Master's Thesis of Irina Aulianisa

Forecasting Epidemiological Impact and Cost-effectiveness of Human papillomavirus (HPV) Vaccination Among Pre-adolescent Females in Indonesia:

a UNIVAC Modelling Study

청소년기 이전의 인도네시아 여성에서 인유두종 바이러스(HPV) 백신의 역학적 영향과 비용효과의 예측: UNIVAC 모델링을 활용하여

February 2023

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Submitting a master's thesis of Public Health

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Confirming the master's thesis written by
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February 2023

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Abstract

Cervical cancer responsible for 32,469 new cases and 18,279 deaths in 2021, causing a catastrophic national healthcare expenditure. The Ministry of Health decreed a regulation to accelerate the HPV vaccination from 2022-2024. This study aims to estimate the epidemiological, cost-effectiveness, and budget impact of a two-year HPV vaccination program. A static cohort model based on Excel called UNIVAC was used to forecast the lifetime costs and health impacts of selecting quadrivalent or bivalent vaccines for 9-year-old girls and varying vaccine costs. Under the cost-effectiveness threshold (CET) range from $687 to $1459 (16% and 34% GDP per capita), the bivalent and quadrivalent HPV vaccination estimate the ICER $322 and $325/DALYs averted at Gavi prices compared to no vaccination. The quadrivalent with government contract price value of ICER was $894/DALYs averted. According to health opportunity cost estimate as the CET ($687), adopting a two-dose HPV vaccination program for pre-adolescent girls in Indonesia would be cost-effective from the government's perspective by using Gavi price. Additionally, all vaccines prices scenarios would be considered cost-effective using the $1459 as CET. Policymakers are advised to invest on a two-dose HPV vaccine at Gavi price as long as Indonesia continues to have procurement during this Gavi transitional phase until 2025.

Keyword: Cost-effectiveness analysis, Cervical cancer, Indonesia, UNIVAC, Human papillomavirus

Student Number: 2021-25757

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Chapter 1. Introduction

1.1 Study Background

1.1.1 Cervical cancer

Human papillomavirus (HPV) has been identified for more than 200 strains by deoxyribonucleic acid (DNA) sequence data worldwide, and 40 strains of HPV can infect the genital region (Kocjan et al., 2015). HPV is the number one prevalent cause of sexually transmitted diseases, where 99.7% is an oncogenic virus that plays a significant role as cervical cancer's leading cause (Veldhuijzen et al., 2010). There are two types of HPV, 16 and 18, which explain 70% of the highest risk of all types of cervical cancer (Kaliff et al., 2018). In 2020, cervical cancer burdened global health with 604,127 new cases and 341,831 mortalities in both sexes, making the cervical cancer as the second-highest incidence and mortality rates among females with the age-standardized incidence and mortality rate of 13.1 and 6.9 per 100,000, respectively (Sung et al., 2021). 85% of these deaths occur in low- and middle-income countries (LMICs) (Salomon et al., 2015), where Indonesia, unfortunately, is also one of them.

With 32,469 new cases and 18,279 deaths (13.9 per 100,000) (Sung et al., 2021), cervical cancer is the second most common cancer among Indonesian women. Since 2000, the deaths of cervical cancer have been decreasing very slowly until this recent period (figure 1). It is predicted that 1.7 million women will die from cervical cancer in Indonesia by 2070, and 3.95 million will die by 2120 without any interference of prevention (Canfell et al., 2020). Fewer than 1 in 10 women in Indonesia have been screened for cervical cancer in the last five years, affecting 76.6 percent of patients who have entered the advanced stage when detected (IARC, 2020; Sumarmi et al., 2021). The Indonesian government spent about $2.5 million on cervical cancer treatment in 2011, which was only provided to low- and middle-income individuals under the Social Health Insurance (JAMKESMAS) system. As of 2014, when Universal Health Coverage has been implemented, cervical cancer's clinical and economic burdens are potentially much higher since the government covers the full cost of treating the disease (Setiawan et al., 2020).

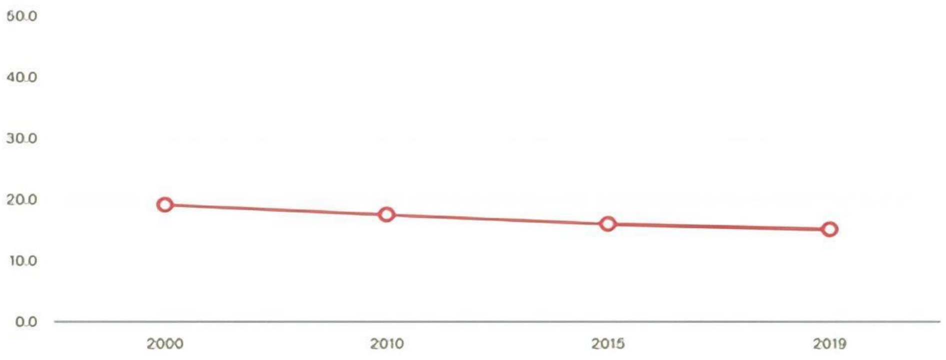

Figure 1 Age-standardized death rate per 100,000 women for cervical cancer in Indonesia (2019)

1.1.2 HPV vaccine

Initial commercial development of HPV vaccines was undertaken by 2 companies, GlaxoSmithKline Biologicals (GSK) and Merck & Co (Inglis et al., 2006). GSK developed a bivalent vaccine (Cervarix), composed of HPV-16 and

HPV-18 virus-like particles (VLP). Merck developed a quadrivalent vaccine (Gardasil), with HPV-16 and HPV-18 as well as HPV-6 and HPV-11 VLPs. Merck later developed a nonvalent vaccine, Gardasil 9, similar to Gardasil but containing L1 VLPs of 5 additions oncogenic types of HPV 31, 33, 45, 52, and 58 and so has the potential to provide type specific protection against approximately 90% of cervical cancers worldwide (de Martel et al., 2017).

Based on USA studies in the past 20 years about HPV vaccination, as early as 4 years after Gardasil licensure, vaccine-type HPV infections had decreased 56% among 14–19-year-old females (Markowitz et al., 2013). Other studies showed that within 12 years of vaccine introduction, infections with the four HPV types prevented by Gardasil decreased 88% among 14–19-year-old females and 81% among 20–24-year-old females in the United States (McClung et al., 2019). Therefore, Indonesia's health ministry generated a decree based on the WHO amendment, to prevent and eliminate cervical cancer by implementing HPV vaccination for adolescents, with the school-based vaccination program, as the first prevention and secondary prevention by pap smear test and Visual Inspection of Acetic Acid (VIA) (McGraw, 2014; Setiawan et al., 2020). HPV vaccination is given to provide protection against infection with the HPV virus, especially those that highly invasive and can cause cervical cancer, namely HPV types 16 and 18 (Patel et al., 2018).

1.1.3 HPV vaccination program in Indonesia

In Indonesia presently, HPV vaccines are exceedingly expensive. Additionally, since Indonesia entered the GAVI accelerated transition phase since 2016, it is currently ineligible for the co-financing policy implementation scheme, which GAVI and Indonesia would equally finance vaccines. Therefore, the government of Indonesia must provide approximately five million doses of HPV vaccination by calculated from two doses multiplied by 2.5 million girls in the age of 10 years-old in each year, furthermore, this self-financing HPV vaccination strategy takes a significant amount of the national budget (Setiawan et al., 2020).

After the introductory of HPV vaccination program from 2016 until 2021, Indonesia Ministry of Health decreed a regulation to accelerate the HPV vaccination program for pre-adolescent girls since 2022 until 2024 because of the excessive burden that caused by cervical cancer (Indonesia Ministry of Health, 2021). The School Child Immunization Month (Bulan Imunisasi Anak Sekolah, (BIAS)) campaign, which targets girls of primary school age, is integrated with the implementation of the 2022–2024 HPV immunization introduction program (Indonesia Ministry of Health, 2021). Jakarta, the capital city, was the pilot to execute the program in 2016 (Ayuningtyas & Sutrisnawati, 2018), followed by Yogyakarta in 2017, and other Indonesian big cities such as Surabaya, Makassar, and Manado in 2018 (Indonesia Ministry of Health, 2017).

After the pilot project, in April 2022, the HPV vaccine was added to the list of routine, free immunizations given across the country to accelerate the program, according to an official announcement made by Indonesian Health Minister, which makes a significant milestone in Indonesia's efforts to eradicate cancer and improve the sexual and reproductive health of women and girls (Bennett & Dewi, 2022). The HPV vaccination program in Indonesia is an elementary school-based program, where the authorities is the one who actively came to the adolescents. It is based on pilot studies that no-cost, voluntary mass vaccinations in schools are well received and result in higher immunization rates, and that improving access to the HPV vaccine is associated with greater improvements in vaccine uptake than other interventions (Walling et al., 2016). Schools have the highest reach to adolescents and demonstrate success in providing vaccines (Hall et al., 2000; Walling et al., 2016). Introducing the HPV vaccine in a school-based setting provides a rare opportunity to build and strengthen school and adolescent health by offering preventive and curative health interventions and education (Bloem & Ogbuanu, 2017).

1.1.4 Health economic evaluation in HPV vaccination

Cost-effectiveness assessment is an essential technique to help decision-makers evaluate the worth of certain initiatives and guide decisions about how to allocate resources (Bardach et al., 2017). In recent decades, pilot studies have been conducted in Indonesia for cervical cancer screening and HPV vaccination (Kim et al., 2013; Kosen et al., 2017; Spagnoletti et al., 2019; Setiawan et al., 2020). Although the research concluded that HPV vaccination is generally affordable and cost-effective, these issues are still major challenge in low-middle income countries (LMICs) such as Indonesia. Due to variances in epidemiological parameters such as the prevalence of specific HPV-related diseases, local treatment practices, and associated costs, the results of the analysis differ greatly from country to country. Most of Asian countries discovered the HPV vaccine for adolescent females to be cost-effective, however, it is crucial for LMICs to lower the cost of the HPV vaccine to a point where HPV vaccination can be implemented at a low cost (Zhu et al., 2022). A national HPV vaccination program as well as cervical cancer screening and treatment programs need to be implemented to reach the elimination targets, and health workforce competencies across all three pillars (HPV vaccination, cervical screening, and treatment) need to be improved for long-term success of HPV vaccination program for pre-adolescent girls (UNFPA Asia-Pacific Regional Office, 2022).

1.2 Purpose of Research

This study will estimate the epidemiological impact, cost-effectiveness, and budget impact of HPV vaccination of pre-adolescent girls in Indonesia through a comprehensive health economic analysis of Indonesia's two-year HPV vaccination program. By comparing different scenarios and forecast outcome, it would provide considerable strategies for Indonesia to arrange the next move in HPV vaccination program implementation.

Chapter 2. Systematic Review as A Pre-study

Health and Economic Evaluation of Pre-Adolescent HPV Vaccination Program in Low and Lower Middle-Income Country

2.1 Introduction

Based on the global cervical cancer trends in 2020, low-income country (LIC) and low-middle-income country (LMIC) countries are the most affected. The incidence reached 23.8 and 17.4 in low-income countries, and mortality reached 16.9 and 10.6 in low-middle-income countries. The mortality gap between high and low-income countries is almost seven times (WHO, 2020a). In 2022, cervical cancer will affect 604,000 women and be responsible for 342,000 deaths, with more than 90% of these deaths occurring in LIC and LMIC (Sung et al., 2021). Since 2009, to overcome the situation, the WHO has advised human papillomavirus (HPV) vaccinations, which have been accessible since 2006 (Bruni et al., 2021). Based on the catastrophic disease development, the WHO developed a global strategy to hasten the eradication of cervical cancer for the years 2020–2030, with one of their top goals being to achieve 90% coverage of girls receiving the HPV vaccine (by 15 years of age) (WHO, 2020b).

