Journal of Health Economic and Policy Research
JHEPR Vol. 2 No. 2 2024
ISSN 3025-5198

Economic Evaluation of Expanding HPV Vaccination Programs for Boys: A Systematic Review

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Article Information:

- ***Submitted*** : *January 26th 2024*
- ***Revised*** : *January 27th 2024*
- ***Accepted*** : *January 29th 2024*

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DOI: https://doi.org/10.30595/jhepr.v2i2.157

Abstract

Background: The human papillomavirus is responsible for almost all cases of cervical and non-cervical cancers. Various treatments have been carried out, but they have not been effective enough in reducing the burden, so a preventive modality is needed. The U.S. Food and Drug Administration has approved three HPV vaccines for use. Since the WHO's recommendation in 2006, HPV infections have significantly decreased by 88% among teen girls and 81% among young adult women. Additionally, research has indicated that the HPV vaccine is cost-effective in preventing both cervical and non-cervical cancers. The primary target group for HPV vaccination is girls aged 9–14, but some countries are starting to expand their programs according to the WHO recommendation for secondary targets: boys and adult women.

Objective: To systematically review the cost-effectiveness of expanding the HPV vaccination program to include boys to prevent HPV-related cancer.

Methods: Two databases, Pubmed and ScienceDirect, from 2013 to 2023, in English or Indonesian, were searched for economic evaluations of the HPV vaccination program for boys. Three search strategies were used, including the terms «economic evaluation», «HPV», and «boys». The PRISMA statement guided the literature screening and selection.

Results: A total of 306 articles were identified. Only 26 of them were deemed relevant. This research compiled studies from countries with varying economic levels on the expansion of vaccination programs in boys to prevent or reduce cervical, anogenital, and HNC cancers. All of the studies used a modelling approach to estimate the number of cases avoided and health care costs. Sixteen studies found that it was cost-effective to expand HPV vaccination programs to include boys. We found that the ICER values were sensitive to the vaccine price, duration of protection, and vaccination coverage.

Conclusion: Expanding HPV vaccination to boys is considered a cost-effective solution for preventing HPV-related cancers, based on studies conducted in many countries. It is recommended to conduct an economic evaluation to estimate the cost-effectiveness of HPV vaccination as a prevention method for HPV-related cancers in low and middle-income countries like Indonesia. We suggest expanding the HPV vaccination target to boys with a lower-priced vaccine and increasing vaccination coverage to initiate the study.

Keywords: *Cost-effectiveness, Human Papillomavirus, Vaccination, Boys.*

Introduction

Human papillomavirus (HPV) is a leading cause of infection-related cancers, contributing to 4.8% of the global cancer burden. HPV is responsible for almost all cervical cancer cases, as well as a significant portion of non-cervical cancers, including anogenital and head and neck cancers. It is a small DNA virus that infects skin and mucosal cells. HPV is mainly transmitted through sexual activities such as vaginal, anal, or oral sex[1]. While many HPV infections go unnoticed and clear up on their own, some persist and can lead to various benign and malignant lesions[2]. Low-risk HPV types usually do not cause disease, but some can lead to the development of warts on the genitals, anus, mouth, or throat. These low-risk types, including HPV 6, 11, 34, 40, 42, 43, and 44, have been associated with low-grade cervical lesions too. Meanwhile, high-risk HPVs have the potential to cause various types of cancer, including approximately 70% of all cervical cancer cases, with HPVs 16 and 18 being responsible for most HPV-related cancers. Cervical cancer is a common cancer and a leading cause of death in low- and middle-income countries. Cancer can develop in areas where high-risk HPVs persistently infect cells, such as the cervix, oropharynx, anus, penis, vagina, and vulva[1,3].

Cancer's impact on health varies around the world. High-income countries have a higher burden of cancer in terms of disability-adjusted life years (DALYs) per population compared to low- and middle-income countries (LMICs)[4]. The projected worldwide economic cost of cancer between 2020 and 2050 is estimated to be $25.2 trillion, adjusted for 2017 prices[5]. In the U.S. in 2017, the economic burden of cancer was approximately 1.8% of gross domestic product (GDP) and estimated cancer healthcare spending was $161.2 billion, while in the European Union, the economic burden of cancer was 1.07% of GDP and healthcare spending was €57.3 billion[6]. In Indonesia, the costs incurred reached IDR 2,7 trillion, with a total of 1,79 million cancer cases in 2018[7].

Although various treatments (surgery, chemotherapy, and radiotherapy) have been carried out, they have not been effective enough in reducing the burden on patients and the government or preventing the recurrence of HPV-related cancer. There is a need for additional modalities for preventive measures, one of which is vaccination. The World Health Organization (WHO) has introduced the HPV vaccine, and the Food and Drug Administration (FDA) has approved three HPV vaccines for use. The bivalent vaccine (2-valent, 2vHPV) contains proteins from HPV types 16 and 18, which are expressed and purified from insect cells. The quadrivalent vaccine (4-valent, 4vHPV) contains proteins from HPV types 6, 11, 16, and 18, which are expressed and purified from yeast cells[1,8]. The nonavalent vaccine (9-valent, 9vHPV) is the third vaccine that provides protection against nine different types of HPV, including HPV types 16 and 18, as well as types 31, 33, 45, 52, and 58, which are responsible for a significant proportion of other cervical cancers[9].

