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Impact, cost-effectiveness, and budget implications of HPV vaccination in Kenya: A modelling study

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ABSTRACT

Background: Sub-Saharan Africa has the highest rate of cervical cancer cases and deaths worldwide. Kenya introduced a quadrivalent HPV vaccine (GARDASIL, hereafter referred to as GARDASIL-4) for ten-year-old girls in late 2019 with donor support from Gavi, the Vaccine Alliance. As Kenya may soon graduate from Gavi support, it is important to evaluate the potential cost-effectiveness and budget impact of the current HPV vaccine, and potential alternatives.

Methods: We used a proportionate outcomes static cohort model to evaluate the annual budget impact and lifetime cost-effectiveness of vaccinating ten-year-old girls over the period 2020–2029. We included a catch-up campaign for girls aged 11–14 years in 2020. We estimated cervical cancer cases, deaths, disability adjusted life years (DALYs), and healthcare costs (government and societal perspective) expected to occur with and without vaccination over the lifetimes of each cohort of vaccinated girls. For each of the four products available globally (CECOLIN©, CERVARIX©, GARDASIL-4©, and GARDASIL-9 ©), we estimated the cost (2021 US$) per DALY averted compared to no vaccine and to each other. Model inputs were obtained from published sources, as well as local stakeholders.

Results: We estimated 320,000 cases and 225,000 deaths attributed to cervical cancer over the lifetimes of the 14 evaluated birth cohorts. HPV vaccination could reduce this burden by 42–60 %. Without cross-protection, CECOLIN had the lowest net cost and most attractive cost-effectiveness. With cross-protection, CERVARIX was the most cost-effective. Under either scenario the most cost-effective vaccine had a 100 % probability of being cost-effective at a willingness-to-pay threshold of US$ 100 (5 % of Kenya's national gross domestic product per capita) compared to no vaccination. Should Kenya reach its target of 90 % coverage and graduate from Gavi support, the undiscounted annual vaccine program cost could exceed US$ 10 million per year. For all three vaccines currently supported by Gavi, a single-dose strategy would be cost-saving compared to no vaccination.

Conclusion: HPV vaccination for girls is highly cost-effective in Kenya. Compared to GARDASIL-4, alternative products could provide similar or greater health benefits at lower net costs. Substantial government funding will be required to reach and sustain coverage targets as Kenya graduates from Gavi support. A single dose strategy is likely to have similar benefits for less cost.

1. Introduction

In 2020, an estimated 600,000 cases of cervical cancer were diagnosed globally, and more than 340,000 women died from the disease [1]. Sub-Saharan Africa accounts for 20 % of cases and 25 % of deaths from cervical cancer globally, [2] yet less than half of African countries have introduced HPV vaccination, and even where implementation has started, coverage has been low [3].

In 2020, Kenya had an estimated 5,236 cervical cancer cases (11.9 % of all cancer cases) and over 3,000 cervical cancer deaths [1]. The National Cancer Control Strategy 2017–2022 identified

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prevention, early detection, and treatment of cancers due to infectious agents as a key strategy for reducing cancer burden in Kenya [4]. However, the current screening strategy, which aims to screen women for human papillomavirus (HPV)—the most common cause of cervical cancer—five times between 25 and 49 years of age, reaches less than one-third of the target population [5]. In October 2019, Kenya launched HPV vaccination (with Gardasil, hereafter referred to as GARDASIL-4, Merck Sharp & Dohme) for 10-year-old girls, using a two-dose health-facility-based vaccination strategy. In 2021, there was a catch-up campaign for any girls aged 10–14 years that had not been vaccinated as part of the routine program [6]. Although 77 % of the targeted girls had received the first dose of the HPV vaccine in 2021, only 31 % had received the second dose [7]. A recent modelling study by the World Bank has recommended a school-based delivery model as the most efficient scale-up strategy to achieve the 90 % World Health Organization elimination target for vaccination. In Kenya, 86.7 % of girls 9–13 years attend school.

To our knowledge, the decision to introduce HPV vaccination in Kenya was not informed by a country-led economic evaluation [6]. In a budget constrained environment, it would be useful for policymakers to understand the value of the current GARDASIL-4 program and consider whether alternative HPV vaccines (CECOLIN, Xiamen Innovax Biotech; CERVARIX, GlaxoSmithKline; and GARDASIL-9, Merck Sharp & Dohme) could offer better value for money. Further, it will be useful to understand the budget impact of these vaccines as the country transitions from Gavi support and will be required to increase its contribution to the full cost of the vaccine by 2027 [8]. A recent study in Kenya has demonstrated that one dose of HPV vaccination could provide similar benefits to two doses [9]. A single dose strategy could make the current program considerably more affordable and is therefore worth serious consideration.

This paper will assess the potential impact, cost-effectiveness, and budget impact of GARDASIL-4 and alternative products in Kenya. This will help to inform prioritization, planning, and advocacy for the national HPV vaccination program.

2. Methods

2.1. Modelling approach

To evaluate the potential impact and cost-effectiveness of introducing HPV vaccination we used the UNIVAC decision-support model, an Excel-based proportionate outcomes static cohort model. We evaluated vaccination of 10-year-old girls over a ten-year period (2020–2029). To estimate the burden of cervical cancer, we multiplied 2019 UN population estimates of the number of girls alive in each single year and single calendar year of life [10] by age-specific rates of cervical cancer cases (local, regional, and distant) and cervical cancer deaths. We estimated the numbers of cases, deaths, and disability adjusted life years (DALYs) with and without vaccination (Fig. 1). Burden estimates were aggregated over the lifetimes of each cohort of vaccinated girls. The direct impact of vaccination is calculated for each year of age by multiplying vaccine coverage by vaccine efficacy (adjusted for the HPV type distribution and assumed efficacy of each vaccine product against each HPV type). The model also estimates HPV vaccination program costs and healthcare costs, with and without vaccination.

The primary outcome measure is the cost (US$) per DALY averted, accounting for all costs and benefits aggregated over the ten cohorts of vaccinated girls (2020–2029). All future costs and health benefits were discounted at 3 % per year, and all costs represent 2021 US$ (KES exchange rate 107.0 as of June 30, 2021) [11].

We estimated the potential cost-effectiveness of four different vaccines (CERVARIX, CECOLIN, GARDASIL-4, and GARDASIL-9), comparing each product to no vaccination (and no change in existing cervical cancer screening and treatment strategies) and to each other. The cost per DALY averted was expressed as a percentage of Kenya's national gross domestic product (GDP) per capita (current US$) to help interpretation of results. The GDP per capita for Kenya was US$ 2,007 in 2021 [12]. Kenya does not have a strict willingness-to-pay (WTP) threshold for determining whether an intervention is cost-effective, so we calculated the probability the vaccine would be cost-effective over a range of alternative possible WTP thresholds between 0 and 0.5 times the national GDP per capita.

For each product, we estimated the cost of the vaccination program that would be borne by the Government in each calendar year between 2020 and 2029. These costs were calculated without discounting to inform realistic planning and budgeting and assume the Government will fully graduate from Gavi donor assistance (i.e., fully finance the vaccination program) by the year 2027.

