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# The projected cost-effectiveness and budget impact of HPV vaccine introduction in Ghana

Elisabeth Vodicka [a,*,1], Justice Nonvignon [b,1], Kwadwo Odei Antwi-Agyei [c], John Bawa [c], Andrew Clark [d], Clint Pecenka [a], D. Scott LaMontagne [a]

[a] PATH, 2201 Westlake Avenue, Suite 200, Seattle, WA 98109, USA
[b] University of Ghana, Department of Health Policy, Planning and Management, P.O Box LG 78, Legon, Accra, Ghana
[c] PATH-Ghana, 14a Ameda Street, Roman Ridge, Accra, Ghana
[d] London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

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ABSTRACT

*Background:* Cervical cancer is responsible for around one-quarter of all cancer deaths among Ghanaian women. Between 2013 and 2015, Ghana conducted a pilot of HPV vaccination among 10–14-year-old girls in four regions; however, the country has yet to introduce the vaccine nationally. This study projected the cost-effectiveness and budget impact of adding HPV vaccination into Ghana's national immunization program.

*Methods:* We used a proportional outcomes model (UNIVAC, version 1.4) to evaluate the cost-effectiveness of introduction with bivalent (Cervarix™) and quadrivalent (Gardasil®) vaccines from government and societal perspectives. Vaccine introduction was modeled to start in 2022 and continue over ten birth cohorts using a combined delivery strategy of school (80%) and community outreach (20%). We modeled vaccination in a single age cohort of 9-year-old girls vs. a multi-age cohort of 9-year-old girls (routine) and 10–14-year-old girls (one-time campaign) compared to no vaccination. Health outcomes included cervical cancer cases, hospitalizations, deaths, and disability-adjusted life years (DALYs). We applied a discount rate of 3% to costs and outcomes. All monetary units are reported in USD 2018.

*Results:* National HPV vaccination in Ghana was projected to be cost-effective compared to no vaccination in all scenarios evaluated. The most cost-effective and dominant strategy was vaccination among 9-year-old girls, plus a one-time campaign among 10–14-year-old with the bivalent vaccine ($158/DALY averted from the government perspective; 95% credible range: $19–$280/DALY averted). Projected average annual costs of the vaccine program ranged from $11.2 to $15.4 M, depending on strategy. This represents 11–15% of the estimated total immunization costs for 2022 ($100,857,875 based on Ghana's comprehensive Multi-Year Plan for Immunization, 2020–2024).

*Discussion:* Our model suggests that introducing HPV vaccination would be cost-effective in Ghana under any strategy when willingness-to-pay is at least 40% GDP per capita ($881). Inclusion of a one-time catch-up campaign is shown to create greater value for money than routine immunization alone but would incur greater program costs.



## 1. Background

In sub-Saharan Africa (SSA), cervical cancer is the leading cause of death due to cancer in women [1]. Despite the preventable, detectable, and treatable nature of cervical cancer – and global progress toward reducing disease burden in high-income countries – trend data from cervical cancer registries in SSA suggest that overall incidence in the region has been increasing over time [2]. In 2018, the highest age-standardized incidence of cervical cancer globally was recorded in 15 countries[2] in SSA where national vaccination, screening, and treatment programs are limited and high HIV prevalence contributes to accelerated risk for cervical cancer [1–3]. In Ghana, the age-standardized incidence rate of cervical cancer is 32.9 per 100,000 women and age-standardized mortality rate is 23.0 per 100,000

* Corresponding author.
*E-mail address:* evodicka@path.org (E. Vodicka).
[1] Authors contributed equally.

[2] eSwatini, Malawi, Zambia, Zimbabwe, Tanzania, Burundi, Uganda, Lesotho, Madagascar, Comoros, Guinea, Burkina Faso, Mali, South Africa, and Mozambique.

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women versus global rates of 13.1 and 6.9 per 100,000 women, respectively [1]. Cervical cancer is responsible for approximately one-quarter of all cancer deaths among Ghanaian women [1].

Given the promising available strategies to prevent, detect, and treat cervical cancer, the World Health Organization (WHO) has called for the elimination of cervical cancer as a public health priority [4]. Disease prevention through vaccination against human papillomavirus (HPV) is a core pillar of the WHO strategy for elimination [4]. As of 2020, three vaccine products have received WHO prequalification for administration: the Cervarix™ bivalent, Gardasil® quadrivalent, and Gardasil-9® nonavalent HPV vaccines.[3] These vaccines have been demonstrated to be safe and efficacious with no evidence of waning immunity [5–8]. All prevent nearly 100% of infections due to HPV types 16 and 18 that cause most cervical cancers, as well as cervical intraepithelial neoplasia (CIN), vulvar and vaginal intraepithelial neoplasia due to HPV types in the vaccines [9]. The Cervarix bivalent vaccine cross-protects against a significant portion of CIN due to non-vaccine HPV types 31, 33, and 45, while the Gardasil quadrivalent and nonavalent vaccines protect against infections due to HPV types 6 and 11 responsible for genital warts [9,10]. The nonavalent provides further direct protection against HPV types 31, 33, 45, 52, and 58 [9].

