Costing and Evaluating Human Papillomavirus (Hpv) Vaccine Strategies in Low- and Middle-Income Countries (Lmics) Utilizing Modeling and Economic Analyses

COSTING AND EVALUATING HUMAN PAPILLOMAVIRUS (HPV) VACCINE STRATEGIES IN LOW- AND MIDDLE-INCOME COUNTRIES (LMICS) UTILIZING MODELING AND ECONOMIC ANALYSES

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A Dissertation Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

For the Degree of *Doctor of Science*

in the Department of Global Health and Population

Harvard University

Boston, Massachusetts

March 2020

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Abstract

As data to inform evidence-based policy of new and existing HPV vaccination strategies in LMICs are limited, this dissertation focuses on the costing and evaluation of the HPV vaccine utilizing modeling and economic analyses.

In Paper 1, we developed a predictive model for estimating standardized immunization delivery unit cost estimates at the country level. The predicted programmatic, economic costs per dose for routine delivery of childhood vaccines was $1.49 (95% uncertainty range: $0.33–4.87) and for HPV vaccines was $2.04 ($0.66–6.20). Country-specific costs modeled within a Bayesian meta-regression framework provide a broad indication of immunization delivery costs that may be preferable to raw country-level data without reliable, standardized review.

In Paper 2, we used a multiple modeling approach to estimate the health and economic outcomes associated with HPV vaccine delivery in Uganda, a low-income country in East Africa, where cervical cancer is the leading cause of cancer among females. Using a wide range of plausible scenarios to assess what might be achieved by a campaign delivery strategy for HPV vaccination against HPV-16/18 infections, we found that campaign strategies yielded greater health benefits if campaigns occurred frequently and targeted a wide age range compared with routine HPV vaccination strategies.

In Paper 3, relying on the methodology of extended cost-effectiveness analysis (ECEA) to examine the distributional and financial risk protection benefits from HPV vaccination in Ethiopia, we found that routine two-dose HPV vaccination could avert 586,000 cervical cancer deaths and 18,900 cases of catastrophic health expenditure over 2019-2118, assuming 40% vaccination coverage and 100% efficacy against HPV-16/18 with lifelong duration of protection. Approximately 30% of health benefits would accrue to the poorest quintile whereas 66% of financial risk protection benefits accrue to the poorest quintile.

Table of Contents

List of Figures

List of Tables

List of Appendix Figures

List of Appendix Tables

Acknowledgements

First, I would like to acknowledge my co-authors on these studies, both for their contribution to the work and for their support of my professional development. Second, I would like to specially thank Dawit Desalegn for his support while I was in Ethiopia and Logan Brenzel for her support of my costing work. Third, I would like to thank the faculty of the Department of Global Health and Population for their valuable comments along the way, particularly Jesse Bump, Marcia Castro, Margaret Kruk, Margaret McConnell, and Christopher Sudfeld. Fourth, I am grateful to the entire community at the Center for Health Decision Science for including me in the community and challenging me to become a more critical thinker. A special thank you to Jamie Cohen for keeping me sane as a classmate, colleague, and friend.

I am grateful for the members of my dissertation committee, Stéphane Verguet, Jane Kim, and Nicolas Menzies. They were all generous with their time throughout my tenure as a doctoral student and I have learned a tremendous amount from each of them. I am also grateful for the funding provided for these studies by the Bill & Melinda Gates Foundation.

I would also like to acknowledge my outside reviewer, Omar Galárraga, for taking the time to read this dissertation and provide feedback. Additionally, I would like to thank Barbara Heil and Allison Conary for their time and effort to ensure I reached the point of graduation. Finally, I am extremely grateful to my loving family. Mom, Dad, and Leah – I would not be at Harvard writing this dissertation without you.

Introduction

Adolescents, aged 10-19 years, make up one sixth of the world's population [1,2]. While adolescents are generally perceived to be healthy, adolescents' decisions about health care and behaviors at this stage of life have critical implications for future health and development as they age [1-5]. Adolescent health sees a rise in preventable causes of death including injury, human immunodeficiency virus (HIV), tuberculosis, and maternal health, particularly in low- and middle-income countries (LMICs) [2,3,6]. Of the approximately one million deaths occurring annually among adolescents worldwide, 70% occurred in the regions of Africa and Southeast Asia [2]. Moreover, the majority is due to preventable causes (Table A) [2,6].

Table A. Top 10 causes of death among adolescents (ages 10-19) in 2012, global [2]

Cause of death	Number of deaths
Road injury	121,000
HIV/AIDS	99,000
Self-harm	82,000
Lower respiratory infections	67,000
Interpersonal violence	67,000
Diarrheal diseases	65,000
Drowning	59,000
Meningitis	48,000
Epilepsy	31,000
Endocrine, blood, immune disorders	31,000

There also tends to be a rise in mental health disorders during this stage of the life course; and adolescents can engage in behaviors that can determine later health status and risk of chronic disease, including tobacco use, alcohol use, as well as unsafe sex [6-8]. Despite these vulnerabilities, there has been less focus on the health measurement and health care provision for this age group [1-4,6]. As the first 1,000 days of life are viewed as a "crucial development period" and under-five mortality is emphasized as an important indicator of population health, younger

children (i.e., those aged under 5 years) have received the greatest focus in data collection and research [3,6]. For example, the Demographic and Health Surveys (DHS) not only focus on infant and child mortality, but also specifically cite under-five mortality as "a leading indicator of the level of child health and overall development in countries" [9,10]. The Multiple Indicator Cluster Surveys (MICS) have routinely included surveys specific to children under five, but have only added a questionnaire for children 5-17 in the sixth round of MICS beginning in 2019 [11]. However, adolescence is likewise a crucial period of development, but is neglected within the realm of research [12,13].

Opportunities to reach adolescents with routine health services with existing health systems infrastructure in LMICs may be limited; however, countries may be able to leverage school health programs that are already in place. The out-of-school rates for lower secondary school (ages 12-14) and upper secondary school (ages 15-17) have decreased from 25 to 16% and 48 to 36%, respectively, since the year 2000 [14]. Therefore, global efforts to increase access to and completion of schooling have the added benefit of providing an improved delivery platform for public health interventions. This builds on the ideas of the "health promoting hospital" (HPH), in which the provision of health care services is one of several intersectoral components for promoting health [15]. Many existing programs are already leveraging school-based delivery, e.g., deworming [16,17]; feeding and nutrition [18,19]; malaria prevention [20]; and immunizations [21,22]. Additional consideration should be given to leverage the existing infrastructure in place to reach adolescents using school-based delivery for important health interventions, without first requiring additional outreach initiatives that may only reach those already accessing routine health services [23].

One such important consideration to support the health and well-being of adolescents is the prevention of human papillomavirus (HPV) infection. Persistent HPV infections can lead to genital warts, cervical cancer, anal cancer, penile cancer, vaginal cancer, vulvar cancer, and cancers of the head and neck, with HPV types 16 and 18 causing 70% of all cases of cervical cancer [24,25]. More than 85% of cervical cancer deaths occur in LMICs [26], with cervical cancer being the leading cause of female cancer death in sub-Saharan Africa [27]. There is also a large economic burden in both the short- and long-term due to persistent HPV infections and induced cancers, which can be averted through both vaccination and cervical cancer screening programs [26]. Of the 800 million people who experienced catastrophic health spending – spending exceeding 10% of household consumption – and the 100 million who experienced impoverishing health spending – household health consumption pushing individuals below the international poverty line of $1.90 per day, Purchasing Power Parity – in 2010 [28,29], a large percentage of the out-of-pocket (OOP) burden may be due to cancer and non-communicable diseases [30,31]. However, while approximately 75% of women in developed countries have received access to cervical cancer screening in the last five years, less than 5% of women in developing countries have [32]. Therefore, without increased screening and vaccine uptake in LMICs, both the health and economic burden due to HPV are likely to continue.

In 2018, the World Health Organization Director General made a global call for action towards the elimination of cervical cancer in part through increased HPV vaccination [33]. The goal of cervical cancer elimination underscores the need to leverage school-based platforms of HPV vaccine delivery, but also provides an opportunity to strengthen intersectoral thinking in countries with ongoing plans to introduce HPV vaccine. Rather than introducing yet another vertical

program with the potential to displace routine health services [34], HPV vaccination programs can instead strengthen linkages between health and education.

Prophylactic HPV vaccination has a direct, proximal effect on whether or not an individual contracts a high-risk HPV infection. Studies on the Gardasil HPV vaccine have shown that it provides almost 100% protection against vaccine-targeted high-risk HPV strains (e.g., HPV-16, -18) [35,36]. As HPV vaccination is recommended to adolescents (typically ages 9 to 14 years), there are several different delivery strategies to administer vaccination, including school-based vaccination, facility-based vaccination, or vaccination combined with the provision of other health interventions (e.g., antenatal or HIV care) [37,38]. As adolescents are not often reached by routine services, particularly in LMICs, HPV vaccine delivery is likely to require an intersectoral approach with school-based delivery or integration into existing health services, as supported by prior evidence from HPV vaccine demonstration projects [38].

As data to inform evidence-based policy of new and existing HPV vaccination strategies in LMICs are limited, this thesis focuses on the costing and evaluation of the HPV vaccine utilizing modeling and economic analyses. More specifically, I examine different HPV vaccine delivery strategies and the costing of those strategies using an individual-based mathematical model of HPV transmission and cervical cancer progression and a predictive model of immunization delivery costs. I employ modeling and quantitative economic evaluation methods in order to:

1. Assess the drivers of country-level costs of routine childhood and HPV vaccine delivery in order to produce standardized country-level estimates of immunization delivery unit costs for LMICs.

2. Compare and assess health and economic outcomes for a range of campaign delivery strategies relative to routine delivery for HPV vaccination in Uganda.
3. Assess the equity benefits (distributional health gains) including financial risk protection benefits across socioeconomic status of routine delivery of the HPV vaccine in Ethiopia.

I employ multiple models and methodologies to answer these questions. In Paper 1, I utilize a publicly-available database of immunization delivery costs in LMIC settings to develop a predictive model for estimating standardized immunization delivery unit cost estimates at the country level with a Bayesian meta-regression approach [39]. These predicted costs per dose estimates can be useful for cost-effectiveness analyses when country level costs are unavailable, uncertain, or old. Country-specific costs modeled within a Bayesian meta-regression framework provide a broad indication of immunization delivery costs that may be preferable to raw country-level data without reliable, standardized review.

In Paper 2, I rely on a multiple modeling approach to estimate the health and economic outcomes associated with HPV vaccine delivery in Uganda, a low-income country in East Africa, where cervical cancer is the leading cause of cancer among females. I use a wide range of plausible scenarios, supported by evidence from childhood vaccination campaigns, to assess what might be achieved by a primary campaign delivery strategy for HPV vaccination. I found that campaign vaccination yielded greater health benefits and was cost-effective if campaigns occurred frequently enough and targeted a wide age range compared with routine HPV vaccination. In settings where routine health systems infrastructure may be limited, reaching adolescent populations with a campaign delivery strategy may be an efficient use of resources.

In Paper 3, I use the methodology of extended cost-effectiveness analysis (ECEA) [40] to examine the distributional and financial risk protection benefits from HPV vaccination in Ethiopia, a low-income country in East Africa, where cervical cancer is the second leading cause of cancer deaths among females [41]. Our analysis shows that routine two-dose HPV vaccination could avert 733,000 cervical cancer cases, 586,000 cervical cancer deaths, and 18,900 cases of catastrophic health expenditure due to cervical cancer treatment, assuming 40% vaccination coverage and 100% efficacy against HPV-16/18 with lifelong duration of protection. Approximately 30% of health benefits would accrue to the poorest quintile whereas 66% of financial risk protection benefits would accrue to the poorest quintile. This information can help policymakers in the decision-making regarding continued routine HPV vaccination, especially in the context of setting pro-poor health policies in Ethiopia.

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Paper 1: Producing standardized country-level immunization delivery unit cost estimates

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Abstract

Background
To plan for the financial sustainability of immunization programs, and make informed decisions to improve immunization coverage and equity, decision-makers need to know how much these programs cost. Cost estimates can significantly influence the cost-effectiveness and budget impact estimates used to allocate resources at the country level. However, many low- and middle-income countries (LMICs) do not have immunization delivery unit cost estimates available, or have estimates that are uncertain, unreliable, or old. While new immunization costing exercises will narrow this evidence gap, such studies are resource-intensive and hard to implement routinely. We undertook a Bayesian evidence synthesis to generate country-level estimates of immunization delivery unit costs for LMICs.

Methods
We extracted estimates of the childhood and HPV delivery cost per dose in 2016 US dollars for routine immunization services from the Immunization Costing Action Network's Immunization Delivery Cost Catalogue. We used these data to construct a prediction model for estimating standardized immunization delivery unit costs. A Bayesian meta-regression approach was used to incorporate country-level gross domestic product per capita, reported diphtheria-tetanus-pertussis third dose (DTP3) coverage, population, and number of doses in the routine vaccination schedule) and study-level (study year, single antigen or programmatic cost per dose, and cost type (financial or economic)) predictors. The fitted prediction model was used to estimate routine immunization delivery costs per dose for childhood and HPV vaccines for each LMIC for 2009-2018. Alternative regression models were specified in sensitivity analyses.

Results
We estimated the prediction model using the results from 33 individual studies, covering 22 countries. The predicted programmatic, economic costs per dose for routine delivery of childhood vaccines was $1.49 (95% uncertainty range: $0.33–4.87) and for HPV vaccines was $2.04 ($0.66–6.20) across all LMICs. By individual cost component, the programmatic economic costs per dose for routine delivery of childhood vaccines were: $0.61 for labor; $0.26 for supply chain; $0.46 for service delivery; and $0.15 for capital.

Conclusions
Immunization delivery costs are a necessary component of high-quality cost-effectiveness models, and are also used to inform budgeting for immunization programs. Our study provides estimates produced via meta-regression analyses that can help refine evaluation of vaccination programs and improve budgeting and planning in situations where empirical cost data are unavailable.

Background

Routine immunization and new vaccine introduction are critical to achieving 14 of the 17 Sustainable Development Goals (SDGs) adopted by countries in 2015 to "ensure prosperity for all" [1]. To monitor progress towards these goals, to plan for the financial sustainability of immunization programs, and to improve program coverage and equity, decision-makers need to know how much country immunization programs cost. Immunization delivery unit cost estimates are essential for budgeting and planning for the introduction of the increasing number of new vaccines available [2], which have even required the development of new financing mechanisms to support the increasing costs of country immunization programs [3]. Moreover, cost estimates can help to identify and evaluate strategies to improve efficiency in vaccine service delivery [4,5]. Cost estimates can significantly influence the cost-effectiveness and budget impact estimates used to allocate resources at the country level [6].

In addition, low- and middle-income countries (LMICs) often require continued updates of immunization program costing to apply for operational support from Gavi, the Vaccine Alliance [4,7]. However, many LMICs have not conducted an empirical study of immunization services costs, or have estimates that are uncertain, unreliable, or old. While this evidence gap has been narrowed by recent efforts to improve the production and collation of immunization costing data [8-10], these efforts would need to be expanded extensively in order to supply all countries with up-to-date and high-quality cost estimates.

The objective of this study was to produce standardized country-level estimates of immunization delivery unit costs for 136 LMICs, via an evidence synthesis of available data on immunization delivery costs [10]. We use these data to describe both routine childhood (i.e., under-five)

vaccination program delivery unit costs, as well as human papillomavirus (HPV) vaccination school-based delivery unit costs. We present immunization delivery costs per dose estimates by year, by cost component (labor, supply chain, service delivery, capital), and by country.

Methods

We developed a predictive model of immunization delivery unit costs in LMICs using Bayesian meta-regression analysis. In this section, we describe the data used to inform the model, modeling methods, and alternative regression specifications.

Data overview

We relied on a publicly-available database describing immunization delivery costs in LMIC settings—the Immunization Delivery Cost Catalogue (IDCC) from the Immunization Costing Action Network (ICAN) [10]. The IDCC is an online web catalog and downloadable Excel spreadsheet of immunization delivery cost evidence in LMIC settings, which describes the results of a systematic review of both the published and grey literature published between January 2005 and January 2018 and screened according to a set of quality criteria. The search of the peer-reviewed literature included six major electronic databases[*] with search terms including three categories of keywords – "immunization" AND "cost" AND delivery" – translated into the query language of each database. The search of the grey literature included advanced searches in Google, conference proceedings, the ProQuest dissertation database, as well as direct requests from 64 key contacts involved in global and national immunization-related work. Calls for grey literature were also posted in eight immunization-related newsletters, communities of practice, and web

[*] EconLit, Embase, Medline (via PubMed), NHS-EED, Web of Science, and WHO Global Index Medicus

discussion forums. All resources with full text availability in English, French, or Spanish, conducted in LMIC settings – determined using World Bank country income classification [11] – that included a form of delivery unit cost data from primary data collection were included. One out of two investigators conducted the title/abstract review, and one out of four investigators conducted the full text review. In addition to extracting relevant contextual and methodological information from each study, the IDCC presents the reported cost results converted to 2016 US dollars. Additional information is available from the ICAN IDCC website on the study methodology (http://immunizationeconomics.org/ican-idcc-methodology).

From the IDCC, we identified studies that included the delivery costs per dose of routine (i.e., fixed facility) vaccine delivery, for which the costs components included in the estimate were defined. We excluded studies that did not report a cost per dose or for which a cost per dose could not be calculated from the reported information, studies that did not define the components included in the costs per dose, and studies that focused solely on the costs of vaccines delivered by supplementary immunization activities (SIAs), i.e., mass vaccination outreach campaigns.

From the identified studies, we extracted estimates of the routine delivery cost per dose for childhood immunization services, defined as vaccinations for children under 5 years of age, as well as school-based delivery of HPV vaccination. We also extracted study-specific contextual information, including the number of sampled sites, when reported by a study, whether the study examined programmatic (i.e., full) costs per dose or single antigen (i.e., incremental) costs per dose, economic and/or financial costs per dose, and component costs per dose. For the observed costs per dose outcome, we extracted the observation with the highest level of granularity available

from a given study. In other words, if the total vaccine delivery costs per dose were also reported as cost components (i.e., labor, supply chain, service delivery, capital), we utilized each component cost as an observation. Otherwise, we utilized the total costs per dose with indicator variables for the components included.

We selected covariates hypothesized to be associated with immunization delivery unit costs: number of doses in the routine vaccination schedule (log(*Doses*)), gross domestic product (GDP) per capita (log(*GDP*)), reported diphtheria-tetanus-pertussis third dose coverage (*DTP3*), and total country population (log(*Pop*)) [12,13]. We reviewed available years of country immunization schedules in order to develop the predictor for the number of doses in the routine vaccination schedule over time [14]. Where individual year schedules were not available, we assumed no changes between available years. We used these data to construct country-level explanatory variables for the prediction model for estimating standardized immunization delivery unit costs.

Prediction model

We used a Bayesian meta-regression approach to regress the log of immunization delivery unit costs against the country-level explanatory variables, as well as study-level explanatory variables, as shown in Table 1.1.

Table 1.1. Model covariates

Covariate name	Description
Year	Study year
Econ	Cost type: financial=0; economic=1; undefined=2
Single	Antigens included: full vaccine program=0; single antigen=1
HPV	Vaccine program type: childhood vaccine=0; HPV=1
log(Doses)	Number of doses in the routine vaccination schedule
log(GDP)	GDP per capita
DTP3	DTP3 coverage
log(Pop)	Country population size

The continuous variables (i.e., *Year*, log(*Doses*), log(*GDP*), *DTP3*, log(*Pop*)) were standardized to mean zero and unit standard deviation before fitting the regression model. This specification of log costs per dose as the dependent variables implies a multiplicative relationship between individual predictors and the costs per dose outcome [15]. The Bayesian framework enabled us to combine the previous country- and study-level data, as well as to combine observations that varied in the definition of what was included in the costs per dose, i.e., the cost components, and synthesize these data across the observed countries. Due to the challenge of studies including an inconsistent set of cost categories, we developed an analytic strategy where each cost category was estimated separately, i.e., *Labor* ($\hat{c}_i^l$), *Supply chain* ($\hat{c}_i^{sc}$), *Service delivery* ($\hat{c}_i^{sd}$), and *Capital* ($\hat{c}_i^c$). We specified a linear equation for the log of each cost category with the previously described predictors:

$$\hat{c}_i^l = \exp(\beta_{0_l} + \beta_1 * Year_i + \beta_2 * Econ_i + \beta_3 * Single_i + \beta_4 HPV_i + \beta_5 * \log(doses)_i + \beta_6 * DTP3_i + \beta_7 * \log(GDP)_i + \beta_8 * \log(pop)_i) \quad (1)$$

$$\hat{c}_i^{sc} = \exp(\beta_{0_{sc}} + \beta_1 * Year_i + \beta_2 * Econ_i + \beta_3 * Single_i + \beta_4 HPV_i + \beta_5 * \log(doses)_i + \beta_6 * DTP3_i + \beta_7 * \log(GDP)_i + \beta_8 * \log(pop)_i) \quad (2)$$

$$\hat{c}_i^{sd} = \exp(\beta_{0_{sd}} + \beta_1 * Year_i + \beta_2 * Econ_i + \beta_3 * Single_i + \beta_4 HPV_i + \beta_5 * \log(doses)_i + \beta_6 * DTP3_i + \beta_7 * \log(GDP)_i + \beta_8 * \log(pop)_i) \quad (3)$$

$$\hat{c}_i^c = \exp(\beta_{0_c} + \beta_1 * Year_i + \beta_2 * Econ_i + \beta_3 * Single_i + \beta_4 HPV_i + \beta_5 * \log(doses)_i + \beta_6 * DTP3_i + \beta_7 * \log(GDP)_i + \beta_8 * \log(pop)_i) \quad (4)$$

The individual indicators for the costs included, i.e., *Labor* (I_l), *Supply chain* (I_{sc}), *Service delivery* (I_{sd}), *Capital* (I_c), were combined with the output of each modeled cost component to calculate the mean estimate of the delivery costs per dose (tc_i) for a given study:

$$tc_i = \hat{c}_i^l * I_l + \hat{c}_i^{sc} * I_{sc} + \hat{c}_i^{sd} * I_{sd} + \hat{c}_i^c * I_c \quad (5)$$

These mean estimates for the total delivery cost per dose were fitted using a Normal likelihood function:

$$\log(y) \sim Normal(tc, \sigma) \quad (6)$$

We extrapolated the observed costs per dose from the 22 LMIC settings to 136 LMICs using the specified formulae. We assumed common variance across all observations; in sensitivity analyses, we relaxed this assumption to explore variance that is inversely proportional to sample size. We assumed informative prior distributions for all model parameters. The predictors were assumed to follow a normal distribution centered at zero with a standard deviation of one [16]. The error term was assumed to follow a half-Cauchy distribution centered at zero with a standard deviation of five [17]. The effect of the log(*Doses*), *DTP3*, and *Single* indicator was constrained to be zero for the HPV vaccine delivery observations, as these were either: (1) not theorized to change expected costs in the case of log(*Doses*) and *DTP3*; or (2) a redundant impact due to HPV vaccine delivery being inherently observations of single antigen costs. The fitted prediction model was used to estimate immunization delivery costs per dose for both economic and financial, both childhood and HPV vaccines, programmatic costs per dose (i.e., as opposed to single antigen studies)

including all cost components for each LMIC for 2009–2018. We tested the predictive performance of the model by comparing our predictions to the observed costs per dose matched to country and year. It is important to note that the uncertainty intervals from a Bayesian framework represent posterior probabilities conditional on priors, likelihood, and regression model, and should not be interpreted as a traditional (i.e., frequentist) 95% confidence interval. The prediction model was estimated in R software [14] using an adaptive Hamiltonian Monte Carlo algorithm using the Stan software package, version 2.20.0, with four chains of 5,000 iterations with 2,500 burn-ins (iterations that were discarded), yielding 10,000 posterior draws for analysis [18,19]. Stan model diagnostics were utilized to determine any problems encountered by the sampler and the potential scale reduction factor (i.e., Rhat) for all parameters were evaluated to determine that the model had successfully converged.

Alternative regression specifications

We estimated several alternative regression specifications: (1) in which the previous model was weighted by sample size; (2) in which HPV vaccine delivery costs per dose were modeled separately from childhood vaccine delivery costs per dose; (3) in which we adopted weakly informative prior distributions, i.e., all predictors were assumed to follow a Normal distribution centered at zero with a standard deviation of 10; and (4) in which we adopted non-informative prior distributions for parameters. In scenario 1, we added weights using the number of sampled sites ($sites_i$) to derive each cost estimate in order to incorporate the precision estimated by the original studies. The overall variance in a particular observation was the linear sum of two variance terms, reflecting (1) study-level factors, e.g., methodology, data collection instruments; and (2) site-level sampling uncertainty. We assumed site-level sampling uncertainty to be common across

countries (on a log scale). The weights were a combination of site-level (σ^2_{site}) and study-level (σ^2_{study}) variance and took the form of the following equation:

$$\sigma_i = \sqrt{\sigma^2_{study} + \sigma^2_{site}/sites_i}\ , \tag{7}$$

$$\text{where } \sigma^2_{study} = \frac{adj}{1-adj} * \sigma^2_{site}\ . \tag{8}$$

In the case where the number of sampled sites for the basis of the cost per dose was not reported in the identified studies, we assumed a sample size of one. The site-level error term was assumed to follow a half-Cauchy distribution centered at zero with a standard deviation of five and the adjustment factor (*adj*) was assumed to follow a Beta distribution with α and β parameters of 2.

Results

Data selection

A total of 77 reported costs per dose estimates from 33 studies covering 22 countries were included in the analysis—52 routine childhood vaccine delivery observations [20-45] and 25 school-based HPV vaccine delivery observations [44-48]. Of the 33 studies, 14 were done in low-income country settings and 19 in middle-income country settings, as classified by 2019 World Bank income level [11]. The observed cost per dose, for estimates with all cost components included, ranged from $0.66 to $9.45. Fifty-nine unit cost estimates (77%) had defined cost components, but the costs could not be disaggregated into those components; the remaining observations could be disaggregated into unique components, bringing the total to 144 observations for analysis. For cost components included in the total cost per dose, 95% of observations included labor, 97% supply chain, 71% service delivery, and 43% capital. Table 1.2 provides summary information on the characteristics of the immunization delivery unit costs per dose analyzed.

Table 1.2. Summary characteristics for immunization delivery unit costs per dose

Reported costs per dose	Estimates (n)
Total cost per dose only	59
Total + cost components	18[a]
Income[b]	Estimates (n)
Low-income	43
Lower middle-income	27
Upper middle-income	7
Vaccine	Estimates (n)
Childhood	52
HPV	25
Antigens costed	Estimates (n)
Single antigen	53
Full vaccination program	24
Cost type	Estimates (n)
Economic	34
Financial	29
Undefined	14

[a] The 18 costs per dose estimates that could be disaggregated into cost components brought the total observations from 77 to 144.
[b] Low income: Gross national income (GNI) per capita of $1025 or less; Lower middle-income: GNI per capita of $1026 to $3995; upper middle-income: GNI per capita of $3996 to $12,375 [12].
Note: The 77 observations represent 22 countries. HPV = human papillomavirus.

For the observed dataset, the mean and standard deviation (in parentheses) of the continuous explanatory variables were: 12 (3) for *Doses*; $1,520 ($1,270) for *GDP*; 0.88 (0.09) for *DTP3*; and 72,400,000 (233,000,000) for *Pop*.

Regression model

Table 1.3 reports the regression model fit to log costs per dose. The predictor log(*Pop*) was statistically significant; all other predictors were not significant in the regression results. In our validation assessment of the model's predictive capacity, our final model provided costs per dose estimates that were in line with those of the original country-based study (Figure 1.1). Ninety-eight percent of our predictions fall within the observed costs per dose range.

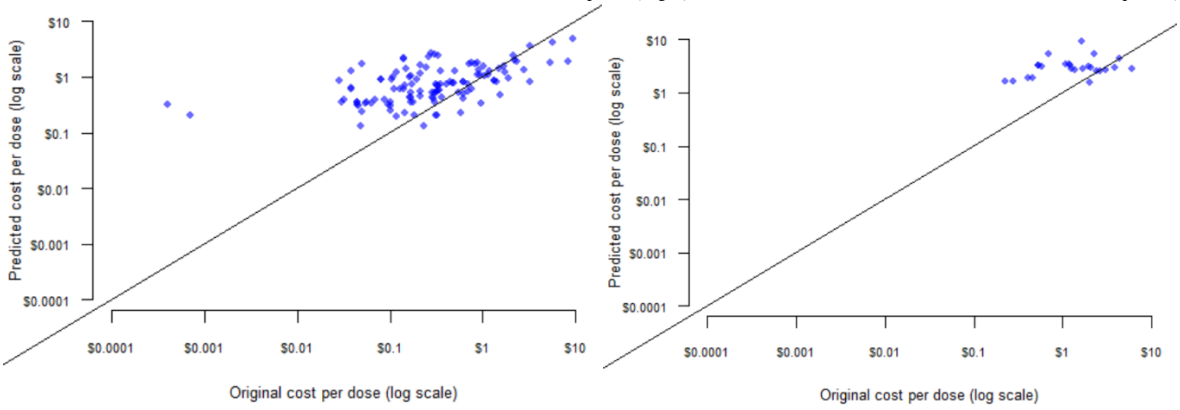
Table 1.3. Results for regressions of log costs per dose on predictors

Variable	Mean coefficient
Labor intercept	-0.55 (0.29)
Supply chain intercept	-1.43 (0.32)*
Service delivery intercept	-0.87 (0.35)*
Capital intercept	-2.00 (0.37)*
Year	-0.15 (0.14)
Economic cost indicator	-0.21 (0.17)
Single antigen indicator	-0.13 (0.27)
HPV indicator	0.27 (0.34)
log(doses)	-0.05 (0.13)
log(GDP per capita)	0.17 (0.13)
log(population)	-0.28 (0.13)*
DTP3 coverage	0.24 (0.14)
Error term	1.28 (0.08)

* Significant at 5% level.

Note: Continuous predictors were standardized to mean zero and unit standard deviation; thus, fitted coefficients for continuous variables (e.g., log(doses)) represent the increase in log costs per dose observed for a 1.0 standard deviation increase in the variable. Values in parentheses represent standard errors. DTP3 = diphtheria-tetanus-pertussis third dose; GDP = gross domestic product; HPV = human papillomavirus.

Figure 1.1. Comparison of predicted costs per dose and published literature costs per dose for routine childhood vaccine delivery (*left*) and HPV vaccine delivery (*right*)



Note: The original costs per dose represent 144 observations (119 childhood and 25 HPV) across 22 countries for currency years between 2001 and 2017. The predicted costs per dose are matched to the country and year of each observation. HPV = human papillomavirus.

As previously described, the prediction model relies on a log-transformed costs per dose outcome and standardized (i.e., mean zero and unit variance) explanatory variables, which results in regression coefficients that can be difficult to interpret. To contextualize the interpretation of Table 1.3, first differences were calculated that describe the percentage difference in the cost per dose produced by a change in an individual predictor (Table 1.4), holding others fixed. The fitted model

demonstrated that routine costs per dose were decreasing as a function of time (i.e., calendar year), population size, and number of doses in the vaccination schedule, and increasing as a function of GDP per capita and DTP3 coverage.

