Chapter seven

COST-EFFECTIVENESS ANALYSIS OF QUADRIVALENT AND NONAVALENT HUMAN PAPILLOMAVIRUS VACCINES IN ETHIOPIA

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ABSTRACT

Background

In Ethiopia, cervical cancer is the second most common cancer among women of the reproductive age group. Since 2018, the quadrivalent human papillomavirus (4vHPV) vaccine targeting four HPV types (6/11/16/18) has been introduced in the national immunization program in Ethiopia. Currently, however, a nonavalent HPV (9vHPV) vaccine which provides broader protection against nine HPV types (6/11/16/18/31/33/45/52/58) is available for global use. Our study, therefore, aims to estimate the cost-effectiveness of 9vHPV vaccine compared to the current HPV vaccination program in Ethiopia.

Method

A static Markov cohort model was used to simulate the progression of HPV infection to cervical cancer for a cohort of 12-years-old girls (N= 100,000) in Ethiopia. The model ran up to the age of 100 years, with a cycle length of 1 year. One-way and probabilistic sensitivity analyses were used to explore the robustness of the model and uncertainties around the parameters included in the model. Cost-effectiveness thresholds of one and three times gross domestic product (GDP) per quality-adjusted life-year (QALY) gained were considered.

Results

At a price of US$ 6.9, the incremental cost-effectiveness ratio (ICER) per QALY gained for the 9vHPV vaccine was US$ 454 compared to the 4vHPV vaccine, which is less than one times GDP per capita of Ethiopia. The ICER was most sensitive to the change in the discount rate of QALYs. Compared to 4vHPV vaccine, for 9vHPV vaccine to remain very cost-effective and cost-effective, its price per dose should not exceed US$ 8.4 and US$ 15, respectively, at a threshold of one and three times GDP per capita.

Conclusion

Compared to the 4vHPV vaccine, the 9vHPV vaccine is a cost-effective option in Ethiopia, given that its price per dose does not exceed US$15.

INTRODUCTION

The Human Papillomavirus (HPV) is the most common cause of infection of the anogenital tract [1]. Although HPV infections are primarily temporary and cleared up within a few months of acquisition, some of them may persist and progress to cancer [2]. HPV infection is linked to almost all cases of cervical cancer [1,3]but the risk associated with the various HPV types has not been adequately assessed. METHODS: We pooled data from 11 case-control studies from nine countries involving 1918 women with histologically confirmed squamous-cell cervical cancer and 1928 control women. A common protocol and questionnaire were used. Information on risk factors was obtained by personal interviews, and cervical cells were collected for detection of HPV DNA and typing in a central laboratory by polymerase-chain-reaction-based assays (with MY09/MY11 and GP5+/6+ primers. Globally, cervical cancer was ranked as the fourth common cancer among women and was responsible for the deaths of some 311,000 women in 2018, with the vast majority occurring in less developed nations [4,5]. In Ethiopia, cervical cancer was the 2nd most common cancer in women aged 15 to 44 years. In 2018, about 6,294 new cervical cancer cases were diagnosed in Ethiopia, and 4,884 women died from the disease [6].

There are currently three HPV vaccines available on the market: a bivalent HPV (2vHPV) vaccine, a quadrivalent HPV (4vHPV) vaccine, and a nonavalent HPV (9vHPV) vaccine. Both 2vHPV and 4vHPV vaccines prevent specific kinds of cancer, including cervical cancer caused by high-oncogenic HPV types 16 and 18, which are associated with about 70% of cervical cancers [3]but the risk associated with the various HPV types has not been adequately assessed. METHODS: We pooled data from 11 case-control studies from nine countries involving 1918 women with histologically confirmed squamous-cell cervical cancer and 1928 control women. A common protocol and questionnaire were used. Information on risk factors was obtained by personal interviews, and cervical cells were collected for detection of HPV DNA and typing in a central laboratory by polymerase-chain-reaction-based assays (with MY09/MY11 and GP5+/6+ primers. The 4vHPV vaccine additionally protects against non-oncogenic HPV types 6 and /11[7,8]. Both 2vHPV and 4vHPV vaccines demonstrated cross-protection against other non-vaccine oncogenic HPV types [9–11]. However, a result from a recent systematic review showed that the cross-protection provided by the 2vHPV and 4vHPV vaccines was inconsistent across non-vaccine HPV types, and its long-term durability has not yet been established [12]. Compared to the 4vHPV vaccine, the 9vHPV vaccine provides protection against additional high-oncogenic HPV types 31/33/45/52/58. With five HPV types, the 9vHPV vaccine can prevent approximately 90% of cervical cancers [13].