The WHO currently recommends HPV vaccination for girls 9–14 years old in all countries [11]. As of June 2020, 107 WHO member states and 21 non-member independent territories—primarily high- or upper-middle-income—have incorporated HPV vaccination into their national immunization programs [12]. In low- and middle-income countries (LMICs), incorporation into national immunization programs has been slower and often initiated as pilot introductions or vaccine demonstration projects with variable coverage [13,14]. In Ghana, HPV vaccination was piloted through a demonstration program in four districts from 2013 to 2015 among in-school and out-of-school girls aged 10–14 years via a three-dose schedule with the quadrivalent vaccine [15]. Subsidized vaccine support is available from Gavi, the Vaccine Alliance for HPV vaccine introduction in eligible LMICs, including Ghana; however, the country's national immunization technical advisory group (NITAG) has yet to recommend introduction in the national immunization schedule.

Potential value for money and financial sustainability, in addition to health impact, are critical components for decision-makers considering new vaccine introduction, product selection, and delivery strategies [16]. Several studies have evaluated the cost-effectiveness of HPV vaccination of girls globally and suggest that it is likely to be a cost-effective public health investment [17–19]. However, there is limited data available on the local costs and cost-effectiveness of national HPV vaccination in Ghana [15]. This study evaluated the projected cost-effectiveness and budget impact of adding HPV vaccine into Ghana's national immunization program through a combined delivery strategy of school-based vaccinations and community outreach to inform the country's vaccine introduction decision.

## 2. Materials and methods

### 2.1. Analytic framework and model

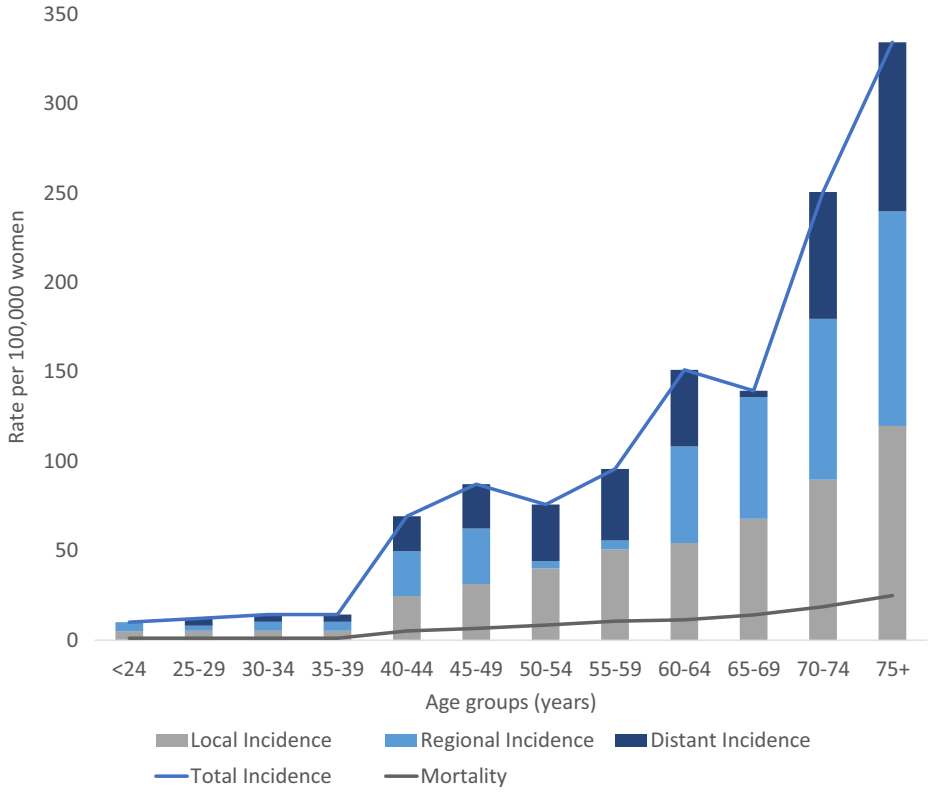
We used the UNIVAC tool (version 1.4) to assess the financial, economic and health impacts of various national HPV vaccination scenarios, each compared to no vaccination in Ghana and among the competing vaccination strategies. UNIVAC is a transparent proportional outcomes model that evaluates vaccine impact and cost-effectiveness of several childhood vaccines, including HPV, with flexibility to examine the impact of different vaccine products and programmatic choices on costs and health outcomes [20]. The model simulates the target population over the individual's lifetime horizon, applies age-specific cervical cancer rates to estimate the expected disease burden with and without vaccination, and assigns outcomes to each cohort of girls. This simple approach does not involve recalculating health states at regular time steps and is static rather than dynamic, i.e., it does not account for potential feedback/interactions between health states over time. Health outcomes include cervical cancer cases stratified by stage, hospitalizations, deaths, and disability-adjusted life years (DALYs). Costs include vaccine price, vaccine introduction and delivery costs, and costs of cervical cancer treatment by stage. Incremental costs and health outcomes are then combined into an average or incremental cost-effectiveness ratio (cost per DALY averted).