Table 1.4. First differences calculated from regression results

Comparison[a]	Percentage difference in unit cost per dose[b]
1 additional calendar year	-4.2% (-13.6, -1.2)
Per capita GDP doubled	18.4% (4.3, 29.1)
Population doubled	-11.6% (-17.4, -7.8)
1 additional dose in schedule	-0.5% (-2.1, 1.2)
1% increase in DTP3 coverage	2.9% (2.7, 3.4)

[a] Values represent posterior means, and values in parentheses represent equal-tailed 95% credible intervals.
[b] Calculated as one minus the average cost per dose for the given scenario divided by average cost per dose in comparator scenario.
DTP3 = diphtheria-tetanus-pertussis third dose, GDP = gross domestic product.

Predicted costs

Overall, the predicted programmatic, economic costs per dose ranged from $0.26 to $11.66 across all LMICs for the year 2018. The average predicted programmatic, economic costs per dose by income level (i.e., the average of country-level point estimates) were: $0.89 ($0.31–1.67) for low-income countries; $1.49 ($0.37–3.83) for lower-middle income countries; and $2.50 ($0.76–7.01) for upper-middle income countries. The predicted economic costs per dose for routine delivery of childhood vaccines were $1.49 ($0.33–4.87) and for HPV vaccines were $2.04 ($0.66–6.20). By individual cost component, the programmatic economic costs per dose for routine delivery of childhood vaccines were: $0.61 for labor; $0.26 for supply chain; $0.46 for service delivery; and $0.15 for capital. Table 1.5 presents the programmatic, economic costs per dose by each stratification by world region, both unweighted and weighted analyses.

Table 1.5. Predicted programmatic, economic costs per dose in 2018 for routine childhood vaccine delivery and HPV vaccine delivery by world region: (A) unweighted and (B) weighted.

A. Unweighted

Region	Mean childhood vaccine delivery cost per dose	Mean HPV vaccine delivery cost per dose
Africa	$1.02 ($0.28–2.82)	$1.47 ($0.66–3.60)
Southeast Asia	$2.04 ($0.63–5.32)	$2.66 ($1.06–6.41)
Eastern Mediterranean	$0.96 ($0.30–1.76)	$1.35 ($0.67–2.32)
Europe	$1.62 ($0.65–2.70)	$2.02 ($1.04–3.27)
Americas	$1.34 ($0.45–3.48)	$1.65 ($0.62–4.20)
Western Pacific	$2.27 ($0.45–7.33)	$3.43 ($0.86–10.24)

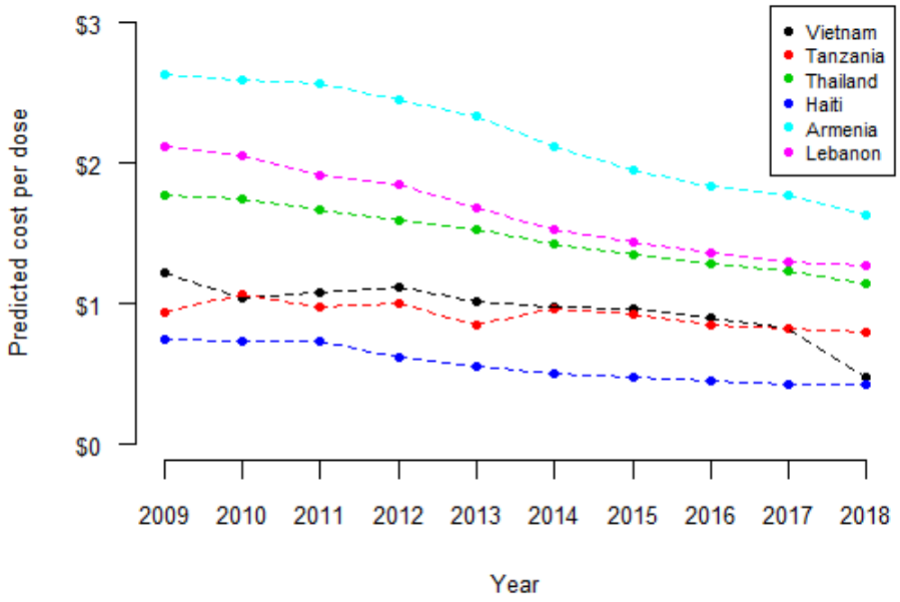
B. Weighted

Region	Mean childhood vaccine delivery cost per dose	Mean HPV vaccine delivery cost per dose
Africa	$1.08 ($0.36–2.87)	$1.67 ($0.80–3.84)
Southeast Asia	$2.17 ($0.75–5.43)	$2.94 ($1.33–6.82)
Eastern Mediterranean	$1.04 ($0.36–1.88)	$1.54 ($0.84–2.61)
Europe	$1.73 ($0.73–2.82)	$2.24 ($1.24–3.71)
Americas	$1.40 ($0.51–3.60)	$1.77 ($0.71–4.36)
Western Pacific	$2.42 ($0.54–7.62)	$3.87 ($1.05–11.03)

Note: Countries included in each World Health Organization (WHO) region are low- and middle-income countries according to World Bank income level [12]. HPV = human papillomavirus.

The full list of predicted programmatic, economic immunization delivery costs per dose in 2018 by country can be found in Appendix Table 1.1. Figure 1.2 presents the predicted programmatic, economic costs per dose for childhood vaccine delivery by year for a set of six example countries selected for differences in region and income level. The predicted costs per dose show a decreasing trend on average over time.

Figure 1.2. Predicted programmatic, economic costs per dose for routine childhood vaccine delivery by year.



Controlling for other covariates, the financial costs per dose predictions did not differ substantially from the economic costs per dose predictions; however, financial cost observations generally reported fewer cost categories, notably capital. The full list of predicted programmatic, financial immunization delivery costs per dose in 2018 by country can be found in Appendix Table 1.2.

Alternative regression specifications

With the first alternative regression specification, incorporating weights for sample size produced small changes in most coefficients (Appendix Table 1.3) and resulted in costs per dose estimates that were approximately 10% higher (Table 1.5).

With the second alternative regression specification, running separate models for childhood and HPV vaccine delivery cost outcomes (Appendix Table 1.4), we predicted costs per dose that were lower on average for childhood vaccine delivery (approximately 40% lower) and higher on average for HPV vaccine delivery (approximately 10% higher) (Table 1.6).

Table 1.6. Predicted programmatic, economic costs per dose in 2018 by world region: fitting childhood vaccine delivery cost per dose and HPV vaccine delivery cost per dose separately

Region	Mean childhood vaccine delivery cost per dose	Mean HPV vaccine delivery cost per dose
Africa	$0.59 ($0.18–1.57)	$1.91 ($1.06–3.45)
Southeast Asia	$1.19 ($0.41–2.87)	$2.59 ($1.17–5.97)
Eastern Mediterranean	$0.58 ($0.17–1.07)	$1.60 ($0.96–2.92)
Europe	$0.96 ($0.40–1.51)	$2.03 ($1.26–3.64)
Americas	$0.78 ($0.29–2.01)	$1.77 ($0.73–3.88)
Western Pacific	$1.29 ($0.29–4.03)	$3.78 ($0.87–9.92)

Note: Countries included in each world region are low- and middle-income countries according to World Bank income level [12]. HPV = human papillomavirus.

Adopting weakly informative (Appendix Table 1.5) or non-informative (Appendix Table 1.6) priors did not affect regression results.

Discussion

Our predicted programmatic, economic costs per dose by income level in 2018 were: $0.89 ($0.31–1.67) for low-income countries; $1.49 ($0.37–3.83) for lower-middle income countries; and $2.50 ($0.76–7.01) for upper-middle income countries. The predicted economic costs per dose for routine delivery of childhood vaccines were $1.49 ($0.33–4.87) and for HPV vaccines were $2.04 ($0.66–6.20). These estimates are consistent with the empirical estimates reported in ICAN IDCC [10]. These predicted costs per dose estimates can be useful for cost-effectiveness analyses when country-level costs are unavailable, uncertain, or old. For example, instead of using neighboring country data or regional data when primary cost data are unavailable, these modeled costs relying on country-level predictors such as GDP per capita and immunization coverage may provide a more informed estimate.

The regression results showed several relationships that might be expected between predictors and immunization delivery costs, but our findings may also be consistent with alternative explanations. While all predictors except log(*Pop*) were not statistically significant in the regression results, the

final model posits that these determinants logically predict immunization delivery unit costs and act as proxies for how costs are likely to differ across countries. The only statistically significant relationship was population size; higher population sizes (a proxy for higher service volume) were strongly associated with lower costs per dose. This relationship is expected as the increasing scale of an immunization program can result in costs savings through both efficiency gains and spreading fixed costs over a larger population (i.e., economies of scale). The higher service volume to lower delivery costs relationship has also been found in previous studies [9]. Additionally, a greater number of doses in the routine immunization schedule was associated with small decreases in unit costs, on the order of 5% for each additional dose (non-significant). Given the fixed costs for personnel and supply chain necessary for routine immunization delivery, additional doses in a recurrent program (i.e., no additional training, social mobilization, or other introduction costs) spreads these costs over a greater number of doses. Greater GDP per capita and DTP3 coverage were both associated with higher costs per dose, likely due to the higher price levels in wealthier countries and the increasing marginal costs with higher vaccine coverage levels, respectively. All of these relationships should be viewed as correlations with predicted costs per dose rather than confirming any specific causal relationship.

The results from the first alternative regression specification incorporating weights for sample size were likely affected due to our assumption of a sample size of one in the case where sample size is not reported, which affected 27 out of 77 total cost per dose observations. The reported sample sizes ranged from two to 112 with an average of 30. Therefore, when taking into consideration the level of precision for the costs per dose estimated by the original studies, we predict costs that are approximately 12% higher. The results from the second alternative regression specification fitting

childhood and HPV vaccine delivery separately resulted in lower and higher predictions, respectively, as the HPV vaccine delivery observations were overall more homogeneous (all observations were reported as total costs per dose, all included labor costs, all excluded capital costs, and only 3 observations did not include supply chain and/or service delivery costs), which increased the impact of predictors on the heterogeneous childhood dataset.

There are several limitations to this analysis. First, we are assuming that the data are an unbiased sample of the true value, but costing studies are inconsistent (i.e., study methodologies are heterogeneous) and samples are not always randomly selected or nationally representative. Costing studies may over- or under-estimate costs due to the costing approach used (i.e., gross costing vs. micro-costing [49]) or may underestimate costs due to the exclusion of relevant intervention cost components [50]. Improving consistency in how costing studies are conducted, how samples are selected, and at what level may resolve part of this bias, but truly random sample selection is unlikely. The inclusion of uncertainty and scenario analyses aimed to address these limitations by estimating uncertainty intervals. However, additional uncertainty due to limitations and quality in the original data might have remained. Large heterogeneity exists in the dataset, which is only partially explained by the regression coefficients. Within this uncertainty, there may be real differences between countries or simply "measurement error" within the empirical study. The "measurement error" may be due to inconsistent definitions of cost components and cost types (i.e., financial vs. economic) within studies in addition to differences in how costs were collected. Second, we assumed that routine childhood vaccine delivery costs are similar regardless of individual vaccine product. However, there may be differences in delivery costs, particularly in the case of injection vs. oral vaccines. Additionally, while we included an indicator for HPV

vaccines to incorporate the mean change in delivery costs compared to childhood vaccines, we did not otherwise include changing delivery costs for reaching older target age groups. Third, we acknowledge that there may be issues raised by log transformations of data containing zeroes. However, within this analysis, while we allowed for zeroes in individual cost categories, the data used were strictly positive. Fourth, while the number of studies is large for a meta-analysis, the number of observations within each of these studies (i.e., number of sites) is small and only 22 countries were represented in the original dataset. A costing study that relies on a small number of sampled sites may produce results that are not representative, if there is likely to be large variation across sites [51]. These countries were generally of lower GDP per capita (average $1,600 vs. $4,000) and higher DTP3 coverage (average 88% vs. 85%) compared to the 136 LMIC prediction populations. Finally, the exclusion of predictors that we were unable to assess or incorporate could result in omitted variable bias (i.e., sources of variation that were not modeled) for our predictions. There may be reasons that the countries and settings included in the sample are unique beyond the variables that we looked at.

While recent costing reference cases provide concrete guidance for implementing and reporting costing studies [5], we are unlikely to have the resources to conduct empirical costing and/or cost-effectiveness analysis for all questions and settings of interest. Therefore, a key strategy for improving the availability of costing data is to determine how and where we can extrapolate from a specific study to learn something more general. Country-specific costs modeled within a Bayesian meta-regression framework provide a broad indication of immunization delivery costs that may be preferable to raw country-level data without reliable, standardized review.

Immunization delivery costs are a necessary component of high-quality cost-effectiveness models, and are also used to inform budgeting for immunization programs. Our study provides estimates produced via meta-regression analyses that can help refine evaluation of vaccination programs and improve budgeting and planning in situations where empirical cost data are unavailable or of low quality.

Acknowledgements

This study was funded by the Bill & Melinda Gates Foundation. Earlier versions of this paper were presented at the 2019 International Health Economics Association World Congress, and we received valuable comments from conference participants. We also received valuable comments from Stéphane Verguet and Jane Kim.

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Appendix

Appendix Table 1.1. Low- and middle-income country parameters with predicted programmatic, economic immunization delivery costs per dose in 2018

Country	World Bank Income Level[a]	WHO Region	GDP per capita (2018 US$)	Population	DTP3 Coverage	Number of Doses in Schedule	Predicted Childhood Vaccine Delivery Costs per Dose	Predicted HPV Vaccine Delivery Costs per Dose
Afghanistan	LIC	EMR	$520	37,200,000	0.66	18	$0.32	$0.70
Albania	UMIC	EUR	$5,250	2,870,000	0.99	11	$2.40	$2.60
Algeria	UMIC	AFR	$4,280	42,200,000	0.91	22	$0.96	$1.30
Angola	UMIC	AFR	$3,430	30,800,000	0.59	11	$0.52	$1.09
Argentina	UMIC	AMR	$11,650	44,500,000	0.86	18	$1.14	$1.63
Armenia	LMIC	EUR	$4,210	2,950,000	0.92	16	$1.72	$2.28
Azerbaijan	UMIC	EUR	$4,720	9,940,000	0.95	17	$1.49	$1.86
Bangladesh	LMIC	SEAR	$1,700	161,000,000	0.98	18	$0.75	$0.86
Belarus	UMIC	EUR	$6,290	9,490,000	0.97	13	$1.79	$2.07
Belize	UMIC	AMR	$5,030	383,000	0.96	12	$3.32	$3.95
Benin	LIC	AFR	$900	11,500,000	0.76	18	$0.58	$1.06
Bhutan	LMIC	SEAR	$3,360	754,000	0.97	13	$2.60	$3.08
Bolivia	LMIC	AMR	$3,550	11,400,000	0.83	18	$0.98	$1.52
Bosnia and Herzegovina	UMIC	EUR	$5,950	3,320,000	0.73	12	$1.25	$2.14
Botswana	UMIC	AFR	$8,260	2,250,000	0.95	13	$2.45	$2.97
Brazil	UMIC	AMR	$8,920	209,000,000	0.83	14	$0.76	$1.10
Bulgaria	UMIC	EUR	$9,270	7,020,000	0.92	11	$1.92	$2.34
Burkina Faso	LIC	AFR	$730	19,800,000	0.91	12	$0.81	$1.01
Burundi	LIC	AFR	$280	11,200,000	0.90	16	$0.69	$0.95
Cabo Verde	LMIC	AFR	$3,650	544,000	0.98	15	$2.84	$3.43
Cambodia	LMIC	WPR	$1,510	16,200,000	0.92	18	$0.93	$1.24
Cameroon	LMIC	AFR	$1,530	25,200,000	0.79	9	$0.72	$1.03
Central African Republic	LIC	AFR	$510	4,670,000	0.47	14	$0.36	$1.02
Chad	LIC	AFR	$730	15,500,000	0.41	17	$0.26	$0.83
China	UMIC	WPR	$9,770	1,393,000,000	0.99	7	$0.98	$0.92
Colombia	UMIC	AMR	$6,650	49,600,000	0.92	13	$1.16	$1.43
Comoros	LIC	AFR	$1,450	832,000	0.91	17	$1.68	$2.35
Congo	LMIC	AFR	$2,150	5,200,000	0.75	16	$0.84	$1.51
Congo, Democratic Republic of the	LIC	AFR	$560	84,100,000	0.81	16	$0.42	$0.66

Appendix Table 1.1 (Continued)

Costa Rica	UMIC	AMR	$12,030	5,000,000	0.94	14	$2.22	$2.75
Côte d'Ivoire	LMIC	AFR	$1,720	25,100,000	0.82	19	$0.67	$1.08
Cuba	UMIC	AMR	$8,100	11,300,000	0.99	12	$1.99	$2.17
Djibouti	LMIC	EMR	$2,050	959,000	0.84	16	$1.49	$2.32
Dominica	UMIC	AMR	$7,030	71,600	0.94	11	$5.20	$6.35
Dominican Republic	UMIC	AMR	$7,650	10,600,000	0.94	9	$1.85	$2.07
Ecuador	UMIC	AMR	$6,340	17,100,000	0.85	16	$1.13	$1.65
Egypt	LMIC	EMR	$2,550	98,400,000	0.95	16	$0.84	$1.00
El Salvador	LMIC	AMR	$4,060	6,420,000	0.81	10	$1.23	$1.76
Equatorial Guinea	UMIC	AFR	$10,170	1,310,000	0.25	16	$0.85	$2.69
Eritrea	LIC	AFR	$730	3,180,000	0.95	10	$1.40	$1.56
Ethiopia	LIC	AFR	$770	109,000,000	0.72	13	$0.35	$0.63
Fiji	UMIC	WPR	$6,200	883,000	0.99	19	$2.88	$3.54
Gabon	UMIC	AFR	$8,030	2,120,000	0.70	9	$1.53	$2.53
Gambia	LIC	AFR	$710	2,280,000	0.93	10	$1.41	$1.64
Georgia	UMIC	EUR	$4,340	3,730,000	0.93	11	$1.84	$2.21
Ghana	LMIC	AFR	$2,200	29,800,000	0.97	5	$1.47	$1.25
Grenada	UMIC	AMR	$10,830	111,000	0.96	11	$5.51	$6.51
Guatemala	LMIC	AMR	$4,550	17,200,000	0.86	15	$1.07	$1.52
Guinea	LIC	AFR	$890	12,400,000	0.45	7	$0.41	$0.92
Guinea-Bissau	LIC	AFR	$780	1,870,000	0.88	17	$1.13	$1.67
Guyana	UMIC	AMR	$4,630	779,000	0.95	14	$2.60	$3.25
Haiti	LIC	AMR	$870	11,100,000	0.64	18	$0.44	$1.00
Honduras	LMIC	AMR	$2,480	9,590,000	0.90	18	$1.10	$1.53
India	LMIC	SEAR	$2,020	1,353,000,000	0.89	14	$0.44	$0.56
Indonesia	LMIC	SEAR	$3,890	267,700,000	0.79	18	$0.51	$0.81
Iran	UMIC	EMR	$5,270	81,800,000	0.99	8	$1.34	$1.30
Iraq	UMIC	EMR	$5,880	38,400,000	0.84	15	$0.93	$1.36
Jamaica	UMIC	AMR	$5,360	2,930,000	0.97	13	$2.18	$2.55
Jordan	UMIC	EMR	$4,250	9,960,000	0.96	17	$1.49	$1.83
Kazakhstan	UMIC	EUR	$9,330	18,300,000	0.98	16	$1.75	$2.03
Kenya	LMIC	AFR	$1,710	51,400,000	0.92	18	$0.77	$1.01
Kiribati	LMIC	WPR	$1,630	116,000	0.95	12	$3.29	$4.02
Korea, Democratic People's Republic of	LIC	SEAR	$1,030	25,500,000	0.97	7	$1.15	$1.09
Kyrgyz Republic	LMIC	EUR	$1,280	6,320,000	0.94	10	$1.31	$1.49
Lao People's Democratic Republic	LMIC	WPR	$2,570	7,060,000	0.68	19	$0.69	$1.43

Appendix Table 1.1 (Continued)

Lebanon	UMIC	EMR	$8,270	6,850,000	0.83	18	$1.37	$2.12
Lesotho	LMIC	AFR	$1,320	2,110,000	0.93	13	$1.51	$1.90
Liberia	LIC	AFR	$670	4,820,000	0.84	16	$0.82	$1.27
Libya	UMIC	EMR	$7,240	6,680,000	0.97	17	$1.91	$2.31
Macedonia, North	UMIC	EUR	$6,080	2,080,000	0.91	14	$2.04	$2.69
Madagascar	LIC	AFR	$460	26,300,000	0.75	17	$0.42	$0.77
Malawi	LIC	AFR	$390	18,100,000	0.92	9	$0.82	$0.92
Malaysia	UMIC	WPR	$11,240	31,500,000	0.99	15	$1.72	$1.93
Maldives	UMIC	SEAR	$10,220	516,000	0.99	17	$3.77	$4.58
Mali	LIC	AFR	$900	19,100,000	0.71	16	$0.48	$0.92
Marshall Islands	UMIC	WPR	$3,620	58,400	0.81	16	$3.03	$5.13
Mauritania	LMIC	AFR	$1,220	4,400,000	0.81	10	$1.00	$1.44
Mauritius	UMIC	AFR	$11,240	1,270,000	0.97	10	$3.38	$3.75
Mexico	UMIC	AMR	$9,700	126,000,000	0.88	14	$0.97	$1.28
Micronesia	LMIC	WPR	$3,060	113,000	0.75	19	$2.09	$4.04
Moldova, Republic of	LMIC	EUR	$3,190	3,550,000	0.93	20	$1.53	$2.07
Mongolia	LMIC	WPR	$4,100	3,170,000	0.99	19	$1.99	$2.39
Montenegro	UMIC	EUR	$8,760	622,000	0.87	9	$2.97	$3.79
Morocco	LMIC	EMR	$3,240	36,000,000	0.99	16	$1.20	$1.35
Mozambique	LIC	AFR	$490	29,500,000	0.80	15	$0.49	$0.79
Myanmar	LMIC	SEAR	$1,330	53,700,000	0.91	9	$0.82	$0.94
Namibia	UMIC	AFR	$5,930	2,450,000	0.89	18	$1.78	$2.54
Nepal	LIC	SEAR	$1,030	28,100,000	0.91	13	$0.80	$1.01
Nicaragua	LMIC	AMR	$2,030	6,470,000	0.98	8	$1.73	$1.71
Niger	LIC	AFR	$410	22,400,000	0.79	16	$0.48	$0.80
Nigeria	LMIC	AFR	$2,030	196,000,000	0.57	18	$0.28	$0.66
Pakistan	LMIC	EMR	$1,470	212,000,000	0.75	16	$0.38	$0.65
Palau	UMIC	WPR	$17,320	17,900	0.95	14	$8.93	$11.66
Panama	UMIC	AMR	$15,580	4,180,000	0.88	17	$2.07	$2.94
Papua New Guinea	LMIC	WPR	$2,720	8,610,000	0.61	13	$0.63	$1.35
Paraguay	UMIC	AMR	$5,870	6,960,000	0.88	17	$1.41	$2.00
Peru	UMIC	AMR	$6,950	32,000,000	0.84	16	$1.00	$1.48
Philippines	LMIC	WPR	$3,100	107,000,000	0.65	16	$0.41	$0.85
Romania	UMIC	EUR	$12,300	19,500,000	0.86	17	$1.36	$1.95
Russian Federation	UMIC	EUR	$11,290	144,000,000	0.97	17	$1.23	$1.41
Rwanda	LIC	AFR	$770	12,300,000	0.97	19	$0.98	$1.20
Samoa	LMIC	WPR	$4,390	196,000	0.34	18	$1.07	$3.39
São Tomé and Principe	LMIC	AFR	$2,000	211,000	0.95	18	$2.70	$3.63

Appendix Table 1.1 (Continued)

Senegal	LIC	AFR	$1,520	15,900,000	0.81	23	$0.68	$1.14
Serbia	UMIC	EUR	$7,230	6,980,000	0.96	8	$2.17	$2.27
Sierra Leone	LIC	AFR	$520	7,650,000	0.90	20	$0.80	$1.15
Solomon Islands	LMIC	WPR	$2,160	653,000	0.85	12	$1.81	$2.59
Somalia	LIC	EMR	$500	15,000,000	0.42	10	$0.29	$0.78
South Africa	UMIC	AFR	$6,340	57,800,000	0.74	18	$0.68	$1.21
South Sudan	LIC	AFR	$780	11,000,000	0.49	15	$0.34	$0.93
Sri Lanka	LMIC	SEAR	$4,100	21,700,000	0.99	20	$1.36	$1.59
St. Lucia	UMIC	AMR	$10,320	182,000	0.95	21	$4.13	$5.65
St. Vincent and the Grenadines	UMIC	AMR	$7,380	110,000	0.97	24	$4.36	$5.95
Sudan	LMIC	EMR	$980	41,800,000	0.93	19	$0.72	$0.94
Suriname	UMIC	AMR	$5,950	576,000	0.95	18	$2.82	$3.72
Swaziland	LMIC	AFR	$4,140	1,140,000	0.90	20	$1.91	$2.77
Syrian Arab Republic	LMIC	EMR	$1,860	16,900,000	0.47	18	$0.36	$1.02
Tajikistan	LMIC	EUR	$830	9,100,000	0.96	20	$1.01	$1.28
Tanzania, United Republic of	LIC	AFR	$1,050	56,300,000	0.98	18	$0.81	$0.95
Thailand	UMIC	SEAR	$7,270	69,400,000	0.97	20	$1.21	$1.44
Timor-Leste	LMIC	SEAR	$2,040	1,270,000	0.83	20	$1.30	$2.16
Togo	LIC	AFR	$670	7,890,000	0.88	18	$0.81	$1.18
Tonga	LMIC	WPR	$4,360	103,000	0.81	24	$2.57	$4.66
Tunisia	LMIC	EMR	$3,450	11,600,000	0.97	19	$1.39	$1.70
Turkey	UMIC	EUR	$9,310	82,300,000	0.98	21	$1.30	$1.50
Turkmenistan	UMIC	EUR	$6,970	5,850,000	0.99	20	$2.01	$2.40
Tuvalu	UMIC	WPR	$3,700	11,500	0.89	21	$5.17	$8.31
Uganda	LIC	AFR	$640	42,700,000	0.93	21	$0.65	$0.86
Ukraine	LMIC	EUR	$3,100	44,600,000	0.50	18	$0.36	$0.96
Uzbekistan	LMIC	EUR	$1,530	33,000,000	0.98	19	$0.97	$1.14
Vanuatu	LMIC	WPR	$3,030	293,000	0.85	20	$2.09	$3.40
Venezuela	UMIC	AMR	$14,200	28,900,000	0.60	23	$0.74	$1.65
Vietnam	LMIC	WPR	$2,560	95,500,000	0.75	15	$0.51	$0.87
Yemen	LMIC	EMR	$940	28,500,000	0.65	18	$0.38	$0.83
Zambia	LMIC	AFR	$1,540	17,400,000	0.90	18	$0.88	$1.21
Zimbabwe	LIC	AFR	$2,150	14,400,000	0.89	19	$0.95	$1.34

[a] LIC: Gross national income (GNI) per capita of $1025 or less; LMIC: GNI per capita of $1026 to $3995; UMIC: GNI per capita of $3996 to $12,375 (World Bank 2019).