The following sections outline the choice of model input parameters and scenarios. These were reviewed during a stakeholder consultation workshop held on July 13, 2022, with participants invited from relevant ministry of health departments (National Vaccines and Immunizations Program [NVIP]; National Cancer Control Program [NCCP]; and Division of Monitoring, Evaluation, Health Policy, and Research) and stakeholders under the National STOP cervical cancer technical working group, including county governments, academia, civil society, and the private sector.

2.2. Disease burden

Inputs for disease burden are summarized in Table 1. We used age-specific rates of cervical cancer cases and deaths estimated for Kenya by GLOBOCAN for the year 2020 [13] and assumed these rates would remain constant over time in the absence of vaccination (Table 1). We assumed cases were distributed into local, regional, and distant cancer categories, using the International Federation of Gynaecology and Obstetrics (FIGO) staging system and information from published local studies and cancer registry reports [14–18]. Disability weights to represent time lost while living with local, regional, and distant cancer were taken from the Global Burden of Disease (GBD) project [19]. Average five-year survival rates were based on a recent analysis of cervical cancer survival in sub-Saharan Africa from population-based cancer registries, as well as from a Kenyan publication by Khaemba et al. [20,21].

2.3. Healthcare costs

Inputs for healthcare costs are summarized in Table 2. In the base case scenario, a government (public sector) perspective was used [22]. This includes costs related to diagnosis, staging, surgery (simple/radical hysterectomy), chemotherapy, radiotherapy, and palliative care. For radiotherapy, the estimated cost includes 25 sessions, while chemotherapy costs include five sessions. Palliative care costs include a palliation care clinic consultation, family therapy, wound dressing, prescriptions refill/renewal, and rehydration services. Direct medical costs for radical hysterectomy, radiotherapy, and chemotherapy represent the procedure fee for each type or combination of treatment services, plus the direct medical costs for (1) staging laboratory investigations and/or imaging, (2) oncology consultation, and (3) medications for pain relief. For comparison, we assumed a modified societal perspective, which includes direct medical (e.g., supplies), non-medical (e.g., patient transportation) and indirect costs (e.g., patient time) [23]. A factor that could explain the high cost of illness for local cervical cancer using

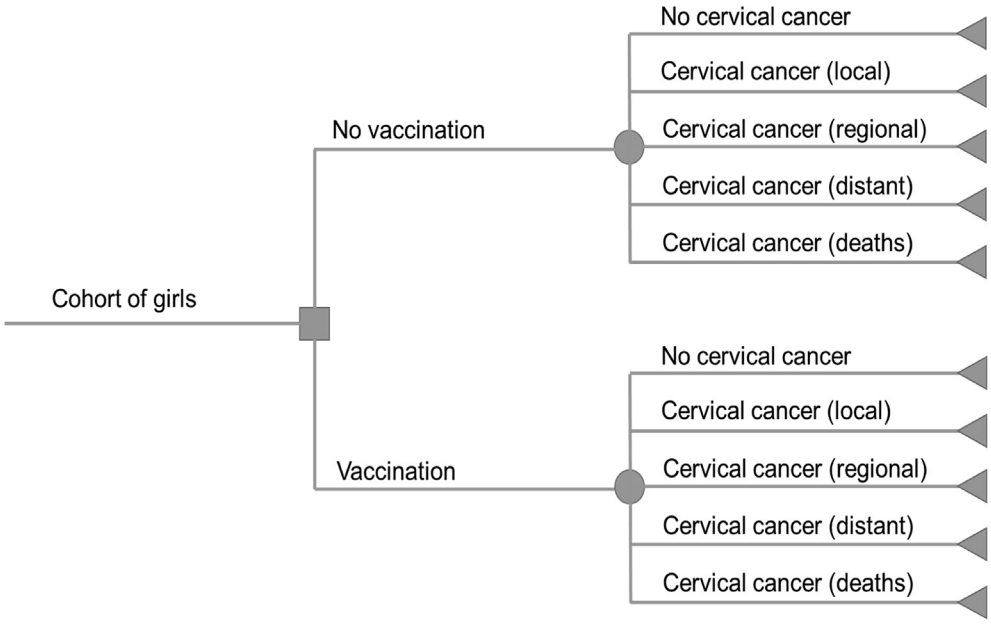

Fig. 1. Schematic diagram of the UNIVAC model for HPV vaccination.

the societal perspective is that the Vodicka et al. study had various treatment scenarios, depending on whether the stage at diagnosis was IA1, IA2, IB1, or IIA1. The most comprehensive treatment was simple hysterectomy combined with radiotherapy, for which costs are much higher than surgery alone.

2.4. Vaccine program costs

Input data for vaccine program costs are summarized in Table 3, and include the costs of the vaccines, syringes, and safety boxes, together with the costs of international handling, international delivery and all other incremental costs to the health system associated with the delivery strategy e.g., additional staff time, training, cold-chain capacity etc. For 2020, we estimated the government would contribute $0.50, $1.00, and $1.00 to the price of CECOLIN, CERVARIX, and GARDASIL-4, respectively, based on current country co-financing levels for routine HPV vaccination. For 2027–2029 we assumed the government would pay the full per dose prices of $3.00, $5.18, and $4.50, respectively, based on current Gavi prices for these vaccines [24]. In the interim years (2021–2026) we estimated a steady increase in the percentage of the price paid by the government (e.g., 20 %, 25 %, 30 %, 46 %, 62 %, 80 %). For completeness we also evaluated GARDASIL-9. This product is not available through the Gavi mechanism, so we assumed a per dose price of $25.00 for the entire period (2020–2029) based on the lowest price negotiated by a non-Gavi country [25]. We assumed that catch-up doses would be provided free of charge by Gavi. We reduced our estimates of the program cost in the first year (2020) to account for a Gavi Vaccine Introduction Grant of $1,626,936 for routine vaccination (677,890 girls aged 10 years in the year 2020 multiplied by $2.40) and $1,713,012 (2,635,404 girls aged 11–14 years in the year 2020 multiplied by $0.65). International handling fees and cost of syringes was obtained from UNICEF [26,28], while the delivery fee as a proportion of vaccine price was sourced from Vodicka et al. [27].

2.5. Vaccine impact calculations

Inputs for vaccine impact calculations are shown in Table 4. In our base case scenario, we assumed 16 % (2020), 31 % (2021), and 90 % (2022–2029) vaccine coverage for two doses. Equivalent coverage for one dose was 60 % (2020), 77 % (2021), and 90 % (2022–2029). The assumptions for years 1 and 2 were based on the real-world coverage reported by the NVIP (unpublished) for the GARDASIL-4 program. The assumption for the remaining years was based on the global target to vaccinate 90 % of girls [29].