Plausible HPV vaccine introduction strategies of interest in Ghana were developed with input from key stakeholders, including the Ghana Ministry of Health Expanded Program on Immunization (EPI). Vaccine introduction was modeled to start in 2022 and continue over ten consecutive birth cohorts using a combined delivery strategy of school-based vaccinations (80%) and community outreach (20%). We modeled national HPV immunization with either the Cervarix bivalent or Gardasil quadrivalent vaccine compared to no vaccination in two potential target populations: 1) a single age cohort of 9-year-old girls (routine only), and 2) a multi-age cohort (MAC) of 9-year-old girls (routine) and 10–14-year-old girls (one-time campaign). Under all scenarios, we assumed that the second dose would be administered six months after initial vaccination, accounting for minimal coverage decreases between dose one and two. The base case analysis was modeled as introduction among 9-year-old girls (routine only) using the quadrivalent vaccine.

Costs and health outcomes for each cohort were then simulated over the lifetime horizon based on population size and life expectancy by age from the United Nations Population Division 2017 Revision [21], age-specific disease incidence and mortality (Fig. 1), vaccine coverage, and vaccine efficacy. We used a pooled odds ratio from the FUTURE and PATRICIA trials as our base case estimate for vaccine efficacy [10]. We also considered the underlying cross-protection provided by each vaccine against non-vaccine types in our sensitivity analyses by incorporating estimates of underlying HPV genotype prevalence in Ghana and cross-protection against each genotype with each vaccine [10,22–24]. A weighted vaccine efficacy was calculated to account for efficacy against specific types.

Expected costs of vaccine program introduction and vaccine delivery were derived from a 2014 cost analysis conducted using the WHO C4P costing tool alongside Ghana's HPV vaccination demonstration project (data not published). This report estimated delivery costs of $9.65 per dose across multiple cohorts. Delivery cost offsets via Gavi subsidies were also included. Recent (2020) guidance from Gavi indicates that operations (Ops) grants for HPV delivery are provided to support campaign operational costs, and amounts are based on the country's Gavi phase. Initial self-financing countries receive $0.65 per targeted person, preparatory transition phase countries receive $0.55 per targeted person, and accelerated transition countries receive $0.45 per targeted person [25]. Gavi vaccine introduction grants (VIGs) subsidize the costs of routine HPV delivery through either a lump sum of $100,000 or $2.40 per targeted girl, whichever is higher [25]. For this analysis, subsidies to the government and vaccine price for each year were determined based on the country's expected co-financing sta-

[3] Cervarix™ (bivalent product by GlaxoSmithKline Biologicals), Gardasil® (quadrivalent product by Merck/MSD), and Garadisil-9® (nonavalent product by Merck/MSD) were the only three WHO prequalified HPV vaccines on the market at the time this analysis was conducted. WHO prequalification is expected in 2021 for the bivalent product Cecolin® by Xiamen Innovax Biotech Co. Limited. Cecolin has demonstrated high safety and efficacy against HPV-16/18-associated cervical intraepithelial neoplasia in clinical trials [42].




*†Estimates were based on data from Globocan 2018* [42]. *Simplified definitions were used for invasive cancer categories based on FIGO staging* [43]. *Local Invasive cancer was defined as FIGO Stage 1a1, 1a2, 1b1, 1b2, 2a1, 2a2. Regional invasive cancer was defined as FIGO Stages 2b1, 2b2, 3a1, 3a2, 3b1, 3b2. Distant invasive cancer was defined as FIGO Stage 4a-4b.*

**Fig. 1.** Age-specific disease burden by stage in Ghana (2018).

tus of accelerated transition phase in the modeled introduction year (2022) and associated co-share amount per dose, with Gavi supplementing any remaining amount of the vaccine tender [25,26]. Therefore, introduction and operational cost subsidies from Gavi assumed a VIG of $2.40 per girl for routine immunization in the first year and an Ops grant of $0.45 per girl for those in the MAC [25].

Local administrative and clinical experts at five health facilities (which together manage most of cervical cancer cases in Ghana) were consulted to ascertain direct medical costs of cervical cancer treatment and typical treatment for cervical cancer by stage. Facilities included three public tertiary hospitals (Korle Bu Teaching Hospital in Accra, Komfo Anokye Teaching Hospital in Kumasi, Tamale Teaching Hospital in Tamale), one public secondary hospital (Greater Accra Regional Hospital, Accra), and one mission hospital (Battor Catholic Hospital, Battor). Information from experts was supplemented by typical treatment strategies outlined by the Federation of International Gynecology and Obstetrics and existing literature on cervical cancer by stage and access to care in Ghana [27–29]. Typical care components captured as part of treatment costs were consult and diagnosis, staging, and treatment strategies for invasive cancer, including radical and simple hysterectomy, chemotherapy, radiotherapy, concomitant delivery of chemo-radiation, and palliation. All women receiving treatment were assumed to have one follow-up visit, including consult, histopathology, and lab testing (full blood count and sickling test). Treatment strategies and their unit costs were allocated to local, regional and distant cancer proportionally, based on staging incidence and probability of treatment.