The HPV vaccine is a highly effective preventive measure, reducing the incidence of HPV-related cancers by more than 90%. Since its recommendation in 2006, HPV infections, including those causing most HPV cancers and genital warts, have decreased significantly by 88% among teen girls and 81% among young adult women. In addition, the HPV vaccine has been shown to reduce the incidence of cervical pre-cancer in young women, and studies have shown that the vaccine provides protection for at least 12 years with no evidence of decline over time. Furthermore, research has indicated that the HPV vaccine is cost-effective in preventing both cervical and non-cervical cancers[10]. Several countries have also tested the provision of HPV vaccination in various communities, including girls, boys, and women[11]. Several studies have investigated the cost-effectiveness of HPV vaccination programs for boys, making this study an update. This information is crucial for health policymakers, who have limited budgets for various health technology options. Some studies have recommended including boys in existing vaccination programs that are currently only for girls, while others have proposed school-based or gender-neutral vaccination programs. This systematic review aimed to evaluate the cost-effectiveness of expanding HPV vaccination programs to include boys in order to prevent HPV-related cancers.

Methods

1. Search strategy

On October 29th – 30th, 2023, a systematic search was conducted in two main databases, PubMed and ScienceDirect, using the following three search terms: economic evaluation, HPV, and boys. The search term used for PubMed was "economic evaluation AND (HPV OR papilloma) AND boys", while the search term used for ScienceDirect was "economic evaluation and (HPV or papilloma) and boys".

2. Selection and eligibility criteria

The screening of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. After obtaining the articles from both databases, the duplicate study was removed. Then, the initial screening process was performed by checking the title and abstract of each previously identified article. Furthermore, the final screening was performed through a thorough reading of the included articles.

We systematically reviewed the worldwide literature and reported it according to the PRISMA guidelines. Studies were eligible for inclusion if they met the following criteria: The studies must have conducted health economic (pharmacoeconomic) studies on HPV vaccination in boys, be written in English, and have been published between 2013 and 2023. We excluded studies with the following characteristics because they were not mentioned or accessible: We excluded studies that were either abstract only or not available in full text, chapter books, reviews, or included comments, debates, discussions, or presentations.

3. Data extraction and analysis method

During the review, the reviewer (DTS) independently extracted information from each selected study's economic evaluation (pharmacoeconomic) analysis. The information extracted from each study was the first author's name and year of publication, country, cancer type prevented, study objective, study method, perspective, time horizon, HPV vaccination details (vaccine type, vaccine price, age target, and coverage), discount rate (cost and benefit), clinical outcome, HPV revaccination program, intervention/scenario, ICER, CET, study conclusion, and sensitivity analysis.

Table 1. Study characteristics of the pharmacoeconomic studies of HPV vaccination for boys

No	Authors, publication year	Country	Cancer type	Study objective
1	Chanthavilay et al., 2016[12]	Lao People's Democratic Republic (Lao PDR)	Cervical cancer.	To evaluate the benefit of complementing vaccination program with additional interventions, such as adding a catch-up vaccination campaign and/or a 10-year-old boy vaccination element.
2	Kitano, 2022[13]	Japan	Head and neck cancer, anal cancer, penile cancer, genital warts, and adult-onset RRP.	To quantify the risk and the benefit of universal male HPV vaccination in Japan.
3	Cheung et al., 2023[14]	Hong Kong	Cervical cancer, CIN 1/2/3, vaginal/vulvar cancers, VIN, anal cancer, head and neck cancer, penile cancer, or genital warts.	To assess the public health impact and cost-effectiveness of routine GNV compared with routine FOV with the 9vHPV vaccine in Hong Kong.
4	Wahab et al., 2023[15]	Singapore	Cervical, anal, vulvar/ vaginal, penile, and oropharyngeal cancer.	To assess if including 13-year-old boys in Singapore's national school-based HPV vaccination programme is economically beneficial from the healthcare payer's perspective.
5	Laprise et al., 2014[16]	Canada	Anogenital warts, cervical, vulva, vagina, anus, penis, and oropharynx cancer.	To estimate the incremental cost-effectiveness of two- and three-dose schedules of girls-only and girls & boys HPV vaccination programmes in Canada.
6	Brisson et al., 2015[17]	United States (US)	Anogenital warts and cervical, anogenital, and oropharyngeal cancers.	To compare population-level effectiveness and cost-effectiveness of 9- and 4-valent HPV vaccination in the United States.
7	Graham et al., 2015[18]	Canada	Oropharyngeal cancer.	To assess the cost effectiveness of male HPV vaccination in Canada with respect to oropharyngeal cancer (OPC).
8	Chesson et al., 2018[19]	United States (US)	Cervical, vaginal, vulvar, anal, and/or penile, oropharyngeal cancer, cervical intraepithelial neoplasia (CIN), genital warts, and RRP.	To assess the health impact and cost-effectiveness of harmonizing female and male vaccination recommendations by increasing the upper recommended catch-up age of HPV vaccination for males from age 21 to age 26 years.
9	Chesson et al., 2020[20]	United States (US)	Cervical, vaginal, vulvar, anal, and/or penile, oropharyngeal cancer, CIN, genital warts, and RRP.	To estimate the potential impact and cost-effectiveness of HPV vaccination for "mid-adults" (adults aged 27 through 45 years) in the United States.
10	Choi et al., 2022[21]	United States (US)	Oropharyngeal cancer.	To evaluate the impact of increased HPV vaccination coverage on HPV-associated OPC incidence and costs.
11	Wolff et al., 2018[22]	Sweden	Cervical, vaginal, vulvar, anal, and oropharyngeal (tonsillar and base of tongue), penile cancer.	To assess cost-effectiveness of expanding the Swedish HPV-vaccination program to include preadolescent boys, by comparing health-effects and costs of HPV-related disease, with a sex-neutral vaccination program versus only vaccinating girls.
12	Burger et al., 2014[23]	Norway	Cervical, oropharyngeal, anal, penile, vaginal, vulvar, genital warts, juvenile RRP.	To assess whether HPV vaccination of pre-adolescent boys is cost-effective.
13	Jiménez et al., 2015[24]	Norway	Genital warts, cervical, vulvar, vaginal, and anal precancerous lesions, and cancer.	To evaluate the epidemiological impact, costs, health benefits and cost-effectiveness of administering the quadrivalent HPV-vaccine to 12-year-old-boys in addition to the current practice of vaccinating 12-year-old-girls.