In Ethiopia, an HPV vaccination program of two-dose 4vHPV vaccine for girls at the age of 14 has already been implemented since 2018 [14]. As evidenced by various epidemiological studies in Ethiopia, however, other high-oncogenic HPV types (31/33/45/52/58) that the 4vHPV vaccine cannot sufficiently protected have also been frequently detected in individuals with cervical cancer [15-17]identifying a prevalence of 67.1% in this population. High-risk HPV types 16 (55.7%. In Ethiopia, the combined prevalence of these other high-oncogenic HPV types is about 28.2 % [18]synthesized data on the genotype distribution of HPV is fundamental that is otherwise missed in Ethiopia. The aim of this study is to compile the findings on HPV genotyping in Ethiopia. Published articles were systematically searched using comprehensive search strings from PubMed/Medline and SCOPUS. Further, Google Scholar and the Google databases were also searched manually for grey literature. The included studies in the review employed 859 women (age range 15–85 years. Hence, switching from the 4vHPV vaccine to the 9vHPV vaccine will provide Ethiopia additional health and economic benefit. Notably, the present study aimed to evaluate the cost-effectiveness of introducing a 9vHPV vaccine compared to the 4vHPV vaccine for the prevention of cervical cancer among 12-year-old girls in Ethiopia where cervical cancer imposes a heavy health and economic burden on women of reproductive age. Additionally, our study sought to determine the maximum price per dose for the 9vHPV vaccine to remain cost-effective in comparison to the 4vHPV vaccine.

METHODS

Model structure

A previously published Markov cohort model, adapted to reflect the setting in Ethiopia, was used in our analysis [19]. The model includes three mutually exclusive health states: susceptible, cervical cancer, and death (Figure 1). Using this model, we analyzed a cohort of 100,000 girls aged 12 years. This group of girls was supposed to be not exposed to HPV. The cohort was followed up to the age of 100 years.

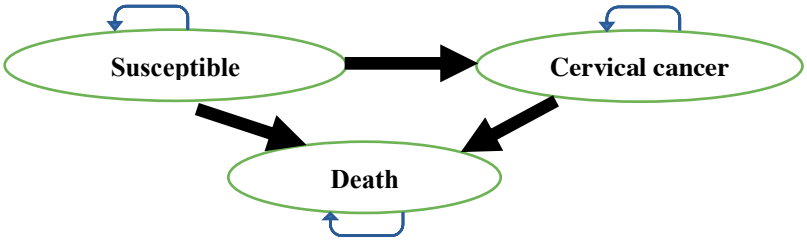

Figure 1: Schematic representation of the Markov model

Input Data

The parameters used in the current study are shown in Table 1. The efficacy data for the 4vHPV and 9vHPV vaccines were derived from clinical trial data and weighted by the proportion of cervical cancer attributed to various HPV strains among Ethiopian women [18,20,21]synthesized data on the genotype distribution of HPV is fundamental that is otherwise missed in Ethiopia. The aim of this study is to compile the findings on HPV genotyping in Ethiopia. Published articles were systematically searched using comprehensive search strings from PubMed/Medline and SCOPUS. Further, Google Scholar and the Google databases were also searched manually for grey literature. The included studies in the review employed 859 women (age range 15–85 years. Lifelong protection from HPV vaccination was assumed in our study. The incidence and mortality data for cervical cancer in Ethiopia was derived from the GLOBOCAN report [6]. Age-specific all-cause mortality among women was obtained from the World Health Organization (WHO) life table for Ethiopia [22]. The cost for treating cervical cancer was obtained from a previous cost-effectiveness analysis [23]. Gavi, the vaccine alliance, prices were used for the vaccines and school-based vaccine delivery cost was adopted from an earlier study [24,25]. Cervical cancer is the leading cause of female cancer-related deaths in Tanzania. Vaccination against human papillomavirus (HPV. All cost estimates were inflated to 2019 values [26].