Societal-level treatment costs included direct medical costs, plus opportunity costs of women's time for procedures (including convalescence if they had hospital stays or recovery time), time waiting for test results (if provided on the same day as procedures), and time costs associated with travel to/from facility visits. The amount of time women spent traveling to/from facilities for cervical cancer treatment was estimated based on a 2013 study presenting average travel times to/from facilities in Ghana for maternity care [30]. For opportunity costs of women's time, we applied the Ghana 2018 minimum wage, reported as 10.65 Ghanaian cedis per day (USD 2018 $2.32) [31]. We valued the time of women at minimum wage regardless of working status. Due to data limitations, we did not include costs for meals purchased, accommodations, fuel or transport fares, or caregiver costs.

We applied a discount rate of 3% to costs and health outcomes. All monetary units are reported in USD 2018. We estimated costs and cost-effectiveness ratios from government and societal perspectives. We compare cost-effectiveness ratios to GDP per capita as a proxy as Ghana does not have an established cost-effectiveness threshold. Key input parameters are described in Table 1.

### 2.2. Uncertainty analyses

We conducted one-way sensitivity analyses for each scenario to assess the impact of individual parameter uncertainty on model results, presented as tornado diagrams. We ran probabilistic sensitivity analyses to assess the impact of combined parameter uncertainty on the cost-effectiveness ratios by varying all parameter

**Table 1**
Key model inputs.

| Parameter | Base Case Estimate | Range | Source |
|---|---|---|---|
| Number of 9-year-old girls in year of modeled vaccine introduction (2022)[a] | 404,578 | N/A | [21] |
| Vaccine coverage | Dose 1: 93%<br>Dose 2: 92% | Dose 1: 73–100%<br>Dose 2: 59–100% | Base case: Coverage estimate from 2014 Ghana HPV demonstration project costing. Assume 1% drop in coverage based on demonstration attrition between doses. Ranges: First/final dose coverage estimates for LMICs [44] |
| Two-dose vaccine efficacy against HPV 16 and 18[b] | 94% | 92–97% | Pooled odds ratio from FUTURE and PATRICIA trials [10] |
| Two-dose cross-protection by HPV type, quadrivalent | Type 31: 70% | 32.1–88.2% | [10] |
| Two-dose cross-protection by HPV type, bivalent | Type 31: 89.4%<br>Type 33: 82.3%<br>Type 45: 100% | 66.5–97.9%<br>53.4–94.7%<br>41.7–100% | [10] |
| Vaccine, price per dose[c] | Bivalent: $4.60<br>Quadrivalent: $4.50 | Bivalent: $3.24–$5.40<br>Quadrivalent: $3.31–$5.52 | Base case: Gavi price per dose [45];<br>Range: ±50% of base case |
| Ghana co-financing share (range for period of analysis) | 32–100%, varied annually | N/A | Annual co-financing share per dose was estimated based on Ghana's 2019 starting fraction of 32%. |
| Vaccine supplies, price per dose | $0.08 | $0.07–$0.09 | 2014 Ghana HPV demonstration costing |
| Wastage | 5% | 4–6% | 2014 Ghana HPV demonstration costing |
| Average health system cost per dose[d] | $9.65 | Varies annually, range from $4.67-$16.58 | Calculation; Low range = 50% of base case. High range = 120% of base case. |
| Average cervical cancer treatment cost per case (government perspective)[e] | Local: $1038<br>Regional: $1906<br>Distant: $1844 | $519–$3113<br>$953–$5717<br>$922–$5531 | Calculation; Low range = 50% of base case. High range = 200% of base case. |
| Average cervical cancer treatment cost per case (societal perspective)[f] | Local: $1090<br>Regional: $1969<br>Distant: $1905 | $545–$3269<br>$985–$5908<br>$953–$5715 | Calculation; low range = 50% of base case; high range = 200% of base case. |
| Disability weights for cervical cancer by stage | Local: 0.288<br>Regional: 0.451<br>Distant: 0.540 | 0.193–0.399<br>0.307–0.600<br>0.377–0.687 | [46] Diagnosis and primary therapy phase of cervical cancer<br>[46] Metastatic phase of cervical cancer<br>[46] Terminal phase of cervical cancer |
| Average duration of illness[g] | Local: 15 years<br>Regional: 7.5 years<br>Distant: 2.5 years | Local: 4.25–18 years<br>Regional: 3.25–9 years<br>Distant: 2–3 years | Calculated based on local and international data |

[a] Year-over-year changes in cohort size and average life-expectancy were obtained from annual UNPop 2017 projections. Average life-expectancy for the 2022 birth cohort was 64.3 years [21].

[b] For those who receive only a single dose, we assume half of the two dose efficacy.