Since 2019, the national vaccination programs of 100 nations had included the

HPV vaccine. However, just 30 percent of the world's population is covered by the 100 countries, and LICs and LMICs have a substantially lower introduction rate of the HPV vaccine than high-income countries (WHO, 2019). Without vaccination, costs for treating cervical cancer patients in LIC and LMIC countries were estimated at more than $100 million, $50 million, and $10 million, as reported in Philippines (Llave et al., 2022), Ghana (Vodicka et al., 2022), and Bangladesh (Mahumud et al., 2020). The significant economic burden of cervical cancer, particularly in LIC and LMIC countries is correlated with its high epidemiological burden (Hull et al., 2020). The vaccination against HPV was also stated to be cost-effective in many LMIC countries, however, many LMIC countries' have not yet implemented an HPV vaccination program through a comprehensive national vaccination plan, although numerous LMIC country studies have demonstrated the cost-effectiveness of the HPV vaccine (Frianto, Setiawan, Diantini, & Suwantika, 2022).

A review study is known to be able to synthesize, gather key data from various studies, and draw essential conclusions from the subjects covered. In light of this, it is essential to carry out thorough reviews of the economic impact of HPV vaccination in nations throughout the world that have implemented targeted vaccination policies (Frianto et al., 2022). There are already several modellings being developed to assess the health and economic impact of vaccination programs which can be applied in LIC and LMIC settings, there are Markov (Wondimu, Postma, & van Hulst, 2022), PRIME (Mahumud et al., 2020), UNIVAC (Anwari et al., 2020; Llave et al., 2022; Luvsan et al., 2022; Vodicka et al., 2022), and CERVIVAC model (Yaghoubi et al., 2018). This systematic review aimed to synthesize the epidemiological impact and cost-effectiveness of introducing the HPV vaccination program in pre-adolescent girls in LIC and LMIC countries.

2.2 Materials and Methods

2.2.1 Search Strategies

A literature search for the period from 1st January 2017 to 1st October 2022 was conducted using two databases, which are PubMed and Embase. Full search strategy was as follow: ("cost-effectiveness" OR "cost utility" OR "cost benefit" OR "economic outcome" OR "economic evaluation" OR "health economics" OR "economic assessment") AND ("human papillomavirus" OR "HPV") AND ("vaccine" OR "vaccination" OR "vaccinated" OR "immunization").

2.2.2 Inclusion and exclusion criteria

Journal articles written in English were included if (1) bivalent, quadrivalent, and nonavalent HPV vaccination was evaluated; (2) assess the HPV vaccination program from LIC and LMIC based on the world bank data (Yonzan, 2022); (3) the study population is 9-14 years girls; and (4) a comprehensive health economic analysis was performed; (5) decision analytic models were applied to evaluate health economics outcomes. The exclusion criteria were the following: (1) the evaluation include other disease than cervical cancer; (2) other vaccine than HPV vaccination;

(3) other interventions such as cervical cancer screening programs; (4) the articles were reviews, protocol papers, letters, editorials, conference abstracts, poster presentations with insufficient details, or case reports. These criteria are demonstrated in the study selection in figure 2.

2.2.3 Quality and Assessment

The Consolidated Health Economic Evaluation Reporting Standards (Husereau, Drummond, Augustovski, de Bekker-Grob, Briggs, Carswell, Caulley, Chaiyakunapruk, Greenberg, Loder, Mauskopf, Mullins, Petrou, Pwu, Staniszewska, et al.) Statement is used to assess the studies. This tool, created by the International Society for Pharmacoeconomics and Outcomes Research, was utilized to evaluate the accuracy of the cost-effectiveness of HPV vaccination reporting in the studies that were included. 24 items made up the CHEERS checklist (Husereau, Drummond, Augustovski, de Bekker-Grob, Briggs, Carswell, Caulley, Chaiyakunapruk, Greenberg, Loder, Mauskopf, Mullins, Petrou, Pwu, Staniszewska, et al., 2022). Studies were categorized as providing decent reporting quality, moderate reporting quality, and low reporting quality if they prove to checklist 20–24 items, 14–19 items, and fewer than 14 items, respectively (Zhu et al., 2022).

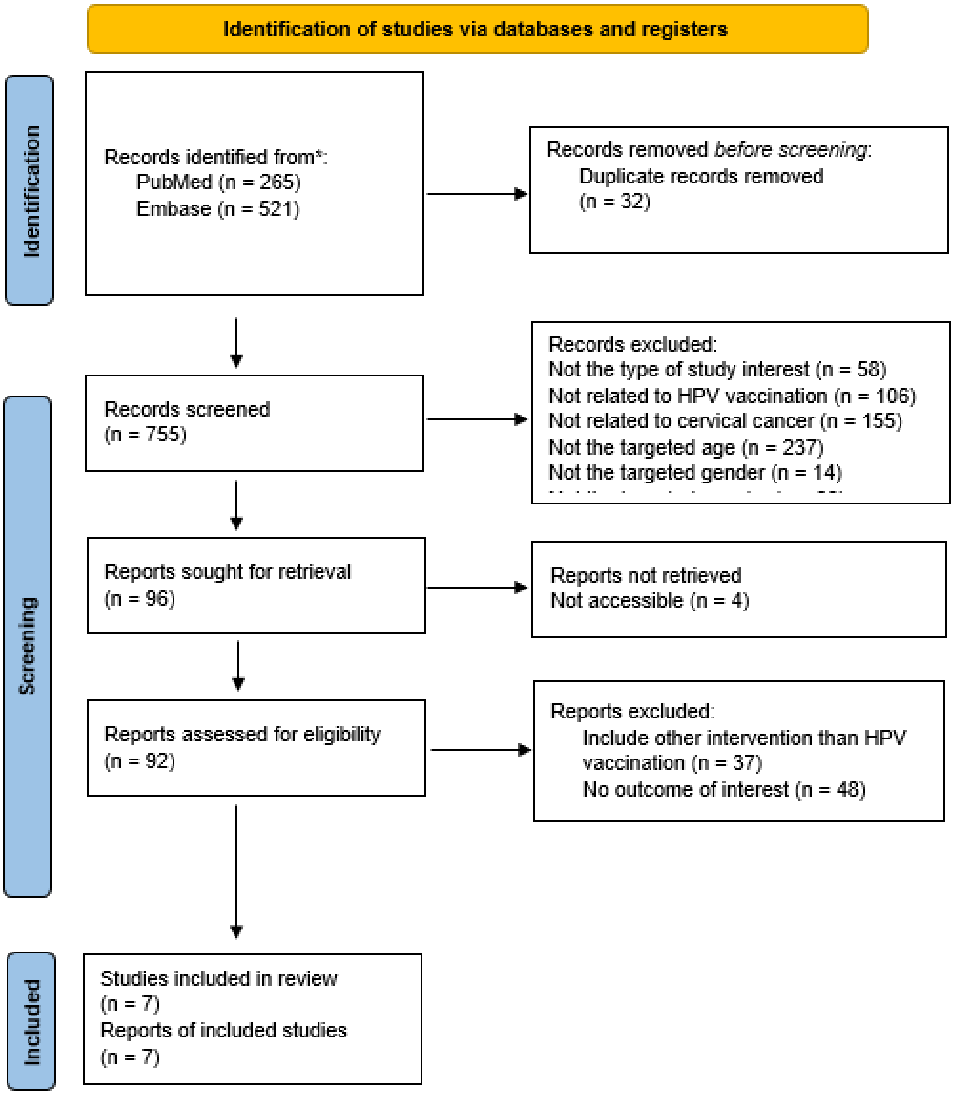

Figure 2 The flowchart of study selection based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Canfell et al., 2020).

2.3 Results

From two databases, 787 articles, approximately, were retrieved (226 articles from PubMed and 521 articles from Embase, respectively). 32 articles were cut from these figures due to duplication. Titles and abstracts of 755 papers were examined. Following the initial screening, 58 articles were excluded because they were on the list of articles with study design exclusions, 106 articles were excluded because they were not related to HPV vaccination, 155 articles were excluded because they were not associated with cervical cancer, 237 articles had populations that were not pre-adolescent, 14 articles had populations that were not specifically female, and 89 articles were excluded because they did not included as LI and LMI countries. In all, 96 articles were sought for retrieval, but 4 were not obtained since the full text was not available. There are about 92 full text articles that have been evaluated for eligibility. In the last screening process, 48 papers failed to indicate the desired outcome, and 37 articles were removed because they had interventions other than HPV vaccination. Finally, as shown in figure 1, we only included 7 articles that fulfilled all inclusion and exclusion requirements.

2.3.1 Characteristic and Study Designs

Seven studies in this review focused on different LIC and LMIC countries which are Mongolia (Luvsan et al., 2022), Philippines (Llave et al., 2022), Ethiopia (Wondimu et al., 2022), Ghana (Vodicka et al., 2022), Afghanistan (Anwari et al., 2020), Bangladesh (Mahumud et al., 2020), and Iran (Yaghoubi et al., 2018). All these studies were conducted from 2018 through 2022. Five studies were conducted in Asia (Anwari et al., 2020; Llave et al., 2022; Luvsan et al., 2022; Mahumud et al., 2020; Yaghoubi et al., 2018), and two were conducted in Africa (Vodicka et al., 2022; Wondimu et al., 2022). Considering countries' income levels, three studies were conducted in low-income countries (Anwari et al., 2020; Mahumud et al., 2020; Wondimu et al., 2022), and four were conducted in lower-middle-income countries (Llave et al., 2022; Luvsan et al., 2022; Vodicka et al., 2022; Yaghoubi et al., 2018). Both government and societal perspectives were applied by five included studies (Anwari et al., 2020; Llave et al., 2022; Luvsan et al., 2022; Vodicka et al., 2022; Yaghoubi et al., 2018), and just government perspective was applied by two studies in Bangladesh and Ethiopia (Mahumud et al., 2020; Wondimu et al., 2022).

Additionally, four different models were applied as the methods. A static Markov cohort model was used by the Ethiopia study (Wondimu et al., 2022). The PRIME (Papillomavirus Rapid Interface for Modelling and Economics) model was utilized by the Bangladesh study (Mahumud et al., 2020), the CERVIVAC model was used by the Iran study (Yaghoubi et al., 2018), and the rest of it used the UNIVAC model (Anwari et al., 2020; Llave et al., 2022; Luvsan et al., 2022; Vodicka et al., 2022). Discount rates for both cost and utility were 3% in six country studies (Anwari et al., 2020; Luvsan et al., 2022; Mahumud et al., 2020; Vodicka et al., 2022; Wondimu et al., 2022; Yaghoubi et al., 2018), only the Philippines study mentioned using 5.33% for the cost, 3% and 10% for the utility discount (Llave et al., 2022). In terms of the vaccine type, three countries include both bivalent and quadrivalent vaccines in their evaluation. The Philippines study assessed four types of vaccine quadrivalent, nonavalent, and two different brands of bivalent vaccine (Llave et al., 2022). On the other hand, Iran and Ethiopia's study evaluate just one type of vaccine (Wondimu et al., 2022; Yaghoubi et al., 2018). Vaccination coverage scenarios for one vaccination dose were applied in Ethiopia (Wondimu et al., 2022), and three doses were applied in Iran (Yaghoubi et al., 2018). The other five countries applied two-doses vaccination (Anwari et al., 2020; Llave et al., 2022; Luvsan et al., 2022; Mahumud et al., 2020; Vodicka et al., 2022). In addition, the vaccine coverage also varies between the countries, range from 32.5% to 95%.