Outcomes

The primary outcome measure used in this study was incremental cost-effectiveness ratio (ICER) of vaccination with the 9vHPV vaccine among 12 years old girls, compared with the 4vHPV vaccine. We also assessed the impacts of the 9vHPV vaccine prices per dose on the ICER values. An ICER that falls below once times the gross domestic product (GDP) per capita is considered very cost-effective, while if the ICER falls between one and three times GDP per capita, it is considered cost-effective. However, when it is more than three times GDP per capita, it is assumed to be cost-ineffective according to WHO's cost-effectiveness threshold [32,33]. The number of cervical cancer cases avoided and life-years saved were also reported. The analysis was done from the perspective of the healthcare system. Both the costs and health outcomes were discounted at the rate of 3%. Discount rates of 0 and 6% were used in the sensitivity analysis.

Sensitivity analyses

To test parameter uncertainty and assess the robustness of the results, both univariate and probabilistic sensitivity analyses (PSA) were performed, with the distributions used in the PSA as listed in Table 1.

Table 1: Model impute parameters, inclusive ranges for the univariate sensitivity analysis and distributions for the probabilistic analysis

Parameter	Base-case value	Range	Distribution (alpha, beta)	Source
The proportion of HPV 16/18 in CC	0.536	0.493 - 0.578	Beta (286, 248)	[18]
The proportion of other HrHPV in CC (31/33/45/52/58)	0.282	0.244 - 0.320	Beta (150.6, 383.4)	[18]
Vaccine efficacy in HPV 16/18 (4vHPV and 9vHPV vaccines)	0.975	0.926 - 0.995	Beta (121.2, 3.1)	[20,21†]
9vHPV vaccine efficacy in other HrHPV (31/33/45/52/58)	0.975	-		[20,21‡]
Vaccine coverage	0.532	0.201 - 0.957	Beta (1066.1, 937.9)	[27]
Cancer treatment Cost	$825.98	619.48 - 1032.47	Gamma (1, 825.98)	[23]
4vHPV vaccine price per dose	$4.50	-		[28]
9vHPV vaccine price per dose	$6.90*	5.18 - 8.63		[29]
Vaccine delivery cost	$4.62	3.47 - 5.78	Gamma (1, 4.62)	[30]
Utilities				
Susceptible	1			
Cancer	0.68	0.48 - 0.84	Beta-PERT (3.2, 2.8)	[31]
Death	0			
Discounting				
Discount rate cost	0.03	0 - 0.06		
Discount rate utility	0.03	0 - 0.06		

HPV: Human papillomavirus; CC: Cervical cancer; HrHPV: High-risk human papillomavirus; 4vHPV vaccine: quadrivalent human papillomavirus vaccine; 9vHPV vaccine: nonavalent human papillomavirus vaccine. * A projected price to be paid by Gavi. † Both vaccines were presumed to be equally effective against HPV type 16/18. ‡ The efficacy of 9vHPV vaccine against HPV types 31/33/45/52/58 was assumed to be the same as that against HPV types 16/18.

RESULTS

Public health impact of HPV vaccine

The public health impact of HPV vaccines in terms of cervical cancer incidence and life-years saved at vaccination coverage of 53.2% are shown in Figure 2. The model estimated that the 4vHPV vaccine and 9vHPV vaccine would prevent 519 and 793 cervical cancer cases by vaccinating 100,000 girls at the age of 12, respectively, when compared with the absence of HPV vaccination. Similarly, 80 (4vHPV vaccine) and 121 (9vHPV vaccine) discounted life-years would be saved in this population. Figure 3 shows cervical cancer cases prevented at different vaccination coverage. The results show that when vaccine coverage increased from about 50% to more than 90%, the number of cervical cancers prevented increased by about 70%.