[c] Year-over-year co-financing projections were estimated based on Ghana's 2019 starting fraction (32.1%) and expected annual transition phase (Year 2 of Preparatory Transition Phase in 2019). Ghana is anticipated to become fully self-financing by 2026 at which point the MOH would be responsible for 100% of the Gavi vaccine price.

[d] Health systems cost was derived from 2014 C4P costing data collected during the Ghana HPV demonstration project and based on 3-dose schedule. Analysis was adapted for a 2-dose delivery schedule. Year 1 estimates assume a Gavi vaccine introduction grant (VIG) subsidy of $2.40 per person for single-aged cohort and operations grant (Ops) subsidy of $0.45 per person for the multi-aged cohort doses provided. Assumes 80% of girls are reached through school-based delivery and 20% are reached through community outreach. On average, school-based delivery was estimated at $9.05 and community outreach at $10.44 per dose. Community outreach costs were higher primarily due to additional transportation costs. Ranges were calculated for each annual delivery cost as +/- 20% of base case annual estimate.

[e] Estimated based on typical patient flow by cervical cancer stage and expected proportion of women in each stage [28,29]. Costs were based fee schedule information for typical treatment services from five facilities and supplemented with literature and expert opinion. Assumed one course of treatment per cervical cancer case. Data on loss to follow-up after treatment referral was sparse. As such, we address potential differences in average treatment costs per case due to loss to follow-up through inclusion of wide sensitivity ranges.

[f] Productivity losses and opportunity costs of missed wages were estimated based on the 2018 daily minimum wage in Ghana (10.65 cedis daily wage in 2018) [31].

[g] Base case average duration of illness was estimated based on SurvCan data from India [47] using the Declining Exponential Approximation of Life Expectancy method to convert five-year survival rates into average duration of life expressed in years [48]. Low range was estimated based on limited 5-year survival data from Ghana [29] using DEALE methodology and life expectancy. High range was estimated as +20% of base case estimate due to limited upper bound data.

estimates simultaneously with random draws from their plausible ranges over 10,000 Monte Carlo simulations. Ninety-five percent uncertainty intervals represent the 2.5th and 97.5th percentiles of probabilistic simulations; for each probabilistic simulation, parameters were drawn from a distribution with a mean equal to the point estimate and range equal to the low and high values of the uncertainty range. In the absence of information about the shape of each distribution, a simple PERT-Beta distribution was assumed for all parameters [32].

## 3. Results

National HPV vaccination in Ghana was projected to be cost-effective compared to no vaccination in all scenarios evaluated.

**Table 2**
Population health impact of HPV vaccination compared to no vaccination by delivery scenario and vaccine selection over 10 birth cohorts.

| Health outcome | Without vaccination | With vaccination | Averted by vaccination |
|---|---|---|---|
| *Bivalent vaccine, routine immunization of 9-year-old girls* | | | |
| Cervical cancer cases | 176,054 | 56,710 | 119,344 |
| *Local invasive* | *88,107* | *28,381* | *59,726* |
| *Regional invasive* | *69,639* | *22,432* | *47,208* |
| *Distant invasive* | *18,307* | *5,897* | *12,410* |
| Deaths | 105,933 | 34,123 | 71,811 |
| DALYs | 345,103 | 111,163 | 233,940 |
| *Bivalent vaccine, routine immunization of 9-year-old girls, plus one-time campaign among 10–14-year-old girls* | | | |
| Cervical cancer cases | 243,375 | 78,395 | 164,980 |
| *Local invasive* | *121,798* | *39,233* | *82,565* |
| *Regional invasive* | *96,269* | *31,010* | *65,259* |
| *Distant invasive* | *25,308* | *8152* | *17,156* |
| Deaths | 147,109 | 47,386 | 99,723 |
| DALYs | 500,118 | 161,096 | 339,023 |
| *Quadrivalent vaccine, routine immunization of 9-year-old girls* | | | |
| Cervical cancer cases | 176,054 | 98,628 | 77,426 |
| *Local invasive* | *88,107* | *49,359* | *38,748* |
| *Regional invasive* | *69,639* | *39,013* | *30,626* |
| *Distant invasive* | *18,307* | *10,256* | *8,051* |
| Deaths | 105,933 | 59,345 | 46,588 |
| DALYs | 345,103 | 193,332 | 151,772 |
| *Quadrivalent vaccine, routine immunization of 9-year-old girls, plus one-time campaign among 10–14-year-old girls* | | | |
| Cervical cancer cases | 243,375 | 136,342 | 107,033 |
| *Local invasive* | *121,798* | *68,233* | *53,565* |
| *Regional invasive* | *96,269* | *53,931* | *42,338* |
| *Distant invasive* | *25,308* | *14,178* | *11,130* |
| Deaths | 147,109 | 82,412 | 64,696 |
| DALYs | 500,118 | 280,173 | 219,945 |

**Table 3**
Discounted costs of HPV vaccination compared to no vaccination by delivery scenario and vaccine selection over 10 birth cohorts from government and societal perspectives.