For the population targeted age girls, five studies chose nine years old girls (Anwari et al., 2020; Llave et al., 2022; Luvsan et al., 2022; Vodicka et al., 2022; Yaghoubi et al., 2018), while Bangladesh applied ten years old (Mahumud et al., 2020), and Ethiopia applied twelve years old (Wondimu et al., 2022). All these studies using cost-effectiveness analysis for the economic evaluation stated their cervical cancer epidemiology situation in their background.

In economic evaluation studies and mathematical modeling research, handling with uncertainty is a crucial matter (Frianto et al., 2022). It is important part of any economic evaluation, and a lack of analysis is evidence of a poor-quality study (Walker & Fox-Rushby, 2001). Five country studies applied one-way and probabilistic sensitivity analysis (PSA) (Anwari et al., 2020; Llave et al., 2022; Luvsan et al., 2022; Vodicka et al., 2022; Wondimu et al., 2022), meanwhile the other two country studies applied one-way sensitivity analysis (Mahumud et al., 2020; Yaghoubi et al., 2018). More detailed information can be seen in table 1.

Table 1 Study characteristic and CHEERS item

Country, income levels (year)	Study Perspective	Methods	Discount Rate		Vaccination			Age	Study Type	Sensitivity Analysis
			Cost	Utility	Type	Coverage	Efficacy			
Mongolia, LMIC (2022)	GP & SP	UNIVAC model	3%	3%	Bivalent & Quadrivalent	93%, 93%	94%	9	CEA	One-way & PSA
Philippines, LMIC (2022)	GP & SP	UNIVAC model	5.33 %	3% & 10%	Bivalent (Cervarix™ & Cecolin®), Quadrivalent, Nonavalent	78%, 60.5%	From 63.4% to 91.4%	9	CEA	One-way & PSA
Ethiopia, LIC (2022)	GP	Markov model	3%	3%	Quadrivalent & Nonavalent	53.2%	97.5%	12	CEA	One-way & PSA
Ghana, LMIC (2021)	GP & SP	UNIVAC model	3%	3%	Bivalent & Quadrivalent	93%, 92%	94%	9	CEA	One-way & PSA
Afghanistan, LIC (2019)	GP & SP	UNIVAC model	3%	3%	Bivalent	70%, 65%	32.5%, 65%	9	CEA	One-way & PSA
Bangladesh, LIC (2019)	GP	PRIME model	3%	3%	Bivalent & Quadrivalent	70% (2 dose)	95%	10	CEA	One-way
Iran, LMIC (2018)	GP & SP	CERVIVAC model	3%	3%	(3 dose) Quadrivalent	85%, 83%, 80%	94.3%	9	CEA	One-way

The vaccination coverage and efficacy are in order by 1st dose, 2nd dose, and 3rd dose. CEA: cost-effectiveness analysis. GP: Government perspective, SP: Societal perspective.

2.3.2 The vaccination strategy and health outcomes

Based on the study in Mongolia, where they calculated the outcome for the vaccination program will reached 20% cervical cancer cases averted, which conclude that the HPV vaccination program was cost-effective compared to no vaccination at all (Luvsan et al., 2022). With modified scenario by applying four different types of HPV vaccines and compared them with no vaccination. Their result when comparing no vaccination, the utility of Cecolin®®, Gardasil™, or Gardasil® in the vaccination program are estimated to be cost-effective, however Gardasil® was the most beneficial compared to others. In a scenario where cross-protection was not considered, results were similar except that Cervarix™™ and Gardasil® were both dominated by Cecolin®. On the other hand, even though it was the highest vaccine type for the case averted, Gardasil®9 was not cost-effective under any of the modeled scenarios (Llave et al., 2022). In contrast with this result, an Ethiopia mentioned nonavalent vaccine was the cost-effective choice with 53.2% avert cases, compared to quadrivalent vaccine (Wondimu et al., 2022).

In the study held in Ghana settings, the intervention projected to avert the cases up to more than 77,000 cases, which makes the program cost-effective under in any scenarios. A one-time catchup campaign is demonstrated to more beneficial than routine immunization alone, even though it would increase program cost (Vodicka et al., 2022). Afghanistan study stated in terms of vaccination strategy scenario, would avert case 45%, compared to no vaccination, they conclude the HPV vaccine program targeting a single cohort might well be cost-effective from both the government and societal perspectives, with additional health benefits generated by a catch-up campaign (Anwari et al., 2020). Meanwhile in Iran study, when they used three-doses of quadrivalent vaccine is not quite cost-cost-effective, even that so the vaccination program would avert case was 182 compared to no vaccination, in addition, a two-dose schedule or lowering vaccination pricing has an impact on final conclusions (Yaghoubi et al., 2018).

A Bangladesh study has a different approach of strategy than others, it measured how cost-effective of the vaccination program when using the bivalent and quadrivalent listed price compared to bivalent Gavi-negotiated vaccination (Mahumud et al., 2020). They declared with Gavi-negotiated costs, implementing a two-dose bivalent HPV vaccination program is cost-effective. The primary factor determining the cost-effectiveness of bivalent and quadrivalent vaccines is vaccine cost. At the listed pricing in Bangladesh, neither quadrivalent nor bivalent vaccine is economically advantageous. However, they succeed to avert the cervical cancer by 1,317 cases for bivalent and 2,575 cases for quadrivalent vaccine (Mahumud et al., 2020). More detailed information can be seen in Table 2.

Table 2 The vaccination strategy and health outcomes

Country (year)	Vaccination Strategy		Epidemiological Impact (Case Averted)	CHEERS
	Current practice	New Intervention		
Mongolia (2022)	No vaccination	With vaccination	20%	27/28
Philippines (2022)	No vaccination	With vaccination	Cervarix: 123,795 cases Cecolin: 99,703 cases Gardasil: 97,922 cases Gardasil9: 127,166 cases	27.5/28
Ethiopia (2022)	Quadrivalent vaccination	Nonavalent vaccination	53.2%	20/28
Ghana (2021)	No vaccination	With vaccination	77,426 cases	28/28
Afghanistan (2019)	No vaccination	With vaccination	45%	23/28
Bangladesh (2019)	Listed vaccine price	GAVI negotiated vaccine price	Bivalent: 1,317 cases Quadrivalent: 2,575 cases	27/28
Iran (2018)	No vaccination	With vaccination	182 cases	27/28

2.3.3 The vaccination program and healthcare cost averted

Vaccine price varied at $4.5-$87.4 from all included studies with the lowest and highest vaccine prices per dose were found in Afghanistan and Bangladesh, respectively (Anwari et al., 2020; Mahumud et al., 2020). In terms of total HPV vaccination program costs, it reported to be in the range $1.3-$637 million, with the lowest and highest program costs were found in Ethiopia and Philippines, respectively (Llave et al., 2022; Wondimu et al., 2022).

In particular, a study in Mongolia calculated treatment cost reduction due to vaccination up to $5 million for bivalent vaccine and more than $4.2 million for quadrivalent vaccine, both in government and societal perspective (Luvsan et al., 2022). With the same scenario comparing the bivalent and quadrivalent vaccine with no vaccination scenario, a study in Ghana using the same price of vaccine per dose with Mongolia (Gavi price), the total program cost using the bivalent and quadrivalent are more than $97 million, respectively. Their treatment cost averted in government and societal perspective, up to $34.3 - $35.6 million for using bivalent vaccine, and $22.2 - $23.1 million for using quadrivalent vaccine, with the ICER range from $266 - $272 per DALYs averted in bivalent vaccine, and $488 - $494 per DALYs averted in quadrivalent vaccine (Vodicka et al., 2022). In Afghanistan, with the strategy of country co-financing and Gavi, the vaccine per dose for using bivalent vaccine would be $0.20 and $4.60, and their total program cost achieved $3.3 million per year. The result came out with $203 thousand treatment cost reduced in societal perspective, the ICER are $400 - $426 in societal and government perspective (Anwari et al., 2020).

In the Ethiopia study, they used Gavi price with the value $4.50 and $6.90 vaccine per dose, and total program cost $1.2 - $1.4 million for quadrivalent and nonavalent vaccine. Their ICER calculation result is $454 per QALY gained (Wondimu et al., 2022). The Philippines study, with their four types of vaccine scenario mentioned that their cervical cancer treatment reduced more than six times in societal perspective compared to government perspective. With the least treatment cost reduced by Gardasil® with $17,8 million in government perspective and the highest reduced is by Gardasil®9 with $151 million in societal perspective (Llave et al., 2022).

The study in Bangladesh, has the highest vaccine price scenario with the bivalent vaccine in Gavi price up to $9 per dose, and listed price $51 for bivalent and $85 for quadrivalent vaccine, with program costs are range from $11 - $87.4. The treatment cost reduction by government perspective achieved $5.9 million for the Gavi bivalent vaccine, $13.3 million for bivalent listed vaccine, and $11.2 million for the quadrivalent vaccine. Their ICER results showed $4.5 thousand per DALYs averted for the Gavi bivalent vaccine price, $14.8 and $33.5 thousand for listed price bivalent and quadrivalent vaccine (Mahumud et al., 2020). The largest dose vaccine scenario being used by Iran study. With three-doses quadrivalent vaccination strategy applied, the vaccine price per dose is $13.75, and total program cost in government perspective is $23 million, societal perspective is $22.7 million, respectively. With that strategy, the results are treatment cost prevented would be around $379 and $692 thousand and the ICERs are $15.2 and $15 million per DALYs averted for government and societal perspective (Yaghoubi et al., 2018). More detailed information can be seen in Table 3.

2.3.4 Cost-effectiveness threshold and value

Estimating the value affected persons place on the efficacy measure, such as a DALY, is one method for creating such thresholds. The one and three times gross domestic product (GDP) per capita threshold, which are frequently employed in global health, are based on the idea of each person's estimation willingness to pay for a change in their own risk are averaged throughout the affected population to arrive at this number, which is then stated as the cost of a life year. The values are scaled to the resources available in each countries using GDP per capita (Robinson et al., 2017). On this review, all the studies used GDP per capita for the CET. The most common used are one time GDP per capita, however the range are from 0,04 until three times GDP per capita.

Range of the willingness to pay (WTP) for the cost-effectiveness threshold are from 20% up to 70%. In Mongolia study, with anticipated ICERs of less than 20% of the country's $3,735 per capita GDP in 2018, vaccination in Mongolia is highly probable to be more cost-effective than a no vaccination. (Luvsan et al., 2022). In Ghana, HPV vaccination would be affordable using any technique if the willingness to pay was at least 40% of the GDP per capita which was $881 (Vodicka et al., 2022). From a governmental and societal perspective, the introduction of the HPV vaccine in Afghanistan targeting a single cohort is potentially cost-effective (0.7 times the $586 GDP per capita), with additional health gains coming from a catch-up campaign (Anwari et al., 2020). Other study in Ethiopia stated given that the cost per dose of the nonavalent vaccine is less than US$15, it is more economical in Ethiopia than the quadrivalent vaccine (Wondimu et al., 2022).

In the terms of four vaccination comparison, Cecolin®, Cervarix™, or Gardasil® are predicted to be more cost-effective in the Philippines than no immunization at a threshold of less than the GDP per capita. However, Gardasil®9 is not cost-effective with WTP 50% GDP per capita (Luvsan et al., 2022). In Bangladesh, HPV vaccination with Gavi costs by implementing a bivalent vaccine is cost-effective, on the other hand, the strategy with listed price vaccination on both bivalent and quadrivalent is not cost-effective (Mahumud et al., 2020). The one and only study that conclude different in their evaluation, is Iran study, where they mentioned a three-dose HPV vaccination program is not cost-effective (Yaghoubi et al., 2018).