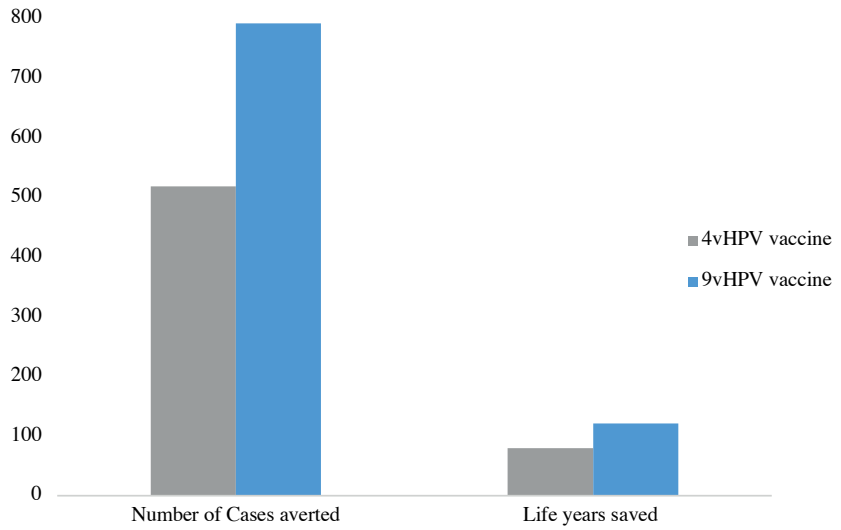

Figure 2: Estimated cases averted and discounted life-years saved by HPV vaccines (N=100,000; HPV: human papillomavirus; 9vHPV vaccine: nonavalent human papillomavirus vaccine; 4vHPV vaccine: quadrivalent human papillomavirus vaccine)

Table 2: Results of cost-effectiveness of analysis

Intervention	Cost (US$)	Effect (QALY)	Δ Cost (US$)	Δ Effect (QALY)	ICER (US$/QALY)
4vHPV vaccine	1,295,065	2,631,913	Reference	Reference	
9vHPV vaccine	1,485,049	2,632,332	189,984	419	454

ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year; 9vHPV vaccine: nonavalent human papillomavirus vaccine; 4vHPV vaccine: Quadrivalent human papillomavirus vaccine; US$: United States dollar

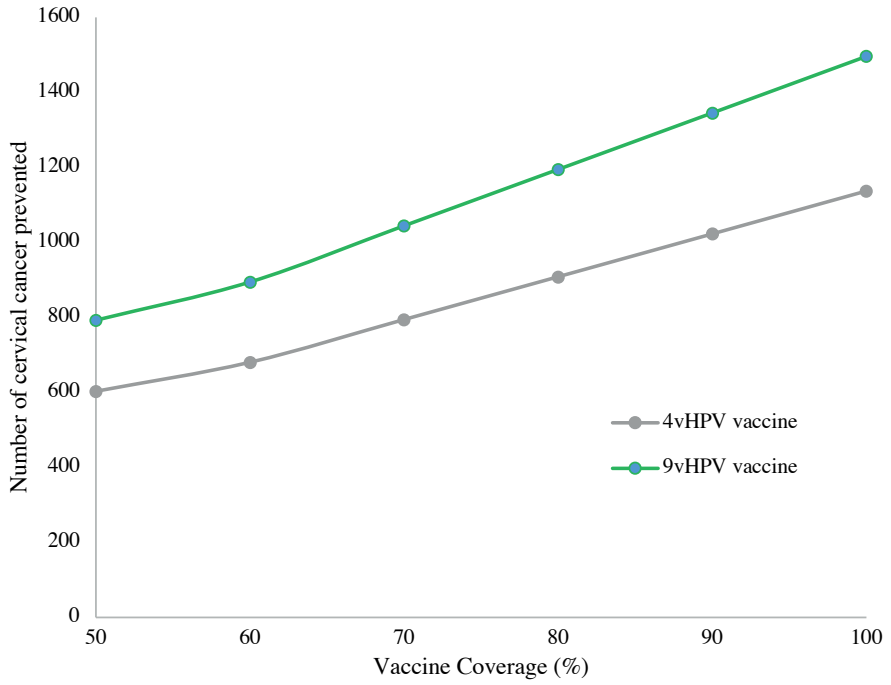

Figure 3: Cervical cases prevented at different HPV vaccine coverage rates (N=100,000; HPV: human papillomavirus; 9vHPV vaccine: nonavalent human papillomavirus vaccine; 4vHPV vaccine: quadrivalent human papillomavirus vaccine).