| Health outcome | Without vaccination | With vaccination | Difference |
|---|---|---|---|
| *Bivalent vaccine, routine immunization of 9-year-old girls* | | | |
| Vaccine program costs | $0 | $97,947,001 | $97,947,001 |
| Health care costs (government perspective) | $50,573,450 | $16,290,474 | -$34,282,975 |
| Health care costs (societal perspective) | $52,564,378 | $16,931,783 | -$35,632,595 |
| *Bivalent vaccine, routine immunization of 9-year-old girls, plus one-time campaign among 10–14-year-old girls* | | | |
| Vaccine program costs | $0 | $103,471,099 | $103,471,099 |
| Health care costs (government perspective) | $73,488,769 | $23,671,845 | -$49,816,924 |
| Health care costs (societal perspective) | $76,381,806 | $24,603,736 | -$51,778,070 |
| *Quadrivalent vaccine, routine immunization of 9-year-old girls* | | | |
| Vaccine program costs | $0 | $97,228,640 | $97,228,640 |
| Health care costs (government perspective) | $50,573,450 | $28,331,946 | -$22,241,503 |
| Health care costs (societal perspective) | $52,564,378 | $29,447,292 | -$23,117,086 |
| *Quadrivalent vaccine, routine immunization of 9-year-old girls, plus one-time campaign among 10–14-year-old girls* | | | |
| Vaccine program costs | $0 | $103,059,374 | $103,059,374 |
| Health care costs (government perspective) | $73,488,769 | $41,169,425 | -$32,319,344 |
| Health care costs (societal perspective) | $76,381,806 | $42,790,145 | -$33,591,661 |

Further, bivalent vaccination with a one-time campaign was the least costly and most impactful scenario and thus dominated all other options. For the base case scenario modeling introduction among 9-year-old girls with the quadrivalent vaccine, vaccination was projected to avert 77,426 total cervical cancer cases, 46,588 cervical cancer deaths, and 151,772 DALYs compared to no vaccination over 10 birth cohorts. Vaccination under this scenario was expected to incur $74,987,137 more in discounted costs from the government perspective and $74,111,553 more from the societal perspective compared to no vaccination. The higher costs with vaccination were primarily associated with new program costs incurred for vaccine introduction and delivery (net $97,228,640 incurred) and offset by downstream costs of cervical cancer treatment averted due to primary prevention of disease through vaccination (net $22,241,503 and $23,117,086 averted from the heath system and societal perspectives, respectively). The cost per DALY averted was estimated to be $494 from the government perspective and $488 per DALY averted from the societal perspective for this scenario.

The most cost-effective strategy modeled was vaccination among 9-year-old girls, plus a one-time campaign among 10–14-year-olds with the bivalent vaccination ($158/DALY averted from the government perspective and $152/DALY averted from the societal perspective). This strategy was dominant because it had the lowest cost and larger effects compared all other strategies. Results for all scenarios evaluated relative to no vaccination are presented in Table 2 (health outcomes) and Table 3 (costs). Incremental costs, DALYs averted and cost per DALY averted compared to the dominant strategy are presented in Appendix Table 1.

One-way sensitivity analyses show that the model outcomes were most influenced by variation in cervical cancer treatment costs and disease event rates, followed by vaccine efficacy, incremental health system costs per dose, vaccine price per dose, and coverage rates (Fig. 2). Across scenarios and perspectives, when varying individual parameters for uncertainty impacts, the cost per DALY averted for vaccination among girls ranged from cost-saving to $862. This represents up to 39% of Ghana's gross domestic product (GDP) per capita of $2202 (USD$ 2018). Results from the probabilistic sensitivity analyses determined 95% credible ranges (CR) around the ratios for each scenario, providing a range of $19–$739 from the government perspective and $18–$733 from the societal perspective (Table 4). This represents 0.8–34% of GDP per capita. Ghana, like many countries, does not have established cost-effectiveness thresholds for health interventions, including vaccination. However, as shown in the cost-effectiveness acceptability curve in Fig. 3, results from the probabilistic sensitivity analysis found that HPV vaccination would be cost-effective compared to no vaccination in 100% of simulations at a willingness-to-pay threshold of $881 per DALY averted. A threshold of $881 per DALY averted corresponds to 40% of GDP per capita.

Projected average annual undiscounted financial costs of the vaccine program over ten birth cohorts range from $11.2-$15.4 M, depending on strategy (Appendix Table 2). This represents 11–15% of the projected total immunization costs for 2022 based on Ghana's comprehensive Multi-Year Plan (cMYP) for immunization (2020–2024). Projected first-year costs were higher for scenarios with a one-time MAC catch-up in addition to the routine immunization single-age cohort compared to scenarios with a single-age cohort only. In our scenario of vaccine introduction in 2022, costs for vaccination with a MAC plus routine immunization were $54,924,813 with the bivalent vaccine and $54,876,175 with the quadrivalent vaccine, representing approximately 54% of Ghana's cMYP projected annual costs for the total immunization program in 2022. In contrast, first-year costs for vaccination with single-


**Fig. 2.** One-way sensitivity analyses for vaccine selection and delivery strategy.

aged routine immunization were projected to be much lower at $12,217,202 with the bivalent vaccine and $12,168,564 with the quadrivalent vaccine. Subsequent year-over-year costs across scenarios ranged from $9,515,968 to $15,363,686. The high outlay that we see in the first year for scenarios with MAC catch-up campaigns is primarily due to the incremental health systems costs of providing two doses of vaccine to five additional cohorts.