For each of the four vaccine products (CECOLIN, CERVARIX, GARDASIL, GARDASIL-9) we derived weighted estimates of HPV vaccine efficacy against cervical cancer cases and deaths (Table 4) by calculating the percentage distribution of HPV types among cervical cancer cases and adjusting for estimates of vaccine efficacy against each HPV type. The HPV type distribution in Kenya was taken from estimates reported by the Catalan Institute of Oncology and the International Agency for Research on Cancer [30]. When summed, the type distribution exceeded 100 %, so we rescaled the distribution to fit within a 100 % envelope. The top three HPV types were 18 (44.0 %), 16 (13.7 %), and 45 (14.5 %). Estimates of vaccine-type efficacy were taken from Qiao *et al.* [31] for CECOLIN; Apter *et al.* [32] for CERVARIX; and Ault *et al.* [33] and Garland *et al.* [34] for GARDASIL-4. A study by Huh *et al.* [35] provided additional efficacy data for GARDASIL-9. The scale of cross-protection to non-vaccine types is uncertain, so we calculated weighted vaccine efficacy with and without cross-protection. For CERVARIX, a study by Wheeler *et al.* [36] was used with cross-protective efficacy against types 31, 33, 45, 51, 52, and 56. For GARDASIL-4, we assumed cross-protection against type 31 based on a study by Brown *et al.* [37] We assumed CECOLIN would have the same cross-protection as GARDASIL-4, and we assumed no cross-protection for GARDASIL-9. With these assumptions, cross-protection had a substantial influence on the efficacy assumed for CERVARIX and a negligible influence on the efficacy of the other three products (Fig. 2). We therefore restricted our primary analysis to five scenarios. The first four scenarios assumed no cross protection for each product. We then ran one additional scenario for CERVARIX with cross-protection. Results for the five scenarios were presented together in tables and figures for ease of comparison and interpretation.

In the base case analysis we assumed one dose of HPV vaccine provided 80 % of the total efficacy estimated for two doses. We also ran a deterministic "what-if" scenario assuming one dose provides

Table 1
Input parameters for estimating cervical cancer disease burden.

Parameter	Value	Low	High	Source
Annual rate of cervical cancer deaths per 100,000 females				
10–14 years	0.03	0.02	0.04	GLOBOCAN 2020 −/+20 % [13]
15–19 years	0.07	0.06	0.08	GLOBOCAN 2020 −/+20 % [13]
20–24 years	0.11	0.09	0.13	GLOBOCAN 2020 −/+20 % [13]
25–29 years	0.82	0.66	0.98	GLOBOCAN 2020 −/+20 % [13]
30–34 years	4.90	3.92	5.88	GLOBOCAN 2020 −/+20 % [13]
35–39 years	12.50	10.00	15.00	GLOBOCAN 2020 −/+20 % [13]
40–44 years	24.80	19.84	29.76	GLOBOCAN 2020 −/+20 % [13]
45–49 years	40.00	32.00	48.00	GLOBOCAN 2020 −/+20 % [13]
50–54 years	59.00	47.20	70.80	GLOBOCAN 2020 −/+20 % [13]
55–59 years	78.00	62.40	93.60	GLOBOCAN 2020 −/+20 % [13]
60–64 years	93.00	74.40	111.60	GLOBOCAN 2020 −/+20 % [13]
65–69 years	98.50	78.80	118.20	GLOBOCAN 2020 −/+20 % [13]
70–74 years	94.10	75.28	112.92	GLOBOCAN 2020 −/+20 % [13]
75–79 years	75.30	60.24	90.36	GLOBOCAN 2020 −/+20 % [13]
80–84 years	44.50	35.60	53.40	GLOBOCAN 2020 −/+20 % [13]
85–89 years	0.00	0.00	0.00	GLOBOCAN 2020 −/+20 % [13]
90–94 years	0.00	0.00	0.00	GLOBOCAN 2020 −/+20 % [13]
95–99 years	0.00	0.00	0.00	GLOBOCAN 2020 −/+20 % [13]
Annual rate of cervical cancer cases per 100,000 females				
10–14 years	0.06	0.05	0.07	GLOBOCAN 2020 −/+20 % [13]
15–19 years	0.20	0.16	0.24	GLOBOCAN 2020 −/+20 % [13]
20–24 years	0.38	0.30	0.46	GLOBOCAN 2020 −/+20 % [13]
25–29 years	3.50	2.80	4.20	GLOBOCAN 2020 −/+20 % [13]
30–34 years	14.40	11.52	17.28	GLOBOCAN 2020 −/+20 % [13]
35–39 years	29.10	23.28	34.92	GLOBOCAN 2020 −/+20 % [13]
40–44 years	50.40	40.32	60.48	GLOBOCAN 2020 −/+20 % [13]
45–49 years	72.90	58.32	87.48	GLOBOCAN 2020 −/+20 % [13]
50–54 years	91.40	73.12	109.68	GLOBOCAN 2020 −/+20 % [13]
55–59 years	109.70	87.76	131.64	GLOBOCAN 2020 −/+20 % [13]
60–64 years	122.30	97.84	146.76	GLOBOCAN 2020 −/+20 % [13]
65–69 years	124.70	99.76	149.64	GLOBOCAN 2020 -/+20 % [13]
70–74 years	114.10	91.28	136.92	GLOBOCAN 2020 −/+20 % [13]
75–79 years	86.40	69.12	103.68	GLOBOCAN 2020 −/+20 % [13]
80–84 years	44.50	35.60	53.40	GLOBOCAN 2020 −/+20 % [13]
85–89 years	0.00	0.00	0.00	GLOBOCAN 2020 −/+20 % [13]
90–94 years	0.00	0.00	0.00	GLOBOCAN 2020 −/+20 % [13]
95–99 years	0.00	0.00	0.00	GLOBOCAN 2020 −/+20 % [13]
% distribution of cervical cancer by severity				
% Local cancer[a] (stage 1 and 2)	45.60 %	36.48 %	54.72 %	Mungo C. et al 2022. [14]
% Regional cancer [b] (stage 3)	41.50 %	33.20 %	49.80 %	Mungo C. et al 2022. [14]
% Distant cancer [c] (stage 4)	12.90 %	10.32 %	15.40 %	Mungo C. et al 2022. [14]
Disability weights for DALYs				
Local cancer	0.29	0.19	0.40	Salomon J. 2015 (proxy: Diagnosis and primary therapy) [19]
Regional cancer	0.45	0.31	0.60	Salomon J. 2015 (proxy: Metastatic phase) [19]
Distant cancer	0.54	0.38	0.69	Salomon J. 2015 (proxy: Terminal phase) [19]
5-year survival rate (% alive after 5 years)				
Local	50.3 %	40.2 %	60.4 %	Khaemba N.E, Mugo C.W, Mutai C. 2013 [21]
Regional	20.5 %	16.4 %	24.6 %	Khaemba N.E, Mugo C.W, Mutai C. 2013 [21]
Distant	0.0 %	0.0 %	0.0 %	Khaemba N.E, Mugo C.W, Mutai C. 2013 [21]

[a] Local cancer refers to FIGO stage 1 and 2 - https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/staged.html.
[b] Regional cancer refers to FIGO stage 3 - https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/staged.html.
[c] Distant cancer refers to FIGO stage 4 - https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/staged.html.

Table 2
Average cost per treated case of cervical cancer (all costs are presented in [2021] US $).