Cost-effectiveness analysis

Table 2 shows the results of a cost-effectiveness analysis. Compared with the 4vHPV vaccine, 419 quality-adjusted life-years (QALYs) would be gained with the 9vHPV vaccine at an incremental cost of US$ 189,984. This resulted in an ICER of US$ 454 per QALY gained. Figure 4 depicts the effect of 9vHPV vaccine price per dose on the ICER. Figure 4 shows that the 9vHPV vaccine is very cost-effective up to US$ 8.4 per dose and will be cost-effective up to US$ 15 per dose, using one- and three-times GDP per capita as cost-effectiveness thresholds, respectively, as recommended by the WHO.

Univariate sensitivity analyses

Results from univariate sensitivity analysis are presented in Figure 5. As displayed in the tornado diagrams, the ICER is mainly sensitive to the discount rate for QALYs.

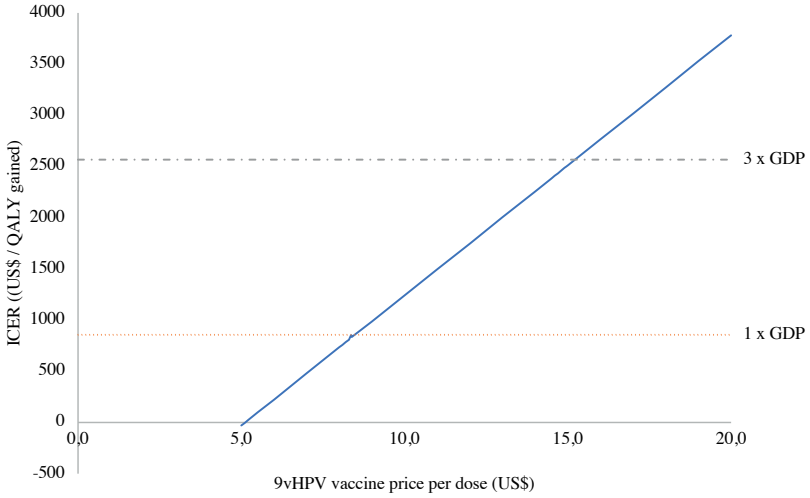

Figure 4: The effect of 9vHPV vaccine price per dose on ICER (US$ / QALY gained) (ICER: incremental cost-effectiveness ratio; 9vHPV vaccine: nonavalent human papillomavirus vaccine; QALY: Quality-adjusted life year; GDP: gross domestic product; US$: United States dollar).

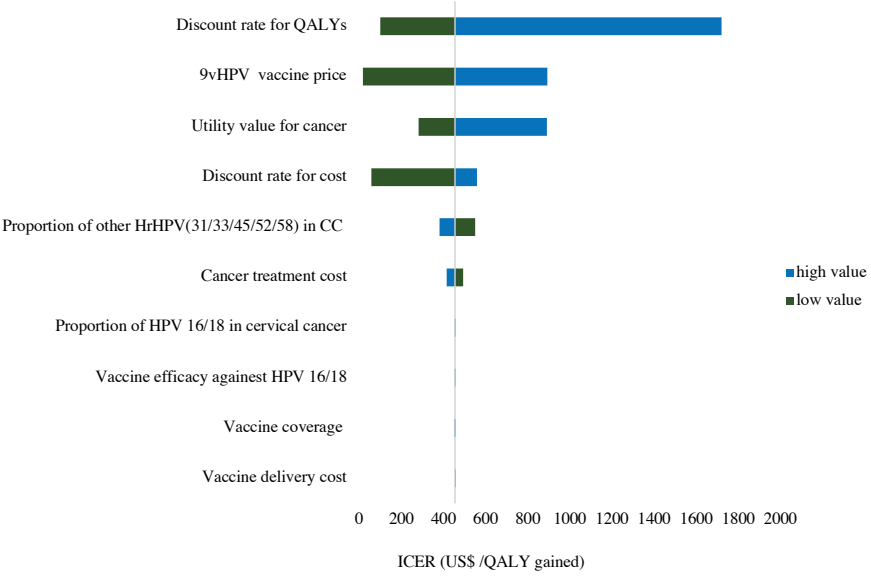

Figure 5: Tornado diagram of the univariate sensitivity analysis showing the impact of varying individual parameters on the ICER for the 9vHPV compared to the 4vHPV in Ethiopia (HPV: human papillomavirus; hrHPV: high-risk human papillomavirus; ICER: incremental cost-effectiveness ratio; 9vHPV: nonavalent human papillomavirus vaccine; 4vHPV: quadrivalent human papillomavirus vaccine; CC: Cervical cancer; QALY: quality-adjusted life year; US$: United States dollar).