Note: AFR = African region; AMR = Region of the Americas; DTP3 = diphtheria-tetanus-pertussis third dose; EMR = Eastern Mediterranean region; EUR = European region; GDP = gross domestic product; HPV = human papillomavirus; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

Appendix Table 1.2. Low- and middle-income country parameters with predicted programmatic, financial immunization delivery costs per dose in 2018

Country	World Bank Income Level[a]	WHO Region	GDP per capita (2018 US$)	Population	DTP3 Coverage	Number of Doses in Schedule	Predicted Childhood Vaccine Delivery Costs per Dose	Predicted HPV Vaccine Delivery Costs per Dose
Afghanistan	LIC	EMR	$520	37,200,000	0.66	18	$0.41	$0.87
Albania	UMIC	EUR	$5,250	2,870,000	0.99	11	$2.99	$3.22
Algeria	UMIC	AFR	$4,280	42,200,000	0.91	22	$1.21	$1.62
Angola	UMIC	AFR	$3,430	30,800,000	0.59	11	$0.68	$1.36
Argentina	UMIC	AMR	$11,650	44,500,000	0.86	18	$1.44	$2.04
Armenia	LMIC	EUR	$4,210	2,950,000	0.92	16	$2.16	$2.84
Azerbaijan	UMIC	EUR	$4,720	9,940,000	0.95	17	$1.86	$2.31
Bangladesh	LMIC	SEAR	$1,700	161,000,000	0.98	18	$0.93	$1.06
Belarus	UMIC	EUR	$6,290	9,490,000	0.97	13	$2.24	$2.56
Belize	UMIC	AMR	$5,030	383,000	0.96	12	$4.15	$4.90
Benin	LIC	AFR	$900	11,500,000	0.76	18	$0.74	$1.31
Bhutan	LMIC	SEAR	$3,360	754,000	0.97	13	$3.25	$3.81
Bolivia	LMIC	AMR	$3,550	11,400,000	0.83	18	$1.23	$1.90
Bosnia and Herzegovina	UMIC	EUR	$5,950	3,320,000	0.73	12	$1.60	$2.68
Botswana	UMIC	AFR	$8,260	2,250,000	0.95	13	$3.07	$3.70
Brazil	UMIC	AMR	$8,920	209,000,000	0.83	14	$0.97	$1.37
Bulgaria	UMIC	EUR	$9,270	7,020,000	0.92	11	$2.42	$2.91
Burkina Faso	LIC	AFR	$730	19,800,000	0.91	12	$1.02	$1.25
Burundi	LIC	AFR	$280	11,200,000	0.90	16	$0.86	$1.16
Cabo Verde	LMIC	AFR	$3,650	544,000	0.98	15	$3.54	$4.24
Cambodia	LMIC	WPR	$1,510	16,200,000	0.92	18	$1.17	$1.54
Cameroon	LMIC	AFR	$1,530	25,200,000	0.79	9	$0.91	$1.28
Central African Republic	LIC	AFR	$510	4,670,000	0.47	14	$0.47	$1.27
Chad	LIC	AFR	$730	15,500,000	0.41	17	$0.35	$1.04
China	UMIC	WPR	$9,770	1,393,000,000	0.99	7	$1.23	$1.15
Colombia	UMIC	AMR	$6,650	49,600,000	0.92	13	$1.45	$1.78
Comoros	LIC	AFR	$1,450	832,000	0.91	17	$2.09	$2.90
Congo	LMIC	AFR	$2,150	5,200,000	0.75	16	$1.08	$1.88
Congo, Democratic Republic of the	LIC	AFR	$560	84,100,000	0.81	16	$0.52	$0.82
Costa Rica	UMIC	AMR	$12,030	5,000,000	0.94	14	$2.79	$3.43
Côte d'Ivoire	LMIC	AFR	$1,720	25,100,000	0.82	19	$0.85	$1.34
Cuba	UMIC	AMR	$8,100	11,300,000	0.99	12	$2.48	$2.70

Appendix Table 1.2 (Continued)

Djibouti	LMIC	EMR	$2,050	959,000	0.84	16	$1.88	$2.88
Dominica	UMIC	AMR	$7,030	71,600	0.94	11	$6.52	$7.88
Dominican Republic	UMIC	AMR	$7,650	10,600,000	0.94	9	$2.33	$2.57
Ecuador	UMIC	AMR	$6,340	17,100,000	0.85	16	$1.43	$2.06
Egypt	LMIC	EMR	$2,550	98,400,000	0.95	16	$1.05	$1.24
El Salvador	LMIC	AMR	$4,060	6,420,000	0.81	10	$1.56	$2.19
Equatorial Guinea	UMIC	AFR	$10,170	1,310,000	0.25	16	$1.14	$3.39
Eritrea	LIC	AFR	$730	3,180,000	0.95	10	$1.74	$1.92
Ethiopia	LIC	AFR	$770	109,000,000	0.72	13	$0.45	$0.78
Fiji	UMIC	WPR	$6,200	883,000	0.99	19	$3.59	$4.38
Gabon	UMIC	AFR	$8,030	2,120,000	0.70	9	$1.97	$3.17
Gambia	LIC	AFR	$710	2,280,000	0.93	10	$1.77	$2.02
Georgia	UMIC	EUR	$4,340	3,730,000	0.93	11	$2.31	$2.74
Ghana	LMIC	AFR	$2,200	29,800,000	0.97	5	$1.85	$1.55
Grenada	UMIC	AMR	$10,830	111,000	0.96	11	$6.91	$8.08
Guatemala	LMIC	AMR	$4,550	17,200,000	0.86	15	$1.35	$1.89
Guinea	LIC	AFR	$890	12,400,000	0.45	7	$0.54	$1.14
Guinea-Bissau	LIC	AFR	$780	1,870,000	0.88	17	$1.42	$2.06
Guyana	UMIC	AMR	$4,630	779,000	0.95	14	$3.26	$4.03
Haiti	LIC	AMR	$870	11,100,000	0.64	18	$0.57	$1.24
Honduras	LMIC	AMR	$2,480	9,590,000	0.90	18	$1.38	$1.90
India	LMIC	SEAR	$2,020	1,353,000,000	0.89	14	$0.55	$0.69
Indonesia	LMIC	SEAR	$3,890	267,700,000	0.79	18	$0.64	$1.01
Iran	UMIC	EMR	$5,270	81,800,000	0.99	8	$1.67	$1.62
Iraq	UMIC	EMR	$5,880	38,400,000	0.84	15	$1.18	$1.70
Jamaica	UMIC	AMR	$5,360	2,930,000	0.97	13	$2.73	$3.16
Jordan	UMIC	EMR	$4,250	9,960,000	0.96	17	$1.86	$2.27
Kazakhstan	UMIC	EUR	$9,330	18,300,000	0.98	16	$2.18	$2.52
Kenya	LMIC	AFR	$1,710	51,400,000	0.92	18	$0.97	$1.25
Kiribati	LMIC	WPR	$1,630	116,000	0.95	12	$4.10	$4.96
Korea, Democratic People's Republic of	LIC	SEAR	$1,030	25,500,000	0.97	7	$1.44	$1.35
Kyrgyz Republic	LMIC	EUR	$1,280	6,320,000	0.94	10	$1.64	$1.84
Lao People's Democratic Republic	LMIC	WPR	$2,570	7,060,000	0.68	19	$0.89	$1.78
Lebanon	UMIC	EMR	$8,270	6,850,000	0.83	18	$1.73	$2.65
Lesotho	LMIC	AFR	$1,320	2,110,000	0.93	13	$1.89	$2.34
Liberia	LIC	AFR	$670	4,820,000	0.84	16	$1.03	$1.57

Appendix Table 1.2 (Continued)

Libya	UMIC	EMR	$7,240	6,680,000	0.97	17	$2.38	$2.87
Macedonia, North	UMIC	EUR	$6,080	2,080,000	0.91	14	$2.56	$3.35
Madagascar	LIC	AFR	$460	26,300,000	0.75	17	$0.53	$0.96
Malawi	LIC	AFR	$390	18,100,000	0.92	9	$1.03	$1.14
Malaysia	UMIC	WPR	$11,240	31,500,000	0.99	15	$2.15	$2.40
Maldives	UMIC	SEAR	$10,220	516,000	0.99	17	$4.70	$5.68
Mali	LIC	AFR	$900	19,100,000	0.71	16	$0.61	$1.15
Marshall Islands	UMIC	WPR	$3,620	58,400	0.81	16	$3.84	$6.38
Mauritania	LMIC	AFR	$1,220	4,400,000	0.81	10	$1.26	$1.78
Mauritius	UMIC	AFR	$11,240	1,270,000	0.97	10	$4.24	$4.66
Mexico	UMIC	AMR	$9,700	126,000,000	0.88	14	$1.22	$1.60
Micronesia	LMIC	WPR	$3,060	113,000	0.75	19	$2.66	$5.02
Moldova, Republic of	LMIC	EUR	$3,190	3,550,000	0.93	20	$1.91	$2.56
Mongolia	LMIC	WPR	$4,100	3,170,000	0.99	19	$2.47	$2.96
Montenegro	UMIC	EUR	$8,760	622,000	0.87	9	$3.77	$4.72
Morocco	LMIC	EMR	$3,240	36,000,000	0.99	16	$1.49	$1.67
Mozambique	LIC	AFR	$490	29,500,000	0.80	15	$0.62	$0.98
Myanmar	LMIC	SEAR	$1,330	53,700,000	0.91	9	$1.02	$1.16
Namibia	UMIC	AFR	$5,930	2,450,000	0.89	18	$2.24	$3.16
Nepal	LIC	SEAR	$1,030	28,100,000	0.91	13	$1.00	$1.25
Nicaragua	LMIC	AMR	$2,030	6,470,000	0.98	8	$2.16	$2.11
Niger	LIC	AFR	$410	22,400,000	0.79	16	$0.60	$0.99
Nigeria	LMIC	AFR	$2,030	196,000,000	0.57	18	$0.36	$0.82
Pakistan	LMIC	EMR	$1,470	212,000,000	0.75	16	$0.48	$0.81
Palau	UMIC	WPR	$17,320	17,900	0.95	14	$11.20	$14.48
Panama	UMIC	AMR	$15,580	4,180,000	0.88	17	$2.62	$3.67
Papua New Guinea	LMIC	WPR	$2,720	8,610,000	0.61	13	$0.82	$1.69
Paraguay	UMIC	AMR	$5,870	6,960,000	0.88	17	$1.78	$2.49
Peru	UMIC	AMR	$6,950	32,000,000	0.84	16	$1.27	$1.85
Philippines	LMIC	WPR	$3,100	107,000,000	0.65	16	$0.53	$1.06
Romania	UMIC	EUR	$12,300	19,500,000	0.86	17	$1.72	$2.44
Russian Federation	UMIC	EUR	$11,290	144,000,000	0.97	17	$1.54	$1.76
Rwanda	LIC	AFR	$770	12,300,000	0.97	19	$1.21	$1.48
Samoa	LMIC	WPR	$4,390	196,000	0.34	18	$1.41	$4.25
São Tomé and Principe	LMIC	AFR	$2,000	211,000	0.95	18	$3.36	$4.48
Senegal	LIC	AFR	$1,520	15,900,000	0.81	23	$0.86	$1.42
Serbia	UMIC	EUR	$7,230	6,980,000	0.96	8	$2.73	$2.81
Sierra Leone	LIC	AFR	$520	7,650,000	0.90	20	$1.00	$1.42

Appendix Table 1.2 (Continued)

Solomon Islands	LMIC	WPR	$2,160	653,000	0.85	12	$2.28	$3.21
Somalia	LIC	EMR	$500	15,000,000	0.42	10	$0.38	$0.97
South Africa	UMIC	AFR	$6,340	57,800,000	0.74	18	$0.87	$1.51
South Sudan	LIC	AFR	$780	11,000,000	0.49	15	$0.44	$1.15
Sri Lanka	LMIC	SEAR	$4,100	21,700,000	0.99	20	$1.69	$1.97
St. Lucia	UMIC	AMR	$10,320	182,000	0.95	21	$5.17	$7.02
St. Vincent and the Grenadines	UMIC	AMR	$7,380	110,000	0.97	24	$5.43	$7.37
Sudan	LMIC	EMR	$980	41,800,000	0.93	19	$0.90	$1.16
Suriname	UMIC	AMR	$5,950	576,000	0.95	18	$3.53	$4.61
Swaziland	LMIC	AFR	$4,140	1,140,000	0.90	20	$2.40	$3.44
Syrian Arab Republic	LMIC	EMR	$1,860	16,900,000	0.47	18	$0.47	$1.28
Tajikistan	LMIC	EUR	$830	9,100,000	0.96	20	$1.26	$1.58
Tanzania, United Republic of	LIC	AFR	$1,050	56,300,000	0.98	18	$1.01	$1.17
Thailand	UMIC	SEAR	$7,270	69,400,000	0.97	20	$1.52	$1.78
Timor-Leste	LMIC	SEAR	$2,040	1,270,000	0.83	20	$1.65	$2.68
Togo	LIC	AFR	$670	7,890,000	0.88	18	$1.01	$1.46
Tonga	LMIC	WPR	$4,360	103,000	0.81	24	$3.25	$5.80
Tunisia	LMIC	EMR	$3,450	11,600,000	0.97	19	$1.73	$2.10
Turkey	UMIC	EUR	$9,310	82,300,000	0.98	21	$1.62	$1.87
Turkmenistan	UMIC	EUR	$6,970	5,850,000	0.99	20	$2.50	$2.98
Tuvalu	UMIC	WPR	$3,700	11,500	0.89	21	$6.46	$10.29
Uganda	LIC	AFR	$640	42,700,000	0.93	21	$0.81	$1.06
Ukraine	LMIC	EUR	$3,100	44,600,000	0.50	18	$0.47	$1.20
Uzbekistan	LMIC	EUR	$1,530	33,000,000	0.98	19	$1.20	$1.41
Vanuatu	LMIC	WPR	$3,030	293,000	0.85	20	$2.63	$4.21
Venezuela	UMIC	AMR	$14,200	28,900,000	0.60	23	$0.96	$2.07
Vietnam	LMIC	WPR	$2,560	95,500,000	0.75	15	$0.65	$1.08
Yemen	LMIC	EMR	$940	28,500,000	0.65	18	$0.49	$1.04
Zambia	LMIC	AFR	$1,540	17,400,000	0.90	18	$1.10	$1.50
Zimbabwe	LIC	AFR	$2,150	14,400,000	0.89	19	$1.19	$1.67

[a] LIC: Gross national income (GNI) per capita of $1025 or less; LMIC: GNI per capita of $1026 to $3995; UMIC: GNI per capita of $3996 to $12,375 (World Bank 2019).

Note: AFR = African region; AMR = Region of the Americas; DTP3 = diphtheria-tetanus-pertussis third dose; EMR = Eastern Mediterranean region; EUR = European region; GDP = gross domestic product; HPV = human papillomavirus; LIC = low-income; LMIC = lower middle-income; SEAR = Southeast Asian region; UMIC = upper middle-income; WPR = Western Pacific region.

Appendix Table 1.3. Sensitivity analysis for regressions of log costs per dose on predictors: using number of sampled sites as weights for precision of cost estimates

Variable	Mean coefficient
Labor intercept	-0.60 (0.29)
Supply chain intercept	-1.46 (0.32)
Service delivery intercept	-0.84 (0.34)
Capital intercept	-2.05 (0.36)
Year	-0.13 (0.14)
Economic cost indicator	-0.20 (0.17)
Single antigen indicator	-0.12 (0.26)
HPV indicator	0.33 (0.33)
log(doses)	-0.04 (0.12)
log(GDP per capita)	0.18 (0.12)
log(population)	-0.27 (0.13)
DTP3 coverage	0.21 (0.15)
Site-level error term	0.73 (0.22)
Study-level error term	1.23 (0.08)

Note: Continuous predictors were standardized to mean zero and unit standard deviation; thus, fitted coefficients for continuous variables (e.g., log(doses)) represent the increase in log costs per dose observed for a 1.0 standard deviation increase in the variable. Values in parentheses represent standard errors. DTP3 = diphtheria-tetanus-pertussis third dose; GDP = gross domestic product; HPV = human papillomavirus.

Appendix Table 1.4. Sensitivity analysis for regressions of log costs per dose on predictors: fitting childhood vaccine delivery cost per dose and HPV vaccine delivery cost per dose separately

Childhood vaccine delivery cost per dose

Variable	Mean coefficient
Labor intercept	-0.77 (0.32)
Supply chain intercept	-1.78 (0.36)
Service delivery intercept	-1.21 (0.40)
Capital intercept	-2.47 (0.42)
Year	-0.27 (0.13)
Economic cost indicator	-0.13 (0.17)
Single antigen indicator	0.25 (0.27)
log(doses)	-0.03 (0.12)
log(GDP per capita)	0.18 (0.14)
log(population)	-0.27 (0.12)
DTP3 coverage	0.23 (0.14)
Error term	1.28 (0.08)

HPV vaccine delivery cost per dose

Variable	Mean coefficient
Intercept	0.59 (0.74)
Economic cost indicator	0.72 (0.36)
Supply chain indicator	-2.59 (0.99)
Service delivery indicator	2.19 (0.61)
log(GDP per capita)	0.01 (0.15)
log(population)	-0.26 (0.15)
Error term	0.71 (0.13)

Note: Continuous predictors were standardized to mean zero and unit standard deviation; thus, fitted coefficients for continuous variables (e.g., log(doses)) represent the increase in log costs per dose observed for a 1.0 standard deviation increase in the variable. Values in parentheses represent standard errors. DTP3 = diphtheria-tetanus-pertussis third dose; GDP = gross domestic product; HPV = human papillomavirus.

Appendix Table 1.5. Sensitivity analysis for regressions of log costs per dose on predictors: weakly informative priors used for regression coefficients and variance terms

Variable	Mean coefficient
Labor intercept	-0.87 (0.31)
Supply chain intercept	-1.83 (0.34)
Service delivery intercept	-1.28 (0.38)
Capital intercept	-2.50 (0.40)
Year	-0.24 (0.14)
Economic cost indicator	-0.03 (0.18)
Single antigen indicator	0.11 (0.29)
HPV indicator	0.48 (0.34)
log(doses)	-0.05 (0.13)
log(GDP per capita)	0.16 (0.13)
log(population)	-0.31 (0.13)
DTP3 coverage	0.30 (0.15)
Error term	1.27 (0.08)

Note: Continuous predictors were standardized to mean zero and unit standard deviation; thus, fitted coefficients for continuous variables (e.g., log(doses)) represent the increase in log costs per dose observed for a 1.0 standard deviation increase in the variable. Values in parentheses represent standard errors. DTP3 = diphtheria-tetanus-pertussis third dose; GDP = gross domestic product; HPV = human papillomavirus.

Appendix Table 1.6. Sensitivity analysis for regressions of log costs per dose on predictors: non-informative priors used for regression coefficients and variance terms

Variable	Mean coefficient
Labor intercept	-0.88 (0.32)
Supply chain intercept	-1.84 (0.35)
Service delivery intercept	-1.29 (0.38)
Capital intercept	-2.52 (0.40)
Year	-0.23 (0.14)
Economic cost indicator	-0.03 (0.18)
Single antigen indicator	0.12 (0.29)
HPV indicator	0.48 (0.37)
log(doses)	-0.04 (0.13)
log(GDP per capita)	0.16 (0.13)
log(population)	-0.30 (0.12)
DTP3 coverage	0.30 (0.15)
Error term	1.27 (0.08)

Note: Continuous predictors were standardized to mean zero and unit standard deviation; thus, fitted coefficients for continuous variables (e.g., log(doses)) represent the increase in log costs per dose observed for a 1.0 standard deviation increase in the variable. Values in parentheses represent standard errors. DTP3 = diphtheria-tetanus-pertussis third dose; GDP = gross domestic product; HPV = human papillomavirus.

Paper 2: Impact and cost-effectiveness of human papillomavirus (HPV) vaccination campaigns: findings from a modeling study in Uganda

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Abstract

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

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

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

Conclusions: We projected that campaign HPV vaccination would provide substantial population health benefits compared with routine vaccination. Expanding the target age range of campaign vaccination up to age 30 may be an efficient strategy, depending on the achievable coverage level and campaign frequency. In settings where routine health systems infrastructure may be limited, reaching adolescent populations with a campaign delivery strategy may be an efficient use of resources.

Background

Persistent human papillomavirus (HPV) infections can cause cervical cancer and can lead to genital warts, other anogenital cancers, and cancers of the head and neck, with HPV types 16 and 18 causing 70% of all cases of cervical cancer [1,2]. More than 85% of the approximately 274,000 cervical cancer deaths each year occur in low- and middle-income countries (LMICs), where fewer than 5% of women have access to preventive screening [3,4]. In Uganda, cervical cancer is the leading cause of female cancer with 29 out of every 100,000 women contracting the preventable disease each year [5]. This is one of the top five highest rates in Africa. There are 11 million women over the age of 15 at risk for cervical cancer in Uganda, but completion of the recommended HPV vaccine schedule is 22% [5,6].

Prophylactic HPV vaccination has a direct, proximal effect on whether or not an individual contracts a high-risk HPV infection. Studies of currently licensed HPV vaccines have shown that they provide almost 100% protection against HPV 16 and 18 [7,8]. Specifically, Merck & Co.'s quadrivalent vaccine (HPV-16/18/6/11) and nonavalent vaccine (HPV-16/18/6/11/31/33/45/52/58) have a reported vaccine efficacy of 98% against HPV 16 and 18 [9,10] and GSK's bivalent vaccine (HPV-16/18) has a reported vaccine efficacy of 95% [11]. By the beginning of 2015, there were an estimated 80 national HPV vaccination programs and 37 pilot programs worldwide [12]. As HPV vaccination is recommended to adolescents (typically ages 9 to 14 years), there are several different delivery strategies to administer vaccination, including school-based vaccination, facility-based vaccination, or vaccination combined with the provision of other health interventions (e.g., antenatal or human immunodeficiency virus (HIV) care).

A routine vaccination strategy is characterized by delivery at fixed sites and adhering to a consistent dosing schedule. This allows for consistent budgeting and allocation of health care workers. However, reaching a target group with limited health services may not be best achieved by a routine vaccination strategy. A campaign delivery strategy differs from routine delivery vaccination in that the scheduling is determined by disease burden and/or programmatic coverage needs. In LMICs, campaigns have typically been used to achieve specific global goals, such as measles elimination or polio eradication, often by the World Health Organization (WHO) [13-15]. During a vaccination campaign, health workers and volunteers establish additional outreach service points or go door to door to offer vaccinations to all members of a target population, irrespective of previous vaccination status. Vaccination campaigns may be conducted nationwide or may target specific districts/regions [16-19].

Because vaccination campaigns require a level of "surge capacity" in terms of human and financial resources for vaccine delivery, there is less consistency in terms of budgeting and allocation of health care workers. Additionally, while a routine strategy can provide flexibility to serve public demand, a campaign strategy only provides limited times during which the vaccine can be accessed. As the HPV vaccine is typically targeted to adolescents not often served by routine health services, characteristics and effectiveness of a potential campaign strategy in LMICs are highly uncertain. Mathematical modeling provides an opportunity to analyze policy choices that can inform future decision-making around HPV vaccine introduction and scale-up in LMICs. In addition to earlier evaluations of the cost-effectiveness of HPV vaccine generally, previous studies have relied on mathematical modeling to evaluate the timeline and strategies for cervical cancer elimination [20,21] and the cost-effectiveness of HPV vaccine introduction in the presence of

cervical cancer screening [22]. However, these analyses assume routine delivery of HPV vaccine in the specified context. This study contributes to this previous work by analyzing, for the first time, a range of plausible scenarios for delivery of the HPV vaccine with mass vaccination campaigns as the primary delivery strategy.

The objective of this analysis was to estimate the health and economic outcomes of female HPV-16/18 vaccination delivered via campaign strategy in Uganda. We examine a range of campaign delivery strategies, varying programmatic features (i.e., campaign coverage, frequency, target age range, cancer treatment costs, and delivery costs) as well as vaccine attributes (i.e., efficacy, duration of protection) to compare the health benefits, costs, and cost-effectiveness of routine and campaign vaccination delivery strategies.

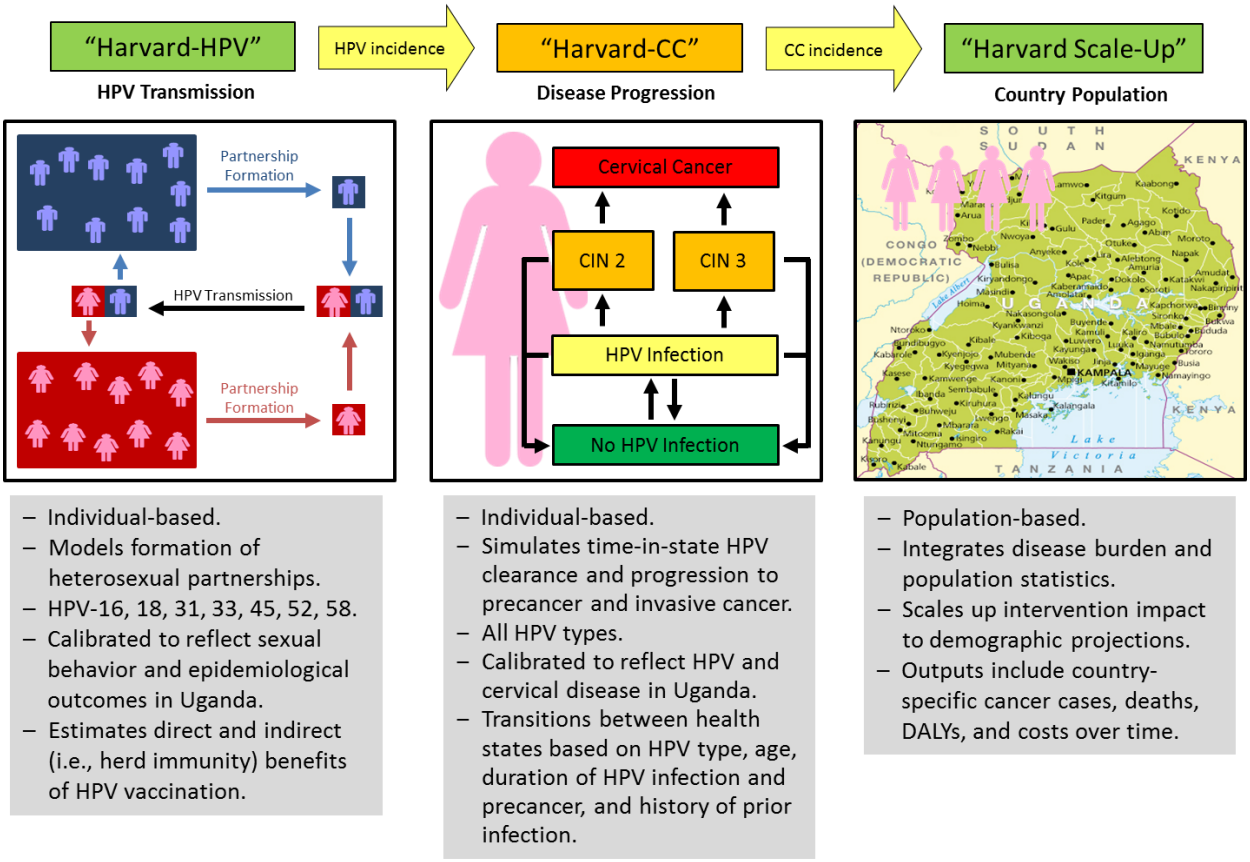
Methods

Analytic overview

We used a multiple modeling approach (Figure 2.1) to estimate the health and economic outcomes associated with various campaign HPV vaccination strategies compared with routine one-dose and two-dose vaccination strategies in Uganda. We linked a dynamic agent-based model of HPV transmission ("Harvard-HPV") to a static individual-based model of cervical cancer development ("Harvard-CC"), which enables us to capture the complex natural history of HPV-induced cervical cancer, the direct benefits of vaccination to vaccinated individuals, and the indirect benefits of vaccination to unvaccinated individuals due to herd immunity. We then used a population-based model ("Harvard-Scale Up") to project the health and economic impact for women in Uganda over time. Model outcomes were aggregated over multiple birth cohorts to capture the lifetime costs and benefits of women aged 9 to 100 years in the year 2019, as well as the lifetime costs and

benefits of girls born between 2020 and 2118 (i.e., 99 additional incoming cohorts). This modeling approach has been previously described in Burger, et al. (2018) [23], but we summarize it briefly here.

Figure 2.1. Overview of multiple modeling approach



Abbreviations. CC: cervical cancer, CIN: Cervical intraepithelial neoplasia, DALYs: disability-adjusted life years, HPV: Human papillomavirus.

Simulation models

As previously described [23], Harvard-HPV is an agent-based dynamic model of partnership acquisition and HPV transmission, stratified by genotype (HPV-16, 18, 31, 33, 45, 52, 58). The model assigns sexual behavior characteristics to individual heterosexual men and women who form partnerships, such as partner concurrency, number of lifetime partners, and duration of current partnership(s). Individuals interact in the model in order to capture both HPV transmission

and the benefits of a proposed HPV vaccination program, directly to the individual and indirectly to unvaccinated partners (i.e., herd immunity). In collaboration with Stephen Sy, Harvard-HPV was updated for this analysis to incorporate functionality to simulate delivery of HPV vaccination over a one-month time window (i.e., the defined length of a vaccination campaign) at assigned frequencies, target age groups, and coverage levels. Inputs for sexual behavior in Uganda, which were collated for this analysis, predominantly varied by the number and duration of heterosexual partnerships and assortativeness by age and sexual activity category (Appendix Figure 2.1). We calibrated Harvard-HPV to reflect these sexual behavior inputs and used the model to estimate HPV incidence reductions over time according to genotype and age. HPV incidence reductions for alternative HPV vaccination strategies then served as inputs into Harvard-CC.

Harvard-CC is a static, individual-based (i.e., microsimulation) model that tracks women beginning at age of vaccination (e.g., 9 years) and as they age and transition through HPV-related health states until death, either due to cervical cancer or background mortality rates. The specific health states included are: no HPV infection, HPV infection, cervical intraepithelial neoplasia grades 2 and 3, cervical cancer, and death. Transitions occur on a monthly time step and depend on age, HPV genotype (HPV-16, -18, -31, -33, -45, -52, -58), duration of infection, and history of prior HPV infection. As previously described and published [24,25], Harvard-CC relies on baseline parameters derived from large, empirical studies [26-29] and calibrated to fit epidemiological outcomes in Uganda [30-32]. Reductions in HPV-16/18 cervical cancer incidence from Harvard-CC then served as inputs into the population-based model, Harvard-Scale Up.

Harvard-Scale Up is a multi-cohort model used to scale the health and economic impacts to the population level [33]. Harvard-Scale Up uses data on the age-specific incidence of cervical cancer [34], HPV-16/18 type distribution in cervical cancer [35], and population demographics at the country or region level over time. We applied the estimated age-specific cancer incidence reductions to the associated incidence rates in Uganda [34]. The Excel-based model then outputs the estimated number of cervical cancer cases and deaths averted, disability-adjusted life years (DALYs) averted, and total economic costs associated with the alternative HPV vaccination strategies.

Scenarios

We conducted analyses to evaluate the impact of campaign HPV vaccination strategies compared to a routine one-dose and two-dose HPV vaccination program. We explored a landscape of plausible strategies guided by other vaccine campaigns and consultation with experts. The following programmatic parameters were varied accordingly – campaign coverage (20%, 40%, or 60%), frequency (every 3, 4, 5, or 6 years), target age range (9- to 14-year-old girls, 9- to 18-year-old girls, 9- to 26-year-old girls, and 9- to 30-year-old girls in 2019), and delivery costs ($0.70 – $1.70 recurrent costs per girl with one-time fixed introduction cost of $2.00 per girl in year one of the program) – to identify thresholds at which the campaign or routine delivery strategy becomes the optimal delivery strategy (Table 1.1). For the base case strategy, we assumed a campaign vaccination coverage level of 40% for 9- to 14-year-old girls every 4 years [36]. We compared campaign HPV vaccination for these strategies to routine one-dose and two-dose HPV vaccination of 9-year-old girls, including temporary one-year vaccination of 10- to 14-year-old girls at 70%

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

Table 2.1. Analytic scenarios

	Campaign Base Case	Routine Strategies	Campaign Strategies	Reference(s)
Frequency	4 years	Annual	3, 4, 5, 6 years	[36,37]
Doses	1 dose	1 or 2 doses	1 dose	[37]
Target age(s)	9-14yo girls	9yo girls	9-14yo, 9-18yo, 9-26yo, 9-30yo girls	[37]
Catch-up age(s)	N/A	10-14yo girls	Not applicable	[37]
Coverage	40%	70%	20, 40, 60%	[36]
Delivery costs	$1.00/girl	$1.70/girl	$0.70, $1.00, $1.20, $1.70/girl	Appendix Figure 2.2

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

Vaccine characteristics

In the base case, we assumed a single HPV vaccine dose conferred 80% protection against incident HPV-16 and -18 infections based on the lower-bound target efficacy for one-dose HPV vaccination in an ongoing randomized control trial (ClinicalTrials.gov Identifier: NCT 03180034). Given the unknown duration of one-dose vaccine protection, we assumed 15 years of full protection followed by waning protection at a constant rate over an additional 20 years. For any second dose given in campaign strategies, and for two-dose routine vaccination, we assumed 100% protection against HPV-16 and -18 infections over the lifetime in the base case. In a scenario analysis, we also considered 100% protection against HPV-16 and -18 infections for 15 years from the point of the second vaccination (i.e., a booster) followed by waning protection at a constant rate over an additional 20 years. In order to address the possibility that vaccine efficacy is lower at older ages,

we also conducted a threshold analysis around vaccine efficacy for girls 19 years of age and older in which we examined one- and two-dose efficacies in 20% decrements from the base case for these ages, including: (1) 60% for one-dose, 80% for two-dose; (2) 40% for one-dose, 60% for two-dose; (3) 20% for one-dose, 40% for two-dose; and (4) 0% for one-dose, 20% for two-dose.

Cost inputs

We assumed a base case HPV vaccine cost of $4.50 per dose [38] for both campaign and routine vaccination, and included costs for vaccine wastage at a rate of 5% for a single dose vial, liquid formulation [39]. For the routine vaccination strategy, we assumed a base case HPV vaccine delivery cost of $1.70 per girl, including costs for personnel, training, social mobilization, disease surveillance, program management, and other recurrent costs; for the campaign vaccination strategy, we assumed a base case HPV vaccine delivery cost of $1.00 per girl. We also examined three additional delivery cost scenarios for campaign vaccination: (1) decreased delivery cost of $0.70 per girl; (2) increased delivery cost of $1.20 per girl; and (3) delivery costs of $1.00 per girl for ages 9-14 and $1.70 per girl for ages 15 and above (i.e., we assume the same delivery costs as routine vaccination for older girls) [40-43]. The appendix outlines the assumptions for these delivery costs (Appendix Figure 2.2).