Tabel 3 The vaccination program and treatment cost averted

Country (year)	Vaccine price per dose	Total Program Cost	Treatment Cost Reduced	
			Government Perspective	Societal Perspective
Mongolia (2022)	$4.60 (B) $4.50 (Q)	$$7,378,136 (B) $7,446,413 (Q)	$5,078,945(B) $4,231,456 (Q)	$5,165,778 (B) $4,303,800 (Q)
Philippines (2022)	Cecolin®: $7.47 Cervarix™: $10.68 Gardasil®: $13.14 Gardasil®9: $44.64	Cecolin: $135,083,980 Cervarix™: $178,500,596 Gardasil®: $211,773,143 Gardasil®9: $637,881,788	Cecolin®: $18,089,110 Cervarix™: $22,460,078 Gardasil®: $17,765,888 Gardasil®9: $23,071,649	Cecolin®: $118,321,721 Cervarix™: $146,912,428 Gardasil®: $116,207,508 Gardasil®9: $150,912,740
Ethiopia (2022)	$4.50 (Q) $6.90 (N)	$1,295,065 (Q) $1,485,049(N)	-	-
Ghana (2021)	$4.60 (B) $4.50 (Q)	$97,947,00 (B) $97,228,640 (Q)	$34,282,975 (B) $22,241,503 (Q)	$35,632,695 (B) $23,117,086 (Q)
Afghanistan (2019)	$0.20 – $4.60 (B)	$3,343,311/year	-	$203,226
Bangladesh (2019)	Gavi price: $9 (B) Listed price: $51.03 (B) $85.03 (Q)	Gavi price: $10.58/dose(B) Listed price: $52.61/dose (B) $87.40/dose (Q)	Gavi price: $5,956,952(B) Listed price: $13,333,764 (B) $11,211,576 (Q)	-
Iran (2018)	$13.75 (Q)	GP: $23,081,251 SP: $22,768,156	$378,646	$691,741

*B: Bivalent, Q: Quadrivalent, N: Nonavalent.

Tabel 4 Cost effectiveness threshold and value (presented in US$)

Country (year)	GDP per capita	Threshold use	ICER**	Conclusion
Mongolia (2022)	$$3,735 in 2018	1x GDP per capita	$747	Compared to NV, WV is cost-effective with WTP less than 20% of GDP per capita
Philippines (2022)	$3,485 in 2019	1x GDP per capita	Cecolin®: $1,210 (GP), $173 (SP) Cervarix™: $1,300 (GP), $263 (SP) Gardasil®: $2,043 (GP), $1,00 (SP) Gardasil®9: $4,986 (GP), $3,949 (SP)	Compared to NV Cecolin®, Cervarix™, and Gardasil® are cost-effective. Gardasil®9 is not cost-effective with WTP 50% GDP per capita
Ethiopia (2022)	$856 in 2019	1x GDP per capita is very cost-effective, 3x GDP per capita is cost-effective	N vaccine $454/QALY gained	Compared to Q vaccine, N is very cost-effective up to a price of US$ 15 per dose
Ghana (2021)	$2202 in 2018	40% to 1x GDP per capita	B: $272 (GP), $266 (SP) Q: $494 (GP), $488 (SP)	Compared to NV, WV is cost-effective with WTP 40% of GDP per capita
Afghanistan (2019)	$586 in 2018	1x GDP per capita	GP: $426, SP: $400	Compared to NV, WV is cost-effective with WTP 70% GDP per capita
Bangladesh (2019)	$1,675 in 2018	4% to 51% of GDP per capita	Gavi price: $4,509 (B) Listed price: $14,817 (B) $33,461 (Q)	B vaccine with Gavi price is highly cost-effective. B and Q vaccines in listed prices were not cost-effective
Iran (2018)	$4,763 in 2015	3x GDP per capita	GP: $15,205, SP: $14,999	Three-dose Q vaccine is not cost-effective

* B: Bivalent, Q: Quadrivalent, N: Nonavalent, GP: Government perspective, SP: Societal perspective, WV: with vaccination, NV: no vaccination, GDP: gross domestic product, WTP: willingness to pay. **All per DALYs averted.

2.4 Discussion

This review explored only 7 studies on economic evaluations of HPV vaccination in LI and LMI categorized by the World Bank in 2022 (Yonzan, 2022), and identified cost-effectiveness of bivalent, quadrivalent, and nonavalent HPV vaccines for pre-adolescents girls. The healthcare delivery systems are not homogenous, and the cost of healthcare is assessed from various angles depending on the country. There have been a few systematic reviews on this subject. A review on bivalent, quadrivalent, and nonavalent vaccine in Asia was carried and included 16 studies, half of them evaluated the cost-effectiveness of HPV vaccination in high-income countries and regions (WHO) while the other eight studies were set in low- and middle-income countries and regions (Zhu et al., 2022). Another review from Indonesia conduct economic evaluation of HPV vaccination included four studies from three LMICs and one upper-middle country (UMC) (Frianto et al., 2022). However, none of them fully assess just for the LIC and LMIC settings.

Every year, infectious diseases lead to around 2 million new cases of cancer worldwide. These are more than 600,000, and human papillomaviruses are responsible.(de Martel, Georges, Bray, Ferlay, & Clifford, 2020) The understanding that infectious agents can result in tumors paved the way for a fresh approach to cancer prevention, which is vaccination. One of the biggest successes in public health has been the development of vaccines against infectious diseases, which have eradicated smallpox and significantly decreased the prevalence and severity of numerous other deadly infectious diseases. By 2030, the World Health Organization (WHO) aims to have eradicated cervical cancer worldwide. This approach aims to vaccinate 90% of girls under the age of 15, screen 70% of women between the ages of 35 and 45 for cervical cancer, and treat 90% of women who are diagnosed with the disease.(Bruni et al., 2021; Colomé-Ceballos et al., 2022) HPV vaccination with cervical screening can be ramped up to reduce cervical cancer incidence annually and seek its eradication by the end of the twenty-first century. (Simms et al., 2019) Combining it with efficient screening techniques can hasten cervical cancer reductions in those nations with the largest burdens. Although HPV vaccination is the primary step towards the global elimination aim, excellent cervical screening tests are also a crucial part of this plan, as is providing proper care to those who have cervical cancer. (Brisson et al., 2020)

In order to determine the most cost-effective technique, these points of distinction should also be taken into account. The evaluation found that, despite differences in the models applied, perspectives adopted, discount rate, vaccine efficacy, cost and coverage, age target, time horizon, effectiveness measurement, and comparators across all studies, all but two of them found that HPV vaccination is cost-effective. Study from Iran did not find the vaccine cost-effective as these studies assumed a very expensive price for the vaccine (Yaghoubi et al., 2018). In addition, this study also adopted three-dose scenario which is exceed the recommendation from CDC, which stated that two HPV vaccination doses given to 9–14-year-olds at least six months apart gave better protection as three doses given to older adolescents or young adults, according to immunogenicity studies (CDC, 2019). And even, other study from WHO Strategic Advisory Group of Experts on Immunization (SAGE) the emerging evidence showing single-dose schedules are just as effective as two- or three-dose regimens during the previous few years (WHO, 2022). There are four models being used, Markov cohort model, PRIME, UNIVAC, and CERVIVAC. All of the models are static, which has the drawback of being unable to account for herd immunity, changes in age distribution, and waning effects, therefore It renders the evaluation of the model a poor reflection of a disease (Abidi, Labani, Singh, Asthana, & Ajmera, 2020). Herd immunity can be highly important in keeping the disease under control because HPV can also be sexually transmitted.

In a prior study, Techakehakih et al. discovered that HPV vaccination was more affordable than screening in Brazil, Canada, the Netherlands, and the United States, with ICERs ranging from US $16,600 to US$27,731.(Techakehakij & Feldman, 2008) For Europe, Giraldi et al. discovered ICERs ranging from €5,815 to €37,700 per QALY.(Giraldi, Martinoli, & De Luca d'Alessandro, 2014) According to Kostaras et al., when protection against anogenital warts (quadrivalent vaccine) was provided, when dynamic models were employed (I$ 26,577 per QALY compared to I$ 41,875 per QALY in static models and to I$ 28,782 per QALY in hybrid models), when vaccine coverage was better than 70%, and (I$ 33,731 compared to I$ 34,412), and when social perspective was accounted.(Kostaras, Karampli, & Athanasakis, 2019) Meanhile, the HPV vaccine and molecular screening are both cost-effective, with the screening and immunization having synergy, according to a systematic analysis of cost-effectiveness studies evaluating various HPV prevention options.(Gervais, Dunton, Jiang, & Largeron, 2017)

Furthermore, this study provides new perspectives on the need of thorough vaccination strategy. A targeted HPV vaccination plan is more preferable to adopt given countries' limited budgets than a widespread vaccination strategy. It should be noted that there are both benefits and drawbacks to doing an economic evaluation of specific health care initiatives. Although it can provide local evidence, the conclusion in the framework of national policy cannot be applied to other places. In this study, five research concentrated on particular areas, including Punjab in India, Vientiane in Lao PDR, Southern Vietnam in Vietnam, and the Brazilian Amazon in Brazil, for a number of key reasons.(Chanthavilay et al., 2016; Fonseca, Ferreira, & Neto, 2013; Prinja et al., 2017; Sharma, Sy, & Kim, 2016) Considering the effects of this program on India's universal immunization program, a cost-effectiveness study of HPV vaccination for adolescent girls in Punjab, India, was initiated by a reputable group of experts. (Prinja et al., 2017) Vientiane was thought to have better access to medical facilities than other areas because it was the capital of the Lao PDR. As a result, it was more practical to concentrate the early implementation of cervical cancer screening and immunization in this area.(Chanthavilay et al., 2016) A study by Sharma et al. considered the addition of vaccination programs for boys by varying vaccination coverage and vaccine price, taking into account that Southern Vietnam is a region with more open attitudes toward sexual behavior and higher rates of premarital sex relations than Northern Vietnam.(Sharma et al., 2016) Furthermore, Da Fonseca et al. decided to study the cost-effectiveness of HPV vaccination in a particular Brazilian region because of the high prevalence of cervical cancer in the Brazilian Amazon.(Fonseca et al., 2013)

Several nations in Asia and Africa are currently considering a targeted HPV vaccination strategy, which uses the implementation of the vaccine at the sub-national level as the first step before vaccination at the national level. To aid in decision-making, these regions urgently need more economic evaluation studies. Additionally, all included studies in this review targeted populations under the age of 12 and had an emphasis on LMICs. To increase vaccine coverage in these nations, a school-based vaccination campaign is strongly advised. It is preferable to pursue a school-based HPV vaccination policy, even in high-income nations like Singapore.(Tay, Hsu, Shcheprov, Walia, & Kulkarni, 2017)

Up to 2016, international non-governmental organizations (INGOs) financed HPV vaccination demonstration projects in more than 40 LMICs.(Gallagher et al., 2017) While a vaccination protection of at least 70% was once considered a limit for efficient cost,(Canfell et al., 2012) in LMICs, additional factors such as the cost of HPV vaccine delivery, tactics for administering catch-up booster shots, coverage of girls who are not enrolled in school, and the price of cervical cancer screening programs also impact the program's overall cost-effectiveness.(Ekwunife et al., 2017)