Cost-effectiveness acceptability curve

The result from probabilistic sensitivity analysis is displayed in Figure 6 as a cost-effectiveness acceptability curve (CEAC). The CEAC shows that at a threshold of $856 per QALY gained (equivalent to one GDP per capita of Ethiopia), the 9vHPV vaccine is cost-effective at a probability of about 91%. The probability of being cost-effective reached 100% when the threshold increased to 3-times GDP per capita (US$ 2567 per QALY gained).

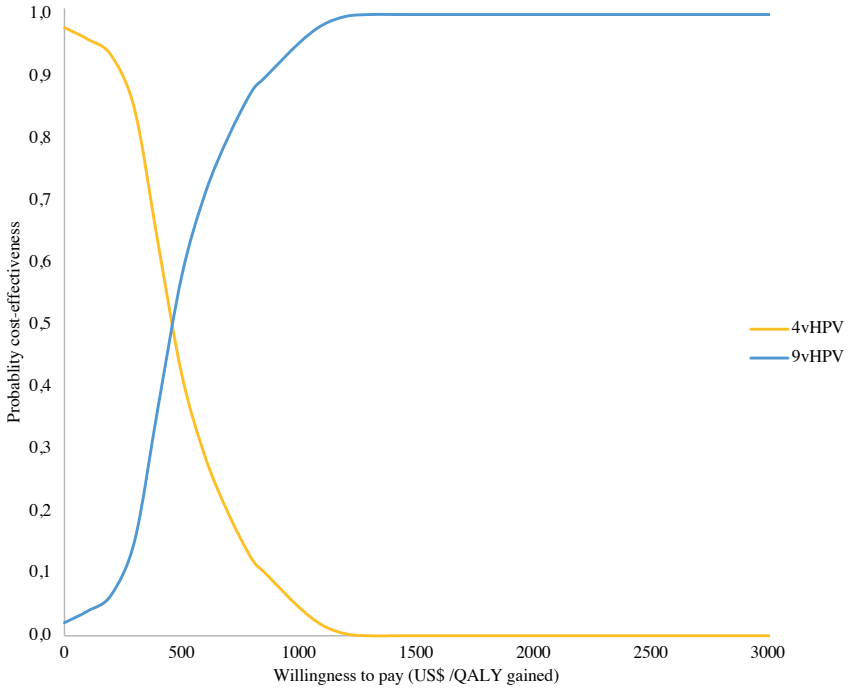

Figure 6: Cost-effectiveness acceptability curves comparing 4vHPV and 9vHPV (9vHPV: nonavalent human papillomavirus vaccine; 4vHPV: quadrivalent human papillomavirus vaccine; QALY: quality-adjusted life year).

DISCUSSION

In this study, the impact and cost-effectiveness of the 9vHPV vaccine compared to the 4vHPV vaccine was assessed in the Ethiopian setting. According to our findings, switching from the 4vHPV vaccine to the 9vHPV vaccine will provide an additional health benefit in terms of both cervical cancer cases avoided and life-years saved per vaccinated cohort of 12-year-old girls. This is of great importance for Ethiopia,

Africa's second-most populous country, where the cohort of 12-year-old girls was estimated to be 1, 338, 291 (in 2018) and cervical cancer is the second leading cause of cancer mortality among women [6,34]. The higher benefit from the 9vHPV vaccine than the 4vHPV vaccine observed in our study was because the former also protects cervical cancer from an additional five HPV subtypes (31/33/45/52/58), which were also identified as being responsible for a significant proportion of cervical cancer in Ethiopia [18]synthesized data on the genotype distribution of HPV is fundamental that is otherwise missed in Ethiopia. The aim of this study is to compile the findings on HPV genotyping in Ethiopia. Published articles were systematically searched using comprehensive search strings from PubMed/Medline and SCOPUS. Further, Google Scholar and the Google databases were also searched manually for grey literature. The included studies in the review employed 859 women (age range 15–85 years. In addition to maximizing the impact, switching from the 4vHPV vaccine to the 9vHPV vaccine will support WHO's cervical cancer elimination target, which calls for cervical cancer incidence to be reduced to less than 4 cases per 100,000 women in every country [35,36]Having adopted the written silence procedure through decision WHA73(7.