We assumed in the base case that all women with detected cervical cancer would have access to cervical cancer treatment and incur the relevant treatment costs. Cervical cancer treatment costs included direct medical costs at a tertiary facility associated with stage-specific International Federation of Gynecology and Obstetrics (FIGO) treatment protocols and assumed to be independent of vaccination coverage [44,45]. We assumed 20% of detected cancers to be local

(i.e., Stage I) and 80% to be late stage (i.e., Stages II-IV). 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 in the following settings: Argentina [46], Brazil [46], Colombia [46], China [47], El Salvador [48], India [49,50], Kenya [49], Mexico [46], Morocco [51], Peru [46,49], South Africa [49], and Thailand [49,52,53]. All costs were converted to 2015 US dollars using local consumer price index (CPI) deflators and exchange rates [54]. To extrapolate published estimates for cervical cancer treatment costs from their original settings, accounting for variation in income level, we adjusted unit costs using an index of tertiary inpatient visit costs from World Health Organization Cost-effectiveness and strategic planning (WHO-CHOICE) and World Bank world development indicators [54,55], resulting in $907 for Stage I and $1,081 for Stage II-IV in Uganda in 2015 US dollars. In a scenario analysis, we assumed that cervical cancer treatment costs only applied to the estimated proportion of women with access to radiation therapy in a given setting (8.5%); the remainder of women incurred no costs for cancer treatment [56].

Outcomes

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

We calculated the incremental cost-effectiveness ratio (ICER) to report cost-effectiveness from a health system perspective. The ICER was defined as the additional cost of a particular strategy divided by the additional health benefits (i.e., DALYs averted), compared to the previous most costly strategy. Strategies that were more costly and less effective ('strongly dominated'), or having higher ICERs than more effective strategies ('weakly dominated'), than an alternative strategy were considered inefficient and were removed from further consideration; the remaining strategies were identified as efficient. The estimated ICERs for the remaining strategies (i.e., the efficient strategies) were compared with a cost-effectiveness threshold (CET) of $674 (2015 US dollars) per DALY averted, the gross domestic product (GDP) per capita in Uganda [57], as well as the average of estimated CETs based on empirical estimates for opportunity costs and the income elasticity for Uganda (i.e., $152) [58].

Results

Health benefits

In the base case, campaign HPV vaccination assuming vaccination coverage of 40%, target age group of 9- to 14-year-old girls, and a frequency of 4 years averted approximately 500,000 cases of cervical cancer across 2019-2118 (i.e., a 15% reduction), compared to a strategy of no HPV vaccination (Table 2.2).

Table 2.2. Cervical cancer cases averted over 2019-2118 by vaccine delivery strategy in the base case

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

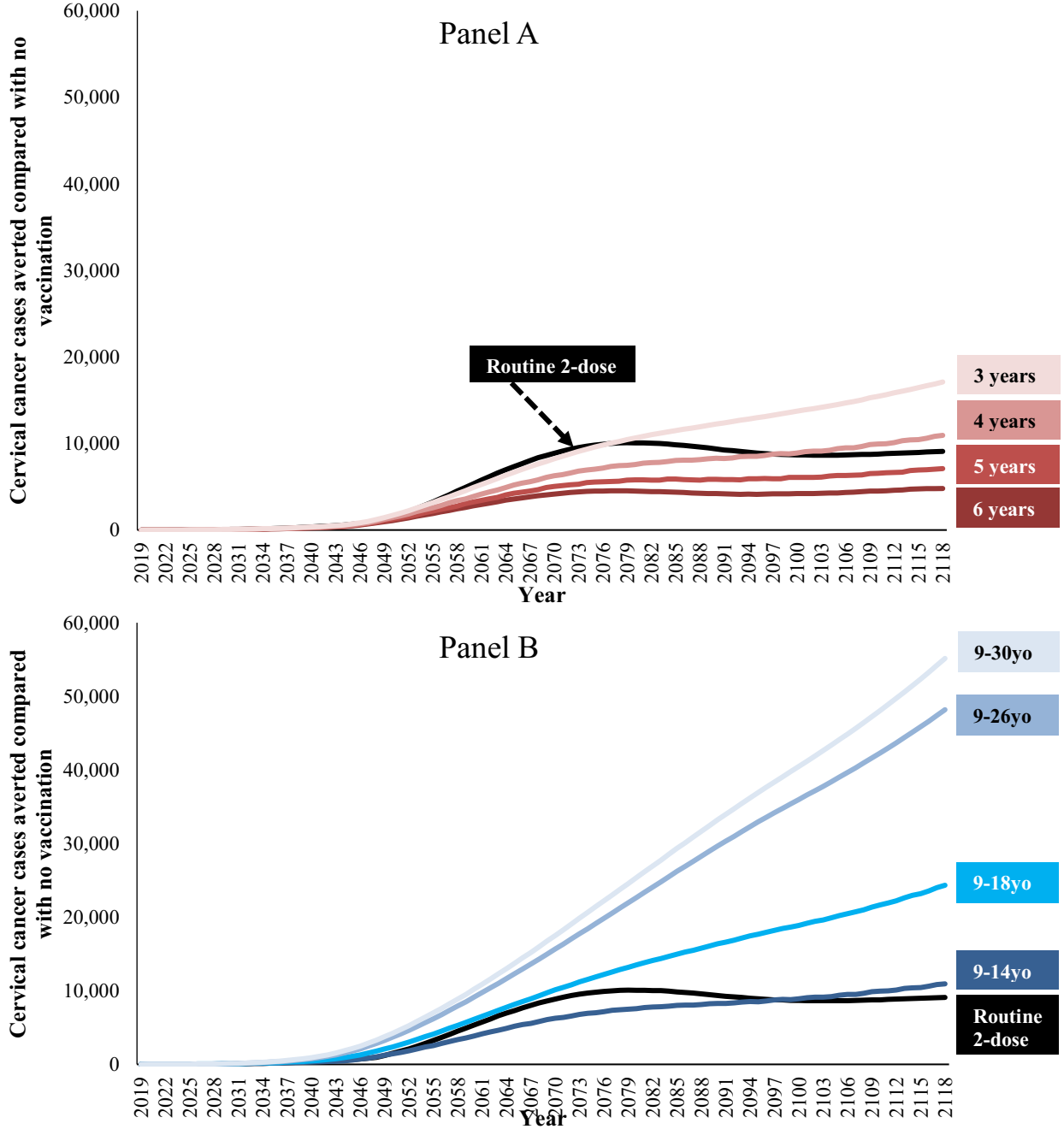
Note: Cervical cancer cases averted are aggregated over 2019-2118 for females currently alive in 2019 plus those women born between 2020 and 2118 and rounded to the nearest thousand. Campaign delivery strategies are presented for 40% coverage in the base case, with 20% and 60% coverage in parentheses.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

These health benefits were comparable to routine two-dose vaccination with 70% coverage and a one-year multi-age vaccination program to age 14 years (Figure 2.2a).

When we varied campaign frequency, the model projected greater benefits for a campaign frequency of 3 years compared to the routine two-dose vaccination delivery strategy. However, campaign vaccination at a frequency of 5 or 6 years yielded fewer health benefits than routine two-dose vaccination. When target age group was varied from the base case, campaign HPV vaccination frequency of 4 years for 9-18, 9-26, or 9-30 year-old girls yielded greater health benefits than routine two-dose vaccination (Figure 2.2b). On average, the 19- to 26-year-old target age group contributed the largest percentage of cervical cancer cases averted, followed by 9- to

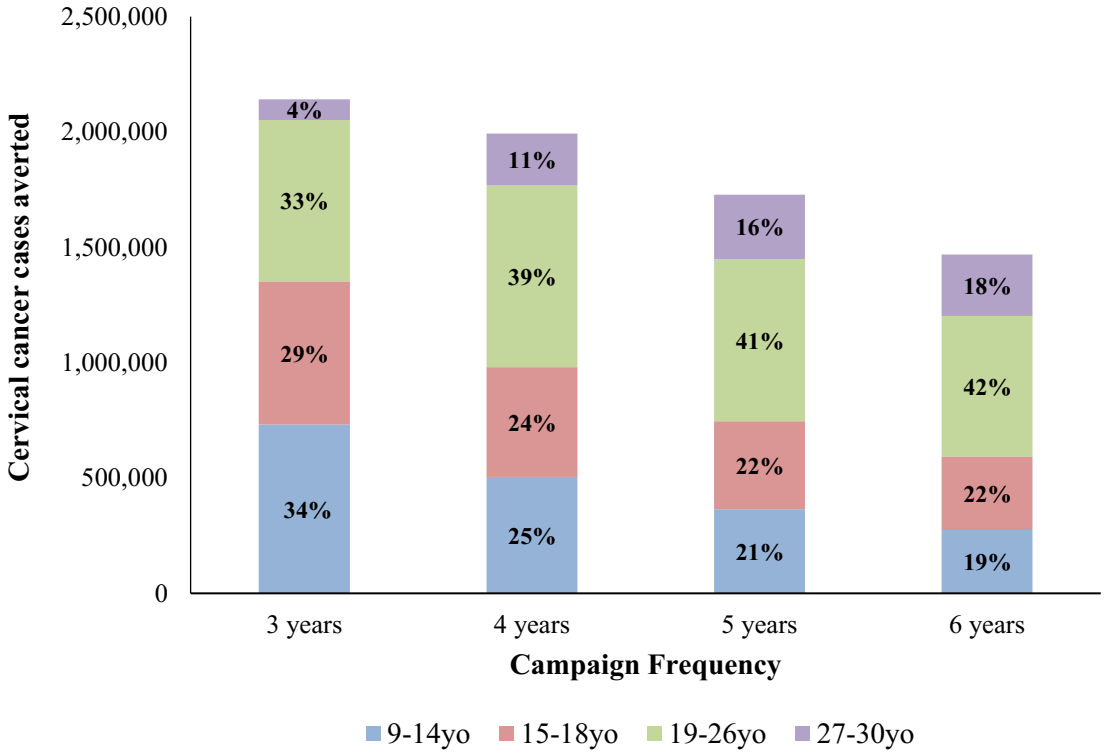
14-year-olds, 15- to 18-year-olds, and 27- to 30-year-olds, as shown in Figure 1.3. When varying vaccination coverage from the base case, campaign vaccination at a coverage level of 20% yielded fewer health benefits than routine two-dose vaccination, whereas campaign vaccination at a coverage level of 60% yielded greater health benefits.

Figure 2.2. Annual number of cervical cancer cases averted: varying campaign frequency (Panel A) and varying target age group (Panel B)



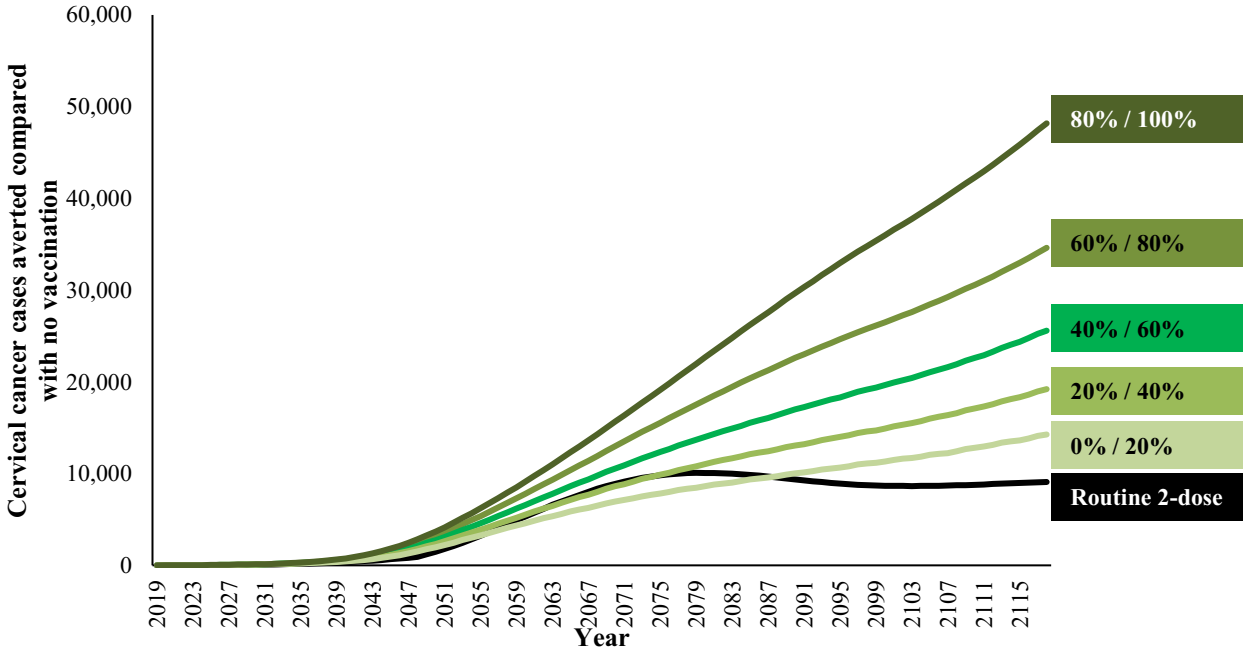
Note: Campaign strategies represent 40% vaccination coverage. Campaign strategies that vary frequency assume vaccination of 9- to 14-year-old (i.e., 9-14yo) girls; campaign strategies that vary target age group strategies assume 4-year frequency. Routine strategies assume 70% vaccination coverage, including a one-year multi-age program of 10-14 year old girls.

Figure 2.3. Cervical cancer cases averted compared to no vaccination by target age group



When we assumed that the second dose boosted the duration of protection by 15 years from the point of the second vaccination rather than provide lifelong protection, the routine two-dose strategy averted more cases of cervical cancer than any campaign frequency at 40% coverage of 9- to 14-year-olds (Appendix Figure 2.3a). However, assuming a campaign frequency of 4 years and campaign vaccination coverage of 40%, campaign HPV vaccination of 9- to 18-, 9- to 26-, or 9- to 30-year-old girls continued to yield greater health benefits than routine two-dose vaccination (Appendix Figure 2.3b). Examining the threshold analysis around vaccine efficacy for girls 19 years of age and older, we found that campaign vaccination at 40% coverage of 9- to 26-year-olds at a 4-year frequency yielded greater health benefits than routine two-dose vaccination as long as the vaccine efficacy was at least 20% for one dose and 40% for two doses (Figure 2.4). This pattern also held for 40% coverage of 9- to 30-year-olds at a 4-year frequency.

Figure 2.4. Annual number of cervical cancer cases averted: varying one- and two-dose vaccine efficacy among 19- to 26-year-old women



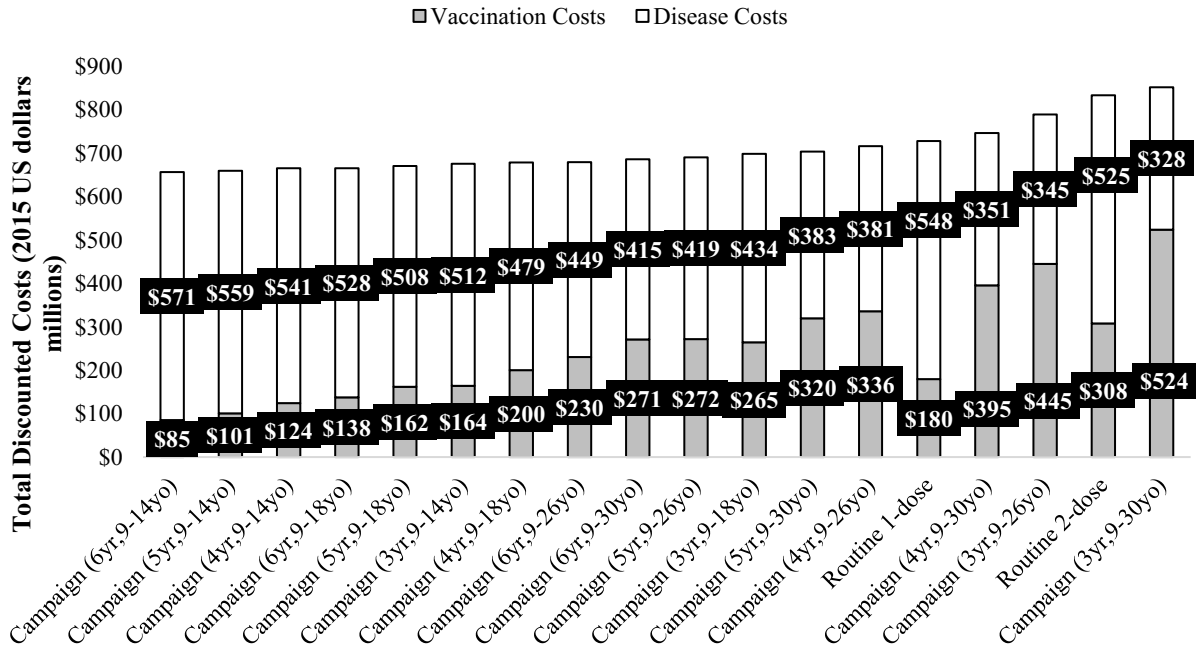
Note: Percentages represent one- and two-dose efficacies, respectively, for 19- to 26-year-old women. For girls under age 19 years, we assumed 80% vaccine efficacy for one dose and 100% vaccine efficacy for two doses. Campaign strategies assume 40% vaccination coverage, 4-year frequency, and 9- to 26-year-old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

Economic outcomes

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

targeting a 9- to 30-year-old age group (assuming 40% coverage and 4-year frequency) was associated with more than three times the initial investment of a vaccination campaign targeting 9- to 14-year-old girls ($395 million compared to $124 million). However, by the same token, the cost offsets due to cervical cancer prevention were 2.5 times higher ($266 million compared to $76 million). While the vaccination program costs would be incurred every four years beginning in 2019, the cost savings due to cervical cancer prevention would begin at fractions of a percent in 2019, reaching 1% in year 10, 10% in year 24, and 50% in year 47.

Figure 2.5. Total discounted costs in 2015 US dollars associated with campaign and routine vaccination strategies

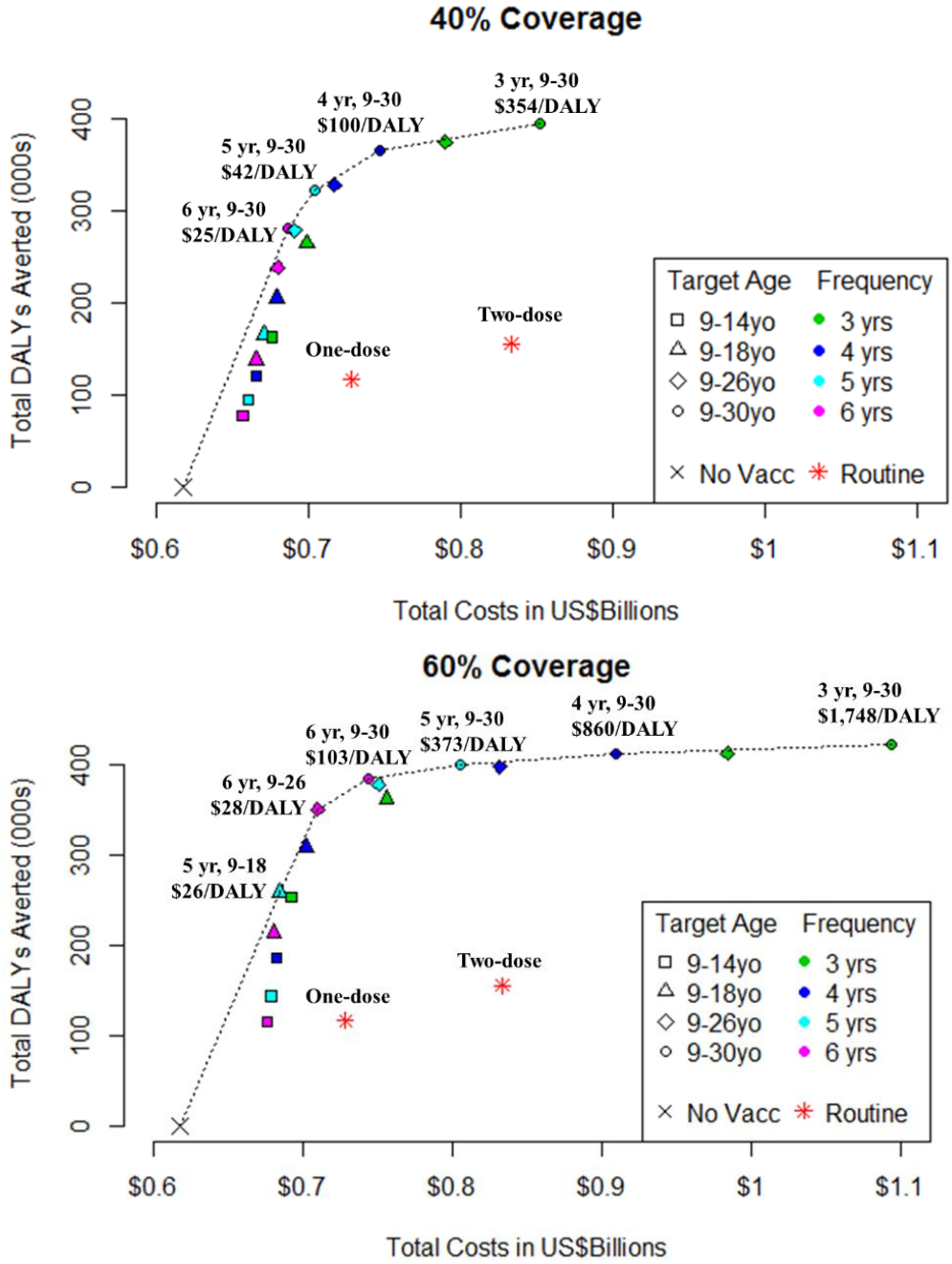


Note: Campaign strategies assume 40% vaccination coverage. Each strategy is labelled with the campaign frequency and target age range in parentheses; for example, "Campaign (6yr,9-14yo)" on the far left refers to a campaign strategy with 6-year frequency and 9- to 14-year-old target age group. Vaccine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

Campaign HPV vaccination strategies were both less costly and more effective than routine one-dose and two-dose HPV vaccination at 20, 40, or 60% coverage (Appendix Table 2.1). Compared to no vaccination, campaign vaccination of 9- to 30-year-old girls at a 3-year frequency and 40% coverage in the base case was the most effective strategy with an ICER below the willingness-to-

pay threshold of Uganda's GDP per capita ($674 in 2015 US dollars [57]) (Figure 2.6). At the same threshold, this strategy was optimal at 20% coverage, but was no longer optimal at 60% coverage. Compared to Uganda's GDP per capita, campaign vaccination of 9- to 30-year-old girls at a 5-year frequency was optimal at 60% coverage. For a lower CET incorporating country-level opportunity costs in Uganda ($152), campaign vaccination of 9- to 30-year-old girls at a 4-year frequency was considered the most cost-effective vaccination delivery approach assuming 40% coverage in the base case. At this lower threshold, campaign vaccination of 9- to 30-year-old girls at a 6-year frequency was optimal at 60% coverage.

Figure 2.6. Discounted incremental cost in 2015 US dollars per disability-adjusted life year (DALY) averted



Note: The base case strategy involved 4-year frequency and a 9- to 14-year-old target age group, assuming one-dose efficacy of 80%, two-dose efficacy of 100%, 15-year duration of protection followed by waning over 20 years with one dose, lifelong duration of protection with two doses, full cancer treatment costs, $1.00 per girl recurrent vaccine delivery cost for campaign vaccination, and $1.70 per girl recurrent vaccine delivery cost for routine vaccination (both campaign and routine vaccination assumed $2.00 per girl introduction cost in year 1). Costs and DALYs were discounted at 3% per year. The incremental cost-effectiveness ratio can be compared to a threshold of the gross domestic product (GDP) per capita in Uganda ($674) or an estimation of the average opportunity costs in Uganda ($152). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year; yo = years old; yr(s) = year(s).

In scenario analyses, when we assumed that the duration of protection was boosted an additional 15 years rather than increased to lifelong protection with two doses, campaign HPV vaccination strategies were still less costly and more effective than routine one-dose and two-dose HPV vaccination at 20, 40, or 60% coverage (Appendix Table 2.2). When we varied the delivery costs, assuming either a lower ($0.70) or higher ($1.20) per girl recurrent HPV vaccine campaign delivery cost rather than the base case assumption of $1.00 per girl, the ICERs changed slightly, but the strategies on the efficiency frontier and their rankings remained unchanged (Appendix Tables 2.3 and 2.4). Additionally, even when we assumed $1.70 per girl for recurrent HPV vaccine delivery cost among those 15 years of age and older, the strategies on the efficiency frontier and their rankings remained the same, with one exception: when we assumed 60% and lifelong duration of protection, the efficiency frontier included a campaign strategy involving 3-year frequency, targeting 9- to 14-year-old girls rather than a campaign strategy involving 5-year frequency, targeting 9- to 18-year-old girls (Appendix Table 2.5). When we adjusted cancer treatment costs to reflect imperfect level of treatment access, campaign strategies with a 5-year frequency targeting 9- to 30-year-olds became more attractive at very low coverage levels (i.e., 20%); optimal strategies remained the same at 40 and 60% coverage (Appendix Table 2.6).

When assuming decreased vaccine efficacy for girls 19 years of age and older, we found that the campaign strategy involving a 3-year frequency targeting 9- to 30-year-old was not efficient if the efficacy of one dose was 40% or less and the two-dose efficacy was 60% or less (Appendix Tables 2.7 – 2.10). At these lower efficacy levels, routine two-dose vaccination became an attractive strategy when campaign coverage was low (i.e., 20%). When a single dose of vaccine was assumed

to confer no protection but two doses were 20% efficacious, vaccinating women aged 19 years and over was not efficient.

Discussion

Using a model-based approach that incorporates HPV transmission dynamics, cervical cancer disease natural history, and population demographics, we projected that campaign HPV vaccination assuming 80% efficacy for one dose against HPV-16/18 infections would provide substantial population health benefits compared with routine one-dose or two-dose vaccination. In settings where routine health systems infrastructure may be limited, reaching adolescent populations with a campaign delivery strategy may be an efficient use of resources. Assuming up to 60% coverage, we found that campaign HPV vaccination can be cost-effective compared to a routine two-dose vaccination program if campaigns occur frequently and target a wide age range (Figure 2.6). This result also held for 20 and 40% campaign vaccination coverage (Appendix Table 2.1). Even without targeting a wide age range, these results indicate that a campaign strategy might still be more attractive than a routine strategy for many 9- to 14-year-old or 9- to 18-year-old target age scenarios. To our knowledge, our study is the first to assess the value of a campaign delivery strategy for HPV vaccination, under scenarios of coverage, frequency, target age range, and delivery costs.

There are several limitations to this analysis. We were restricted in modeling assumptions due to limited data. First, the natural history of HPV infection in older women is highly uncertain and vaccine effectiveness has been shown to be lower among individuals with prevalent HPV infections, which might impact the effectiveness of vaccination at older ages [59-61]. Due to this limited data, we calibrated the dynamic model "Harvard HPV" with all age groups weighted

equally, resulting in a balanced fit across age groups rather than a fit prioritizing a specific age group. In order to partially address this uncertainty, we conducted a threshold analysis of vaccine efficacy for women 19 to 30 years old, and found that strategies to vaccinate women in this age group were no longer efficient at a two-dose efficacy of 20%. We found that, on average, the 19- to 26-year-old target age group contributed the largest percentage of cervical cancer reductions, but this is likely due to the sheer number of women included in this larger age group bucket and does not mean that we would not see diminishing returns by age.

Second, as a campaign delivery strategy has not yet been implemented for HPV vaccination, empirical data to support modeling assumptions are lacking. We relied on information from an alternate childhood vaccination program (i.e., measles) [36]. National multi-age cohort measles campaigns had an estimated mean coverage of 70% (population-adjusted national coverage; standard deviation: 30%). Alternatively, when we estimated national coverage from sub-national (rather than national) multi-age cohort measles campaign coverage, we found a mean coverage of 40% (standard deviation: 20%). We chose the coverage levels derived from sub-national campaign levels to represent what might be feasible for an HPV vaccination campaign, given older target ages outside of routine infant vaccination. The most common age range targeted by the measles campaign data we reviewed is 9 months to 14 or 15 years of age, which indicates that the wide target age ranges examined in this analysis might be reached by a campaign delivery strategy. To counteract the uncertainty of these assumptions, we included scenario analyses aimed at addressing this limitation by presenting a plausible landscape for HPV vaccination campaigns (i.e., coverage, target ages, frequency, and delivery costs).

Third, we did not include freight costs or program costs for reaching older target age groups and increasing coverage. Furthermore, our base case scenario of vaccination of 9- to 14-year-olds at 40% coverage amounts to approximately 0.8% of the annual health expenditure of Uganda in the year the campaign is conducted, which would only increase as the campaign target age range widens [57]. As a result, the findings should be interpreted with caution, particularly if the delivery costs associated with expanding the vaccination program increase with higher coverage. However, we did include a scenario in which we assumed increased delivery costs ($1.70 per girl) for girls ages 15 and older in order to address how costs might increase when targeting older ages. It is important to note that while campaign vaccination of 9- to 30-year-old girls was identified as efficient in the cost-effectiveness analysis, the number of additional cervical cancer cases averted was relatively small in this age group. For example, at the level of 40% campaign coverage, vaccinating girls ages 27- to 30-years-old contributed less than or equal to 18% of the cervical cancer cases averted at all campaign frequencies (Figure 2.3). Additionally, the optimal vaccination strategy varied according to the selection of CET, which may be much lower than GDP per capita [58]. While this analysis identified multiple campaign vaccination strategies as efficient, the selection of CET creates additional uncertainty around which strategy might be considered optimal. Moreover, these strategies were only identified as efficient when vaccine efficacy was assumed to be similar to that of younger girls, such that the strategy involving a 3-year frequency targeting 9- to 30-year-old was not efficient when vaccine efficacy associated with one dose was less than or equal to 40% and vaccine efficacy associated with two doses was less than or equal to 60% (Appendix Tables 2.7 – 2.10). We also did not assume economies of scale for increasing the target age range or increasing the coverage level, which might offset the lack of programmatic costs and even result in more cost-effective results for campaign strategies.

In addition, this analysis captured the costs of the vaccination program over 100 years including the disease costs and health benefits over the lifetimes of women alive in 2019 up to age 100 years. However, it is possible that the context of HPV vaccination and cervical cancer will change over time given new interventions, improved health technologies, reformed health systems, among many possible changes. We assumed that cervical cancer incidence rates were stable over the analyzed time period. We likewise assumed that the vaccine price will remain stable, but it is also possible that HPV vaccine price and financing will be affected as Uganda transitions out of current funding support from Gavi, the Vaccine Alliance [62]. Vaccine efficacy against high-risk HPV types other than HPV-16/18 (i.e., cross-protection) was not included. This assumption and the assumption of 80% vaccine efficacy for a single HPV dose suggest that our results are conservative regarding the impact of HPV campaign vaccination.

This analysis did not consider the likely changes to the incidence of cervical cancer and efficacy of HPV vaccination among individuals with HIV infection. Studies show that HIV may impact the immunogenicity of vaccines [63-67]. Therefore, including women aged 19 years and older in an HIV-endemic setting may not yield as much benefit.

We did not examine cervical cancer screening programs in this analysis and assumed that any ongoing screening programs did not change as HPV vaccination introduction and delivery changed. We also did not incorporate an examination of the budgetary impact of HPV campaign vaccination. Finally, given limited data on the burden of other HPV-related diseases in LMICs, we did not evaluate the impact HPV vaccination may have on non-cervical cancers in women and men, which likely increases the value of all HPV vaccination strategies.