The WHO recommended using a two-dose HPV vaccination schedule to increase compliance and lower costs(Jit, Brisson, Laprise, & Choi, 2015) as vaccine costs are a significant factor in government-funded immunization programs. The choice of vaccine should be based on locally relevant data, such as the scope of prevalent HPV strains and the population for which it is approved. Effective vaccination campaigns and high vaccination rates have significant herd and cross-protection benefits in older women and boys in addition to protecting the vaccinated.(Drolet et al., 2015) Countries must assess their immunization project goals, the factors associated with a successful vaccination strategy, and critical elements in the field application of vaccines in order for vaccination programs to achieve disease reduction targets in the population.(Hardt et al., 2016)

Following the unveiling of the WHO 2030 strategy, numerous nations have already committed at the policy level to eradicating cervical cancer. Committed infrastructure for vaccine supply and administration, funding for the services, and monitoring and evaluating vaccine coverage are all necessary for vaccination plans.(Hardt et al., 2016) Adequate health education, financial incentives, and laws that support mandated vaccination are all interventions that can increase the field level HPV vaccine uptake amongst teenagers.(Abdullahi, Kagina, Ndze, Hussey, & Wiyson ge, 2020) Regarding the delivery method, HPV uptake grew with class-based delivery in schools (RR 1.09) and multi-component provider treatments including an education course, repeated contacts, personalized feedback and incentives, as well as parent interventions such as providing information and sharing educational materials like pamphlets and audio-visual materials.(Dorji, Nopsopon, Tamang, & Pongpirul, 2021)

There are several strengths and limitations from this study. Firstly, this systematic review is the first to address the cost-effectiveness aspect of HPV vaccination program in adolescents specifically in low and lower-middle income countries. Nevertheless, the author could address several limitations in terms of limited number of included studies. Regarding this issue, we have tried to use as highly sensitive search terms as we could to reduce the risk of publication bias in our systematic review. Moreover, the authors are aware that the calculation of cost-effectiveness in all of the included studies were using US dollars and that the articles did not provide the exchange rate to local currency. Therefore, we would have to expect that there might be a slight bias in terms of the absolute value of cost spent in each different country. However, it is very important to note that these differences might not significantly affect the results from our included studies.

2.5 Conclusion

Low human papillomavirus vaccination uptake in low- and lower-middle income countries have been an urgent issue to be discussed. This systematic review presents current best evidence on the cost-effectiveness analysis of the HPV vaccination program among adolescents by using several models of analysis, namely Markov cohort model, PRIME, UNIVAC, and CERVIVAC. The results from included studies have presented overall cost-effective program of HPV vaccination in low- and lower-middle income countries. However, there are still some studies that reported contradictory results due to the very expensive vaccines available in those countries. Therefore, governments are highly recommended to be able to facilitate HPV vaccination program by controlling the vaccine cost, monitoring the supply process of the vaccine, as well as providing adequate educational promotions among pre- adolescents to optimize the vaccination program, especially to reach the target of HPV cases eradication in 2030.

Chapter 3. Methodology

3.1 Study design

Bivalent and quadrivalent HPV vaccines, both of which are offered through Indonesia's pre-adolescent HPV vaccination program, have been evaluated and compared with various cost and health outcome scenarios. Over a two-year period from 2022 to 2024 based on the decree of Indonesia Ministry of Health to accelerate the HPV immunization program for the pre-adolescents girls (Indonesia Ministry of Health, 2017). The HPV vaccination was given to Indonesian girls aged 9 by applying the costs from the government's perspective, including the price of vaccination programs and the net cost of cervical cancer treatment when the government is the payer. The first comparison was between vaccination and no immunization in terms of the possible health effects of anticipated cervical cancer cases, disability-adjusted life years (DALYs), and deaths prevented. The incremental cost-effectiveness ratio (ICER) was subsequently determined using the formula shown below:

$$\frac{HPV\ vaccination\ program\ costs -\ cervical\ cancer\ treatment\ cost\ saverted}{DALYs\ averted}$$

The cost per DALYs saved by each vaccination product in comparison to no vaccination, as well as the comparison of these results among the two HPV vaccinations, are the key findings of this study. There are also presented additional outcomes, such as costs, cases, and mortality.

3.2 Model

The model used for this study analysis is a universal framework for evaluating vaccine policy options in low-middle income country called UNIVAC (version 1.4). UNIVAC is a static proportional impact model developed in Excel (Clark, 2022), which estimates the impact of multiple-age cohort vaccination. The impact of vaccination is measured by the reduction of cervical cancer incidence, prevalence, and mortality in relation to vaccine coverage, efficacy, and distribution of HPV types with high risk. Herd effects and cross-protection are not considered. Therefore, the estimated health benefits of HPV vaccination for 9‒14-year-old girls are conservative. Vaccinating girls before sexual debut fully protects them from developing cervical cancer caused by high-risk HPV types, in accordance with the efficacy observed in vaccine trials. The model assumes a two-dose schedule with perfect timeliness to the target ages given in the coverage estimates. Model equations and parameters have been extensively described elsewhere.

3.3 Methods, data source, and expert input

The methodology is aligned with the established guidelines in the 2017 Indonesian Health Technology Assessment (HTA) Guideline (Indonesian Health Technology Assessment Committee (InaHTAC), 2017) to ensure relevance to local decision-making. The target population's demographic data, cervical cancer incidence and mortality by age and stage (categorized as local, regional, and distant), disability weights for the disease, average illness duration, costs of cervical cancer treatment, vaccine coverage, vaccine efficacy, and vaccination program costs were all model parameters (including vaccine price, vaccine supplies and wastage, and delivery costs).

Between 2020 and 2022, the data collected from peer-reviewed journals, health agencies, and government institutions. The preference was given to using local data as input parameters whenever possible. In the absence of locally accessible data, we extrapolated values from nations with economic standing comparable to Indonesia in terms of GDP per capita, HPV vaccination administration method, geographic location, and population density. The base case is the most possible case for each data item. In terms of each parameter, it determined the low and high range estimations to account for possible variations from our base case values. In the absence of formal estimates of variance (such as 95% confidence intervals), we used a proportional estimate of variation from the base case (such as 25% of base case estimate).

The univariate sensitivity analyses were performed to assess individual parameter variation on estimates of cost-effectiveness and to identify drivers of model outcomes. Probabilistic sensitivity analysis (PSA) evaluated joint parameter uncertainty on outcomes and estimated 95% credible ranges for results by running 1,000 Monte Carlo simulations in which values were drawn from each parameter’s uncertainty range simultaneously. A PERT-Beta distribution was being used for all parameters due to lack of information about each distributional shape (Ekwunife et al., 2017). The PERT-Beta distribution is commonly used in simulations and is defined by a minimum possible value, the most likely value and a maximum value (Hajdu & Bokor, 2016). The following parameters were varied over their low and high ranges: disease rates, vaccine coverage rates, vaccine efficacy, vaccine program costs, and healthcare costs of treating cervical cancer.

This study uses two cost-effectiveness thresholds (CET) to depict the willingness to pay (WTP). First threshold is 0.34 time of GDP per capita which is $1459 ($4,291 as 2021 GDP per capita) represent the cost-effective threshold. This is based on previous systematic review study that assessed the cost-effectiveness thresholds based on Human Development Index (HDI) and GDP (Daroudi et al., 2021). Second threshold is the health opportunity cost which define as the amount of health (which being presented as DALY or QALY) that a health care system currently delivers with more or less resources (Ochalek & Lomas, 2020). Based on the health opportunity cost calculation, Indonesia health has a range between $535 - $778 (in 2015 USD) or 16%-23% GDP per capita (Ochalek & Lomas, 2020). In this study, 0.16 times of GDP per capita ($687, respectively) is being utilized as the second threshold.

3.4 Data Inputs

3.4.1 Cervical cancer disease and hospitalization burden

The international estimate based on GLOBOCAN 2020 being utilize, which was provided by International Agency for Research on Cancer (IARC) to forecast the burden. of cervical cancer in Indonesia due to the absence of data from local studies and national registry (IARC, 2020). The numbers of age-specific incidence and mortality rates used in this study were listed in figure 1 and 2. Based on the Federation of International Gynecology and Obstetrics (FIGO) classification for cervical cancer to define local stage (IA, IIA, and IB1), regional stage (IB2, IIB, and IIIB), and distant stage (IVB and IVA) (Dhamija et al., 2021; Marth et al., 2017). More detailed information can be seen in appendix 3.

The disability-adjusted life years (DALY) measure the number of years of life lost (YLL) owing to illness-related mortality and the number of years of life lived with the disease (YLD). As a result, this single composite benefit metric includes both morbidity and mortality. The YLD was weighted to account for the deterioration in quality of life. YLL was determined using a single age's average life expectancy and the calendar year of death. The disability weights being applied for cervical cancer of 0.29, 0.45, 0.54 for local, regional, and distant stages respectively. (Salomon et al., 2015). For the estimation of the cervical cancer hospitalization rate, the treatment seeking proportion from previous local study being calculated based on the Cipto Mangungkusumo Hospital Based Cancer Registry, which is the center of Indonesia national referral hospital in Indonesia capital city, Jakarta

(Gondhowiardjo et al., 2020), and it assumed it could represent the cervical cancer hospitalization rate by stage in Indonesia. For the estimated cervical cancer illness by stage mean duration, we used the assumption of 8, 5, and 2 years for local, regional, and distant cases respectively based on expert consultation and Chennai 5-year survival rate (table 1).

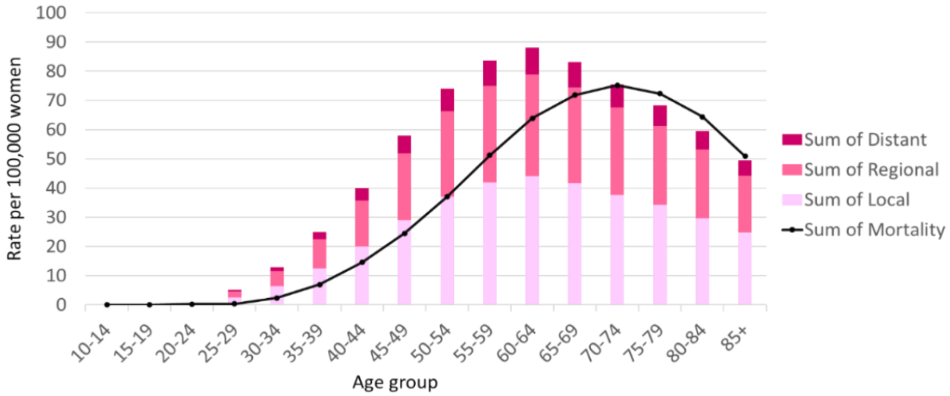

Figure 3 Indonesia age-specific disease burden by cervical cancer based on the FIGO cervical cancer stage in 2020

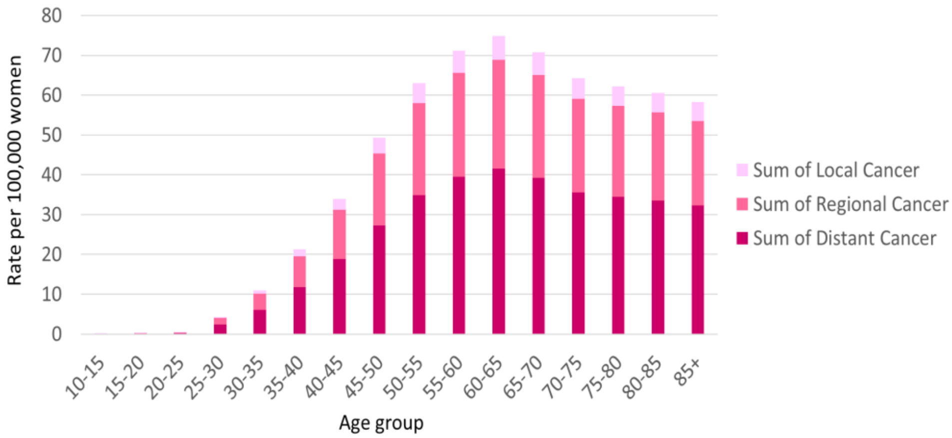

Figure 4 Indonesia age-specific hospitalization rate based on the FIGO cervical cancer stage in 2020

Table 5 The disability weights and estimated mean duration of cervical cancer by stage for calculating DALYs

Parameter	Base case (range)	Reference
Disability weights for cervical cancer by stage		
Local	0.29 (0.19-0.40)	(Salomon et al., 2015)
Regional	0.45 (0.31-0.60)	
Distant	0.54 (0.38-0.69)	
Estimated mean duration of cervical cancer by stage		
Local	0.80 (0.60-1.00)	Assumption by expert consultation
Regional	0.50 (0.38-0.63)	(Balasubramaniam et al., 2021)
Distant	0.20 (0.15-0.25)	Assumption by expert consultation

3.4.2 Vaccine efficacy and coverage

Based on WHO and UNICEF data of immunization coverage, the estimation of HPV vaccination coverage are 0.83 and 0.80 for the first and second dose (WHO, 2022). Th vaccine efficacy for each vaccine using pooled odds ratio estimates from PATRICIA & FUTURE trials weighted by genotype prevalence in Indonesia. Vaccine efficacy for bivalent was 63.4 and 70.4 for dose 1 and dose 2, where quadrivalent was 62.9 for dose 1 and 69.9 for dose 2, respectively (Lehtinen et al., 2012; Setiawan et al., 2020). For more detailed information see table 2.