Parameter	Value	Low	High	Source
Government perspective:				
Local cervical cancer[a]	$1,436.10	$1,148.80	$1,723.20	Atieno et al, 2018 [22]
Regional cervical cancer[b]	$2,995.90	$2,396.70	$3,595.10	Atieno et al, 2018 [22]
Distant cervical cancer[c]	$4,097.20	$3,277.80	$4,916.60	Atieno et al, 2018 [22]
Societal perspective:				
Local cervical cancer[a]	$5,827.42	$2,913.50	$8,741.00	Vodicka et al, 2019 [23]
Regional cervical cancer[b]	$5,630.49	$2,815.30	$8,445.80	Vodicka et al, 2019 [23] [23]
Distant cervical cancer[c]	$5,671.18	$2,835.60	$8,506.80	Vodicka et al, 2019 [23]

[a] Local cancer cost per treated woman include simple hysterectomy plus radiotherapy.
[b] Regional cancer cost per treated woman include radiotherapy and chemotherapy.
[c] Distant cancer cost per treated woman include chemotherapy, radiotherapy, and palliative care.

Table 3
Input parameters for estimating HPV vaccine program costs.

Parameter	Value	Low	High	Source
Price of vaccine doses				
CECOLIN	$3.00	$3.00	$3.00	Gavi: vaccine profiles [24]
CERVARIX	$5.18	$5.18	$5.18	Gavi: vaccine profiles [24]
GARDASIL-4	$4.50	$4.50	$4.50	Gavi: vaccine profiles [24]
GARDASIL-9	$25.00	$25.00	$25.00	World Health Organization [25]
International handling fee (% of price)				
CECOLIN	3 %	2 %	4 %	UNICEF [26]
CERVARIX	3 %	2 %	4 %	UNICEF [26]
GARDASIL-4	3 %	2 %	4 %	UNICEF [26]
GARDASIL-9	3 %	2 %	4 %	UNICEF [26]
International delivery (% of price)				
CECOLIN	10 %	8 %	12 %	Vodicka et al, 2022 [27]
CERVARIX	10 %	8 %	12 %	Vodicka et al, 2022 [27]
GARDASIL-4	10 %	8 %	12 %	Vodicka et al, 2022 [27]
GARDASIL-9	10 %	8 %	12 %	Vodicka et al, 2022 [27]
Wastage percentage				
CECOLIN	5 %	4 %	6 %	Gavi: vaccine profiles [24]
CERVARIX	5 %	4 %	6 %	Gavi: vaccine profiles [24]
GARDASIL-4	5 %	4 %	6 %	Gavi: vaccine profiles [24]
GARDASIL-9	5 %	4 %	6 %	Gavi: vaccine profiles [24]
Costs of syringes				
Price per dose:	$0.07	$0.06	$0.08	UNICEF [28]
Percentage international handling:	3 %	2 %	4 %	Assumption
Percentage international delivery:	10 %	8 %	12 %	Assumption
Percentage wastage[a]	5 %	4 %	6 %	Assumption
Costs of safety box				
Price per box:	$1.30	$1.30	$1.30	UNICEF [28]
Total number of syringes per safety box (Kenya NVIP)	100	100	100	Kenya NVIP
Price per syringe/dose:	$0.0103	$0.0103	$0.0103	Derived
Percentage international handling:	3 %	2 %	4 %	Assumption
Percentage international delivery:	10 %	8 %	12 %	Assumption
Percentage wastage[a]	5 %	4 %	6 %	Assumption
Incremental health system costs				
Cost per year per dose	$4.97	$3.98	$5.97	World Bank investment case for Kenya −/+20 %, table A5 with the assumption of 85 % school-based, 10 % facility-based and 5 % outreach

[a] The % wastage is converted into a factor (1/[1 - % wastage]) which is multiplied by the expected number of doses required to meet the anticipated level of coverage.

the same protection as two doses based on evidence from a recent study in Kenya [9,38].

2.6. Uncertainty analysis

For each vaccine, we ran a probabilistic sensitivity analysis with 1,000 runs per scenario. The low, mid, and high values for each input parameter were assumed to represent the mode and range within a series of PERT-Beta distributions. All parameters were varied across their uncertainty range except for vaccine price. Probabilistic results were represented as clouds on a cost-effectiveness plane and used to inform cost-effectiveness acceptability curves (i.e., the probability that the vaccine would be cost-effective at different WTP thresholds). In addition, we ran deterministic sensitivity analyses to show the effect on the cost-effectiveness ratio of changing one input in isolation. We ran the same set of "what-if" scenarios for each vaccine.

3. Results

Table 5 summarizes the costs and benefits of each vaccine option compared to no vaccine and to each other. Vaccinating 10-year-old girls each year (2020–2029) and running a catch-up campaign in year 1 (for girls aged 11–14 years) involves vaccinating 14 birth cohorts of girls (born 2007–2020). Over the lifetimes of these 14 birth cohorts, we estimate there could be around 320,000 cases and 225,000 deaths attributed to cervical cancer. Over the same period, the discounted cost of cervical cancer treatment was estimated to be around US$ 175 million from a government perspective and US$ 415 million from a societal perspective.

Without cross-protection, CECOLIN, CERVARIX, and GARDASIL-4 would each have a similar projected health impact (~42 % reduction in cervical cancer cases and deaths). This is equivalent to around 137,000 cases and 97,000 deaths averted during the lifetimes of the vaccinated cohorts. The impact of GARDASIL-9 is estimated to be around 60 %. The discounted program cost associated with introducing each vaccine would be US$ 74, US$ 90, US$ 86, and US$ 380 million, respectively, compared to no HPV vaccination. From a government perspective, the healthcare costs averted by the three Gavi-supported vaccines (CECOLIN, CERVARIX, GARDASIL-4) would represent 98 %, 87 %, and 79 % of the vaccine program costs, respectively. From a societal perspective, the healthcare costs averted were substantial and for all three vaccines exceeded the cost of introducing the vaccination program (cost-saving). For GARDASIL-9, the healthcare costs averted represented 27 % (government perspective) and 64 % (societal perspective) of the vaccine program costs. CECOLIN has the lowest net cost and most attractive cost-effectiveness ($3 per DALY averted from a government perspective and cost-saving from a societal perspective). If all four products were available and cross-protection were not considered, CERVARIX would be dominated by CECOLIN because CERVARIX would generate less impact at a higher net cost. The incremental cost-effectiveness of the remaining alternatives (GARDASIL-4 compared to CECOLIN and GARDASIL-9 compared to GARDASIL-4) would exceed 0.45 times the national GDP per capita from either a government or societal perspective (Table 5).

With cross-protection, the health impact of CERVARIX increased to 57 % and it became the most cost-effective option in both a government perspective (cost-saving) or societal perspective

Table 4
Input parameters used to calculate the impact of HPV vaccination in Kenya.