## 4. Discussion

Our findings suggest that introducing HPV vaccination would be cost-effective compared to no vaccination in Ghana in all scenarios evaluated. Further, bivalent vaccination with a campaign had higher impact and lower cost and thus dominated the other scenarios. While Ghana does not currently have a prespecified threshold for determining whether an intervention represents good value and former WHO guidance suggesting thresholds of 1–3 times GDP per capita are no longer recommended [33], recent econometric modeling based on opportunity costs and income elasticity suggest potential cost-effectiveness thresholds for Ghana of 4–40% GDP per capita [34]. Our results suggest that national HPV vaccine introduction would be cost-effective under any scenario at willingness to pay thresholds of at least 40% of the 2018 GDP per capita. At willingness to pay thresholds lower than 40% of the 2018 GDP per cap-

**Table 4**
Cost per DALY averted for each scenario compared to no vaccination.

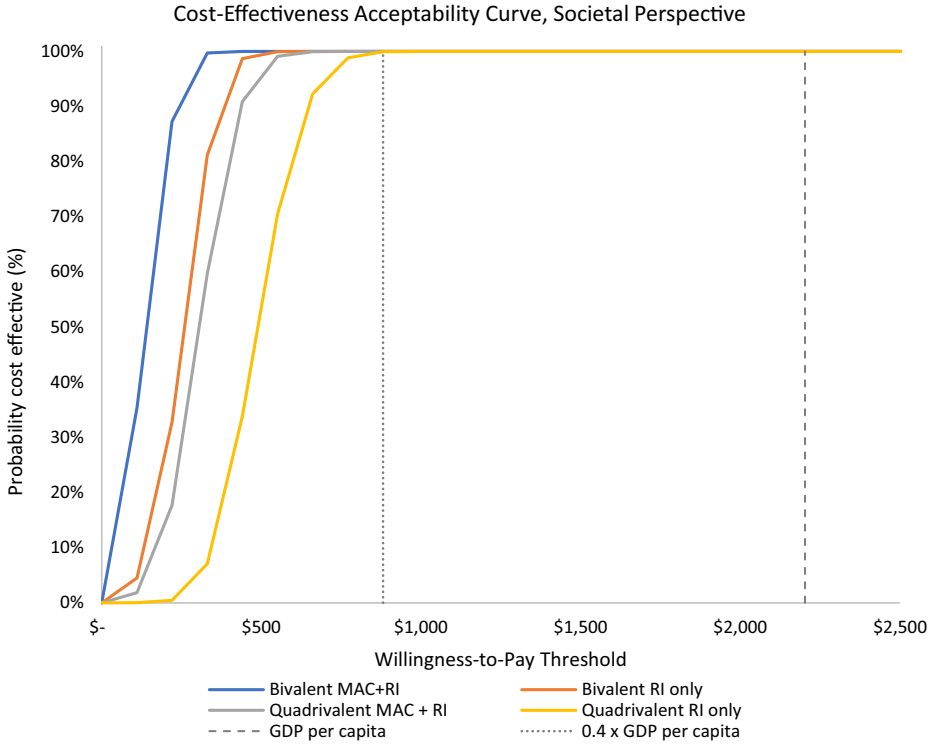
| Target population | Vaccine selection | Cost per DALY averted | |
|---|---|---|---|
| | | *Government perspective* | *Societal Perspective* |
| Routine vaccination among 9-year-olds without campaign | Quadrivalent | $494 (95% CR: $289–$739) | $488 (95% CR: $279–$733) |
| | Bivalent | $272 (95% CR: $101–$422) | $266 (95% CR: $90–$417) |
| Routine vaccination among 9-year-olds, plus campaign among 10–14-year-olds | Quadrivalent | $322 (95% CR: $135–$510) | $316 (95% CR: $123–$504) |
| | Bivalent* | $158 (95% CR: $19–$280) | $152 (95% CR: $18–$276) |

CR: Credible range; DALY: Disability-adjusted life year.
* This strategy dominates all others in an incremental cost-effectiveness analysis.

ita, the probability of cost-effectiveness is dependent on strategy with bivalent vaccination via a MAC campaign followed by routine immunization being the most favorable approach.

Inclusion of a one-time catch-up campaign is expected to create greater value for money than routine immunization alone, but also incur higher costs in the first year due to greater delivery costs. The bivalent vaccination may generate better value than quadrivalent due to relevant cross-protection against HPV types 31, 33 and 45, which have been shown to be prevalent among 5.1%, 0.7% and 21.9% of cervical cancer cases in Ghana, respectively [24]. Importantly, economic evidence needs to be considered alongside short-term budget impact and financial sustainability. We projected that introducing national HPV vaccine program would cost the MOH an average of $10.9-$15.4 M per year (undiscounted), depending on the strategy. First-year costs were estimated to be higher than subsequent years; this was particularly true for strategies incorporating a one-time campaign among a MAC due to the additional per-person delivery costs and health system costs associated with vaccination of multiple cohorts.