This analysis does not address the integration of a routine and campaign delivery program within the same health system, which may affect the overall impact of vaccination campaigns. We also do not address the normative discussion of whether or not a campaign strategy should be implemented for HPV vaccination. There are conflicting views regarding the impact of 'vertical' delivery of specific health interventions on the 'horizontal' delivery of primary and preventive services in the health system, and the broader benefits and disadvantages of a campaign delivery strategy for public health interventions. Previous findings examining the impact of measles vaccination delivered by a campaign vaccination strategy on the broader health system have ranged from positive to negative associations with system functioning [68-74]. Furthermore, others have proposed that campaign efforts should focus specifically on strengthening the routine vaccination program, integrating vaccination with other health services, and encouraging donor support of primary health care [75]. These are important considerations for the decision-making process regarding HPV vaccine delivery, particularly if the goals of an HPV campaign vaccination strategy include combination with other interventions or programs.

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

are effective and cost-effective. This analysis can help to inform HPV vaccine introduction strategies in LMICs, and can serve to elucidate the potential impact of campaign delivery.

Acknowledgements

This study was funded by the Bill & Melinda Gates Foundation. Earlier versions of this paper were presented at the 2018 International Papillomavirus Conference, 2018 Society for Medical Decision-Making Conference, and 2019 Institute for Disease Modeling Symposium, and we received valuable comments from conference participants. We also received valuable comments from Stéphane Verguet and Nicolas Menzies.

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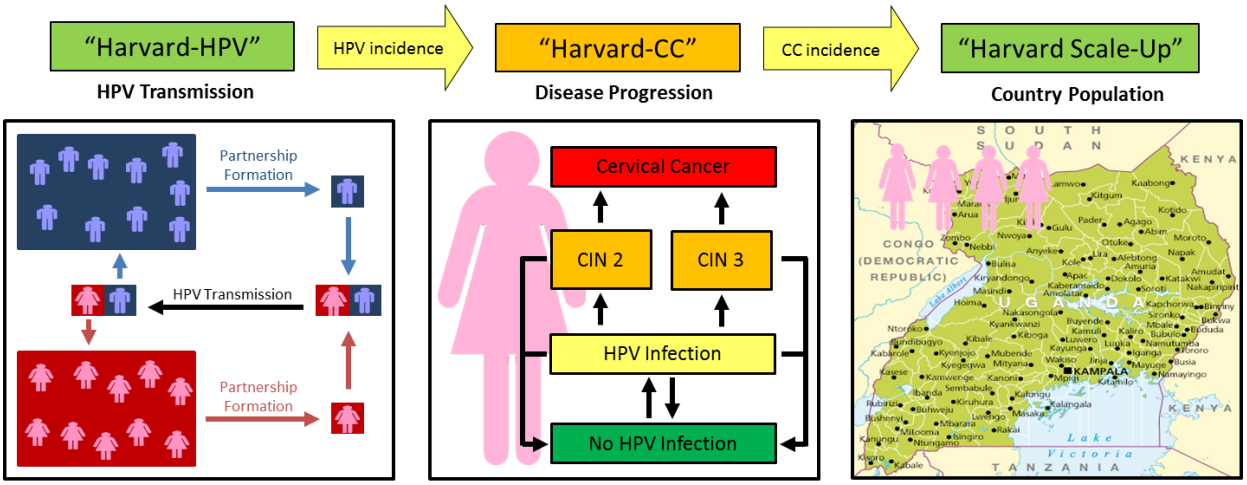
Appendix

Appendix Figure 2.1. Overview of simulation models

As previously described [1], we used a multi-modeling approach involving the linkage of a dynamic transmission model of HPV transmission ("Harvard-HPV"), an individual-based model of cervical carcinogenesis ("Harvard-CC") and a companion multi-country population model ("Harvard-Scale Up") to project the population health and economic consequences for alternative HPV vaccination scenarios for women over time. Harvard-HPV, Harvard-CC, and Harvard-Scale Up can be used independently, or they can be linked to include direct and indirect benefits from HPV vaccination, and synergies between vaccination and long-term vaccination benefits. Harvard-HPV is an agent-based model that simulates heterosexual HPV transmission and projects the impact of HPV vaccination policy on HPV incidence and prevalence among men and women. Model outputs from Harvard-HPV can inform the complex natural history model of cervical squamous cell carcinoma (Harvard-CC), which simulates individual women from an early age over their lifetime through health states including no HPV infection, HPV infection status, cervical precancer (i.e., cervical intraepithelial neoplasia grade 2 or 3) and cancer. Harvard-Scale Up is a multi-cohort, Excel-based companion model used to capture current and future health and economic benefits at the population level taking into account changing demographics (e.g., population size, mortality rates) over time.



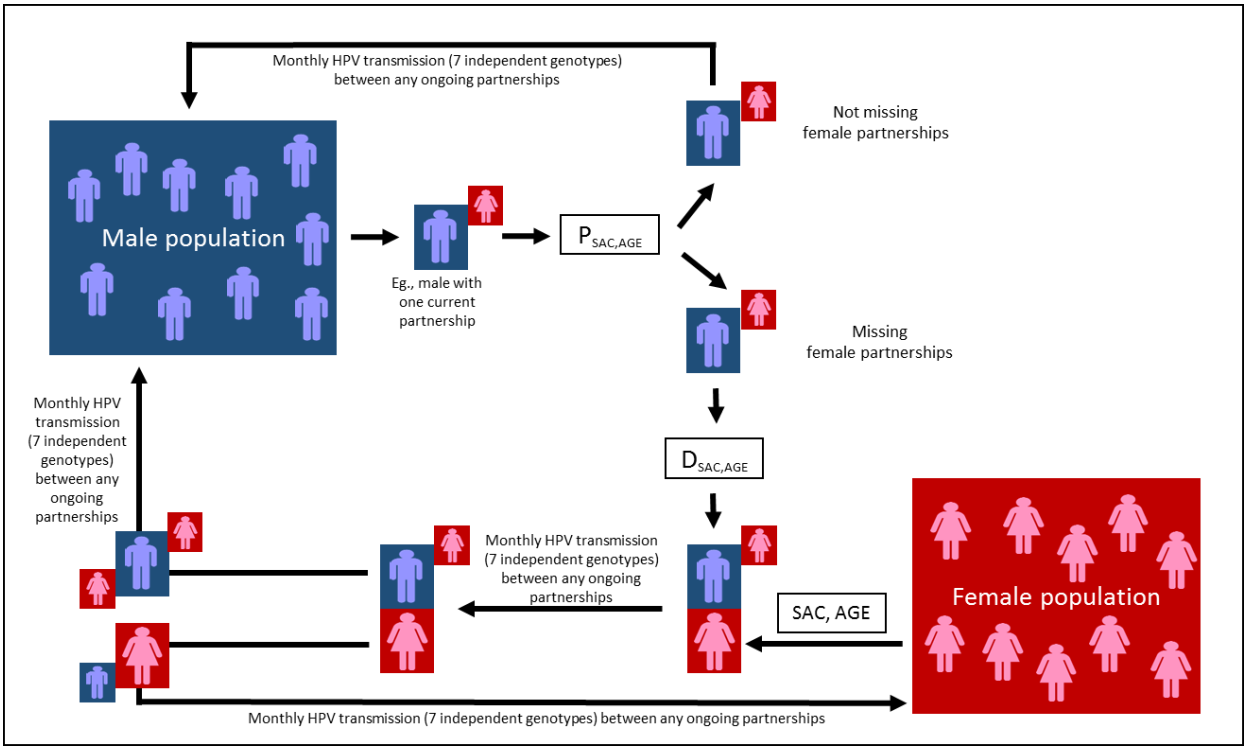
- Individual-based.
- Models formation of heterosexual partnerships.
- HPV-16, 18, 31, 33, 45, 52, 58.
- Calibrated to reflect sexual behavior and epidemiological outcomes in Uganda.
- Estimates direct and indirect (i.e., herd immunity) benefits of HPV vaccination.

- Individual-based.
- Simulates time-in-state HPV clearance and progression to precancer and invasive cancer.
- All HPV types.
- Calibrated to reflect HPV and cervical disease in Uganda.
- Transitions between health states based on HPV type, age, duration of HPV infection and precancer, and history of prior infection.

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

Abbreviations. CC: cervical cancer, CIN: Cervical intraepithelial neoplasia, HPV: Human papillomavirus

Schematic of the agent-based model of HPV transmission ("Harvard-HPV"). The agent-based dynamic model simulates heterosexual partnership acquisition and dissolution, and independent transmission of seven HPV genotypes (HPV-16, -18, -31, -33, -45, -52, -58). Individuals are stratified by sex, age, and sexual activity category (SAC; four categories: none (0); low (1); medium (2); high (3)), which govern initial sexual mixing in the population. Each month, individuals in the model cycle through four steps: (1) sexual mixing; (2) HPV infection; (3) HPV clearance and natural immunity; (4) aging, births, and deaths. For each male in the population, the annual number of partnerships (P) is assigned as a function of SAC and age. Partnership assessment occurs at the start of each year of each male's life, and any new partnerships are formed randomly during the course of the upcoming year. For males who are missing one or more female partner(s), a new partnership is formed, with the duration (D) of each partnership randomly drawn from age- and SAC-specific normal distributions. HPV transmission may occur between discordant partners. Sex-specific clearance of an HPV infection allows HPV natural immunity to increase exponentially with each acquisition and clearance of the same HPV genotype. Individuals are eligible to form another partnership, irrespective of ongoing partnerships. Model version 3.06.



For the current analysis, we adapted our dynamic model of HPV transmission [1] to reflect sexual mixing behavior in Uganda. Baseline inputs on sexual behavior were derived from the Ugandan Demographic Health Survey (2016) and fit to Ugandan-specific HPV prevalence among females [2,3] and males [4]. For females calibration targets included an IARC study among women aged 15-24 years and adjusted START-UP prevalence by age and HPV genotype (Odida proportion, RLU cutoff 0.5) [2,3]. For males, calibration targets include a study among uncircumcised men aged 15-49 years in Rakai (HIV+: 30%) [4].

Baseline sexual mixing inputs for each setting varied by the number of heterosexual partnerships in the last 12 months by age and four sexual activity categories (SACs), the duration of heterosexual partnerships by age and SAC, and assortativeness by age (probability of finding partnerships within age bucket, one age-bucket older or one age-bucket younger) and SAC (probability of mixing with partner in the same SAC). Baseline inputs, including HPV genotype-specific natural immunity and monthly transmission probabilities were fit (i.e., calibrated) to lifetime number of partnerships, and age- and genotype-specific HPV prevalence. Our multi-parameter calibration approach, which has been explained previously, involves a likelihood-based approach to fit to HPV prevalence by uniformly varying the sex- and genotype-specific natural immunity, and uniformly varying the sex- and genotype-specific monthly partnership transmission probability [5]. Following 100,000 model draws, we identified the 50 best-fitting parameters sets that fit to the calibration targets (see figures below). Analyses were performed using the best-fitting parameter set.

Mean annual number of male partnerships[a] as a function of age and sexual activity category (Uganda DHS 2016). Number of partnerships were adjusted to balance those reported by females.

Age, Years	SAC1-mean	SAC2-mean	SAC3-mean	SAC4-mean
12-14	0	0	1	3
15-24	0	1	3	10
25-49	0	1	3	12
50-59	0	1	3	13

Abbreviations: HPV, human papillomavirus; SAC, Sexual activity category.
[a]Values are rounded to nearest discrete value.

Monthly duration of male sexual partnership, by age and sexual activity category (SAC) (Uganda DHS 2016).

Age, Years	SAC1-mean	SAC2-mean	SAC3-mean	SAC4-mean
10-14[a]	0	0	6	6
15-19	0	24	12	6
20-24	0	24	12	6
25-29	0	36	18	6
30-34	0	42	24	12
35-39	0	60	60	24
40-59	0	127.5	106.5	77

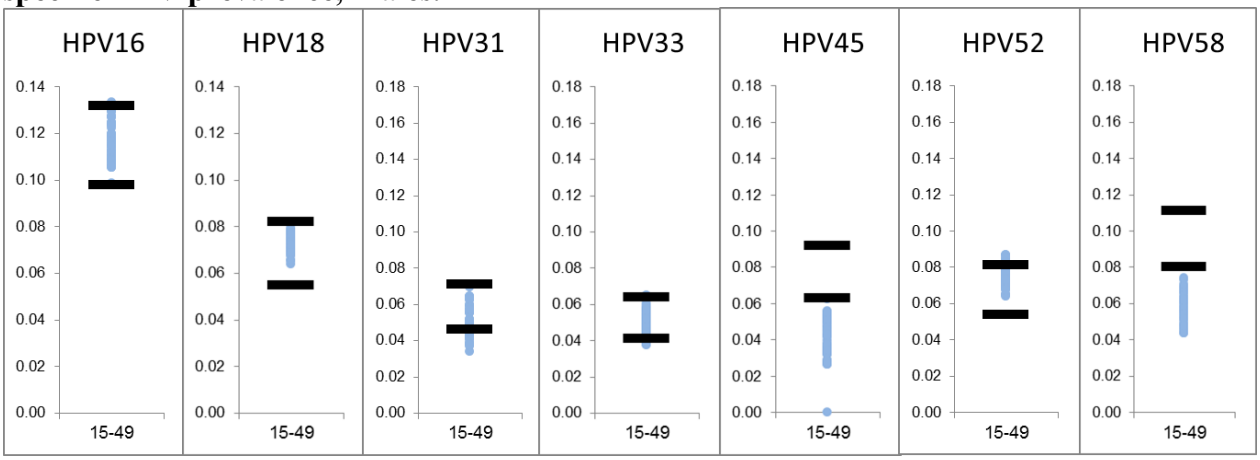
Assortativeness sexual mixing parameter by age (Uganda DHS 2016).

Parameter, males	Value
Probability partner within age bucket	0.2282
Probability partner one age bucket younger	0.0362
Probability partner one age bucket older	0.4630

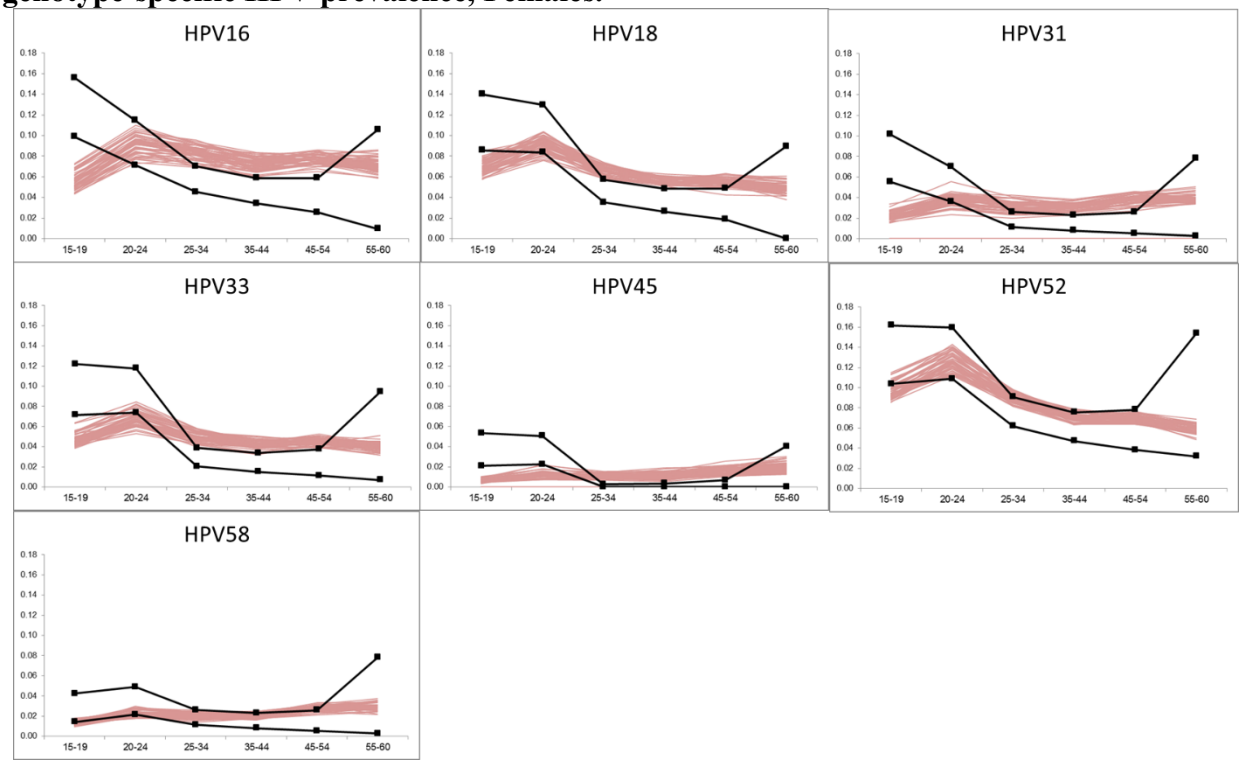
Calibrated parameter set used in analysis.

Calibration parameter	Search range	Best-fitting parameter set
Male to female HPV transmission, monthly per partner		
HPV 16	0.01-female	0.010412
HPV 18	0.01-female	0.037160
HPV 31	0.01-female	0.010496
HPV 33	0.01-female	0.028631
HPV 45	0.01-female	0.010896
HPV 52	0.01-female	0.052502
HPV 58	0.01-female	0.010965
Female to male HPV transmission, monthly per partner		
HPV 16	0.01-0.10	0.061951
HPV 18	0.01-0.10	0.082025
HPV 31	0.01-0.10	0.054081
HPV 33	0.01-0.10	0.071582
HPV 45	0.01-0.10	0.086559
HPV 52	0.01-0.10	0.062630
HPV 58	0.01-0.10	0.084088
Natural immunity, males		
HPV 16	0.00-0.10	0.016181
HPV 18	0.00-0.10	0.076011
HPV 31	0.10-0.50	0.045512
HPV 33	0.10-0.50	0.043114
HPV 45	0.10-0.50	0.067366
HPV 52	0.10-0.50	0.094761
HPV 58	0.10-0.50	0.060315
Natural immunity, females		
HPV 16	0.10-0.50	0.467665
HPV 18	0.10-0.50	0.480271
HPV 31	0.10-0.50	0.472950
HPV 33	0.10-0.50	0.498096
HPV 45	0.10-0.50	0.475061
HPV 52	0.10-0.50	0.491974
HPV 58	0.10-0.50	0.492951
Abbreviations: HPV, human papillomavirus		

Harvard-HPV calibration targets (black bars) [4] and model fit (blue dots) to genotype-specific HPV prevalence, Males.



Harvard-HPV calibration targets (black lines) [2,3] and model fit (red lines) to age- and genotype-specific HPV prevalence, Females.



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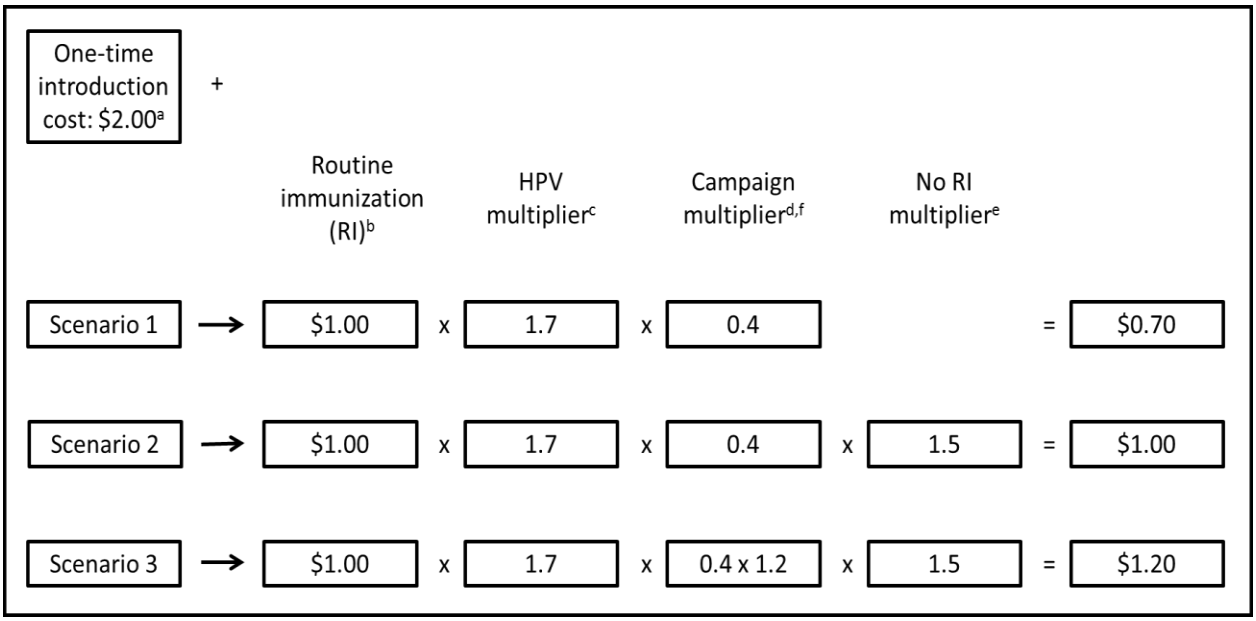
Appendix Figure 2.2. Delivery cost assumptions

This analysis of HPV vaccination campaigns included three scenarios for recurrent vaccine delivery costs as outlined in the Figure below. In the first year of a campaign or a routine vaccination program, there is a one-time introduction cost of $2.00 per targeted girl. Routine vaccination recurrent costs are assumed to be $1.00. Scenario 1 assumed that recurrent routine vaccination costs must be adjusted for HPV vaccine and the economies of scale from a multi-age cohort campaign, resulting in $0.70. Scenario 2 adjusted Scenario 1 for the fact that there is no established routine vaccination program in the case of introducing HPV vaccine via a standalone campaign delivery platform, resulting in $1.00. Scenario 3 adjusted Scenario 2 for the higher expected recurrent costs for the larger healthcare workforce and additional costs of the greater depth and scope of campaigns for HPV (i.e., suggesting that an HPV campaign differs from an HPV routine program), resulting in $1.20. All costs are rounded to the nearest tenth.



[a] One-time introduction cost of $2.00 per targeted girl: This fixed unit cost represents non-recurrent introduction activities: planning, training, social mobilization, and information, education, communication (IEC). Given that the amount of $2.40 per targeted girl for the Gavi vaccine introduction grant for HPV vaccines is based on 80% of estimated average per girl introduction costs according to country expenditure data, we can assume approximately $3.00 per girl is required in the year of introduction [1]. Relying on an assumption of $1.00 per targeted girl for recurrent costs (below), we can also assume approximately $2.00 for fixed costs.

[b] Routine immunization (RI) unit cost of $1.00 per girl: The assumption of $1.00 represents the recurrent costs for ongoing vaccination activities, as evidenced by the operational cost of $0.80 per targeted individual according to Gavi, which can be assumed to go towards ongoing recurrent costs of vaccination for each campaign [1], $1.20 for routine service delivery according to Portnoy, et al. [2], and average operational costs per dose of approximately $1.00 according to Gandhi and

Lydon [3]. Therefore, our assumption for recurrent childhood vaccination delivery costs would be approximately $1.00.

[c] HPV multiplier of 1.7: Whereas the routine vaccination unit costs are based on childhood vaccination data, we can assume that routine vaccination of HPV would be higher given the different target age group and delivery infrastructure required. While the Gavi vaccine introduction grant subsidy is $1.60 higher per targeted person for HPV compared to childhood vaccinations [1], Botwright, et al. estimated $1.80 as the cost for school-based delivery of HPV vaccine [4]. Therefore, we assume 1.7 as the base case multiplier for the increased delivery cost of HPV (representing $1.70 as the routine delivery cost per targeted girl).

[d] Campaign multiplier of 0.4: From the Portnoy, et al. analysis of baseline comprehensive multi-year plan (cMYP) data, when comparing the routine delivery costs per dose to campaign delivery costs per dose, the campaign delivery cost per dose is 60% less [2]. This difference represents the economies of scale gains from multi-age cohort campaigns of infant and childhood vaccinations. Therefore, we assume 0.4 as the base case multiplier for the campaign multiplier.

[e] "No routine immunization (RI) program" multiplier of 1.5: Whereas current vaccination campaigns such as measles or adult influenza experience the specified economies of scale gains from a multi-age cohort campaign, HPV vaccine campaigns conducted without an established routine program would require additional support for the same introduction activities that a routine program would require, such as training of personnel and social mobilization. Using data from Botwright, et al. [4], the introduction cost components represent approximately 50% of the financial cost per dose for HPV vaccine introduction across Gavi-supported demonstration projects of HPV vaccine. We might expect that in the case of vaccination campaigns without an established routine that subsequent campaigns beyond the first would have lower overall delivery costs, but may be higher compared to campaigns supplementing an established routine program given some loss of knowledge and skills in the health care workforce every few years. Therefore, we will assume 1.5 as the base case multiplier for the "no routine immunization (RI) program" multiplier.

[f] HPV campaign multiplier of 1.2: Given the larger health care workforce required for a campaign as compared to the introduction of a new vaccine into a routine program, the recurrent costs of campaigns might be expected to exceed that of a routine program. Additionally, we might expect that the social mobilization and IEC activities would differ in depth and scope given the adolescent and young adult target population, as well as the sexual transmission component of HPV. While not as evidence-based as the other multipliers, we will assume a small multiplier of 1.2 in the base case.

References

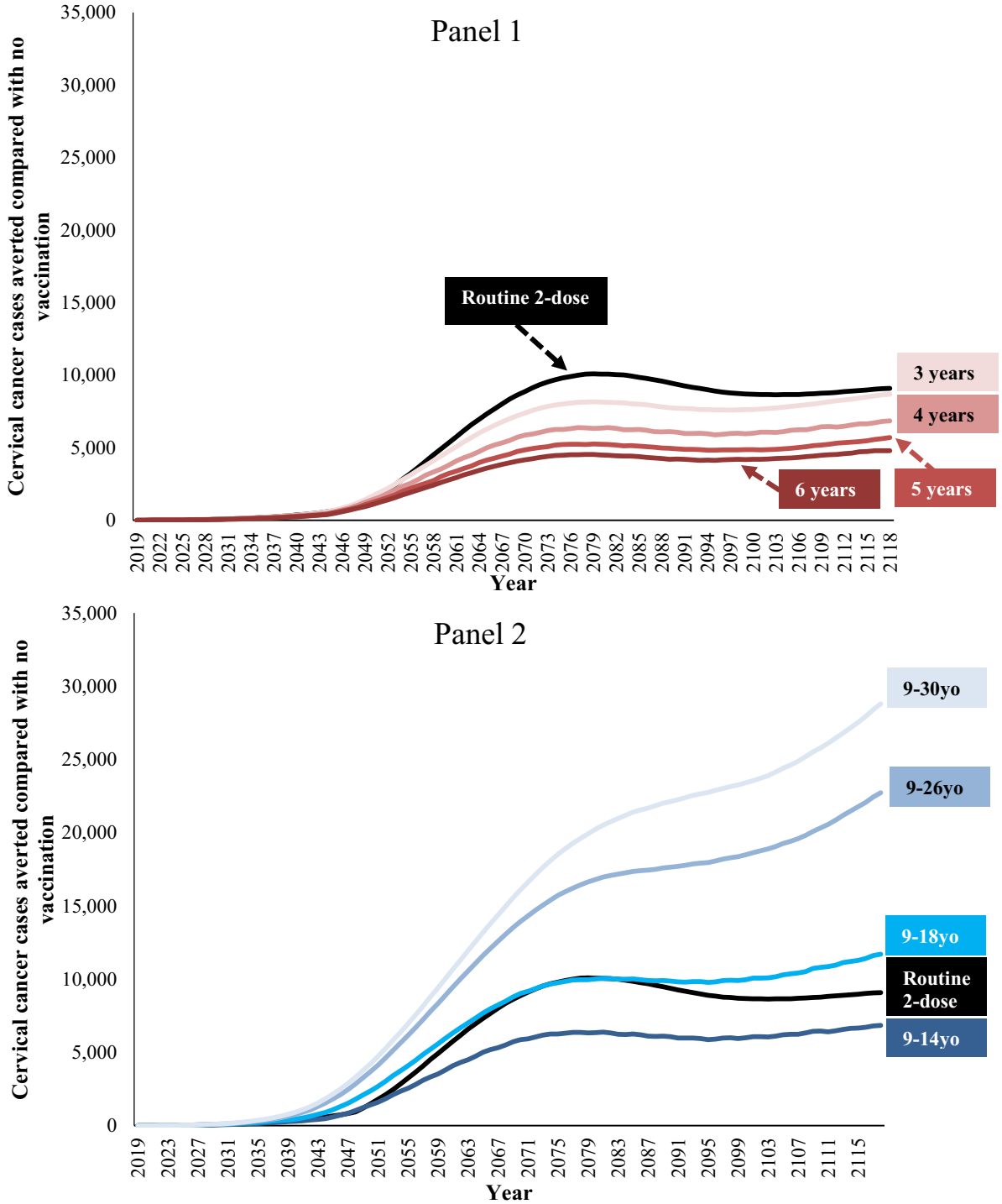
[1] Gavi The Vaccine Alliance. GAVI Alliance Vaccine Introduction Grant and Operational Support for Campaigns Policy. Version No. 1.0. Geneva: Gavi, The Vaccine Alliance. Last updated: 2 April 2013. [Online] Accessed 12 July 2018. Available at: www.gavi.org **2013**.

[2] Portnoy A, Ozawa S, Grewal S, Norman BA, Rajgopal J, et al. Costs of vaccine programs across 94 low- and middle-income countries. Vaccine **2015**; 33(Suppl 1): A99-108.

[3] Gandhi G, Lydon P. Updating the evidence base on the operational costs of supplementary immunization activities for current and future accelerated disease control, elimination and eradication efforts. BMC Public Health **2014**; 14(67.

[4] Botwright S, Holroyd T, Nanda S, Bloem P, Griffiths UK, et al. Experiences of operational costs of HPV vaccine delivery strategies in Gavi-supported demonstration projects. PLoS One **2017**; 12(10): e0182663.

Appendix Figure 2.3. Annual number of cervical cancer cases averted: varying campaign frequency (Panel A) and varying target age group (Panel B), assuming 15-year boost to duration of protection



Note: Campaign strategies represent 40% vaccination coverage. Campaign strategies that vary frequency assume vaccination of 9- to 14-year-old (i.e., 9-14yo) girls; campaign strategies that vary target age group strategies assume 4-year frequency. Routine strategies assume 70% vaccination coverage, including a one-year multi-age program of 10-14 year old girls.

Appendix Table 2.1. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with lifelong duration of protection

2.1a. Assuming campaign coverage of 20% (base case: 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$637,905,527	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$640,160,331	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$643,924,934	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$644,812,698	648,975	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$648,311,225	782,049	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$650,278,012	778,847	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$652,898,253	994,528	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$654,482,774	1,141,588	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$655,933,840	1,378,363	--	--	Weakly dominated[e]
5 years, 9- to 26-year-olds	$658,568,294	1,371,567	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$660,855,556	1,643,546	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$661,806,689	1,329,153	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$666,156,840	1,705,025	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$670,144,215	2,026,372	$53,092,871	2,026,372	$26[g]
3 years, 9- to 26-year-olds	$682,762,600	2,215,207	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$691,321,526	2,600,624	$21,177,311	574,252	$37[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]

Appendix Table 2.1 Continued.