Parameter	Value	Low	High	Source
Coverage of two doses (Kenya NVIP)				
2020	16.00 %	14.00 %	18.00 %	Kenya NVIP
2021	31.00 %	28.00 %	34.00 %	Kenya NVIP
2022–2029	90.00 %	81.00 %	99.00 %	Kenya NVIP
Vaccine efficacy against all types (with cross-protection)				
CECOLIN				
1 dose	48.**09** %	27.02 %	48.48 %	Assumption (80 % of 2-dose VE)
2 doses	60.12 %	33.77 %	60.60 %	Bruni et al 2021; [30] Qiao et al 2019 [31]
CERVARIX				
1 dose	61.72 %	45.62 %	63.37 %	Assumption (80 % of 2-dose VE)
2 doses	77.15 %	57.03 %	79.21 %	Bruni et al 2021; [30] Wheeler et al 2012; [36] Falcaro et al 2021; [39] Tsang et al 2020; [40] Hoes et al 2022 [41]
GARDASIL-4				
1 dose	47.04 %	42.24 %	48.13 %	Assumption (80 % of 2-dose VE)
2 doses	58.80 %	52.80 %	60.16 %	Bruni et al 2021; [30] Ault 2007; [33] Garland et al 2007 [34]
GARDASIL-9				
1 dose	65.27 %	57.48 %	66.81 %	Assumption (80 % of 2-dose VE)
2 doses	81.59 %	71.85 %	83.51 %	Bruni et al 2021; [30] Ault 2007; [33] Garland et al 2007; [34] Huh et al [35]
Vaccine efficacy against vaccine types (no cross-protection)				
CECOLIN				
1 dose	46.14 %	26.00 %	46.14 %	Assumption (80 % of 2-dose VE)
2 doses	57.68 %	32.50 %	57.68 %	Bruni et al 2021; [30] Qiao et al 2019 [31]
CERVARIX				
1 dose	45.51 %	38.06 %	46.14 %	Assumption (80 % of 2-dose VE)
2 doses	56.89 %	47.58 %	57.68 %	Bruni et al 2021; [30] Apter et al 2015 [32]
GARDASIL-4				
1 dose	45.71 %	41.63 %	46.45 %	Assumption (80 % of 2-dose VE)
2 doses	57.13 %	52.04 %	58.06 %	Bruni et al 2021; [30] Ault 2007; [33] Garland et al 2007 [34]
GARDASIL-9				
1 dose	65.27 %	57.48 %	66.81 %	Assumption (80 % of 2-dose VE)
2 doses	81.59 %	71.85 %	83.51 %	Bruni et al 2021; [30] Ault 2007; [33] Garland et al 2007; [34] Huh et al [35]

NVIP, National Vaccination and Immunization Program; VE, vaccine efficacy.
Due to the similarity in efficacy with and without cross-protection for CECOLIN, GARDASIL-4 and GARDASIL-9 (also see Fig. 2), we did not run scenarios with cross-protection for these three products in our primary analysis.
Cross-protection for CERVARIX has also been demonstrated through real world data in vaccination programs [39,40,41].

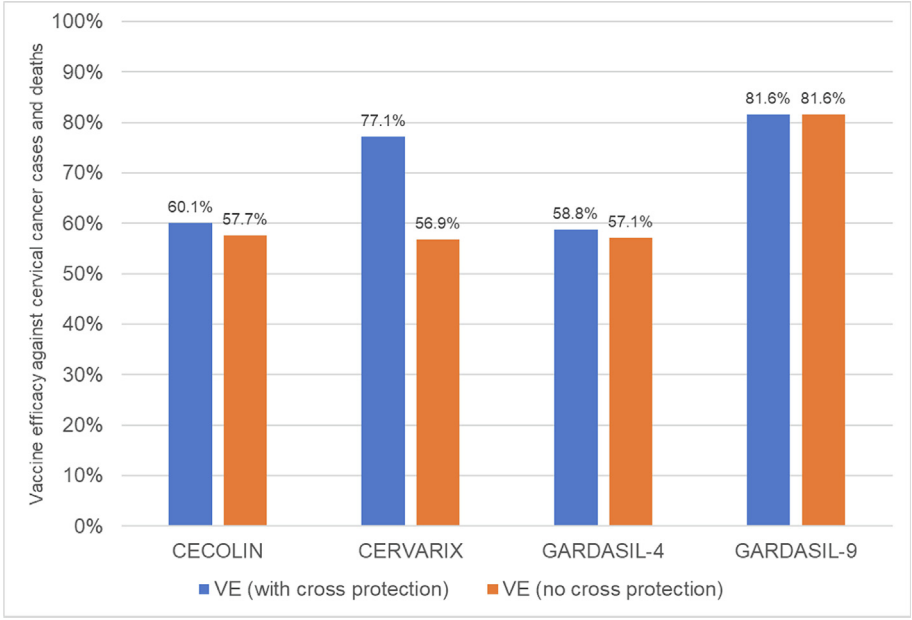

Fig. 2. Vaccine efficacy (VE) against cervical cancer cases and deaths in Kenya by vaccine product, with and without cross-protection to non-vaccine types. Due to the similarity in efficacy with and without cross-protection for CECOLIN, GARDASIL-4 and GARDASIL-9, we did not run scenarios with cross-protection for these three products in our primary analysis.

(cost-saving). Fig. 3 shows the influence of cross-protection on the results for CERVARIX. Without cross-protection, the results for the three GAVI supported vaccines are similar, and probabilistic uncertainty clouds overlap. However, with cross-protection, CERVARIX is a far more attractive option. GARDASIL-9 is unlikely to be affordable or cost-effective given the available alternatives.

Table 5
Lifetime costs and effects of HPV vaccination for Kenyan girls aged 10 years (2020–2029) with catch-up for girls aged 11–14yrs (2020).