In Ghana, the first-year undiscounted financial costs for delivery to 9-year-old girls plus a one-time campaign among 10–14-year-old girls to total over $54 M with either the bivalent or quadrivalent vaccine. While inclusion of a MAC in the first year would be more cost-effective, the first-year financial costs represent approximately 54% of projected annual costs for the total immunization program based on cMYP estimates for 2022 which may limit the budget feasibility of a MAC. This illustrates the difficult tradeoffs and choices that governments in LMICs face between investing in higher-value public health strategies and real-world budget constraints, even with subsidies and introduction support from external partners like Gavi. As Ghana moves toward a transition out of Gavi eligibility to become fully self-financing in the coming decade, the country's co-financing share of Gavi vaccine price per dose will move from 32% to 100%. This may bring challenges of vaccine affordability, and budget prioritization across the EPI portfolio will be amplified. And the country is hardly alone. An analysis estimating the funding gap for immunization across 94 LMICs projected that the delivery of full vaccine programs would lead to a routine immunization funding gap of over $7 billion between 2016 and 2020 (USD 2010) [35]. New vaccines with similar efficacy as existing products coming to market at reportedly lower prices may support countries in reducing the budget impact of vaccine procurement for introduction. Future research on vaccine financing mechanisms and vaccine delivery may support more cost-efficient allocation of resources.




*MAC: Multi-age cohort; RI: routine immunization.*

**Fig. 3.** Cost-effectiveness acceptability curve from the societal perspective demonstrating likelihood of vaccine cost-effectiveness across varying willingness to pay thresholds.

Our estimates of the cost-effectiveness of HPV vaccination are similar to other estimates for Ghana presented as part of multi-regional analyses in the literature. A study by Goldie et al on the health and economic impact of vaccination against HPV 16 and 18 in 72 Gavi-eligible countries estimated a cost per DALY averted of $310–$810 in Ghana (USD 2005) [18]. A second study by Jit et al evaluating vaccine cost-effectiveness in 178 countries projected a cost per DALY averted with HPV vaccination of $436 for vaccinating 12 year old girls (USD 2011) [36]. These findings are in line with the cost-effectiveness ratios estimated in our study for each scenario: $158–$494 per DALY averted from the government perspective and $152–$488 per DALY averted from the societal perspective (95% credible ranges of $19–$739 and $18–$733 from government and societal perspectives, respectively).

This study has some limitations. First, proportionate outcomes models are relatively simple and do not account for more complicated health state transitions (i.e., progression and regression of disease). However, they have the advantage of being transparent and relatively easy to communicate. They have also been shown to generate cost-effectiveness results consistent with more complex models in low- and middle-income countries [36]. Second, the model does not incorporate costs or disease burden associated with prevention, detection, or treatment of pre-cancerous lesions, which contribute to the overall cervical cancer burden of disease. However, Ghana does not have a national cervical cancer screening program and current screening rates are low [37]. Therefore, while the model may underestimate the potential disease burden associated with pre-cancerous lesions, estimates of treatment costs likely reflect the current care practice in Ghana with few women receiving screening and referral to treatment for early detection of pre-cancerous lesions [37]. Additionally, the model does not consider potential herd effects associated with HPV vaccine, although some evidence of immunity in vaccinated groups may reduce the prevalence of vaccine-targeted HPV types among unvaccinated groups [38–41]. While this analysis incorporates data on cross-protection, recently published estimates find lower levels of cross-protection relative to inputs in this analysis. This implies that our impact estimates may be slight overestimates [42]. Finally, while the model incorporates locally specific data on vaccine delivery and cervical cancer treatment costs, data on household level costs to be included in the estimates were limited. Therefore, the societal perspective is conservative and likely underestimates the household level-costs associated cervical cancer care. Due to data limitations, the probabilistic simulations utilized a PERT-Beta distribution for cost data instead of a Gamma or log-normal distribution. Despite the limitations, our findings were in line with global projections of HPV vaccination cost-effectiveness and, to our knowledge, is the first economic evaluation specific to Ghana that incorporates non-vaccine type cross-protection and estimates the financial implications of vaccine delivery strategies.

Evidence suggests that without significant and urgent scaling up vaccination, screening and treatment, cervical cancer-related deaths in LMICs could rise by up to 50% by 2040 [43]. Our findings indicate that national introduction of HPV vaccination among girls in Ghana would be a cost-effective approach to significantly reduce the cervical-cancer related disease burden compared to no vaccination. Importantly, economic evidence needs to be considered alongside budget impact, affordability, feasibility, equity, and other local considerations.

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## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Justice Nonvignon received consulting fees from PATH for this work. There are no other interests to declare.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.07.027.

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