2.1b. Assuming campaign coverage of 40% (base case)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$656,437,779	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$659,830,257	938,428	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$665,043,876	1,202,381	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$665,498,237	1,372,025	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$670,209,585	1,652,910	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$675,645,607	1,620,475	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$678,910,364	2,049,504	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$679,680,405	2,377,978	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$685,909,860	2,804,103	$68,858,517	2,804,103	$25[g]
5 years, 9- to 26-year-olds	$690,670,885	2,780,468	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$698,496,286	2,646,970	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$703,346,743	3,214,803	$17,436,882	410,701	$42[g]
4 years, 9- to 26-year-olds	$716,419,654	3,276,830	--	--	Weakly dominated[e]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$746,136,160	3,641,857	$42,789,417	427,053	$100[g]
3 years, 9- to 26-year-olds	$789,363,769	3,741,105	--	--	Weakly dominated[e]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$852,131,262	3,941,650	$105,995,102	299,794	$354[g]

Appendix Table 2.1 Continued.

2.1c. Assuming campaign coverage of 60% (base case: 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-old girls	$675,816,813	1,151,813	--	--	Weakly dominated[e]
5 years, 9- to 14-year-old girls	$678,251,561	1,432,060	--	--	Weakly dominated[e]
6 years, 9- to 18-year-old girls	$680,353,599	2,135,705	--	--	Weakly dominated[e]
4 years, 9- to 14-year-old girls	$681,965,686	1,860,268	--	--	Strongly dominated[f]
5 years, 9- to 18-year-old girls	$683,700,752	2,580,867	$66,649,409	2,580,867	$26[g]
3 years, 9- to 14-year-old girls	$691,822,121	2,525,703	--	--	Strongly dominated[f]
4 years, 9- to 18-year-old girls	$702,057,499	3,078,743	--	--	Weakly dominated[e]
6 years, 9- to 26-year-old girls	$709,392,092	3,501,014	$25,691,340	920,147	$28[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
6 years, 9- to 30-year-old girls	$743,454,390	3,830,226	$34,062,298	329,213	$103[g]
5 years, 9- to 26-year-old girls	$750,675,178	3,771,217	--	--	Strongly dominated[f]
3 years, 9- to 18-year-old girls	$755,576,438	3,618,549	--	--	Strongly dominated[f]
5 years, 9- to 30-year-old girls	$804,467,345	3,994,013	$61,012,955	163,787	$373[g]
4 years, 9- to 26-year-old girls	$831,359,392	3,971,640	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
4 years, 9- to 30-year-old girls	$908,888,369	4,115,389	$104,421,024	121,375	$860
3 years, 9- to 26-year-old girls	$984,249,294	4,115,578	--	--	Weakly dominated[e]
3 years, 9- to 30-year-old girls	$1,094,205,052	4,221,430	$185,316,683	106,042	$1,748

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.2. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with 15-year boost to duration of protection

2.2a. Assuming campaign coverage of 20% (base case: lifelong protection and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$637,905,527	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$641,392,280	433,508	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$646,790,520	538,686	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$648,759,924	602,503	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$654,151,086	715,084	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$656,949,109	700,328	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$662,703,827	881,893	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$665,694,344	1,016,707	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$670,270,541	1,220,564	$53,219,197	1,220,564	$44[g]
5 years, 9- to 26-year-olds	$674,872,877	1,191,255	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$680,155,246	1,119,902	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$680,596,613	1,427,056	$10,326,073	206,491	$50[g]
4 years, 9- to 26-year-olds	$690,289,025	1,439,663	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$698,565,607	1,713,584	$17,968,994	286,529	$63[g]
3 years, 9- to 26-year-olds	$721,364,925	1,788,452	--	--	Weakly dominated[e]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$734,760,328	2,121,771	$36,194,721	408,186	$89[g]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]

Appendix Table 2.2 Continued.

2.2b. Assuming campaign coverage of 40% (base case: lifelong protection)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$656,437,779	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$664,741,477	881,250	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$677,322,525	1,059,702	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$680,132,409	1,205,750	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$692,868,291	1,397,053	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$700,747,755	1,329,790	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$715,091,411	1,646,752	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$719,205,656	1,942,497	--	--	Weakly dominated[e]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$731,083,555	2,310,807	$114,032,211	2,310,807	$49[g]
5 years, 9- to 26-year-olds	$742,838,645	2,207,777	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$758,181,545	1,983,794	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$760,052,266	2,595,304	$28,968,711	284,497	$102[g]
4 years, 9- to 26-year-olds	$784,009,319	2,543,340	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$810,301,696	2,954,637	$50,249,430	359,333	$140[g]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$865,494,585	2,943,344	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$910,519,968	3,351,564	$100,218,272	396,927	$252[g]

Appendix Table 2.2 Continued.

2.2c. Assuming campaign coverage of 60% (base case: lifelong protection and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$675,816,813	1,151,813	$58,765,469	1,151,813	$51[g]
5 years, 9- to 14-year-olds	$689,052,872	1,309,141	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$710,016,547	1,540,453	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$714,252,281	1,758,422	$38,435,468	606,608	$63[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
5 years, 9- to 18-year-olds	$735,711,357	2,003,450	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$748,636,176	1,884,089	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$774,766,003	2,283,472	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$781,405,778	2,727,628	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$807,493,603	3,156,207	$93,241,322	1,397,786	$67[g]
5 years, 9- to 26-year-olds	$826,265,499	2,979,970	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$849,998,673	2,618,971	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$863,206,293	3,401,150	$55,712,691	244,943	$227[g]
4 years, 9- to 26-year-olds	$902,876,035	3,258,848	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$957,966,244	3,653,541	$94,759,951	252,391	$375[g]
3 years, 9- to 26-year-olds	$1,047,185,986	3,530,163	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$1,133,355,348	3,884,862	$175,389,104	231,321	$758

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.3. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with campaign delivery costs of $0.70 per girl

2.3a. Assuming campaign coverage of 20% (base case: campaign delivery costs of $1.00 per girl and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$635,748,061	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$637,602,593	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$640,752,248	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$641,330,912	648,975	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$644,182,972	782,049	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$646,060,891	778,847	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$647,775,659	994,528	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$648,637,958	1,141,588	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$649,050,750	1,378,363	--	--	Weakly dominated[e]
5 years, 9- to 26-year-olds	$651,636,774	1,371,567	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$652,692,116	1,643,546	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$654,994,138	1,329,153	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$657,549,935	1,705,025	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$660,004,491	2,026,372	$7,312,375	2,026,372	$4[g]
3 years, 9- to 26-year-olds	$671,304,041	2,215,207	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$677,815,243	2,600,624	$17,810,752	574,252	$31[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]

Appendix Table 2.3 Continued.

2.3b. Assuming campaign coverage of 40% (base case: campaign delivery costs of $1.00 per girl)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$652,122,847	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$654,714,781	938,428	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$658,534,665	1,372,025	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$658,698,506	1,202,381	--	--	Strongly dominated[f]
5 years, 9- to 18-year-olds	$661,953,079	1,652,910	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$667,211,365	1,620,475	--	--	Strongly dominated[f]
6 years, 9- to 26-year-olds	$667,990,773	2,377,978	--	--	Weakly dominated[e]
4 years, 9- to 18-year-olds	$668,665,176	2,049,504	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$672,143,680	2,804,103	$55,092,337	2,804,103	$20[g]
5 years, 9- to 26-year-olds	$676,807,844	2,780,468	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$684,871,184	2,646,970	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$687,019,863	3,214,803	$14,876,182	410,701	$36[g]
4 years, 9- to 26-year-olds	$699,205,845	3,276,830	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$725,856,712	3,641,857	$38,836,849	427,053	$91[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$766,446,652	3,741,105	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$825,118,696	3,941,650	$99,261,984	299,794	$331[g]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]

Appendix Table 2.3 Continued.

2.3c. Assuming campaign coverage of 60% (base case: campaign delivery costs of $1.00 per girl and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$669,344,414	1,151,813	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$669,908,242	2,135,705	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$670,578,347	1,432,060	--	--	Strongly dominated[f]
5 years, 9- to 18-year-olds	$671,315,992	2,580,867	$54,264,649	2,580,867	$21[g]
4 years, 9- to 14-year-olds	$672,447,630	1,860,268	--	--	Strongly dominated[f]
3 years, 9- to 14-year-olds	$679,170,760	2,525,703	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$686,689,717	3,078,743	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$691,857,642	3,501,014	$20,541,650	920,147	$22[g]
6 years, 9- to 30-year-olds	$722,805,120	3,830,226	$30,947,478	329,213	$94[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$729,880,618	3,771,217	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$735,138,785	3,618,549	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$779,977,025	3,994,013	$57,171,905	163,787	$349[g]
4 years, 9- to 26-year-olds	$805,538,678	3,971,640	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$878,469,197	4,115,389	$98,492,173	121,375	$811
3 years, 9- to 26-year-olds	$949,873,619	4,115,578	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$1,053,686,203	4,221,430	$175,217,006	106,042	$1,652

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.4. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with campaign delivery costs of $1.20 per girl

2.4a. Assuming campaign coverage of 20% (base case: campaign delivery costs of $1.00 per girl and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$639,343,838	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$641,865,490	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$646,040,057	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$647,133,888	648,975	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$651,063,394	782,049	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$653,089,426	778,847	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$656,313,316	994,528	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$658,379,318	1,141,588	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$660,522,567	1,378,363	--	--	Weakly dominated[e]
5 years, 9- to 26-year-olds	$663,189,307	1,371,567	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$666,297,849	1,643,546	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$666,348,390	1,329,153	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$671,894,776	1,705,025	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$676,904,031	2,026,372	$59,852,687	2,026,372	$30[g]
3 years, 9- to 26-year-olds	$690,401,639	2,215,207	--	--	Weakly dominated
3 years, 9- to 30-year-olds	$700,325,714	2,600,624	$23,421,684	574,252	$41[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]

Appendix Table 2.4 Continued.

2.4b. Assuming campaign coverage of 40% (base case: campaign delivery costs of $1.00 per girl)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$659,314,401	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$663,240,575	938,428	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$669,274,123	1,202,381	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$670,140,618	1,372,025	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$675,713,923	1,652,910	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$681,268,434	1,620,475	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$685,740,489	2,049,504	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$687,473,494	2,377,978	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$695,087,314	2,804,103	$78,035,970	2,804,103	$28[g]
5 years, 9- to 26-year-olds	$699,912,912	2,780,468	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$707,579,687	2,646,970	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$714,231,329	3,214,803	$19,144,016	410,701	$47[g]
4 years, 9- to 26-year-olds	$727,895,527	3,276,830	--	--	Weakly dominated[e]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$759,655,791	3,641,857	$45,424,462	427,053	$106[g]
3 years, 9- to 26-year-olds	$804,641,848	3,741,105	--	--	Weakly dominated[e]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$870,139,639	3,941,650	$110,483,848	299,794	$369[g]

Appendix Table 2.4 Continued.

2.4c. Assuming campaign coverage of 60% (base case: campaign delivery costs of $1.00 per girl and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$680,131,746	1,151,813	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$683,367,037	1,432,060	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$687,317,171	2,135,705	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$688,311,056	1,860,268	--	--	Strongly dominated[f]
5 years, 9- to 18-year-olds	$691,957,259	2,580,867	$74,905,915	2,580,867	$29[g]
3 years, 9- to 14-year-olds	$700,256,363	2,525,703	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$712,302,687	3,078,743	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$721,081,724	3,501,014	$29,124,466	920,147	$32[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$757,220,570	3,830,226	$36,138,846	329,213	$110[g]
5 years, 9- to 26-year-olds	$764,538,219	3,771,217	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$769,201,540	3,618,549	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$820,794,225	3,994,013	$63,573,655	163,787	$388[g]
4 years, 9- to 26-year-olds	$848,573,202	3,971,640	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$929,167,816	4,115,389	$108,373,592	121,375	$893
3 years, 9- to 26-year-olds	$1,007,166,412	4,115,578	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$1,121,217,618	4,221,430	$192,049,801	106,042	$1,811

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.5. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with campaign delivery costs of $1.00 per girl for ages 9-14 years and $1.70 per girl for ages 15 years and higher

2.5a. Assuming campaign coverage of 20% (base case: campaign delivery costs of $1.00 per girl and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$637,905,527	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$640,160,331	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$643,924,934	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$647,902,776	648,975	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$650,278,012	778,847	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$651,975,761	782,049	--	--	Weakly dominated[e]
4 years, 9- to 18-year-olds	$657,448,040	994,528	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$663,086,591	1,141,588	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$666,960,295	1,378,363	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$667,862,693	1,329,153	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$668,773,785	1,371,567	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$673,935,527	1,643,546	--	--	Weakly dominated[e]
4 years, 9- to 26-year-olds	$678,836,685	1,705,025	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$686,400,638	2,026,372	$69,349,295	2,026,372	$34[g]
3 years, 9- to 26-year-olds	$699,659,289	2,215,207	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$712,996,238	2,600,624	$26,595,600	574,252	$46[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]

Appendix Table 2.5 Continued.

2.5b. Assuming campaign coverage of 40% (base case: campaign delivery costs of $1.00 per girl)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$656,437,779	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$659,830,257	938,428	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$665,043,876	1,202,381	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$671,678,394	1,372,025	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$675,645,607	1,620,475	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$677,538,656	1,652,910	--	--	Weakly dominated[e]
4 years, 9- to 18-year-olds	$688,009,938	2,049,504	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$696,888,039	2,377,978	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$707,962,770	2,804,103	$90,911,427	2,804,103	$32[g]
3 years, 9- to 18-year-olds	$710,608,294	2,646,970	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$711,081,868	2,780,468	--	--	Strongly dominated[f]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$729,506,685	3,214,803	$21,543,914	410,701	$52[g]
4 years, 9- to 26-year-olds	$741,779,345	3,276,830	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$778,649,006	3,641,857	$49,142,322	427,053	$115[g]
3 years, 9- to 26-year-olds	$823,157,147	3,741,105	--	--	Weakly dominated[e]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$895,480,686	3,941,650	$116,831,679	299,794	$390[g]

Appendix Table 2.5 Continued.

2.5c. Assuming campaign coverage of 60% (base case: campaign delivery costs of $1.00 per girl and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$675,816,813	1,151,813	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$678,251,561	1,432,060	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$681,965,686	1,860,268	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$689,623,835	2,135,705	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$691,822,121	2,525,703	$74,770,778	2,525,703	$30[g]
5 years, 9- to 18-year-olds	$694,694,358	2,580,867	--	--	Weakly dominated[e]
4 years, 9- to 18-year-olds	$715,706,860	3,078,743	--	--	Weakly dominated[e]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
6 years, 9- to 26-year-olds	$735,203,541	3,501,014	$43,381,420	975,310	$44[g]
3 years, 9- to 18-year-olds	$773,744,450	3,618,549	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$776,533,755	3,830,226	$41,330,213	329,213	$126[g]
5 years, 9- to 26-year-olds	$781,291,653	3,771,217	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$843,707,258	3,994,013	$67,173,503	163,787	$410[g]
4 years, 9- to 26-year-olds	$869,398,928	3,971,640	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$957,657,639	4,115,389	$113,950,381	121,375	$939
3 years, 9- to 26-year-olds	$1,034,939,360	4,115,578	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$1,159,229,188	4,221,430	$201,571,549	106,042	$1,901

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.6. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with cancer treatment costs incurred by 8.5% of women with cancer based on level of treatment access

2.6a. Assuming campaign coverage of 20% (base case: cancer treatment costs incurred by 100% of women with cancer and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$52,449,364	--	$52,449,364	--	--
6 years, 9- to 14-year-olds	$93,255,351	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$100,436,254	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$111,493,991	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$117,735,373	648,975	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$129,320,878	782,049	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$130,271,149	778,847	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$147,073,206	994,528	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$161,041,594	1,141,588	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$177,339,185	1,329,153	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$179,772,213	1,378,363	--	--	Weakly dominated[e]
5 years, 9- to 26-year-olds	$180,364,070	1,371,567	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$202,547,070	1,643,546	$150,097,706	1,643,546	$91[g]
4 years, 9- to 26-year-olds	$210,263,403	1,705,025	--	--	Weakly dominated[e]
Routine 1-dose	$226,168,156	1,160,599	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$237,844,993	2,026,372	$35,297,922	382,826	$92[g]
3 years, 9- to 26-year-olds	$261,468,335	2,215,207	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$298,429,394	2,600,624	$60,584,401	574,252	$106[g]
Routine 2-dose	$352,411,048	1,549,362	--	--	Strongly dominated[f]

Appendix Table 2.6 Continued.

2.6b. Assuming campaign coverage of 40% (base case: cancer treatment costs incurred by 100% of women with cancer)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$52,449,364	--	$52,449,364	--	--
6 years, 9- to 14-year-olds	$133,863,973	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$148,130,823	938,428	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$170,049,472	1,202,381	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$182,419,937	1,372,025	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$205,396,663	1,652,910	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$207,424,913	1,620,475	--	--	Strongly dominated[f]
Routine 1-dose	$226,168,156	1,160,599	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$240,861,090	2,049,504	--	--	Weakly dominated[e]
6 years, 9- to 26-year-olds	$268,593,950	2,377,978	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$301,543,417	2,646,970	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$306,338,012	2,804,103	$253,888,648	2,804,103	$91[g]
5 years, 9- to 26-year-olds	$307,478,555	2,780,468	--	--	Strongly dominated[f]
Routine 2-dose	$352,411,048	1,549,362	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$352,533,170	3,214,803	$46,195,158	410,701	$112[g]
4 years, 9- to 26-year-olds	$368,175,815	3,276,830	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$425,187,043	3,641,857	$72,653,873	427,053	$170[g]
3 years, 9- to 26-year-olds	$473,962,949	3,741,105	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$551,765,286	3,941,650	$126,578,244	299,794	$422[g]

Appendix Table 2.6 Continued.

2.6c. Assuming campaign coverage of 60% (base case: cancer treatment costs incurred by 100% of women with cancer and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$52,449,364	--	$52,449,364	--	--
6 years, 9- to 14-year-olds	$174,544,572	1,151,813	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$195,719,260	1,432,060	--	--	Weakly dominated[e]
Routine 1-dose	$226,168,156	1,160,599	--	--	Strongly dominated[f]
4 years, 9- to 14-year-olds	$228,248,197	1,860,268	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$246,608,936	2,135,705	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$280,757,837	2,580,867	$228,308,472	2,580,867	$88[g]
3 years, 9- to 14-year-olds	$283,797,435	2,525,703	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$334,405,452	3,078,743	--	--	Weakly dominated[e]
Routine 2-dose	$352,411,048	1,549,362	--	--	Strongly dominated[f]
6 years, 9- to 26-year-olds	$376,530,002	3,501,014	$95,772,165	920,147	$104[g]
3 years, 9- to 18-year-olds	$427,480,846	3,618,549	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$435,247,134	3,830,226	$58,717,132	329,213	$178[g]
5 years, 9- to 26-year-olds	$436,964,685	3,771,217	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$507,502,769	3,994,013	$72,255,635	163,787	$441[g]
4 years, 9- to 26-year-olds	$531,585,765	3,971,640	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$619,903,715	4,115,389	$112,400,946	121,375	$926
3 years, 9- to 26-year-olds	$693,961,733	4,115,578	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$812,008,623	4,221,430	$192,104,908	106,042	$1,812

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.7. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with 60% one-dose and 80% two-dose efficacy for girls ages 19 and older

2.7a. Assuming campaign coverage of 20% (base case: one-dose efficacy of 80%, two-dose efficacy of 100%, and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$637,905,527	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$640,160,331	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$643,924,934	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$644,812,698	648,975	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$648,311,225	782,049	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$650,278,012	778,847	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$652,898,253	994,528	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$661,806,689	1,329,153	$44,755,346	1,329,153	$34[g]
6 years, 9- to 26-year-olds	$668,448,380	954,752	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$675,893,796	1,143,674	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$676,955,210	1,103,926	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$686,082,209	1,316,294	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$688,827,626	1,410,720	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$702,421,835	1,610,842	--	--	Weakly dominated[e]
3 years, 9- to 26-year-olds	$713,788,737	1,815,024	--	--	Weakly dominated[e]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$735,525,595	2,035,827	$73,718,905	706,675	$104[g]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]

Appendix Table 2.7 Continued.

2.7b. Assuming campaign coverage of 40% (base case: one-dose efficacy of 80% and two-dose efficacy of 100%)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$656,437,779	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$659,830,257	938,428	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$665,043,876	1,202,381	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$665,498,237	1,372,025	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$670,209,585	1,652,910	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$675,645,607	1,620,475	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$678,910,364	2,049,504	$61,859,020	2,049,504	$30[g]
3 years, 9- to 18-year-olds	$698,496,286	2,646,970	$19,585,922	597,466	$33[g]
6 years, 9- to 26-year-olds	$713,525,749	1,942,129	--	--	Strongly dominated[f]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$733,438,657	2,235,129	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$734,477,225	2,184,648	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$758,666,510	2,515,677	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$766,449,251	2,649,348	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$802,930,718	2,931,259	--	--	Weakly dominated[e]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$836,762,418	3,155,286	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$897,369,829	3,382,577	$198,873,543	735,606	$270[g]

Appendix Table 2.7 Continued.

2.7c. Assuming campaign coverage of 60% (base case: one-dose efficacy of 80%, two-dose efficacy of 100%, and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$675,816,813	1,151,813	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$678,251,561	1,432,060	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$680,353,599	2,135,705	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$681,965,686	1,860,268	--	--	Strongly dominated[f]
5 years, 9- to 18-year-olds	$683,700,752	2,580,867	$66,649,409	2,580,867	$26[g]
3 years, 9- to 14-year-olds	$691,822,121	2,525,703	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$702,057,499	3,078,743	$18,356,747	497,876	$37[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$755,576,438	3,618,549	$53,518,939	539,806	$99[g]
6 years, 9- to 26-year-olds	$761,171,072	2,855,640	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$800,602,861	3,155,213	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$800,877,079	3,113,824	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$850,878,279	3,420,117	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$872,034,942	3,476,140	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$943,999,689	3,684,870	--	--	Weakly dominated[e]
3 years, 9- to 26-year-olds	$1,014,345,420	3,751,677	--	--	Weakly dominated[e]
3 years, 9- to 30-year-olds	$1,121,287,510	3,893,587	$365,711,072	275,037	$1,330

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.8. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with 40% one-dose and 60% two-dose efficacy for girls ages 19 and older

2.8a. Assuming campaign coverage of 20% (base case: one-dose efficacy of 80%, two-dose efficacy of 100%, and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$637,905,527	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$640,160,331	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$643,924,934	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$644,812,698	648,975	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$648,311,225	782,049	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$650,278,012	778,847	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$652,898,253	994,528	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$661,806,689	1,329,153	$44,755,346	1,329,153	$34[g]
6 years, 9- to 26-year-olds	$678,874,757	812,553	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$689,069,572	966,366	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$698,870,569	825,723	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$705,671,344	1,186,275	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$714,360,994	962,343	--	--	Strongly dominated[f]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$736,573,442	1,517,728	$74,766,753	188,576	$396[g]
4 years, 9- to 30-year-olds	$739,234,236	1,157,770	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$786,734,416	1,413,754	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	$96,530,974	31,634	$3,052

Appendix Table 2.8 Continued.

2.8b. Assuming campaign coverage of 40% (base case: one-dose efficacy of 80% and two-dose efficacy of 100%)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$656,437,779	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$659,830,257	938,428	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$665,043,876	1,202,381	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$665,498,237	1,372,025	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$670,209,585	1,652,910	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$675,645,607	1,620,475	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$678,910,364	2,049,504	$61,859,020	2,049,504	$30[g]
3 years, 9- to 18-year-olds	$698,496,286	2,646,970	$19,585,922	597,466	$33[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
6 years, 9- to 26-year-olds	$738,984,228	1,609,823	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$764,199,096	1,836,737	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$788,806,362	1,522,195	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$806,490,701	2,134,746	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$824,961,429	1,712,575	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$885,567,374	1,937,261	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$888,058,886	2,509,720	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$996,268,385	2,205,929	--	--	Strongly dominated[f]

Appendix Table 2.8 Continued.

2.8c. Assuming campaign coverage of 60% (base case: one-dose efficacy of 80%, two-dose efficacy of 100%, and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$675,816,813	1,151,813	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$678,251,561	1,432,060	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$680,353,599	2,135,705	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$681,965,686	1,860,268	--	--	Strongly dominated[f]
5 years, 9- to 18-year-olds	$683,700,752	2,580,867	$66,649,409	2,580,867	$26[g]
3 years, 9- to 14-year-olds	$691,822,121	2,525,703	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$702,057,499	3,078,743	$18,356,747	497,876	$37[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$755,576,438	3,618,549	$53,518,939	539,806	$99[g]
6 years, 9- to 26-year-olds	$805,648,575	2,287,177	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$852,678,636	2,499,775	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$889,283,880	2,052,098	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$932,571,205	2,726,850	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$950,357,496	2,235,209	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$1,050,535,073	2,433,699	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$1,080,357,285	2,948,485	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$1,230,216,340	2,633,701	--	--	Strongly dominated[f]

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.9. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with 20% one-dose and 40% two-dose efficacy for girls ages 19 and older

2.9a. Assuming campaign coverage of 20% (base case: one-dose efficacy of 80%, two-dose efficacy of 100%, and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$637,905,527	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$640,160,331	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$643,924,934	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$644,812,698	648,975	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$648,311,225	782,049	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$650,278,012	778,847	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$652,898,253	994,528	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$661,806,689	1,329,153	$44,755,346	1,329,153	$34[g]
6 years, 9- to 26-year-olds	$687,373,090	696,045	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$699,745,132	819,443	--	--	Weakly dominated[e]
6 years, 9- to 30-year-olds	$705,173,127	727,473	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$719,252,698	1,003,232	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$720,514,180	859,607	--	--	Strongly dominated[f]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$745,446,323	1,046,803	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$754,464,959	1,279,072	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$792,645,329	1,294,815	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	$171,297,727	220,210	$778

Appendix Table 2.9 Continued.

2.9b. Assuming campaign coverage of 40% (base case: one-dose efficacy of 80% and two-dose efficacy of 100%)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$656,437,779	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$659,830,257	938,428	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$665,043,876	1,202,381	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$665,498,237	1,372,025	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$670,209,585	1,652,910	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$675,645,607	1,620,475	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$678,910,364	2,049,504	$61,859,020	2,049,504	$30[g]
3 years, 9- to 18-year-olds	$698,496,286	2,646,970	$19,585,922	597,466	$33[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
6 years, 9- to 26-year-olds	$758,615,178	1,348,149	$30,574,818	187,550	$163[g]
5 years, 9- to 26-year-olds	$788,207,292	1,520,689	$29,592,114	172,540	$172[g]
6 years, 9- to 30-year-olds	$798,503,424	1,353,083	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Weakly dominated[e]
5 years, 9- to 30-year-olds	$834,360,720	1,540,555	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$836,349,118	1,748,205	$48,141,826	227,516	$212[g]
4 years, 9- to 30-year-olds	$895,567,256	1,749,427	--	--	Weakly dominated[e]
3 years, 9- to 26-year-olds	$925,681,570	2,025,912	$89,332,453	277,707	$322[g]
3 years, 9- to 30-year-olds	$1,009,186,802	1,972,304	--	--	Strongly dominated[f]

Appendix Table 2.9 Continued.

2.9c. Assuming campaign coverage of 60% (base case: one-dose efficacy of 80%, two-dose efficacy of 100%, and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$675,816,813	1,151,813	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$678,251,561	1,432,060	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$680,353,599	2,135,705	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$681,965,686	1,860,268	--	--	Strongly dominated[f]
5 years, 9- to 18-year-olds	$683,700,752	2,580,867	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$691,822,121	2,525,703	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$702,057,499	3,078,743	--	--	Weakly dominated[e]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$755,576,438	3,618,549	--	--	Weakly dominated[e]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
6 years, 9- to 26-year-olds	$838,337,842	1,863,056	$221,286,498	1,863,056	$119[g]
5 years, 9- to 26-year-olds	$890,552,797	2,012,112	$52,214,956	149,056	$350[g]
6 years, 9- to 30-year-olds	$903,361,945	1,808,702	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$964,854,770	1,981,710	--	--	Weakly dominated[e]
4 years, 9- to 26-year-olds	$977,570,309	2,152,407	--	--	Weakly dominated[e]
4 years, 9- to 30-year-olds	$1,069,465,216	2,120,161	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$1,130,217,774	2,319,622	$239,664,977	307,510	$779
3 years, 9- to 30-year-olds	$1,253,953,800	2,258,915	--	--	Strongly dominated[f]

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Appendix Table 2.10. Discounted[a] incremental costs, disability-adjusted life years (DALYs) averted and cost-effectiveness of campaign one-dose[b] HPV vaccination strategies versus routine one-dose[b] and two-dose HPV vaccination with 0% one-dose and 20% two-dose efficacy for girls ages 19 and older

2.10a. Assuming campaign coverage of 20% (base case: one-dose efficacy of 80%, two-dose efficacy of 100%, and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$637,905,527	366,100	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$640,160,331	448,571	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$643,924,934	572,389	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$644,812,698	648,975	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$648,311,225	782,049	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$650,278,012	778,847	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$652,898,253	994,528	--	--	Weakly dominated[e]
3 years, 9- to 18-year-olds	$661,806,689	1,329,153	$44,755,346	1,329,153	$34[g]
6 years, 9- to 26-year-olds	$694,942,194	592,370	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$708,375,585	702,385	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$716,626,985	571,796	--	--	Strongly dominated[f]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$730,460,967	850,687	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$733,772,748	681,016	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$761,878,568	827,329	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$769,404,303	1,078,952	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$813,088,217	1,023,548	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	$171,297,727	220,210	$778

Appendix Table 2.10 Continued.

2.10b. Assuming campaign coverage of 40% (base case: one-dose efficacy of 80% and two-dose efficacy of 100%)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$656,437,779	765,683	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$659,830,257	938,428	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$665,043,876	1,202,381	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$665,498,237	1,372,025	--	--	Weakly dominated[e]
5 years, 9- to 18-year-olds	$670,209,585	1,652,910	--	--	Weakly dominated[e]
3 years, 9- to 14-year-olds	$675,645,607	1,620,475	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$678,910,364	2,049,504	$61,859,020	2,049,504	$30[g]
3 years, 9- to 18-year-olds	$698,496,286	2,646,970	$19,585,922	597,466	$33[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
6 years, 9- to 26-year-olds	$775,005,420	1,127,380	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$807,732,208	1,259,352	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$821,644,558	1,046,192	--	--	Strongly dominated[f]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$860,532,306	1,428,152	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$860,720,281	1,191,412	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$926,736,420	1,340,275	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$954,926,252	1,643,752	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$1,045,635,785	1,496,714	--	--	Strongly dominated[f]

Appendix Table 2.10 Continued.