	No vaccine	Cross-protection	No cross-protection			
		CERVARIX	CECOLIN	GARDASIL-4	CERVARIX	GARDASIL-9
Lifetime costs and effects						
Cervical cancer cases (local)	146,403	62,927	83,994	82,782	84,849	58,123
Cervical cancer cases (regional)	133,240	57,269	76,442	75,339	77,220	52,897
Cervical cancer cases (distant)	41,417	17,802	23,762	23,419	24,003	16,443
Cervical cancer cases with treatment	321,059	137,998	184,198	181,539	186,072	127,464
Cervical cancer deaths	226,986	97,543	130,211	128,331	131,536	90,094
DALYs (discounted)	1,069,819	476,912	626,548	617,934	632,616	442,793
Vaccine program costs (discounted)	$0	$90,099,683	$74,077,106	$85,518,188	$90,099,683	$380,488,211
Government healthcare costs (discounted)	$175,494,548	$78,362,449	$102,876,354	$101,465,159	$103,870,410	$72,773,031
Societal healthcare costs (discounted)	$414,061,290	$184,888,119	$242,726,148	$239,396,579	$245,071,523	$171,700,462
Differences (comparator = no vaccine)						
Cervical cancer cases (local)	–	83,476	62,409	63,621	61,554	88,280
Cervical cancer cases (regional)	–	75,970	56,797	57,901	56,020	80,342
Cervical cancer cases (distant)	–	23,615	17,655	17,998	17,413	24,974
Cervical cancer cases with treatment	–	183,061	136,861	139,521	134,988	193,596
Cervical cancer deaths	–	129,444	96,775	98,656	95,450	136,893
DALYs (discounted)	–	592,908	443,271	451,885	437,203	627,026
Vaccine program costs (discounted)	–	$90,099,683	$74,077,106	$85,518,188	$90,099,683	$380,488,211
Government healthcare costs (discounted)	–	-$97,132,099	-$72,618,195	-$74,029,390	-$71,624,138	-$102,721,518
Societal healthcare costs (discounted)	–	-$229,173,172	-$171,335,142	-$174,664,711	-$168,989,768	-$242,360,828
Cost (US$) per DALY averted (comparator = no vaccine)						
Government cost perspective						
Cost (discounted)	–	-$7,032,416	$1,458,911	$11,488,798	$18,475,546	$277,766,694
DALYs averted (discounted)	–	592,908	443,271	451,885	437,203	627,026
Cost per DALY averted (discounted)	–	Cost-saving	$3	$44	$42	$443
Societal cost perspective						
Cost (discounted)	–	-$139,073,488	-$97,258,036	-$89,146,524	-$78,890,084	$138,127,383
DALYs averted (discounted)	–	592,908	443,271	451,885	437,203	627,026
Cost per DALY averted (discounted)	–	Cost-saving	Cost-saving	Cost-saving	Cost-saving	$220
Cost (US$) per DALY averted (comparator = next least costly non-dominated[a] option)						
Government cost perspective						
Cost (discounted)	–	-$7,032,416	$1,458,911	$10,029,887	Dominated **	$266,277,896
DALYs averted (discounted)	–	$592,908	443,271	8,614	Dominated **	175,141
Cost per DALY averted (discounted)	–	Cost-saving	$3	$1,164	Dominated **	$1,520
Societal cost perspective						
Cost (discounted)	–	-$139,073,488	-$97,258,036	$8,111,513	Dominated **	$227,273,906
DALYs averted (discounted)	–	$592,908	443,271	8,614	Dominated **	175,141
Cost per DALY averted (discounted)	–	Cost-saving	Cost-saving	$942	Dominated **	$1,298

[a] CERVARIX (no cross-protection) is dominated by CECOLIN and GARDASIL-4 because it averts fewer DALYs and costs more than both of these options.

From a government perspective, the product with the most favorable cost-effectiveness (CECOLIN without cross-protection and CERVARIX with cross-protection) would have a 100 % probability of being cost-effective at a WTP threshold set at $100 (5 % of Kenya's national GDP per capita) when compared to no vaccination (Fig. 4).

Should Kenya reach its target of 90 % coverage, then the undiscounted vaccine program cost could exceed US$ 10 million per year by the time Kenya has fully graduated from Gavi donor support (Fig. 5). However, a substantial proportion of this cost is associated with the non-vaccine incremental health system costs associated with setting up and maintaining the HPV vaccination program. For the three Gavi-supported vaccines, these incremental health system costs represent around 90 % of the vaccine program costs in 2020, reducing to around half of the costs in 2029. For GARDASIL-9, these costs represent around 14 % of the total vaccine program cost for the full period 2020–2029.

Results from the deterministic scenario analysis (Table 6) showed that a one-dose strategy would be cost-saving compared to no vaccination for all three Gavi-supported vaccines. If Kenya were to adopt a single dose strategy, then the total cost of the vaccination program over the period 2020–2029 would be US$ 43–222 million depending on the product used; this compares to US $ 84–443 million for a two-dose strategy. For GARDASIL-4 (the current product in use in the Kenyan HPV vaccination program), switching to a one-dose strategy would save around US$ 50 million over the 10-year period.

Assuming higher vaccine prices and/or a higher annual discount rate (10 % rather than 3 %) made HPV vaccination far less favorable.

4. Discussion

We found that routine HPV vaccination for 10-year-old girls (with catch-up for girls aged 11–14 years in the first year) could substantially reduce cervical cancer cases and deaths over the lifetimes of the vaccinated girls. Our results were sensitive to the choice of vaccine product, cross-protection assumptions, vaccine price, and discount rate. Without cross-protection, vaccinating the 14 cohorts with any of the three Gavi-supported vaccines could avert around 137,000 cervical cancer cases and 97,000 deaths. With cross-protection assumed for CERVARIX, this could increase to 183,000 averted cases and 129,000 averted deaths. We found that the product with the most favorable cost-effectiveness (CECOLIN without cross-protection, or CERVARIX with cross-protection) would be cost-effective at a WTP threshold of $100 (around 5 % of the national GDP per capita for Kenya). This is below the WTP threshold (20–50 % of national GDP per capita) previously estimated for Kenya based on health opportunity costs by Ochalek *et al.* [42] However, we find that substantial government funding

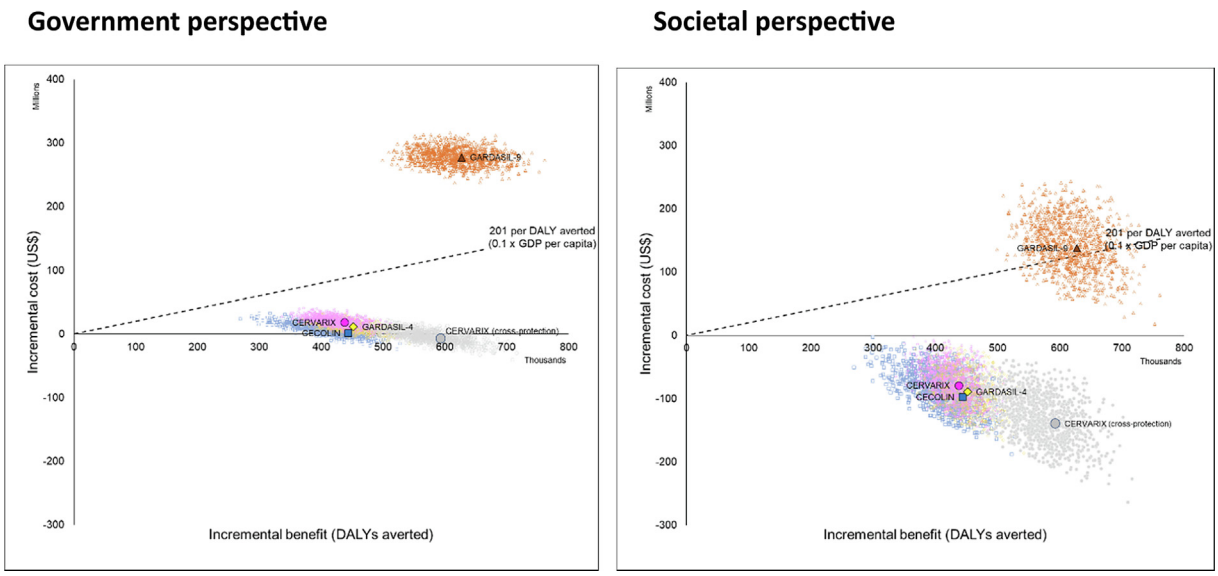

Fig. 3. Probabilistic clouds showing the incremental cost (US$) and benefit (DALYs averted) of each HPV vaccine product compared to no vaccine, and to each other (government and societal perspective). With cross-protection, CERVARIX (grey) had the most favorable cost-effectiveness from both a government and societal perspective, and the incremental benefit of the only non-dominated product (GARDASIL-9 [orange]) would not be worth the incremental cost. Without cross-protection, all three products currently supported by Gavi (CECOLIN [blue], CERVARIX [pink], GARDASIL-4 [yellow]) had similar costs and benefits compared to no vaccination from both a government and societal perspective. CECOLIN had the most favorable cost-effectiveness, but GARDASIL-9 provided greater health benefits and could also be considered if affordable. It should be noted that vaccine prices were fixed for the probabilistic sensitivity analysis, and the relative position of the probabilistic clouds will therefore be very sensitive to changes in vaccine price. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