Not surprisingly, our study also suggests that the benefit from the HPV vaccine in Ethiopia can be maximized by increasing the vaccine uptake rate. As evidenced in other developing countries, the burden associated with cervical cancer in Ethiopia could be significantly reduced by building public awareness about HPV immunization and improving HPV vaccine uptake. For instance, Rwanda, a low-income country in Africa, has reached 90% of HPV vaccine uptake as a result of population-based policy interventions [37]. High vaccination coverage will ensure immunization equity and allow all vulnerable and at-risk populations to benefit from the HPV vaccine. According to a previous study conducted in Ethiopia, the poorest wealth quintile would receive roughly one-third of the health benefits and 50% of the financial risk protection benefits from HPV vaccination[38]where CC screening is extremely limited. An evaluation of the population health and financial risk protection benefits, and their distributional consequences across socioeconomic groups, from human papillomavirus (HPV.

The current study showed that switching from the 4vHPV vaccine to the 9vHPV vaccine would be very cost-effective in Ethiopia and the result was insensitive to changes in most parameters, showing the robustness of the conclusion. However, despite remaining below the threshold, the ICER was most influenced by the change in discount rates for QALYs. This is because the discount rate reduces the benefit of the HPV vaccine, as the benefit occurs many years after vaccination. The United Kingdom Joint Committee on Vaccination and Immunization recommended a non-reference-case discount rate of 1.5% instead of the usually applied 3.5% in the United Kingdom

(UK) when the benefit of intervention is sustained over a long period (at least 30 years) [39]. The PSA also demonstrated that when compared to 4vHPV vaccine, 9vHPV vaccine has a higher chance of being cost-effective (>90%).

The results from the present analysis showed that the 9vHPV vaccine would be very cost-effective up to a price of about US$ 8.4 per dose and cost-effective up to a price of US$ 15 per dose, according to WHO criteria of cost-effectiveness. The results could contribute to future price negotiations between Gavi and vaccine manufacturers. Despite the differences in the type of model employed, several previous economic evaluation studies confirmed the cost-effectiveness of the 9vHPV vaccine when compared to 4vHPV vaccine. The price at which the 9vHPV vaccine is cost-effective varies across the countries [40–43]. However, a Chinese study found that the 9vHPV vaccine was not a cost-effective option. The authors hypothesized that the relatively higher price difference between the 9vHPV and 4vHPV vaccines in China was primarily responsible for inconsistent results [44].

Although this analysis concludes that the 9vHPV vaccine would be (very) cost-effective compared to the current 4vHPV vaccine, the decision to switch to the 9vHPV vaccine would be associated with significant budget impact in Ethiopia, where the national domestic general government health expenditure amounts to only 0.77% of the GDP [45]. Hence, the affordability and sustainability of the vaccination program through self-financing seems debatable. Therefore, as the 9vHPV vaccine is not yet included in the Gavi support list for low-income countries, the country could seek support from other potential international partners to switch from 4vHPV vaccine based universal vaccination to 9vHPV vaccine based universal vaccination.

The current study is subject to some caveats. First, the cohort model used in our research will underestimate the impact of the HPV vaccine as it fails to capture the indirect benefits of vaccination gained from herd immunity. Besides, the current analysis also disregards the effect of HPV vaccines on the genital wart and non-cervical cancers, including vulvar, anal, oropharyngeal, and vaginal cancers. Therefore, this will further underestimate the potential benefit of the vaccines.

CONCLUSIONS

Compared to Ethiopia's current vaccination program with the 4vHPV vaccine, the 9vHPV vaccine has the potential to provide significant additional public health benefits. By switching to the 9vHPV vaccine, 274 additional cervical cancer cases will be avoided, and 42 life years will be gained per 100,000 vaccinated girls in Ethiopia. The 9vHPV vaccine is also (very) cost-effective when compared with the 4vHPV vaccine. The 9vHPV vaccine remains cost-effective up to a price of US$ 15 per dose.

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