2.10c. Assuming campaign coverage of 60% (base case: one-dose efficacy of 80%, two-dose efficacy of 100%, and 40% coverage)

Scenario	Total costs[c]	Total DALYs averted[d]	Incremental cost	Incremental DALYs averted	Cost (USD) per DALY averted
No vaccination	$617,051,343	--	$617,051,343	--	--
6 years, 9- to 14-year-olds	$675,816,813	1,151,813	--	--	Weakly dominated[e]
5 years, 9- to 14-year-olds	$678,251,561	1,432,060	--	--	Weakly dominated[e]
6 years, 9- to 18-year-olds	$680,353,599	2,135,705	--	--	Weakly dominated[e]
4 years, 9- to 14-year-olds	$681,965,686	1,860,268	--	--	Strongly dominated[f]
5 years, 9- to 18-year-olds	$683,700,752	2,580,867	$66,649,409	2,580,867	$26[g]
3 years, 9- to 14-year-olds	$691,822,121	2,525,703	--	--	Strongly dominated[f]
4 years, 9- to 18-year-olds	$702,057,499	3,078,743	$18,356,747	497,876	$37[g]
Routine 1-dose	$728,040,360	1,160,599	--	--	Strongly dominated[f]
3 years, 9- to 18-year-olds	$755,576,438	3,618,549	$53,518,939	539,806	$99[g]
Routine 2-dose	$833,104,416	1,549,362	--	--	Strongly dominated[f]
6 years, 9- to 26-year-olds	$864,801,140	1,512,933	--	--	Strongly dominated[f]
5 years, 9- to 26-year-olds	$920,446,000	1,619,287	--	--	Strongly dominated[f]
6 years, 9- to 30-year-olds	$937,028,494	1,369,035	--	--	Strongly dominated[f]
5 years, 9- to 30-year-olds	$1,002,211,491	1,493,637	--	--	Strongly dominated[f]
4 years, 9- to 26-year-olds	$1,012,464,154	1,697,305	--	--	Strongly dominated[f]
4 years, 9- to 30-year-olds	$1,110,312,501	1,589,071	--	--	Strongly dominated[f]
3 years, 9- to 26-year-olds	$1,168,795,013	1,818,197	--	--	Strongly dominated[f]
3 years, 9- to 30-year-olds	$1,297,437,366	1,696,076	--	--	Strongly dominated[f]

[a]Costs and DALYs discounted at 3% per year; [b]One-dose HPV vaccine efficacy of 80% and 15-year duration of protection; two-dose vaccine efficacy of 100% and lifelong duration of protection; [c]Total costs reflect vaccine program costs associated with 100 incoming birth cohorts from years 2019-2118, and disease cost offsets over the lifetimes of women aged <100 years alive in year 2019; [d]Total DALYs averted are aggregated over multiple birth cohorts and capture the benefits over the lifetimes of women aged <100 years alive in year 2019; [e]Weakly dominated strategies have higher ICERs than a more effective strategy; [f]Strongly dominated strategies are more costly and less effective than another strategy; [g]The incremental cost-effectiveness ratio is less than the gross domestic product per capita in Uganda (i.e., $674). Abbreviations. HPV: Human papillomavirus; DALY: disability-adjusted life year.

Paper 3: Health gains and financial protection from human papillomavirus (HPV) vaccination in Ethiopia: results from an extended cost-effectiveness analysis

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Abstract

Background
High out-of-pocket (OOP) medical expenses for cervical cancer can lead to catastrophic expenditure or medical impoverishment in many low- and middle-income countries. There are 32 million women over the age of 15 years at risk for cervical cancer in Ethiopia, but cervical cancer screening coverage is less than 1%. An evaluation of both the health gains and financial risk protection benefits, and their distributional consequences across socioeconomic groups, from routine human papillomavirus (HPV) vaccination will be critical to support cervical cancer prevention in this setting.

Methods
We used a multiple modeling approach that captures HPV transmission, cervical carcinogenesis, and population demographics to project health and economic outcomes associated with routine HPV vaccination in Ethiopia. Health outcomes included number of cervical cancer cases, and costs included vaccination and operational costs in 2015 US dollars over years 2019–2118 and cervical cancer costs over the lifetimes of the current female population in Ethiopia. We estimated household OOP expenditures averted (assuming 34% of direct medical expenditures were financed out of pocket) and cases of catastrophic health expenditures (CHE) averted. These cases averted depended on household consumption expenditures by wealth quintile, disease incidence, health care use, and OOP payments. CHE cases were defined as 40% of household consumption expenditures.

Results
Our analysis shows that, at 80% coverage, assuming 100% vaccine efficacy against HPV-16/18, routine two-dose HPV vaccination could avert up to 1,390,000 cases of cervical cancer over 2019-2118, which translates to approximately 1,110,000 lives saved. Additionally, routine two-dose HPV vaccination could avert 36,000 cases of CHE in this scenario. At 80% vaccine efficacy and 80% coverage, HPV vaccination could avert 26,000 cases of CHE. Approximately one third of health benefits would accrue to the poorest quintile whereas two thirds of financial risk protection benefits would accrue to the poorest quintile.

Conclusions
HPV vaccination reduces disparities in cervical cancer incidence, mortality, and household health expenditures. Our approach incorporates financial risk protection and distributional assessment into the economic evaluation of routine HPV vaccination in Ethiopia. This understanding and our findings can help policymakers in decisions regarding cervical cancer control efforts and investment in a routine HPV vaccination program following an initial catch-up program.

Background

Ethiopia is a large, low-income country (per capita gross domestic product of $770 in 2018) in East Africa with 24% of the population living below the national poverty line [1]. Ethiopia is also very resource-constrained with an annual per capita health expenditure of $28 [1], compared to $70 in neighboring Kenya or $46 in Uganda, and more than one third of health expenditures in Ethiopia are financed by out-of-pocket (OOP) payments [2]. Cervical cancer is the second leading cause of female cancer death in this setting [3] and estimated to be one of the top 20 causes of medical impoverishment [4]. While the cervical cancer incidence rate is lower compared to neighboring Kenya or Uganda, the number of women over the age of 15 at risk for cervical cancer is more than double in Ethiopia at 32 million, but cervical cancer screening coverage in this setting is less than 1% [5]. The disease burden attributable to cervical cancer and other human papillomavirus (HPV) induced anogenital and oropharyngeal cancers is largely preventable with HPV vaccination, but uptake of HPV vaccines remains low. The currently planned HPV vaccination program in Ethiopia involves yearly catch-up vaccination of single-age cohorts from years 2018 to 2021, as restricted by the current global vaccine shortage [6]. However, there are no additional plans to implement routine HPV vaccination beyond this campaign.

Cervical cancer treatment creates a large financial burden on households, with direct medical costs of approximately $330 per patient for consultations, investigations, and drugs [7], without counting for the additional burden of indirect costs such as time and transportation. Assuming 75% treatment care-seeking, direct medical OOP costs for cervical cancer could result in as many as 3,200 cases of medical impoverishment annually [4]. Public finance of HPV vaccination has the potential to increase uptake of the vaccine and decrease mortality due to cervical cancer, but also can eliminate the incidence of these potentially large OOP expenditures associated with care-

seeking for cervical cancer treatment, and thus can provide financial risk protection (FRP) benefits to individuals and their households. Public finance of HPV vaccination can also improve the distribution of both health and financial outcomes in the population [8]. Additionally, increased HPV vaccination coverage may also reduce HPV-related hospitalizations, prevent HPV-related impoverishment, and bring significant cost savings to poor women and their households [9-11]. Public finance of HPV vaccination therefore contributes to three global goals: (1) the Sustainable Development Goals (SDGs) 1 and 3 to "end poverty in all its forms everywhere" and to "achieve universal health coverage, including financial risk protection for all," respectively [12]; (2) the World Bank objective to raise incomes of the bottom 40% of populations in order to boost shared prosperity [13]; and (3) the World Health Organization's global call to action for the elimination of cervical cancer (in part) through increased HPV vaccination [14]. An evaluation of continued routine HPV vaccination in terms of both the health gains – prevention of cervical cancer cases and deaths – and FRP benefits – prevention of medical impoverishment from OOP health-related expenditures, and their distributional consequences across socioeconomic groups, will be critical to support cervical cancer prevention in Ethiopia.

Traditional economic evaluations such as cost-effectiveness analysis (CEA) often account only for direct health impacts and medical costs averted [15], neglecting the potentially significant benefits accruing beyond this narrow scope, such as large equity and distributional dimensions of health policies and interventions [16,17]. As decision-makers evaluate HPV vaccination decisions, the ability to demonstrate the broader economic impact of vaccination will be critical. One possibility is to use extended cost-effectiveness analysis (ECEA) methods [8,18,19], which can complement traditional CEA in assessing the equity, FRP, and distributional (e.g., across population subgroups

including socioeconomic or income groups) components of HPV vaccination programs. These considerations for reducing disparities in health arising from socioeconomic inequalities and reducing financial effects of ill health are recommended priority-setting criteria in guidance on priority-setting and health system performance [20-22]. ECEA therefore can help document performance along the dimensions of both efficiency and equity, toward accounting for tracking progress with respect to global goals including both SDGs 1 and 3. The objective of this analysis is therefore to evaluate the health, equity, and FRP benefits of routine HPV vaccination in Ethiopia.

Methods

We conducted an economic evaluation of routine HPV vaccination by quantifying the health, FRP, and distributional benefits of rolling out HPV vaccination nationally in Ethiopia using ECEA methods [8,18,19].

General ECEA approach

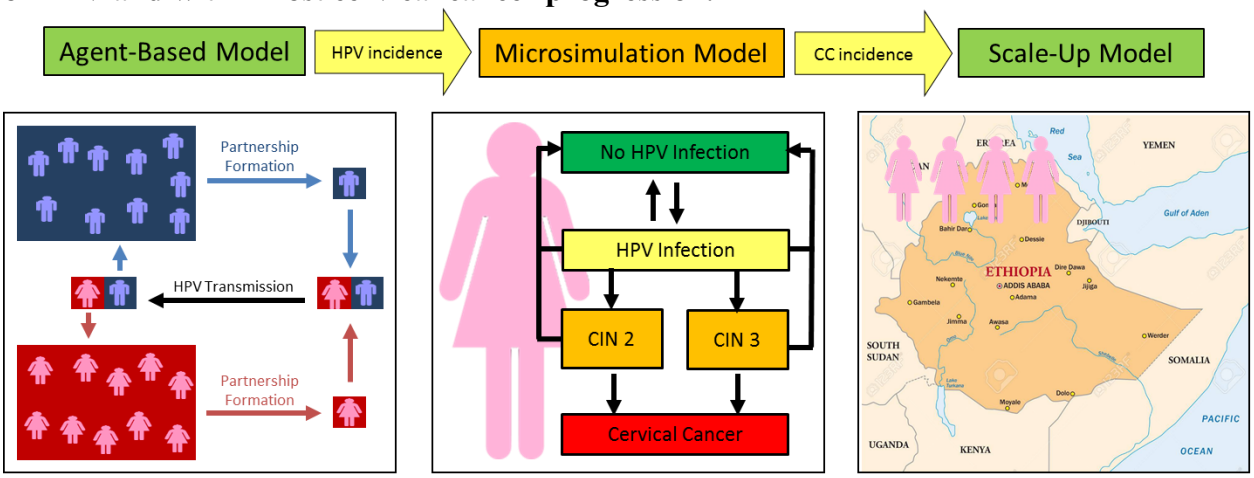
We conducted an ECEA from a health system perspective to evaluate a hypothetical publicly financed program for routine HPV vaccination in Ethiopia. ECEA expands on the standard approach to economic evaluation proposed by CEA, by evaluating equity-related aspects of health policies, including FRP provision and distributional dimensions, which are important for policymakers [8,11,18,23,24]. In addition to health benefits (in this case, HPV-induced cervical cancer deaths averted), ECEA estimates the impact of policies along three dimensions: (1) household OOP health-related expenditures averted by HPV vaccination; (2) FRP benefits provided tied to the reduction of OOP health-related expenditures by HPV vaccination; and (3)

distributional consequences across the wealth strata (e.g., income quintiles) of a country population [8,19].

Disease modeling – cervical cancer cases

We used a previously published multiple modeling approach (Figure 3.1) to estimate the number of cervical cancer cases and deaths averted associated with various HPV vaccination strategies in Ethiopia. As previously described in Paper 1, we linked a dynamic agent-based model of HPV transmission to a static individual-based model of cervical cancer development in order to capture both the direct and indirect benefits of HPV vaccination [25]. We then used a population-based model to project the health impact for women in Ethiopia over time [9].

Figure 3.1. Overview of multiple modeling approach linking population-level transmission of HPV and within host cervical cancer progression.



- Individual-based.
- Models formation of heterosexual partnerships.
- Calibrated to reflect sexual behavior in Ethiopia and epidemiological outcomes in Uganda.
- Estimates direct and indirect (i.e., herd immunity) benefits of vaccination.

- Individual-based.
- Simulates time-in-state HPV clearance and progression to precancer and invasive cancer.
- Calibrated to reflect HPV and cervical cancer in Uganda.
- Transitions between health states based on HPV type, age, duration of HPV infection and precancer, and history of prior infection.

- Population-based.
- Integrates disease burden and population statistics from Ethiopia.
- Scales up intervention impact to demographic projections.
- Outputs include country-specific cancer cases and discounted costs.

Abbreviations. CC: cervical cancer, CIN: Cervical intraepithelial neoplasia, HPV: Human papillomavirus.

The agent-based dynamic model simulating both partnership acquisition and HPV transmission reflects sexual behavior, mortality, and population structure in Ethiopia [26,27] and epidemiological outcomes in Uganda (Paper 1). We used this model to estimate HPV incidence reductions (including herd immunity effects) by genotype (i.e., HPV-16/18) and age over time.

The HPV incidence reductions from the vaccination strategies generated in the agent-based model were used as inputs into the microsimulation model in order to project reductions in cervical cancer incidence attributable to HPV-16/18 by age associated with alternative HPV vaccination strategies. As this model requires highly-detailed data on age-specific HPV prevalence by genotype that are limited in the setting of Ethiopia, we used a version of the model that reflects epidemiological outcomes in Uganda [28-30], a neighboring low-income East African country. Details of the model parameterization process, including calibration and adaptation to the Ugandan setting have been published previously [31,32]. Reductions in HPV-16/18 cervical cancer incidence from the microsimulation model then served as inputs into the population-based scale-up model.

The population-based scale-up model uses data on the age-specific incidence of cervical cancer [33], HPV-16/18 type distribution in cervical cancer [34], and demographics (e.g., population size, mortality rates) over time [12]. We applied the age-specific cancer incidence reductions projected from the microsimulation model to the baseline age-specific cancer incidence rates in Ethiopia [33], provided in Table 3.1, in order to estimate the number of cervical cancer cases averted associated with the alternative HPV vaccination strategies, adjusting for population growth over time.

Table 3.1. National estimates of cervical cancer incidence by age group in Ethiopia [33].

Age group (years)	Cervical cancer incidence rate per 100,000 women
0-4	4
5-9	4
10-14	4
15-19	4
20-24	4
25-29	4
30-34	4
35-39	4
40-44	33
45-49	43
50-54	78
55-59	78
60-64	81
65-69	69
70-74	70
75-79	43
80-84	43
85-99	43

Vaccination scenarios

We conducted analyses to evaluate the impact of routine (i.e., fixed facility delivery) two-dose HPV vaccination of 9-year-old girls at 40 and 80% coverage levels. We examined both 80 and 100% protection against HPV-16 and -18 infections over the lifetime of vaccinees for a two-dose vaccination schedule. In a scenario analysis, we also considered that this protection would drop off completely (i.e., 0% protection) after a 20-year duration. Cases and costs averted were calculated in comparison with a strategy of no HPV vaccination (i.e., Ethiopia's status quo and not the planned single-age cohort campaign).

Cervical cancer costs

Cervical cancer treatment costs included direct medical costs for cancer staging, treatment, palliative care, and follow-up associated with stage-specific International Federation of Gynecology and Obstetrics (FIGO) treatment protocols, assuming that cancer treatment costs were not dependent upon vaccination coverage level [10,35]. We assumed 20% of detected cancers to be local (i.e., Stage I) and 80% to be late stage (i.e., Stages II-IV). We assumed that all cancer staging, treatment, palliative care, and follow-up took place at a tertiary facility. As described in Paper 1, to estimate the unit cost of each procedure, we identified available data from the published literature [26,36-41] and unpublished data [42]. All costs were converted to 2015 US dollars using local consumer price index (CPI) deflators and exchange rates [43]. To extrapolate published estimates for cervical cancer treatment costs from their original settings, accounting for variation in income level, we adjusted unit costs using an index of tertiary inpatient visit costs from WHO-CHOICE [43,44], resulting in about $700 provider cost for the cervical cancer treatment cost (per person) in Ethiopia in 2015 US dollars.

Vaccination costs

We assumed a vaccine cost of $4.50 per dose for HPV vaccine [45], which corresponds to the subsidized cost of HPV vaccine procured by Gavi, the Vaccine Alliance, for low-income countries such as Ethiopia. We also included costs for vaccine wastage at a rate of 5% for a single dose vial, liquid formulation [46]. Lastly, we assumed a one-time introduction cost of $2.00 per girl in the first year of the vaccination program, followed by a recurrent delivery cost of $1.70 per girl, including costs for personnel, training, social mobilization, disease surveillance, program management, and other recurrent costs [47,48].

Financial risk protection

Household medical expenditures related to the treatment of cervical cancer cases can be averted with rollout of HPV vaccination that reduces incidence of cervical cancer cases. Such household OOP direct medical costs averted would then depend on the number of cervical cancer cases, probability of seeking care, and cost of health care. Thirty-four percent of health expenditures are financed by OOP payments in Ethiopia [2]. Therefore, we assumed that an individual's OOP burden for treating cervical cancer would be about 34% of the total treatment cost for cervical cancer, and the government would cover the remaining 66% of the costs, in the base case. The base case OOP payments for cervical cancer treatment in Ethiopia would be $241 (i.e., 34% of $700).

By avoiding OOP expenditures related to the treatment of cervical cancer cases, rollout of HPV vaccination also provides FRP benefits to the population. There are two metrics of (lack of) FRP commonly used in the literature and also by the World Bank and the World Health Organization in tracking progress toward universal health coverage (UHC) [49]: on the one hand, catastrophic health expenditures (CHE), which count the number of individuals for whom OOP direct medical expenditures surpass a certain threshold of total consumption expenditures; on the other hand, impoverishing health expenditures (IHE), which count the number of individuals for whom OOP direct medical expenditures push individuals below a defined poverty line (e.g., international poverty line of $1.90 per day, Purchasing Power Parity) [50-52].

Here, we quantify the FRP benefits of HPV vaccination by estimating the number of cases of CHE that would be averted, counting the number of occurrences when OOP payments tied to direct

medical costs of cervical cancer treatment would no longer surpass a certain threshold of total household consumption expenditures [50,51]. In this analysis, we assumed a 40% threshold for CHE in the base case, as it is the most commonly used in the literature [51]. Under this definition of CHE at a 40% threshold, cervical cancer treatment would be considered catastrophic for the poorest, poorer, and middle quintiles. In order to estimate the number of cases of CHE averted, we compared the household expenditures for cervical cancer treatment costs to household consumption expenditure quintiles for Ethiopia [39]. We first stratified the cervical cancer cases into quintiles in using the distribution of sexually transmitted disease (STD) prevalence from the Ethiopia Demographic and Health Survey (DHS) as a proxy for cervical cancer prevalence, given that HPV is a sexually transmitted infection and the main cause of cervical cancer [26,53]. We also used the average access proportion for radiotherapy, a key component of cancer management, across low-income countries (8.5%) [54] as a proxy for cervical cancer care-seeking, which accounts for both barriers to access as well as other barriers to seeking care [55]. We stratified this proportion into the associated consumption expenditure quintiles using the relative care-seeking percentages for STDs in the Ethiopia DHS [26]. Table 3.2 presents the CHE input assumptions by quintile.

Table 3.2. Financial risk protection assumptions by household consumption quintile in Ethiopia.

Quintile	Household consumption expenditure	Sexually transmitted disease prevalence	Cervical cancer care-seeking
Poorest	$218	26%	6%
Poorer	$367	6%	7%
Middle	$501	7%	5%
Richer	$682	8%	9%
Richest	$1,418	36%	12%

Source: Ethiopia Household Consumption Expenditure Survey 2015/16 [39]; Ethiopia Demographic and Health Survey (DHS) 2016 [26]. Note: DHS inputs in wealth quintiles were mapped into inputs for consumption quintiles.

Analysis outcomes

The primary outcomes of the analysis included household OOP expenditures and cases of CHE averted related to the prevention of cervical cancer cases by quintile. Health outcomes included the number of cervical cancer cases and associated deaths. We discounted future costs at a discount rate of 3% annually. Model outcomes were aggregated over multiple birth cohorts to capture the lifetime costs and benefits of women aged 9 to 100 years in the year 2019, as well as the lifetime costs and benefits of girls born between 2020 and 2118 (i.e., 99 additional incoming cohorts).

Scenario analysis

We analyzed five extensions to the base-case scenario: (1) changes in the vaccine price; (2) changes to the level of care-seeking; (3) changes to the level of OOP payments by quintile; (4) changes to the distribution of cervical cancer incidence by quintile; and (5) changes to the CHE threshold.

In the first scenario analysis, we used a vaccine price of $0.20 per dose, as this is the co-financing level offered by Gavi, the Vaccine Alliance, to introduce new vaccines in low-income countries such as Ethiopia [56]. In the second scenario analysis, we assumed that 50% of cervical cancer cases would seek care, compared to 8.5% in the base case. In the third scenario analysis, we distributed OOP payments by wealth quintile following a lognormal distribution given a shape parameter of the Gini coefficient for Ethiopia (0.39 in 2015 [1]) to account for variations in ability to pay across socioeconomic groups: $93 for poorest; $161 for poorer; $198 for middle; $242 for richer; and $365 for richest. For this scenario analysis, cervical cancer treatment is considered catastrophic for the poorest and poorer quintiles at a 40% threshold. In the fourth scenario analysis, we assumed a linear gradient in CC incidence by quintile: 33% of CC incidence experienced by

the poorest; 27% poorer; 20% middle; 13% richer; and 7% richest. In the fifth scenario analysis, we examined 10% and 25% CHE thresholds (instead of 40%).

Results

Health benefits of HPV vaccine

Routine HPV vaccination assuming lifelong duration of protection against HPV-16/18 infections could avert 733,000 cases of cervical cancer over 2019-2118 in the most likely scenario (i.e., 40% coverage and 100% efficacy), compared to a strategy of no HPV vaccination (Figure 3.2). This translates to approximately 586,000 lives saved. When 80% vaccination coverage was assumed instead of 40%, routine HPV vaccination could avert 1,390,000 cases of cervical cancer, or 1,110,000 lives saved. Approximately 30% of these health benefits would accrue to the poorest quintile compared with 40% to the richest quintile (Figure 3.3a-b).

Figure 3.2. Annual number of cervical cancer cases over 2019-2118 in Ethiopia assuming lifelong duration of protection against HPV-16/18 infections.

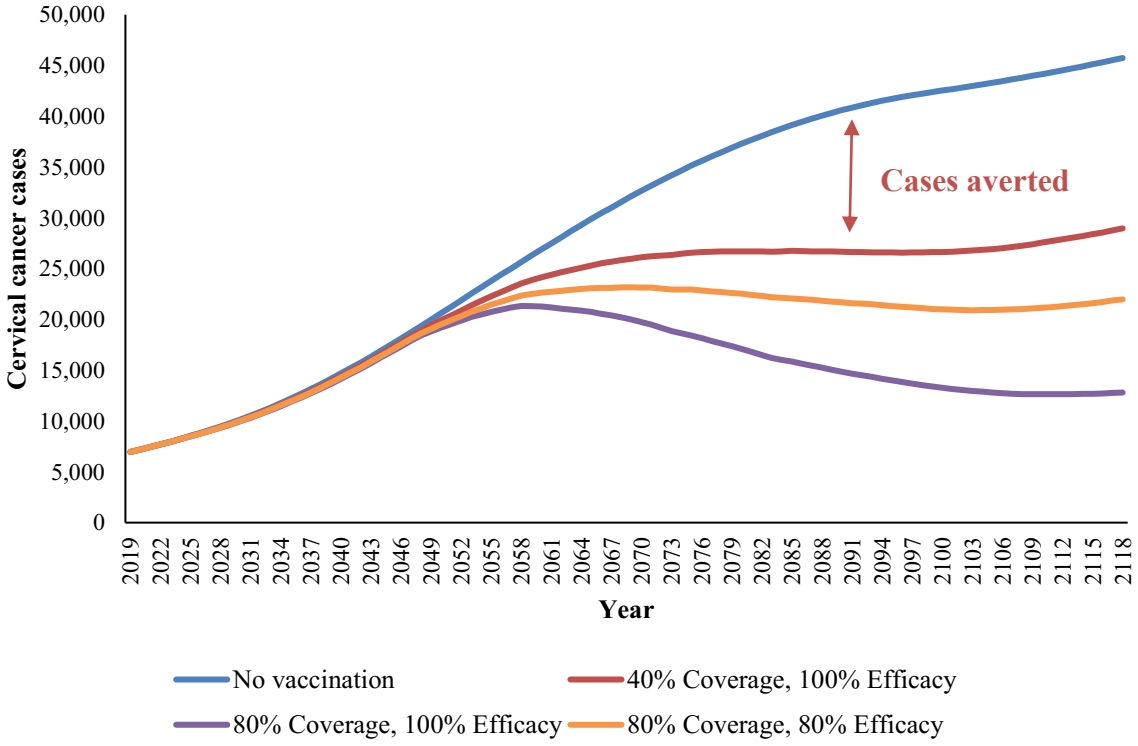
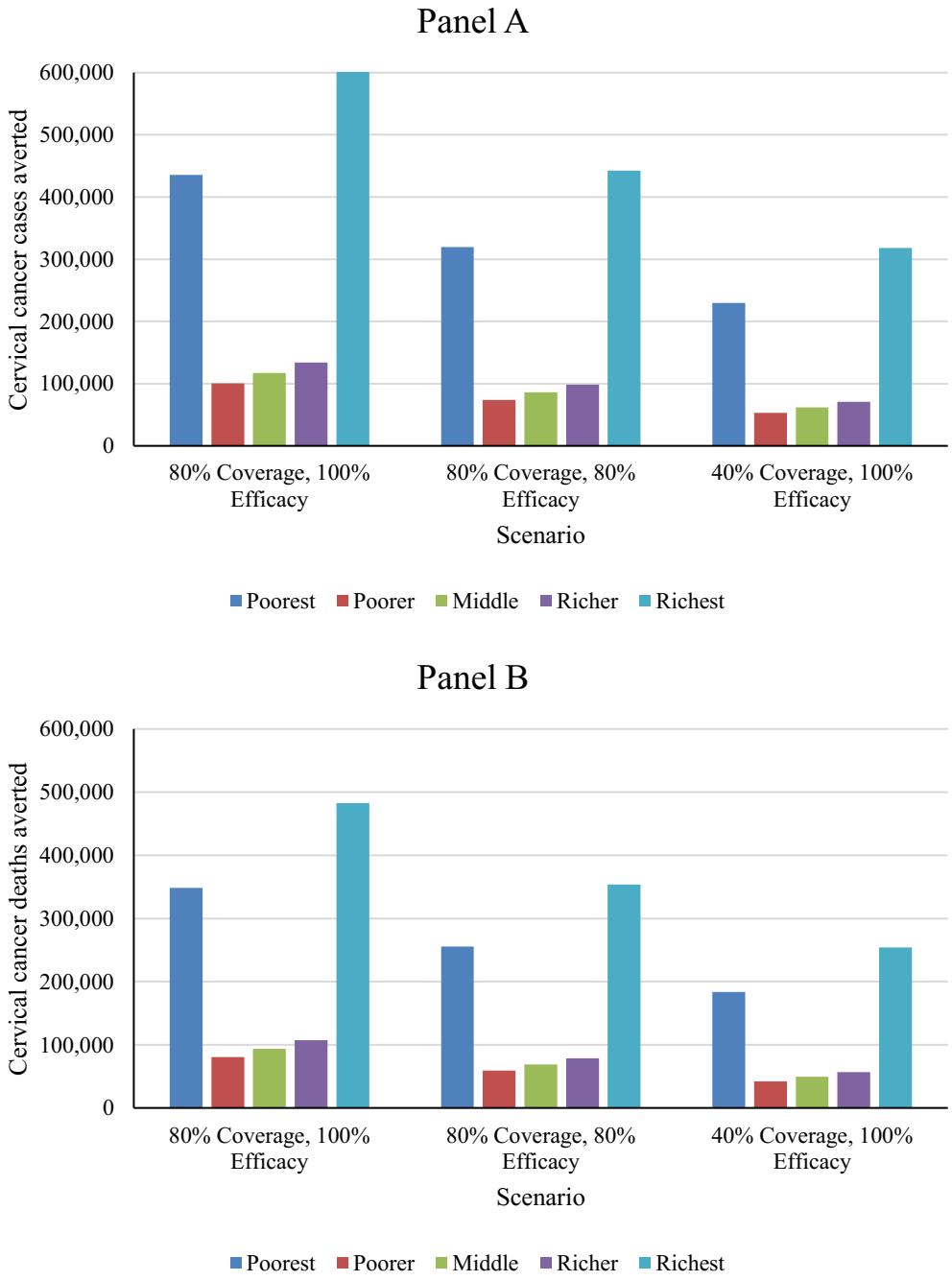


Figure 3.3. Cervical cancer cases (Panel A) and deaths (Panel B) averted by vaccination scenario and consumption quintile assuming lifelong duration of protection against HPV-16/18 infections.

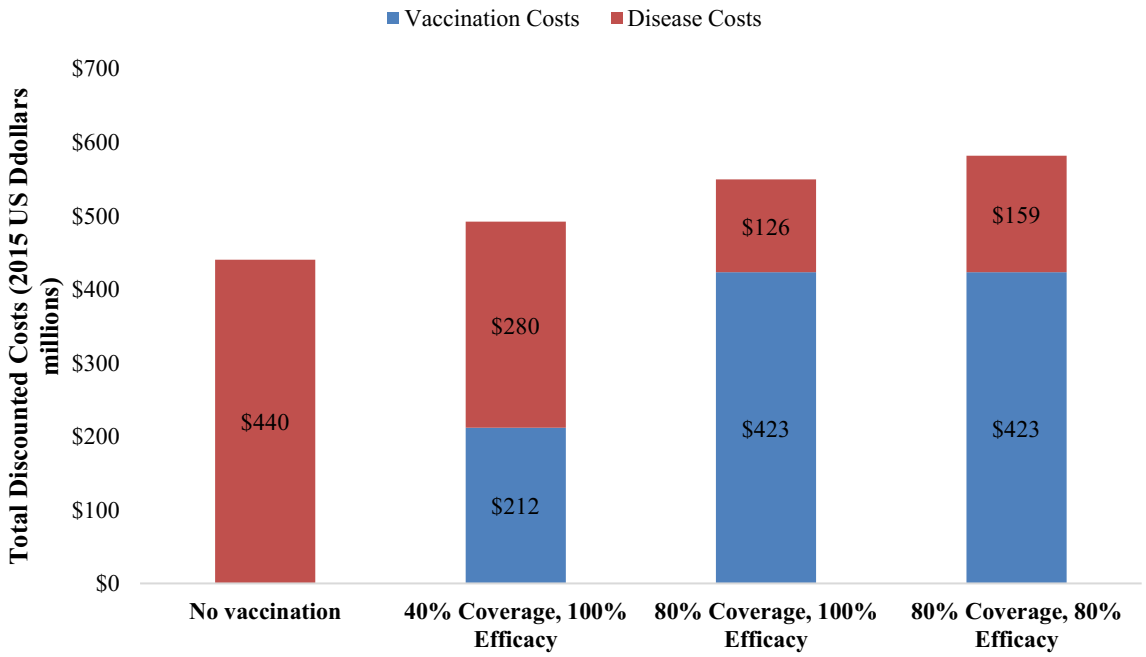


When 20-year duration of protection was assumed instead of lifelong duration of protection, routine HPV vaccination could avert 138,000 cases of cervical cancer at 40% coverage, or 290,000 at 80% coverage.

