Countries in Latin America: A Preliminary Economic Analysis. 2008.
21. Shi JF, Chen JF, Canfell K, et al. Estimation of the costs of cervical cancer screening, diagnosis and treatment in rural Shanxi Province, China: a micro-costing study. *BMC Health Serv Res* 2012;12:123.
22. Ranson MK and John KR. Quality of hysterectomy care in rural Gujarat: the role of community-based health insurance. *Reprod Health Matters* 2002;10(20):70-81.
23. Berraho M, Najdi A, Mathoulin-Pelissier S, et al. Direct costs of cervical cancer management in Morocco. *Asian Pac J Cancer Prev* 2012;13(7):3159-3163.
24. Termrungruanglert W, Havanond P, Khemapech N, et al. Cost and effectiveness evaluation of prophylactic HPV vaccine in developing countries. *Value Health* 2012;15(1 Suppl):S29-34.

25. Katanyoo K, Praditsitthikorn N, Tangjitgamol S, et al. Cost-utility analysis of treatments for stage IB cervical cancer. *J Gynecol Oncol* 2014;25(2):97-104.
26. Agency. USCI. The World Factbook.
27. Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006;95 Suppl 1:S43-103.