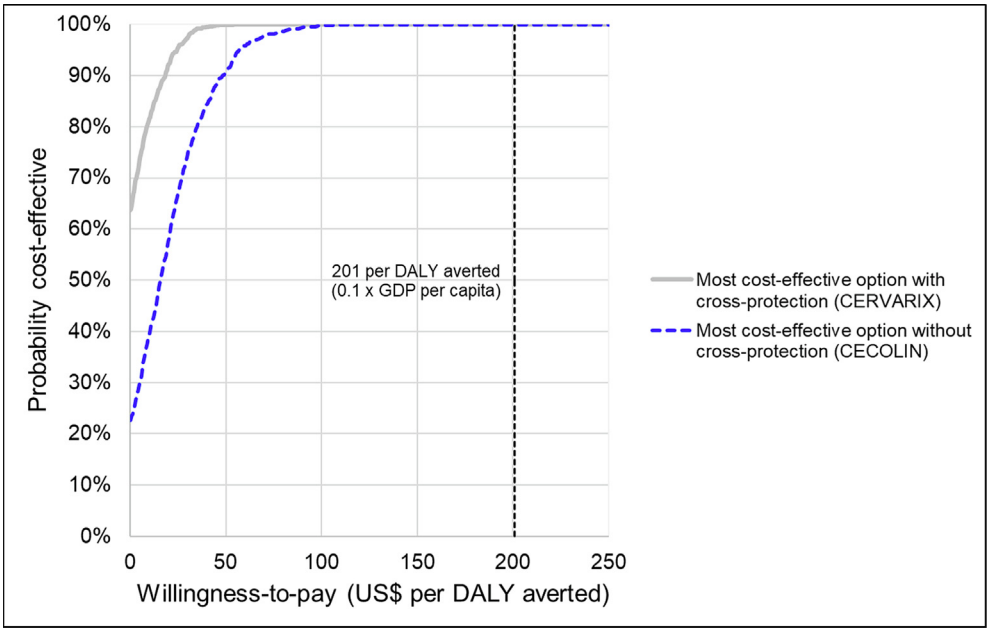

Fig. 4. Probability the most cost-effective option (CECOLIN without cross-protection, CERVARIX with cross-protection) will be cost-effective compared to no vaccination, at different willingness-to-pay thresholds (government perspective).

will be required, possibly exceeding $10 million (undiscounted) per year, to reach ambitious coverage targets (90 % coverage) and sustain the program as Kenya graduates from Gavi support.

The Strategic Advisory Group of Experts on Immunization convened by the World Health Organization in April 2022 recommended the use of either a single- or two-dose strategy for national HPV immunization programs [43]. A recent study in Kenya has demonstrated that a single dose strategy could offer similar health benefits to a two-dose strategy [9]. This would cost substantially less than the current strategy and is therefore worth serious consideration. A single dose schedule may also be a more feasible strategy for achieving the ambitious 90 % coverage target. We assumed high incremental health system costs would be required throughout the period of the analysis to achieve this, representing more than half the total cost of the vaccination program each year. However, this assumption is uncertain. A more thorough analysis of the programmatic barriers to high coverage and the strategies and costs required to overcome them is needed.

All currently available vaccines against HPV have demonstrated high efficacy in both preventing vaccine-targeted HPV infections as

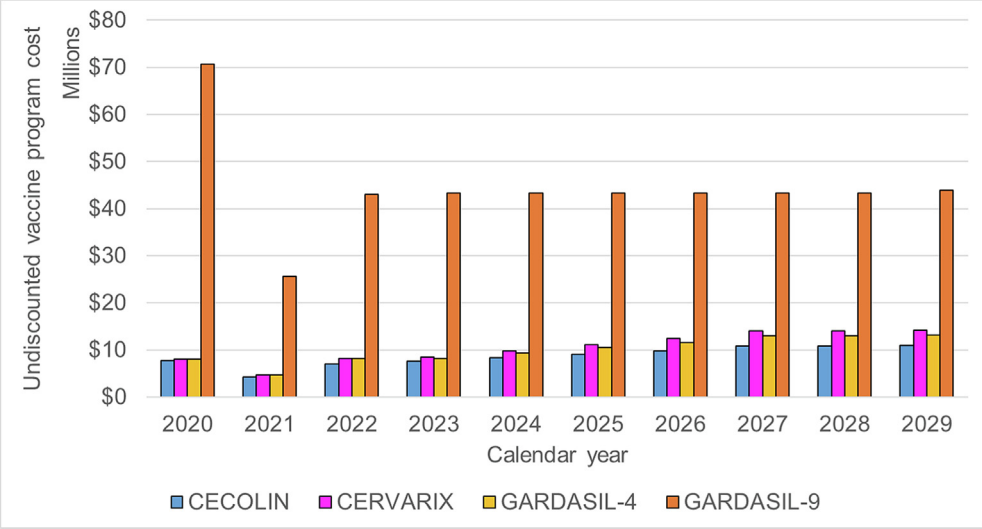

Fig. 5. Undiscounted vaccine program costs (including incremental health system costs) by calendar year and type of HPV vaccine product. In the year 2020, system costs represented 94 %, 91 %, 91 %, and 14 % of the total program costs of CECOLIN, CERVARIX, GARDASIL-4, and GARDASIL-9, respectively. Equivalent values for the year 2029 were 58 %, 44 %, 48 %, and 14 %. Higher costs in year 1 reflect the cost of vaccinating 10-year-old girls plus a catch-up campaign for girls aged 11–14 years, despite lower coverage assumptions in the first year (2020). Dose 1 coverage is assumed to be 60 % (2020), 77 % (2021), and 90 % (2022–2029). Dose 2 coverage is assumed to be 16 % (2020), 30 % (2021), and 90 % (2022–2029). For Gavi-supported vaccines, a Gavi Vaccine Introduction Grant has been included for routine and catch-up doses in the first year (2020) together with a Gavi-subsidized dose price. The increase over time reflects the gradual increase in the government's contribution to the price of each vaccine as it transitions from Gavi support.

Table 6
Cost (US$) per DALY averted for alternative deterministic scenarios (comparator = no vaccine).