Financial outcomes of HPV vaccine

The total vaccine-related costs associated with the scenario of 40% coverage, 100% efficacy, and lifelong duration of protection exceeded $212 million (discounted net present value) between 2019 and 2118, but resulted in long-term cost offsets from future averted cervical cancer cases of $160 million, or 36% of cervical cancer treatment costs with no vaccination (Figure 3). With increased coverage of 80%, the vaccination program would cost $423 million over the same time period, but would avert $314 million associated with cervical cancer treatment costs (i.e., 71%).

Figure 3.4. Total discounted costs in 2015 US dollars (millions) associated with HPV-16/18 vaccination strategies.

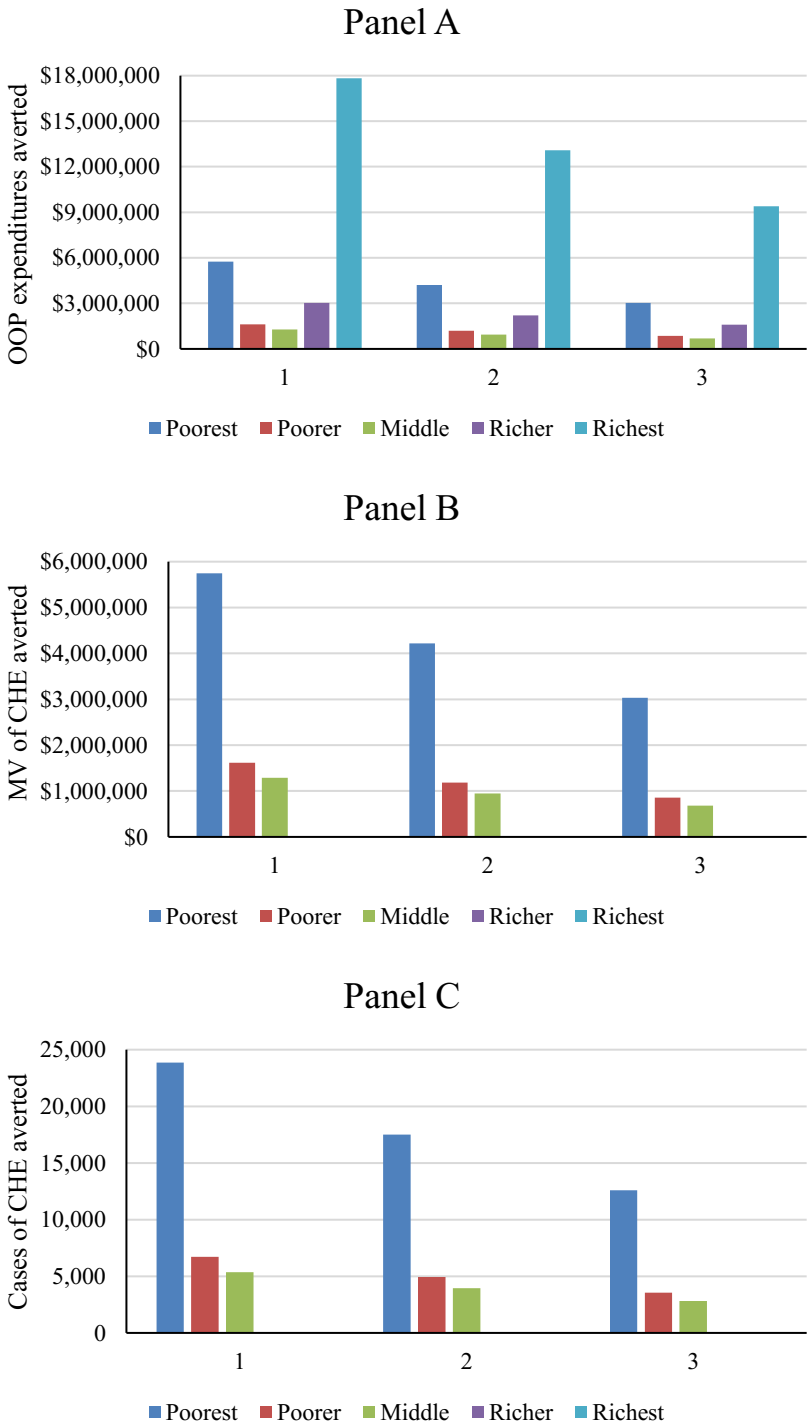


Note: Vaccination program costs (blue bars) reflect 100 cohorts of 9-year-old girls from years 2019-2118. Cervical cancer costs (red bars) reflect disease offsets over the lifetimes of women alive in year 2019 as well as girls born between 2020 and 2118 (i.e., 99 additional incoming cohorts). HPV = human papillomavirus.

Financial risk protection benefits of HPV vaccine

Assuming 100% efficacy against HPV-16/18 infections and lifelong duration of protection, our analysis shows that routine two-dose HPV vaccination could avert $15,600,000 (40% coverage) to $29,500,000 (80% coverage) in total OOP expenditures over 2019-2118, with the bottom two quintiles accounting for 25% of all OOP expenditures averted (Figure 3.5a). This equates to $4,560,000 at 40% coverage and $8,650,000 at 80% coverage corresponding to the monetary value for the amount of CHE averted for the poorest, poorer, and middle quintiles at a 40% CHE threshold (Figure 3.5b). In terms of individual cases of CHE averted between 2019 and 2118, routine two-dose HPV vaccination could avert 18,900 cases of CHE at 40% coverage and 35,900 cases of CHE at 80% coverage (Figure 3.5c). When examining the FRP benefits by wealth quintile, approximately 66% of these FRP benefits would be experienced by the poorest quintile (Table 3.3). Per dollar spent by the Ethiopian government, routine two-dose HPV vaccination at 40% coverage could avert 148 cervical cancer deaths and 46 cases of associated CHE per $100,000 spent.

Figure 3.5. Out-of-pocket (OOP) expenditures, monetary value (MV) of catastrophic health expenditures (CHE), and cases of CHE averted by vaccination scenario and consumption quintile.



Note: The findings assume a $241 OOP payment for cervical cancer treatment, which is considered a case of catastrophic health expenditure (CHE) for the poorest, poorer, and middle consumption quintiles at a 40% threshold. Scenario 1 = 80% coverage, 100% efficacy, lifelong protection; Scenario 2 = 80% coverage, 80% efficacy, lifelong protection; Scenario 3 = 40% coverage, 100% efficacy, lifelong protection.

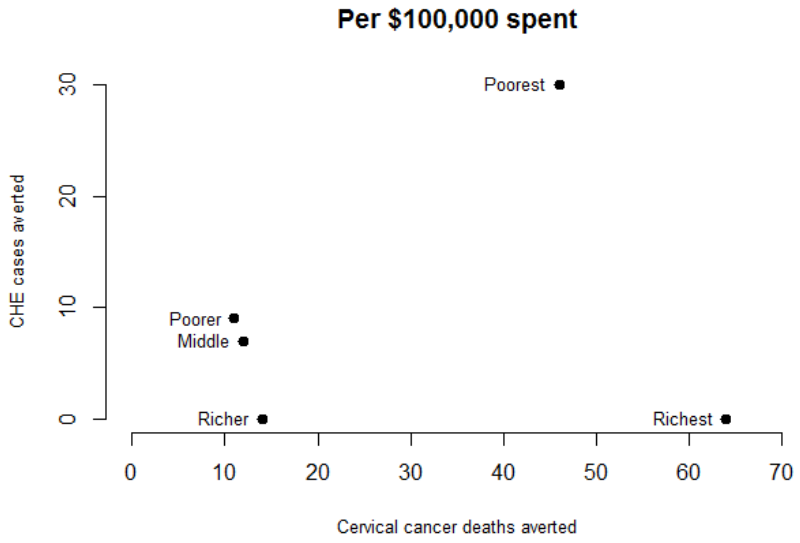
Table 3.3. Cases of catastrophic health expenditure (CHE) averted by routine two-dose human papillomavirus (HPV) vaccination scenario in Ethiopia, assuming lifelong duration of protection against HPV-16/18 infections.

Scenario	Poorest	Poorer	Middle	Richer	Richest	Total
80% Coverage, 100% Efficacy	23,900	6,720	5,360	0	0	35,900
80% Coverage, 80% Efficacy	17,500	4,930	3,930	0	0	26,400
40% Coverage, 100% Efficacy	12,600	3,542	2,830	0	0	18,900

Note: The findings assume a $241 out-of-pocket payment for cervical cancer treatment, which is considered a case of catastrophic health expenditure for the poorest, poorer, and middle wealth quintiles at a 40% threshold.

The number of cervical cancer deaths and CHE cases averted for the most likely scenario, achieving 40% coverage with a vaccine that is 100% efficacious against HPV-16/18 infections, is shown in Figure 3.6. While the combination of disease incidence and care-seeking by quintile yields the greatest number of deaths averted for the richest quintile, the poorest quintile would experience the greater FRP benefits at 30 cases of CHE averted per $100,000 spent.

Figure 3.6. Cervical cancer deaths and cases of catastrophic health expenditures (CHE) averted by routine two-dose human papillomavirus (HPV) vaccination in Ethiopia, per government budget expenditure



Note: The scenario assumes 40% vaccination coverage, 100% vaccine efficacy, and lifelong duration of protection (i.e., no waning) against HPV-16/18.

Scenario analysis

In the first scenario analysis, if Ethiopia were to introduce the HPV vaccine with Gavi support and face a vaccine price of $0.20 per dose (rather than $4.50 per dose as in the base case), the $212 million in vaccination program costs at 40% coverage and $423 million at 80% coverage would substantially be reduced to $32 million and $64 million (discounted at 3%), respectively (Appendix Figure 3.1). In the second scenario analysis, if our assumed proxy for care-seeking percentage is increased from 8.5% in the base case to 50%, the number of CHE cases averted would greatly increase, as expected, with routine two-dose HPV vaccination averting 20,900 cases of CHE in the most pessimistic scenario and up to 211,000 cases of CHE in the most optimistic scenario (Appendix Table 3.1). In the third scenario analysis, assuming a distribution of OOP payments by quintile, CHE averted would decrease as the poorest and poorer quintile would face lower OOP payments relative to the base case (Appendix Table 3.2). Cases of CHE averted would also decrease as the middle wealth quintile would no longer experience CHE. In the fourth scenario analysis, when cervical cancer incidence is evenly distributed on a linear gradient with the poorest quintile experiencing the greatest disease burden down to the richest quintile experiencing the least disease burden, the total number of cases of CHE averted would increase by 30 to 130% (Appendix Table 3.3). In the fifth scenario analysis, a CHE threshold of 25% would add the richer quintile to the group of quintiles experiencing CHE, increasing the number of cases of CHE averted by 35%. A CHE threshold of 10% would further add the richest quintile to the group of quintiles experiencing CHE, increasing cases of CHE averted by 240% (Table 3.4).

Table 3.4. Cases of catastrophic health expenditure (CHE) averted by routine two-dose human papillomavirus (HPV) vaccination scenario in Ethiopia: varying the CHE threshold (40, 25, and 10% of consumption expenditures).

Scenario	Wealth Quintile					Total by CHE Threshold		
	Poorest	Poorer	Middle	Richer	Richest	40%	25%	10%
80% Coverage, 100% Efficacy	23,900	6,720	5,360	12,500	74,100	35,900	48,500	123,000
80% Coverage, 80% Efficacy	17,500	4,930	3,930	9,210	54,300	26,400	35,600	89,900
40% Coverage, 100% Efficacy	12,600	3,542	2,830	6,610	39,000	18,900	25,600	64,600

Note: The findings assume a $241 out-of-pocket payment for cervical cancer treatment and lifelong duration of protection against HPV-16/18 infections. At a 40% threshold, the poorest, poorer, and middle wealth quintiles would experience a case of CHE. At a 25% threshold, the poorest, poorer, middle, and richer wealth quintiles would experience a case of CHE. At a 10% threshold, all wealth quintiles would experience a case CHE.

Discussion

Using a model-based approach that incorporates HPV transmission dynamics, cervical cancer disease natural history, population demographics, financial risk protection and distributional analysis, we projected that routine two-dose HPV-16/18 vaccination could avert 586,000 cervical cancer deaths and 18,900 cases of CHE over 2019-2118 in the most likely scenario (40% coverage and 100% efficacy against HPV-16/18 infections). This percentage is highly sensitive to the rate of care-seeking for cervical cancer that we assumed in this population (8.5%). Approximately 30% of the health benefits from HPV vaccination would accrue to the poorest quintile, whereas approximately 66% of the FRP benefits would accrue to the poorest quintile. While the combination of disease incidence and care-seeking by quintile would yield the greatest health benefits for the richest quintile, the magnitude of the FRP benefits experienced by the poorest quintile indicates that routine two-dose HPV vaccination could be equity-improving overall. These results underscore the importance of considering perspectives of both total health gains and equity when evaluating public health interventions.

Given the focus of the SDGs on poverty reduction and FRP [12,13], and the 24% of the population living under the national poverty line in Ethiopia [1], the incorporation of equity dimensions in this analysis brings valuable contextual elements for policymaking in Ethiopia. In the particular case of HPV vaccination in Ethiopia, our analysis points to the potentially strong pro-poor dimension of HPV prevention and control in the country when viewed from an FRP perspective. However, it is important to note that our base case analysis assumed a cost of $10.70 per girl for routine HPV vaccination (in the years following introduction), which amounts to approximately 0.4% of the current annual health expenditure of Ethiopia at 80% vaccination coverage [1]. Therefore, the price of the vaccine is an important consideration for the budgetary impact for the Ethiopian government. In our scenario analysis examining a reduced vaccine price of $0.20 per dose, the cost of HPV vaccination would change to $2.10 per girl or approximately 0.1% of the current annual health expenditure at 80% coverage, which still may be a significant percentage given the many competing uses for limited budget dollars.

There are several limitations to this analysis. First, we were restricted in our modeling assumptions due to limited data. As age-specific HPV prevalence by genotype was not available in Ethiopia, we were unable to fully calibrate the agent-based and microsimulation models in this setting. However, while age-standardized incidence and mortality rates were higher in Uganda compared to Ethiopia, we used HPV and cervical cancer incidence reductions (i.e., percentages) from these models and projected these reductions onto the age-specific cancer incidence and HPV type distribution for Ethiopia, which also has a larger at-risk population compared to Uganda. We also assumed that the Ethiopian population was fully naïve to HPV vaccination in the rollout of a routine HPV vaccination program, while there is a currently planned and ongoing nationwide

single cohort catch-up program for 14-year-old girls due to the current global HPV vaccine shortage [6]. However, this strategy is unlikely to interrupt transmission beyond the single vaccinated cohort, given the high prevalence of HPV (i.e., a large core population is affected) [57].

Second, in order to stratify cervical cancer cases by quintile, we assumed that cervical cancer incidence and deaths within each wealth quintile would mimic the distribution of STD prevalence across wealth quintiles in Ethiopia [26]. As a result, the STD prevalence rankings by quintile – Richest > Poorest > Richer > Middle > Poorer – largely drove the distribution in health benefits and their rankings across quintiles. Stratifying by STD prevalence is only one possible stratification approach. We might also expect that the level of household consumption expenditure would be correlated with health outcomes, such that richer households can afford greater expenditures on health care. According to the Global Burden of Disease study, we might also expect to see the highest HPV disease burden in the poorest quintile [58], which would then lead to an increase in the impact of HPV vaccination among the poorest individuals. Therefore, we included a scenario analysis applying a linear gradient to CC incidence by quintile in order to demonstrate what this impact might look like.

Third, we have only estimated FRP benefits from HPV vaccine using CHE as a commonly used metric to assess (lack of) FRP [50]. Other FRP measures include estimating the incidence of impoverishing health expenditures, i.e., the number of households for whom OOP health-related expenditures would push them below a defined poverty line (e.g., international poverty line of $1.90 per day, Purchasing Power Parity), or the estimation of a money-metric value of insurance [8,50,52]. Importantly, due to lack of empirical data on OOP costs related to cervical cancer

treatment, this analysis assumed OOP levels at 34% of the total treatment cost based on Ethiopia's national health accounts [1]. In addition, our estimation of FRP gains did not include direct non-medical costs such as transportation, which may differ by wealth quintile and geography (79% of individuals live in rural areas in Ethiopia [1]), nor indirect costs (e.g., wages lost and time losses), which may significantly augment the potential FRP benefits of HPV vaccination.

Fourth, this analysis captured the costs of the vaccination program over 100 years including the disease costs and health benefits over the lifetimes of women alive up to age 100 years in 2019; and we assumed that cervical cancer incidence rates would be stable over this time period. Decreasing the duration of protection to 20 years rather than lifelong led to increasing cervical cancer incidence over time due to decreased natural immunity in the vaccinated population, which may not reflect the true impact of vaccination. Vaccine efficacy against high-risk HPV types other than HPV-16/18 (i.e., cross-protection) was also not included; and we did not examine cervical cancer screening programs in this analysis and assumed that any ongoing screening programs did not change as HPV vaccination introduction and delivery changed. Finally, given limited data on the burden of other HPV-related diseases in low- and middle-income countries, we did not evaluate the impact HPV vaccination may have on non-cervical cancers in women and men, which likely would increase the value of all HPV vaccination strategies.

The results of our work regarding the potential equity-improving impact of vaccination are consistent with previous work on the equity impact of vaccines [59-61]. The potential for HPV vaccination to provide financial risk protection to the poorest households is also consistent with a previous ECEA of routine HPV vaccination in China [11]. This further underscores the need for

additional metrics beyond traditional CEA [15] in order to account for the broader value of vaccination [16,17]. Complementary analyses such as ECEA that address the potentially large equity and distributional aspects of policies can support decision-makers evaluating public health interventions.

Our approach incorporates financial risk protection and equity dimensions into the economic evaluation of routine HPV vaccination in Ethiopia, a resource-constrained setting with low cervical cancer screening coverage. This analysis can help policymakers in making decisions regarding routine HPV vaccination and emphasize the continued priority of routine HPV vaccination once the global vaccine shortage is overcome. The results of this analysis can inform priority setting and health outcomes in Ethiopia, and may also be used to inform decisions in countries with similar demographic and economic characteristics.

Acknowledgements

This study was funded by awards received from the Harvard T.H. Chan School of Public Health, including the 2018 Uwe Brinkmann Memorial Travel Fellowship, 2019 Michael von Clemm Traveling Fellowship, and 2019 Clarence James and Sarah Bradley Gamble Scholarship. Earlier versions of this paper were presented at the 2019 International Health Economics Association World Congress, and seminars at the University of Washington and Harvard University, where we received valuable comments from seminar participants. We also received valuable comments from Jesse Bump, Margaret Kruk, Margaret McConnell, and Nicolas Menzies.

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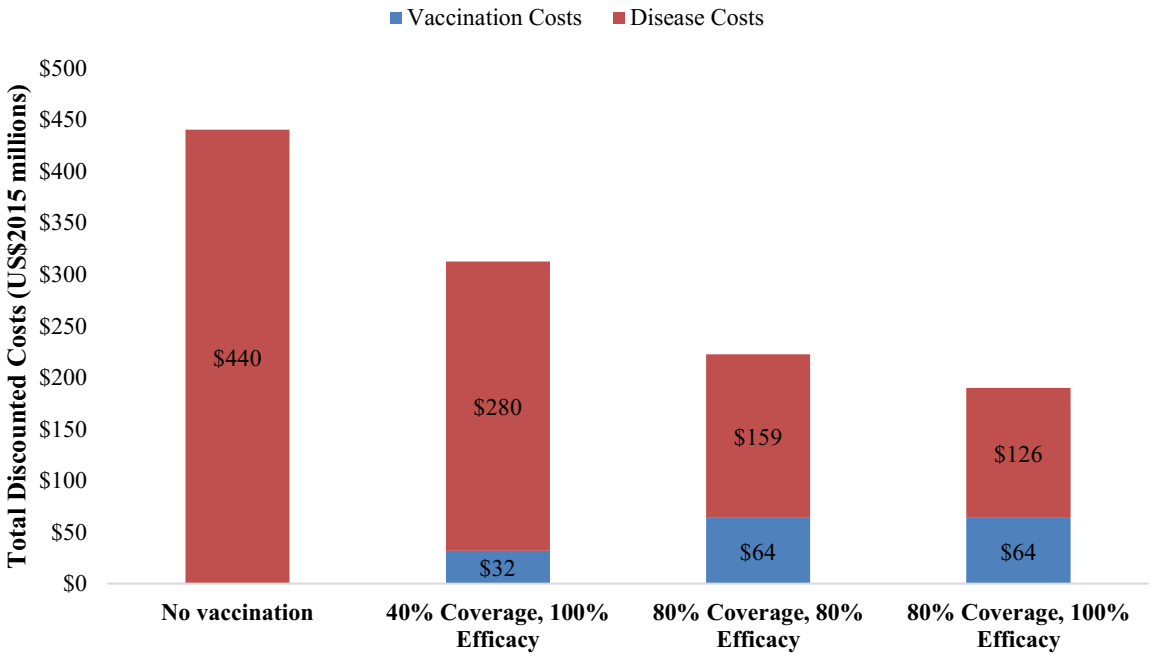
Appendix

Appendix Figure 3.1. Total discounted costs in 2015 US dollars associated with HPV-16/18 vaccination strategies: assuming lifelong duration of protection and $0.20 vaccine price for the Ethiopian government



Note: Vaccination program costs (blue bars) reflect 100 cohorts of 9-year-old girls from years 2019-2118. Cervical cancer costs (red bars) reflect disease offsets over the lifetimes of women alive in year 2019. HPV = human papillomavirus.

Appendix Table 3.1. Cases of catastrophic health expenditure (CHE) averted by routine two-dose human papillomavirus (HPV) vaccination scenario in Ethiopia: assuming 50% care-seeking in population

Scenario	Poorest	Poorer	Middle	Richer	Richest	Total
80% Coverage, 100% Efficacy	140,000	39,500	31,500	0	0	211,000
80% Coverage, 80% Efficacy	103,000	29,000	23,100	0	0	155,000
40% Coverage, 100% Efficacy	74,000	20,800	16,600	0	0	111,000

Note: The findings assume a $241 out-of-pocket payment for cervical cancer treatment and lifelong duration of protection against HPV-16/18 infections. At a 40% threshold, the OOP payment for cervical cancer treatment is considered a case of catastrophic health expenditure for the poorest, poorer, and middle wealth quintiles.

Appendix Table 3.2. Monetary value of catastrophic health expenditures (CHE) averted by routine two-dose human papillomavirus (HPV) vaccination scenario in Ethiopia: assuming a distribution of out-of-pocket payments by wealth quintile

Scenario	Poorest	Poorer	Middle	Richer	Richest	Decrease from base case
80% Coverage, 100% Efficacy	$2,220,000	$1,080,000	$0	$0	$0	$5,350,000
80% Coverage, 80% Efficacy	$1,630,000	$794,000	$0	$0	$0	$3,930,000
40% Coverage, 100% Efficacy	$1,170,000	$570,000	$0	$0	$0	$2,820,000

Note: The findings assume lifelong protection against HPV-16/18 infections and a distribution of OOP payments for cervical cancer treatment: $93 for poorest; $161 for poorer; $198 for middle; $242 for richer; and $365 for richest. The base case assumed a flat OOP payment of $241. The OOP payments are considered a case of catastrophic health expenditure for the poorest and poorer wealth quintiles at a 40% threshold.

Appendix Table 3.3. Cases of catastrophic health expenditure (CHE) averted by routine two-dose human papillomavirus (HPV) vaccination scenario in Ethiopia: assuming a linear gradient of cervical cancer incidence

Scenario	Poorest	Poorer	Middle	Richer	Richest	Total
80% Coverage, 100% Efficacy, No Waning	25,400	24,800	12,700	0	0	62,900
80% Coverage, 80% Efficacy, No Waning	18,600	18,200	9,300	0	0	46,100
40% Coverage, 100% Efficacy, No Waning	13,400	13,070	6,700	0	0	33,200

Note: The findings assume a $241 out-of-pocket payment for cervical cancer treatment and lifelong duration of protection against HPV-16/18 infections. At a 40% threshold, the OOP payment for cervical cancer treatment is considered a case of catastrophic health expenditure for the poorest, poorer, and middle wealth quintiles.

Conclusion

In this thesis, I examined different human papillomavirus (HPV) vaccine delivery strategies and the costing of those strategies using modeling and economic analyses in order to contribute to the evidence base for HPV vaccination policy in low- and middle-income countries (LMICs).

In Paper 1, we produced standardized immunization delivery cost estimates for routine childhood and HPV vaccination using meta-regression analyses to support the evaluation of vaccination programs, to further monitor progress towards the Sustainable Development Goals (SDGs) [1], to plan for the financial sustainability of immunization programs, and to improve immunization programs coverage and equity. Immunization delivery costs are a necessary component of high-quality vaccine cost-effectiveness models [2], and our country-specific costs modeled within a Bayesian meta-regression framework can help refine economic evaluation of vaccination programs and improve budgeting and planning in situations where empirical cost data are unavailable. We found that predicted economic costs per dose for HPV vaccine delivery were overall greater than for childhood vaccine delivery, which might be expected when new platforms are likely required in order to target an adolescent population not always reached by fixed health care facilities and established routine immunization programs in the Expanded Programme on Immunization (EPI). The uncertainty around what might be required for new HPV vaccine programs, potentially including new delivery platforms such as school-based delivery, further underscores how predicted delivery costs can provide a more informed estimate for budgeting vaccine introduction. My research highlights the need for additional facility-based costing studies, particularly in LMICs and particularly with regard to HPV vaccination. While some studies have developed and reported their results using systematic costing guidance [3], future studies would

benefit from standardized reporting in order to get the most out of data collection. Future research might also examine different assumptions for quantitative synthesis of the available data, which will be further informed as new data become available.

In Paper 2, we projected that HPV vaccination delivered via immunization campaigns could provide substantial population health benefits compared with routine vaccination. We determined that reaching adolescent populations with a campaign delivery strategy may be an efficient use of resources. In settings where routine health systems infrastructure may be limited, countries may be able to leverage existing school infrastructure to establish school-based immunization campaigns. This intersectoral approach can not only contribute to the World Health Organization's global call to action for the elimination of cervical cancer [4], but also to the SDGs concerning both health and education [1,5]. While drawing from the prior experience of campaign delivery for childhood vaccination and the demonstration projects for HPV vaccine can provide a broad overview of HPV delivery costs, the costs of reaching an adolescent population with a likely new delivery platform remain uncertain. One reason that campaign delivery was robustly preferred to routine delivery is the wide targeted age range, but the cost, feasibility, and efficacy of reaching older women are likewise uncertain. We included a threshold analysis of vaccine efficacy at older ages, but this is only a broad example of how changes to this assumption might impact the effectiveness of a vaccination program before additional trial data of vaccine efficacy at older ages are published. When considering the full benefits of a campaign vaccination program, policymakers might also need to consider the cross-protective effects, as well as the impact on HPV-induced cancers beyond cervical cancer. Additionally, it would be important to consider the

costs and implications of a routine and campaign delivery strategy integrated within the same health system.

In Paper 3, we described the potentially large equity and redistributive aspects of routine HPV vaccination in Ethiopia. We found that, in addition to 30% of the health gains (e.g., cervical cancer deaths averted), approximately two-thirds of the financial risk protection benefits from routine HPV vaccination in Ethiopia would accrue to the poorest quintile, underscoring the equity-improving impact of vaccination and the need for complementary analyses beyond traditional cost-effectiveness analysis (CEA) in order to account for the broader value of vaccination. While our analysis found HPV vaccination to be a modestly pro-poor policy in terms of health gains, an examination of the broader value of HPV vaccination including financial risk protection (FRP) benefits elucidated its pro-poor impact. Complementary analyses such as extended cost-effectiveness analysis (ECEA) that address metrics beyond direct medical costs and aggregated health gains such as disability-adjusted life years (DALYs) averted can support decision-makers evaluating public health interventions, which may improve priority setting and health outcomes and equity in Ethiopia and other LMICs. Our results were highly sensitive to the care-seeking assumption (8.5% for cervical cancer in low-income settings [6]) as well as the stratification of cervical cancer cases by quintile [7]. While we incorporated scenario analyses to examine changes to these assumptions, this research could be supported by better empirical evidence and modeled approaches on the distribution of disease burden [8]. Furthermore, it would also be refined by additional data collection on both out-of-pocket (OOP) payments for cervical cancer treatment (vs. other disease treatments) and catastrophic health expenditure (CHE) levels by socioeconomic status [9-11].

Overall, in the case of HPV vaccine delivery, many LMICs have limited experience reaching adolescents with routine health services [12]. Therefore, a better understanding of program and vaccine delivery costs across settings will be essential for policy and planning, underscoring the need for additional empirical costing studies. Given the need to deliver HPV vaccine outside the traditional EPI, countries may be able to leverage school health programs, i.e., health services and health education that promote student health, already in place [13]. Future policy for delivering HPV vaccine can benefit from lessons learned from existing programs leveraging school-based delivery, e.g., deworming [14,15]; feeding and nutrition [16,17]; malaria prevention [18]; and immunizations [19,20]. HPV vaccination campaigns might provide a new opportunity for a combination of adolescent health programs, such as HIV prevention [21], or might be combined with existing programs [22]. Additional consideration should be given to not only leverage the existing infrastructure in place to reach adolescents using school-based delivery [23], but also to consider the context of the target population. Campaign or school-based delivery may be equally likely to reach individuals not currently reached by routine health services in Ethiopia and Uganda, as both countries have a similar percentage of the population living in urban compared to rural areas. However, Ethiopia as a much larger country with less health expenditures per capita might require campaigns at more frequent intervals to reach the same coverage levels. Decision-makers may also vary the policy recommendations for HPV vaccine introduction and scale up depending on the cultural context. While Uganda's vaccine policy is likely to include the 9- to 14-year-olds recommended for the HPV vaccine by WHO, the context in Ethiopia might restrict vaccination to older adolescents (i.e., 14 and above). Equity analyses like Paper 3 further enable the targeting of important populations defined by socioeconomic status or geographic location, which is useful in large, federal countries like Ethiopia with regional autonomy. Future research should explore the

design, budget, and implementation of potential campaign or school-based HPV vaccine delivery. The policy surrounding the introduction and scale up of HPV vaccination will also need to consider and adapt to increasing coverage of cervical cancer screening programs in LMICs.

There is great potential for delivery strategies of HPV vaccination to not only be cost-effective, but also be equity-improving in LMIC settings like Uganda and Ethiopia. These analyses can help to inform the selection of delivery strategies for HPV vaccine introduction in LMICs, as well as to elucidate the potential impact of those strategies in terms of health gains, economic costs and benefits, and equity and redistributive aspects [24]. The ECEA methodology can also enable better description of the "real-world" impact of different delivery platforms in reducing health inequalities and improving equity at the global and local levels, and can further highlight the important role that vaccination can play for children from poorer households. This understanding can inform the efficient allocation of resources and support policymakers in decisions regarding HPV vaccination and cervical cancer control. However, decision-makers will also need to weigh this important information against health systems strengthening considerations when considering how to address disease prevention and control.

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