Table 6 Vaccine coverage and efficacy

Parameter	Base case (range)	Reference
Vaccine coverage		
Dose 1	0.83 (0.76-0.90)	WHO/UNICEF Estimates of National Immunization Coverage (WHO, 2022)
Dose 2	0.80 (0.72-0.88)	
Vaccine efficacy		
Bivalent		The range was pooled odds ratio estimates from PATRICIA & FUTURE trials weighted by genotype prevalence in Indonesia
Dose 1	63.4 (49.9–64.0)	
Dose 2	70.4 (55.5–71.2)	
Quadrivalent		
Dose 1	62.9 (56.5–63.7)	
Dose 2	69.9 (62.8–70.7)	

3.4.3 Vaccination program cost

HPV vaccination program costs are summarized in Table 3. Bivalent and quadrivalent price were based on the recent Gavi price, additionally quadrivalent listed price of $11.62 were also added based on the current Indonesia government contract price with the pharmaceutical industry. However, there is no official information available about the bivalent contract price (Setiawan et al., 2020). Since there are no local data available, this study used the vaccine supplies price from international pricing data. Another assumption used in the analysis was that other charges both from international handling and international delivery were 0.10 for each (UNICEF, 2022a). As the use of vaccine would also cause wastage, Bivalent (Cervarix) was 0.10 and 0.50 for Quadrivalent (Gardasil-4) (Gavi, 2021). Syringe price and safety boxes per vaccine dose are 0.07 and 0.01, respectively (PAHO/WHO, 2022a, 2022b). The expected health systems costs per dose for each type of vaccine delivery for $3 was calculated by the mean price of health system cost from previous immunization program (ICAN, 2019). For more detailed information see table 3.

3.4.4 Healthcare cost

The estimates of healthcare cost per treated case were $4,998 for local stage, $9,877 for regional stage, and $3,570 for distant stage. With the specific expenditure details for local stage are hysterectomy and radiation treatment, for regional stage are radiation, chemotherapy, and hysterectomy, and finally in distant stage the treatments are radiation, chemotherapy, and also palliative care. These all are treatments that being suggested in each cervical cancer by the gynecologist experts in from the Cipto Mangungkusumo Hospital Based Cancer Registry according to Indonesia Case-Based Groups (InaCBGs) where the government made a list recommendation price for each treatment, therefore this healthcare expenditures are representing the government perspective (Kosen et al., 2017) and converted to 2022 USD. For more detailed information see table 3.

Table 7 Healthcare costs and vaccination program costs

Healthcare costs per treated case	Estimate (range)	Reference
Local	$4,998 ($2,999-$6,497)	(Kosen et al., 2017) with the expert consultation in advance
Regional	$9,877 ($5,926-$12,840)	
Distant	$3,570 ($2,142-$4,461)	
HPV vaccination program cost		
Expected vaccine price per dose		
Bivalent Gavi price	$5.18	(Gavi, 2021; UNICEF, 2022b)
Quadrivalent Gavi price	$4.50	
Quadrivalent government contract price	$11.62	(Setiawan et al., 2020)
Fixed price assumptions for other vaccine supplies		
Syringe price per dose	0.07 (0.06-0.08))	(PAHO/WHO, 2022a)

Healthcare costs per treated case	Estimate (range)	Reference
Safety box/bag price per dose	0.01 (0.005-0.15)	(PAHO/WHO, 2022b)
Other charges (% of vaccine price)		
% International handling	0.10 (0.08-0.12)	(UNICEF, 2022a)
% International delivery	0.10 (0.08-0.12)	
Percentage wastage		
Bivalent	0.10 (0.08-0.12)	(Gavi, 2021)
Quadrivalent	0.50 (0.40-0.60)	
Syringes	0.05 (0.04-0.06)	(UNICEF, 2020)
Safety boxes/bags	0.05 (0.04-0.06)	
Expected health systems costs per dose for each vaccine delivery	$3.00 ($2.25-$3.75)	(ICAN, 2019)

Chapter 4. Result

By comparing bivalent with Gavi price, quadrivalent with Gavi price, and quadrivalent listed price, the forecast being performed by the lifetime costs and impact of routine HPV vaccination of 9-year-old females who were vaccinated throughout the years 2022–2024.

4.1 No vaccination scenario

According to the UNIVAC model, Indonesia would have a total of 113,774 deaths, 326,701 DALYs, 143,261 total hospital visits and 163,759 cases of cervical cancer without vaccination. Without the vaccination, the anticipated total healthcare expenses for the government (discounted) for treating cervical cancer in this population would be $168,651,589, respectively. For more detailed information see table 4.

Table 8 Lifetime epidemiological and economic outcomes of HPV vaccination of a single cohort of 9-year-old girls

Lifetime costs (US$) and effects	No Vaccine	Bivalent Gavi Price	Quadrivalent Gavi price	Quadrivalent Government Contract Price
Total cervical cancer cases	**163,759**	**68,415**	**75,814**	
Local	**81,954**	**34,239**	**37,942**	
Regional	**64,776**	**27,062**	**29,989**	
Distant	**17,029**	**7,114**	**7,884**	
Total cervical cancer hospital visits	**143,261**	**59,851**	**66,323**	
Local	**11,448**	**4,783**	**5,300**	
Regional	**52,355**	**21,872**	**24,238**	
Distant	**79,457**	**33,196**	**36,786**	
Deaths	**113,774**	**47,532**	**52,673**	
DALYS (discounted)	**326,701**	**136,489**	**151,250**	
Total healthcare cost (discounted)	**$168,651,589**	**$70,459,261**	**$78,079,054**	
Total vaccine program cost (discounted)	**$0**	**$149,751,279**	**$138,515,094**	**$222,479,342**
Averted (comparator = no vaccine)				
Total cervical cancer cases	**-**	**95,344**	**87,946**	
Local	**-**	**47,715**	**44,013**	
Regional	**-**	**37,715**	**34,788**	
Distant	**-**	**9,915**	**9,145**	
Total cervical cancer hospital visits	**-**	**83,409**	**76,936**	

Local	**-**	**6,665**	**6,148**	
Regional	**-**	**30,482**	**28,117**	
Distant	**-**	**46,262**	**42,672**	
Deaths	**-**	**66,241**	**61,101**	
DALYS (discounted)	**-**	**190,212**	**175,451**	
Total healthcare cost (discounted)	**-**	**$98,192,328**	**$97,492,424**	
Total vaccine program cost (discounted)	**-**	**$149,751,279**	**$138,515,094**	**$222,479,342**
Cost per DALY averted (discounted)	**-**	**$322**	**$325**	**$895**
Health impact	**-**	**58.1%**	**53.7%**	

4.2 Bivalent vaccine with the Gavi price

In comparison to no vaccination, it was projected that a two-year vaccination program utilizing the bivalent vaccine with Gavi price will prevent 95,344 cervical cancer cases, 190,212 DALYs, and 66,241 cervical cancer deaths. In this case, the total cost of the immunization program over two years would be $149,751,279, saving the government $98,192,328 in healthcare expenses (table 4). In addition, the base case ICER result calculated is $322 per DALY averted. In the univariate sensitivity analysis from the figure 3, the better strategy than the base case are high input of treatment cost and low input of system cost projection with ICER $138 and $216/DALYs averted, followed by high vaccine efficacy and low coverage projections. On the other hand, compared to base case, low vaccine efficacy and treatment cost were the most least economical with ICER $573 and $569 DALYs averted, followed by high system cost and high coverage projections (figure 5)

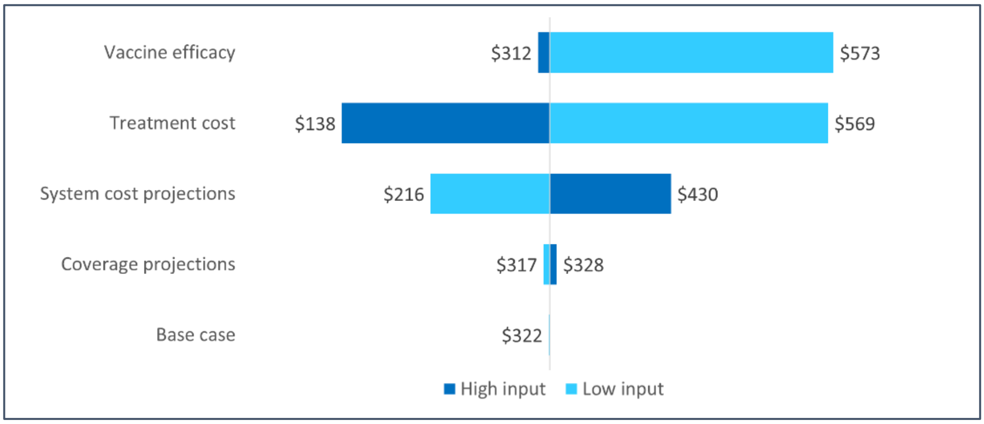

Figure 5 One-way sensitivity analysis shows the ICER/DALYs averted for each scenario in bivalent with Gavi price

4.3 Quadrivalent vaccine with the Gavi price

It was projected using the quadrivalent vaccine with a Gavi price would save 87,946 cases of cervical cancer, 175,451 DALYs, and 61,101 cervical cancer deaths as compared to no vaccination. In this instance, the vaccination program would cost $138,515,094 over the course of two years, saving the government $97,492,424 in healthcare costs (table 4). The base scenario ICER result determined is $325 per averted DALYs. The one-way sensitivity analysis result is presented based on each scenario. Different than the bivalent vaccine, the most cost-effective scenario is high input of treatment cost with the ICER $140/DALYs averted, low input system cost projection, followed by high input vaccine efficacy and low input coverage projection. On the opposite side, the low input cost is the least cost-effective scenario with the ICER $571/DALYs averted, followed by high system cost projection, low vaccine efficacy and high coverage projection (figure 6),