Vaccine	Scenario	Government perspective[b]	% Change	Societal perspective[b]	% Change
CECOLIN	**Central inputs (US$ 3.00 per dose + assumptions[a]), no cross protection**	**3**	-	**Cost-saving**	-
	Cross protection	**7**	133%	Cost-saving	-
	Vaccine price = 25% lower (US$ 2.25 per dose)	Cost-saving	-	Cost-saving	-
	Vaccine price = Highest (US$ 47.70 per dose)	938	31,167%	716	-
	Discount rate = 10%	3081	102,600%	2709	-
	One-dose schedule (with full 2-dose protection)	Cost-saving	-	Cost-saving	-
CERVARIX	**Central inputs (US$ 5.18 per dose + assumptions[a]), no cross protection**	**42**	-	**Cost-saving**	-
	Cross protection	Cost-saving	-	Cost-saving	
	Vaccine price = 25% lower (US$ 3.90 per dose)	Cost-saving	-	Cost-saving	-
	Vaccine price = Highest (US$ 14.14 per dose)	147	250%	Cost-saving	-
	No cross-protection	42	0%	Cost-saving	-
	Discount rate = 10%	2734	4,200%	2361	-
	One-dose schedule (with full 2-dose protection)	Cost-saving		Cost-saving	-
GARDASIL-4	**Central inputs (US$ 4.50 per dose + assumptions[a]), no cross protection**	**44**	-	Cost-saving	-
	Cross protection	38	-14%	Cost-saving	
	Vaccine price = 25% lower (US$ 3.38 per dose)	15	-66%	Cost-saving	-
	Vaccine price = Highest (US$ 47.70 per dose)	920	1,990%	628	-
	Discount rate = 10%	3492	7,836%	3119	-
	One-dose schedule (with full 2-dose protection)	Cost-saving	-	Cost-saving	
GARDASIL-9	**Central inputs (US$ 25.00 per dose + assumptions[a]), no cross protection**	**443**	-	**220**	-
	Cross protection	443	-	220	-
	Vaccine price = 25% lower (US$ 18.75 per dose)	331	-25%	108	-51%
	Vaccine price = Highest (US$ 113.50 per dose)	2028	358%	1805	720%
	Discount rate = 10%	12556	2,734%	12184	5438%
	One-dose schedule (with full 2-dose protection)	292	-34%	69	-69%

[a]Central inputs assume 'mid' estimates defined in tables 1-4 and no cross-protection for each product.
[b]A graded color scale is used to distinguish favorable (green), borderline (amber) and unfavorable (red) cost-effectiveness ratios compared to no vaccination.

well as precancerous lesions in individuals without previous infection with the targeted types. However, some options would make a more compelling economic case for vaccination scale-up in Kenya, especially in the context of transitioning from Gavi support. Compared to the current HPV vaccine in use (GARDASIL-4), we found that alternative products (CECOLIN without cross-protection, or CERVARIX with cross-protection) could provide similar or greater health benefits at lower net costs. Without cross-protection assumptions, all of the Gavi-supported vaccines would have similar net costs and benefits compared to no vaccination, and the rank

order of these three products is very sensitive to changes in vaccine price. With cross-protection assumptions, switching the current product to CERVARIX is clearly worth serious consideration, particularly during a period when Gavi financing is available. However, we did not consider the potential costs associated with switching products, nor did we include the other health benefits associated with GARDASIL-4, namely the reduction in genital warts associated with HPV types 6 and 11. As Kenya transitions from Gavi support, relevant stakeholders may need to assess the best strategy between continuing with the current product and adopting options that could provide similar or greater health benefits at lower net costs. The estimated percent reduction in cervical cancer deaths (42–60 % reduction) compares with a systematic review of modelling studies in low- and middle-income countries (LMICs) by Frianto *et al.*, which estimated reduction of cervical cancers by HPV vaccination at 20–72 % and showed that HPV vaccination could be cost-saving in several instances [44]. Most HPV vaccination economic evaluation studies have demonstrated cost-effectiveness for different implementation strategies. A regression *meta*-analysis of cost-effectiveness for 195 countries demonstrated mean Incremental Cost-Effectiveness Ratio (ICER) of US$ 800 per DALY averted in 64 countries, the majority of which were in sub-Saharan Africa and South Asia [45]. Our study showed a wide range of cost-effectiveness, ranging from cost-saving to $443 per DALY averted (or 22 % GDP per capita) compared to no vaccination. Another study specific to selected LMIC (Uganda, Vietnam, Nigeria, and India) also had a comparable range, of $28–$1406 per DALY averted (5–27 % GDP per capita) [46]. A study in Ethiopia showed that for GARDASIL-9 to be cost-effective, the price per dose should not exceed US$ 15 [47]. Expressing ICER as a proportion of GDP per capita has been proposed as a more effective way of communicating cost-effectiveness to decision-makers [48].

Our study focused exclusively on HPV vaccination for young girls and did not consider possible enhancements to the cervical cancer screening program for females above the eligible age of vaccination. However, with challenges in rolling out interventions in the other two pillars of the cervical cancer elimination strategy (namely screening and treatment), investing in HPV vaccination should be a useful complementary tool for reducing the overall burden of cervical cancer in Kenya. Preliminary findings from a recent investment case for cervical and breast cancer in Kenya completed in 2022 (unpublished) found that with an optimized HPV vaccination program, cervical cancer incidence rates will decrease such that even a scaled-up screening program will detect much fewer cases.

4.1. Strengths and limitations

This study had several strengths. First, national stakeholders were invited to a consultation workshop (held on July 13, 2022) and invited to review and inform inputs to the model. Such a participatory framework is advisable for ensuring that findings are considered relevant and adopted into policy and practice. Second, as far as possible, we used data and scenarios that were relevant to the Kenyan context. Our study also has some limitations. During the stakeholder consultation workshop some stakeholders expressed an interest in simultaneously modelling the costs and benefits of vaccination and screening strategies, but this was outside the scope of the UNIVAC model and the aims of our study. Where other inputs and assumptions were uncertain and influential, we ran probabilistic and/or deterministic uncertainty analyses to show the impact of those assumptions on the results (e.g., cost-effectiveness with and without cross-protection assumptions). We opted to use simple PERT-Beta distributions for our PSA so did not account for other distribution shapes or potential correlation between different combinations of input parameters. This would not have altered our central results, but our estimates of probabilistic uncertainty should be interpreted with this limitation in mind.

5. Conclusion

Our study provides guidance for HPV vaccination program planning within Kenya and lessons for countries with similar disease burden and economic contexts. We find that investing in the HPV vaccination program over the next decade would not only be cost-effective but could even be cost-saving from a societal perspective. Compared to the HPV vaccine currently used in Kenya, alternative products could provide similar or greater health benefits at lower net costs and are therefore worth serious consideration. Substantial government funding will be required to reach ambitious coverage targets and sustain the program as Kenya graduates from Gavi support. A single-dose strategy provides one option for reducing the cost of the HPV vaccination program going forward.

CRediT authorship contribution statement

Lucy Mecca: Conceptualization; data curation; writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Clint Penceka reports financial support was provided by German Federal Ministry of Education and Research.

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