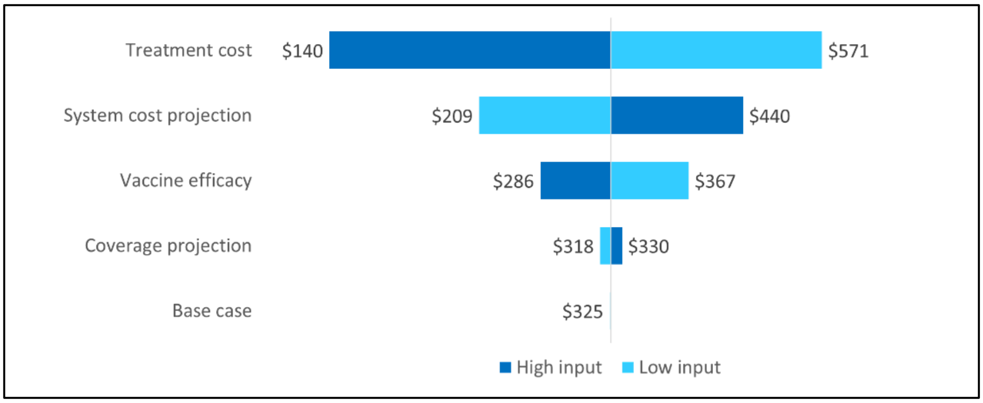

Figure 6 One-way sensitivity analysis shows the ICER/DALYs averted for each scenario in quadrivalent with Gavi price

4.4 Quadrivalent vaccine with the contract price

In comparison to no vaccination, it was anticipated that a two-year vaccination program utilizing quadrivalent government contract price, will spent $222,479,342 on the vaccination program, saving the government $97,492,424 in healthcare budget. From a governmental point of view, this equates to $894/DALY averted, respectively. In the sensitivity analysis tornado graph (figure 5), the most cost effectiveness strategy is high treatment cost with ICER $709/DALYs averted by using the high treatment cost, then low system cost projection, high vaccine efficacy, and low coverage projections. The least cost effectiveness was low treatment cost with ICER $1,140/DALYs averted, followed by high system cost projection, low vaccine efficacy, and high coverage projection (figure 7).

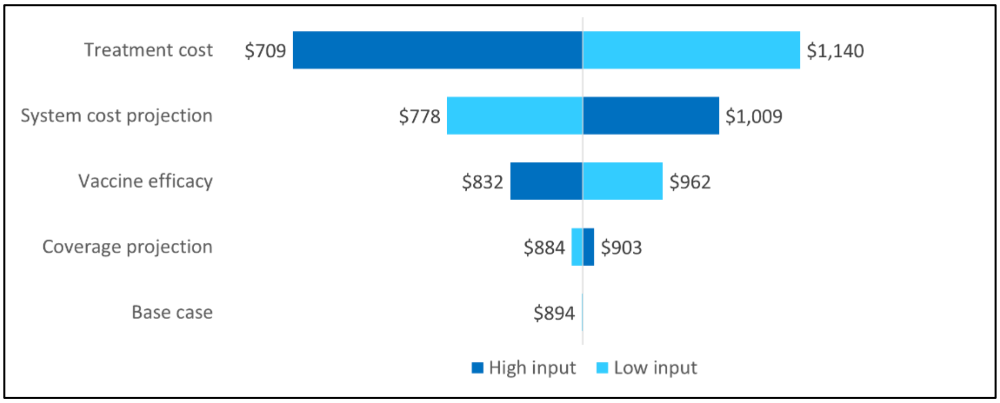

Figure 7 One-way sensitivity analysis shows the ICER/DALYs averted for each scenario in quadrivalent with contract price

4.5 Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis by UNIVAC model estimated two-years vaccination program among 9-year-old girls by using the willingness to pay (WTP) of 16% and 34% GDP per capita depicts by figure 6. The bivalent vaccine with the Gavi price ICERs ranged from $184 to $372/DALYs averted is considered cost-effective scenario with the base case ICER $322/DALYs averted. Followed by quadrivalent with the Gavi price with ICERs ranged from $194 to $383/DALYs averted, which also consider cost-effective with the base case ICER $325/DALYs averted.

On the other hand, quadrivalent with the government contract price are almost three times compared to others with the base case ICER $894/DALYs averted (0.51 times of 34% GDP per capita threshold) and the range $468 to $970, however, with the CET 34% of GDP per capita the quadrivalent with the government contract price still considerably cost-effective (figure 8).

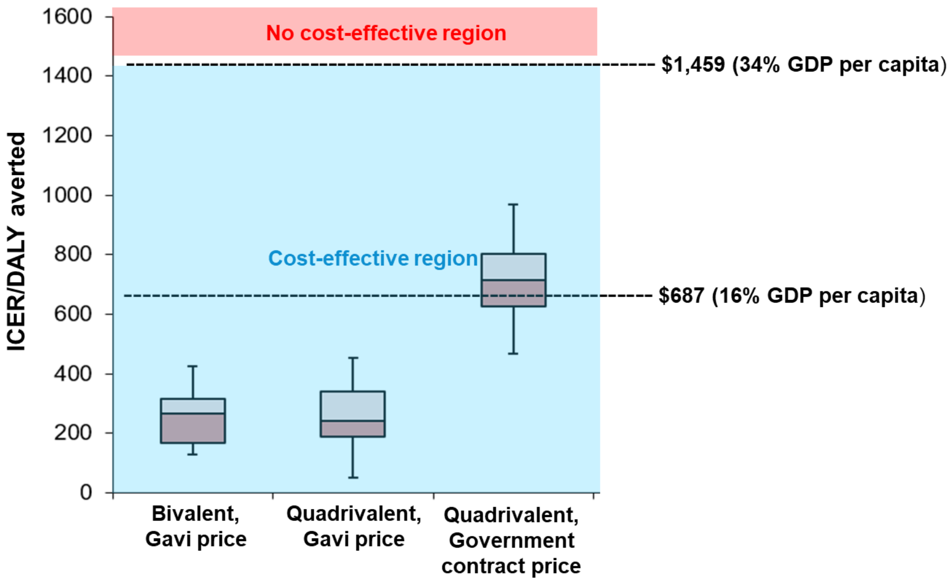

Figure 8 The Probabilistic Sensitivity Analysis (PSA) of all scenarios

Chapter 5. Discussion

Before performing this cost-effectiveness analysis study, the UNIVAC model was selected based on the systematic review results. When numerous models were applied to various LICs and LMICs, UNIVAC stood out as the model used by LICs and LMICs the most, had the most thorough analysis, and produced the most comprehensive range of results, which might be the best model to be applied for Indonesia case.

The Indonesia Health Technology Assessment (HTA) suggested that since no threshold has been determined, Indonesia will use the GDP per capita criteria that has been adjusted for purchasing power parity (PPP) until Indonesia has its threshold value (WTP). However, several systematic reviews of cost-effectiveness thresholds (CET) suggest implementing the threshold to be lower than GDP per capita in terms of LICs and LMICs. Therefore, 34% and 16% being chosen as Indonesia WTP for this study. The health opportunity cost is preferred as very cost-effectiveness threshold because the calculation does not just include the GDP per capita but also depends on each nation's death rates, demographic characteristics, and epidemiology situation (Ochalek & Lomas, 2020). Hence, it would represent more accurate threshold for Indonesia.

Under the model forecast, HPV vaccines with the Gavi price would be a better value for money compared to no vaccination with the government contract price. The other country studies from the Philippines and Bangladesh mentioned that their quadrivalent government contract price is $13.34 to $85.03 (Llave et al., 2022; Mahmud et al., 2020), which makes the quadrivalent vaccine unfavorable compared to the bivalent vaccine, compared to Indonesia quadrivalent government price, it can be stated that Indonesia has more reasonable quadrivalent contract price. Another interesting part is since 2022, Cervarix™ has increased of price from $4.60 to $5.18. Although this study did not analyze the old cost of Cervarix™ price for comparison, the new price would still be reasonable as a result, coming to be very cost-effective using the new price.

Assumptions in terms of vaccine prices have a significant impact on model outcomes. Numerous studies have explored vaccine cost as a critical factor influencing cost-effectiveness in LICs and LMICs (Mahmud et al., 2020; Wondimu et al., 2022; Llave et al., 2022). However, vaccination tender prices differ significantly between nations not eligible for Gavi financing. Indonesia is one of the seventeen countries that transitioned out of Gavi support (WHO, 2017). Despite being a Gavi Accelerated Transition Country since 2016, Indonesia still applicable for GAVI vaccine price, as long as the procurement is carried out through UNICEF until 2025 (Setiawan et al., 2020). The Gavi price used in this study was the actual procurement pricing based on indicated pricing for Gavi-eligible countries could not represent actual present or future tender prices. However, to anticipate the limitation by conducting a wide range of deterministic sensitivity analyses to evaluate the effect of various pricing assumptions on results to address the issue.

In Indonesia, the only two HPV vaccines on the market are Cervarix™ from GlaxoSmithKline of the United Kingdom and Gardasil® from made by Merck Sharp & Dohme (Setiawan et al., 2020). Two other types of vaccine that are not available yet in Indonesia are Gardasil®9 and Cecolin®. Based on other countries, studies showed that the very high price of Gardasil®9 makes it unfavorable from an economic perspective (Llave et al., 2022; Wondimu et al., 2022). On the contrary, the introduction of Cecolin® to the international market would loosen supply restrictions and lower prices even more, which will be the hope of eradicating cervical cancer (Zou et al., 2020). This would increase the vaccine's commercial viability and fund continuous HPV immunization programs.

The disease burden used in the study was pooled from the GLOBOCAN 2020, which was collected based on Hospital-Based Cancer Registry (HBCR) data from Cipto Mangunkusumo Hospital, Indonesia (Gondhowiardjo et al., 2020). These only include cases observed in the national hospitals and do not accurately reflect the actual proportion of cervical cancer in the entire population in Indonesia, including cases that go unreported or untreated. More accurate cost-effectiveness estimations may be the result of the underestimating of the local cervical cancer burden.

The health system costs were adopted from the Immunization Costing Action Network, representing all Indonesian vaccination programs in the last few years. On account of no official statement of the HPV vaccination program, this study calculated from the previous school-based immunization program already being held in Indonesia. Without local and official data from the Indonesian government, this study implemented the parameter in the one-way sensitivity analysis with the incremental health system cost per dose ranging from $2.25 to $3.75.

Other critical parts in this study are the healthcare costs. The previous study captured the healthcare costs (Kosen et al., 2017) based on the national referral center hospital, Cipto Mangunkusumo Hospital. The gynecologist experts from the Female Cancer Program (FCP) Indonesia contributed to calculating the direct cost of cervical cancer. They measured by adjusting the type and frequency of the treatment and weighted with Indonesia Case-Based Groups (InaCBGs). InaCBGs are the government recommendation for the treatment price in a healthcare facility. However, because the national referral hospital has the highest treatment price among other healthcare facilities, it might influence the high input treatment cost most likely to yield more ICER/DALYs averted in all scenarios compared to no vaccination.

Finally, high vaccination efficacy is always more cost-effective than the base case in all three scenarios. A lower vaccination coverage input strategy, on the other hand, would result in fewer ICER/DALYs averted than a high vaccine coverage strategy. Because the more coverage there is, the more vaccine being used, which is not cost-effective. However, high vaccine coverage would increase the epidemiological impact. When the percentage of coverage increases by 7%, even just for the first dose, the health impact overall will increase by nearly 5% for both quadrivalent and bivalent vaccine.

The main strength is this study is assessed the cost-effectiveness analysis between two different vaccines with (quadrivalent and bivalent) and verified the results with two different vaccine prices. Although Indonesia now is in the transition to be fully independent in terms of vaccination funding, the vaccines with Gavi price still would be an economical option. Furthermore, even when Indonesia is not eligible, the government contract could also be cost-effective if the contract could provide the affordable price.

The study has a number of limitations. First, the UNIVAC model does not take into account the indirect effects of vaccination on diseases other than cervical cancer, such as anogenital warts, herd immunity, or precancerous lesions. Second, the cancer registry has a single source hospital. Despite being the country's primary referral hospital, the Cipto Mangunkusumo Hospital, the number may not accurately reflect Indonesia's overall cervical cancer picture. Third, because there were insufficient local data sources available, this study collected data from international sources, which might not adequately reflect Indonesia's vaccination costs

Chapter 6. Conclusion

According to health opportunity cost estimate as the CET ($687), adopting a two-dose HPV vaccination program for pre-adolescent girls in Indonesia would be cost-effective from the government's perspective by using Gavi price. Additionally, all vaccines prices scenarios would be considered cost-effective using the $1459 as CET. Policymakers are advised to invest on a two-dose HPV vaccine at Gavi price as long as Indonesia continues to have procurement during this Gavi transitional phase until 2025.

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Appendix

Appendix 1. Cochrane risk of bias tools 2.0

Domain 1: Risk of bias arising from the randomization process

Signaling questions	Mongolia (2022)	Philippines (2022)	Ethiopia (2022)	Ghana (2021)	Afghanistan (2019)	Bangladesh (2019)	Iran (2018)
1.1 Was the allocation sequence random?	Y	Y	Y	Y	Y	Y	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Y	Y	Y	Y	Y	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N	N	N	N
Risk-of-bias judgement	Low	Low	Low	Low	Low	Low	Low

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signaling questions	Mongolia (2022)	Philippines (2022)	Ethiopia (2022)	Ghana (2021)	Afghanistan (2019)	Bangladesh (2019)	Iran (2018)
2.1. Were participants aware of their assigned intervention during the trial?	N	N	N	N	N	N	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	N	N	N	N	N	N
2.3. [If applicable:] IfY/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	NA	NA	NA	NA	NA	NA
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	N	N	N	PN	PN	PN
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	N	N	N	PN	PN	PN
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	NA	NA	NA	NA	NA	NA
Risk-of-bias judgement	Low	Low	Low	Low	Low	Low	Low

Domain 3: Missing outcome data

Signaling questions	Mongolia (2022)	Philippines (2022)	Ethiopia (2022)	Ghana (2021)	Afghanistan (2019)	Bangladesh (2019)	Iran (2018)
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Y	Y	Y	Y	Y	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA	NA	NA	NA	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA	NA	NA	NA	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA	NA	NA	NA	NA	NA
Risk-of-bias judgement	Low	Low	Low	Low	Low	Low	Low

Domain 4: Risk of bias in measurement of the outcome

Signaling questions	Mongolia (2022)	Philippines (2022)	Ethiopia (2022)	Ghana (2021)	Afghanistan (2019)	Bangladesh (2019)	Iran (2018)
4.1 Was the method of measuring the outcome inappropriate?	N	N	N	N	N	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	N	N	N	N	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N	N	N	N	N	N	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA	NA	NA	NA	NA	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA	NA	NA	NA	NA	NA
Risk-of-bias judgement	Low	Low	Low	Low	Low	Low	Low

Domain 5: Risk of bias in selection of the reported result

Signaling questions	Mongolia (2022)	Philippines (2022)	Ethiopia (2022)	Ghana (2021)	Afghanistan (2019)	Bangladesh (2019)	Iran (2018)
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Y	Y	Y	Y	Y	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...							
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	PN	N	N	N	N	N
5.3 ... multiple eligible analyses of the data?	N	N	N	N	N	N	N
Risk-of-bias judgement	Low	Low	Low	Low	Low	Low	Low

Y: Yes, PY: Probability yes, PN: Probability no, N: No, NI: No information.

The conclusion of the risk of the bias outcome is low risk.

Appendix 2. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022

Section	Recommendation	Countries study						
		Mongolia	Philippines	Ethiopia	Afghanistan	Bangladesh	Iran	Ghana
Title	Identify the study as an economic evaluation and specify the interventions being compared.	Y	Y	Y	Y	Y	Y	Y
Abstract	Provide a structured summary that highlights context, key methods, results, and alternative analyses	Y	P	Y	Y	Y	Y	Y
Introduction								
Background and objectives	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Y	Y	Y	Y	Y	Y	Y
Methods								
Health economic analysis plan	Indicate whether a health economic analysis plan was developed and where available.	Y	Y	Y	Y	Y	Y	Y
Study population	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics)	Y	Y	P	Y	P	Y	Y
Setting and location	Provide relevant contextual information that may influence findings costs being evaluated	Y	Y	N	Y	Y	Y	Y
Comparators	Describe the interventions or strategies being compared and why chosen.	Y	Y	Y	Y	Y	Y	Y
Perspective	State the perspective(s) adopted by the study and why chosen	Y	Y	Y	Y	Y	Y	Y
Time horizon	State the time horizon for the study and why appropriate.	Y	Y	P	Y	Y	Y	Y
Discount rate	Report the discount rate(s) and reason chosen	Y	Y	P	Y	Y	Y	Y

Section	Recommendation	Countries study Mongolia	Philippines	Ethiopia	Afghanistan	Bangladesh	Iran	Ghana
Selection of outcomes	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Y	Y	Y	Y	Y	Y	Y
Measurement of outcomes	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	N	Y	N	Y	Y	Y	Y
Valuation of outcomes	Describe the population and methods used to measure and value outcomes.	Y	Y	Y	Y	P	Y	Y
Measurement and valuation of resources and costs	Describe how costs were valued	Y	Y	Y	Y	Y	Y	Y
Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion	Y	Y	Y	Y	N	Y	Y
Rationale and description of model	If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.	Y	Y	Y	Y	Y	Y	Y
Analytics and assumptions	Describe any methods for analyzing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Y	Y	Y	Y	Y	Y	Y
Characterizing heterogeneity	Describe any methods used for estimating how the results of the study vary for subgroups	Y	Y	N	Y	Y	Y	Y
Characterizing distributional effects	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations	Y	Y	N	Y	N	Y	Y

Section	Recommendation	Countries study Mongolia	Philippines	Ethiopia	Afghanistan	Bangladesh	Iran	Ghana
Characterizing uncertainty	Describe methods to characterize any sources of uncertainty in the analysis.	Y	Y	Y	Y	Y	Y	Y
Approach to engagement with patients and others affected by the study	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Y	Y	N	Y	N	Y	Y
Results								
Study parameters	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Y	Y	Y	Y	Y	Y	Y
Summary of main results	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	Y	Y	Y	Y	Y	Y	Y
Effect of uncertainty	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Y	Y	Y	Y	Y	Y	Y
Effect of engagement with patients and others affected by the study	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Y	Y	N	Y	N	N	N
Discussion								
Study findings, limitations, generalizability, and current knowledge	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Y	Y	P	Y	Y	Y	Y

Section	Recommendation	Countries study						
		Mongolia	Philippines	Ethiopia	Afghanistan	Bangladesh	Iran	Ghana
Other relevant information								
Source of funding	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Y	Y	Y	Y	Y	Y	Y
Conflicts of interest	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Y	Y	Y	Y	Y	Y	Y

The total CHEERS items for each country

Country	Total Y	Total N	Total P	Total NA	Total Score
Mongolia	26	1	0	0	27/28
Philippines	26	0	1	0	27.5/28
Ethiopia	17	6	4	0	20/28
Afghanistan	27	0	0	0	28/28
Bangladesh	21	4	2	0	23/28
Iran	26	1	0	0	27/28
Ghana	26	1	0	0	27/28

Appendix 3. The FIGO and the treatment based on stages

Region	Stage		Description	Treatment Needed
Local Cervical Cancer	IA1, IA2, IB1, IIA	IA1	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion < 5 mm. Measured stromal invasion ≤ 3mm in depth.	Hysterectomy and/or radiation
		IA2	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion < 5 mm. Measured stromal invasion >3 mm and <5 mm in depth	
		IB1	Invasive carcinoma with measured deepest invasion > 5 mm (greater than stage IA), lesion limited to the cervix uteri, independent of lateral extension. Invasive carcinoma > 5 mm depth of stromal invasion and ≤ 2 cm in greatest dimension.	
		IIA	The carcinoma invades beyond the uterus but has not extended onto the lower third of the vagina or to the pelvic wall. Involvement limited to the upper two-thirds of the vagina without parametrial involvement. IIA1 Invasive carcinoma ≤ 4 cm in greatest dimension. IIA2 Invasive carcinoma ≥ 4 cm in greatest dimension.	
Regional Cervical Cancer	IB2, IIB, IIIA, IIIB, IIIC	IB2	Invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA), lesion limited to the cervix uteri, independent of lateral extension. Invasive carcinoma > 2 cm and ≤ 4 cm in greatest dimension	Radiation and/ or chemotherapy and/ or hysterectomy
		IIB	With parametrial involvement but not up to the pelvic wall.	
		IIIA	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or paraaortic lymph nodes. Carcinoma involves the lower third of the valinamide no extension to the pelvic wall.	

Region	Stage		Description	Treatment Needed
		IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause).	
		IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)	
Distant Cervical Cancer	IIIC1, IIIC2, IVB, IVA	IIIC1	Pelvic lymph node metastasis only	Radiation and/ or chemotherapy and palliative
		IIIC2	Paraaortic lymph node metastasis	
		IVA	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV. Spread of the growth to adjacent organs.	
		IVB	Spread to distant organs	

Abstract in Korean

2021년 자궁경부암은 인도네시아의 32,469명의 신규 환자와 1만8,279명의 사망자를 발생시켜 의료비 지출에 국가적 재앙을 초래했다. 이에, 인도네시아 보건복지부는 2022년부터 2024년까지 HPV백신 접종을 필수화 하는 법안을 제정했다. 따라서 본 연구의 목적은 2년간의 HPV 백신 접종의 역학적 효과, 비용 효과 와 예산 효과를 추정하는 것이다. 유니백(UNIVAC)은 엑셀 기반 프로그램으로 정적 코호트 모델을 사용한다. 유니백 프로그램을 활용하여 2022년부터 9세 여아를 대상으로 HPV 4가 또는 2가 백신을 선택할 때 발생하는 평생 비용과 건강 영향을 예측하였다. 그 결과 비용 효과 임계값(CET) $687에서 $1459달러 범위(2021년 1인당 GDP의 16%와 34%)에서 2가 및 4가 HPV 백신은 예방 접종을 하지 않는 것에 비해 가비 가격(Gavi prices)으로 환산한다면 ICER $322과 DALYs $325의 가치를 지닌다. HPV 4가 백신의 효과로는 정부계약금을 ICER $894/DALY만큼 감소시킬 수 있다. 건강 기회 비용 추정치인 CET(687달러)에 따르면 인도네시아에서 사춘기 이전 소녀들을 위한 HPV 2회 접종 프로그램을 채택하는 것이 정부의 관점에서 Gavi 가격을 사용함으로써 비용 효과적일 것이다. 또한 모든 백신 가격 시나리오는 $1459를 CET로 사용하여 비용 효율적인 것으로 간주된다. 따라서, 정책 결정자들은 2025년까지 인도네시아에 HPV백신 물량을 공급하는 과도기 기간동안 가비가격의 원조를 받아 2회 접종 HPV 백신 프로그램을 채택하는 것이 합당하다.

Keyword: 비용 효과분석, 자궁경부암, 인도네시아, 유니벡, 인유두종바이러스, HPV