ISSN 3025-5198

14	Boiron et al., 2016[25]	Austria	Genital warts; RRP; cervical intraepithelial neoplasia (CIN); cervical, vulvar, vaginal, penile, anal, and head/ neck cancers.	To estimate the public health impact and the incremental cost-effectiveness of a universal (girls and boys) vaccination program with a nonavalent HPV vaccine as compared to the current universal vaccination program with a quadrivalent HPV vaccine in Austria.
15	Mennini et al., 2017[26]	Italy	Genital warts; RRP; cervical intraepithelial neoplasia (CIN); cervical, vulvar, vaginal, penile, anal, and head/ neck cancers.	To provide realistic estimates of the epidemiological and economic impact of the implementation of the 9-valent HPV vaccine program for both girls and boys compared to current clinical practice using a 4-valent or bivalent vaccine for girls only.
16	Qendri et al., 2017[27]	Netherlands	Cervical, vulvar, vaginal, anal, penile cancer.	To evaluate the cost-effective of current girls-only vaccination program versus boys vaccination program.
17	Datta et al., 2019[28]	United Kingdom (UK)	Cervical, anal, vaginal, vulvar, penile, oropharyngeal cancers.	To estimate the incremental cost-effectiveness of vaccinating boys as well as girls.
18	Qendri et al., 2020[29]	11 countries in European (Austria, Belgium, Croatia, Estonia, Italy, Latvia, The Netherlands, Poland, Slovenia, Spain, And Sweden)	Cervical, vulvar, vaginal, anal, and oropharyngeal cancers, and in men anal, oropharyngeal, and penile cancers.	To investigate if sex-neutral HPV vaccination can be considered cost-effective compared with girls-only vaccination at uptake levels equal to those among girls and under tender-based vaccination costs achieved throughout Europe.
19	Simons et al., 2020[30]	Netherlands	Anal, penile, and oropharyngeal cancers.	To assess the cost-effectiveness of a gender-neutral HPV vaccination program in the Netherlands.
20	Majed et al., 2021[31]	France	Genital warts, cervical, vulvar, vaginal, and anal cancers.	To assess the public health impact and cost-effectiveness of a 9-valent GNV compared with girls-only vaccination program (GOV).
21	Portnoy et al., 2021[32]	Norway	Cervical cancer.	To assess how the HPV vaccination and cervical cancer screening policy decisions, and whether elimination could be expedited by switching the routine program to 9-valent HPV vaccine.
22	Daniels et al., 2022[33]	United Kingdom (UK)	Cervical, vaginal, vulvar, anal, oropharyngeal, penile cancers, genital warts and RRP.	To investigate the impact of switching from a 2-dose HPV vaccination program to 1-dose on health and economic outcomes.
23	Linertová et al., 2022[34]	Spain	CIN, cervical cancer, anal cancer, VIN, VAIN, RRP, head and neck and penile cancers.	To determine the cost-effectiveness of extending HPV vaccination to include boys, given that the adolescent female population is already being vaccinated.
24	Blakely et al., 2014[35]	New Zealand	Cervical cancer, pre-cancer, genital warts, anal, vulvar, oropharyngeal cancer.	To assess the health impact (QALY), cost, and cost-effectiveness for 3 interventions compared with no vaccination programme.
25	Pearson et al., 2014[36]	New Zealand	CIN I-III, cervical, anal, oropharyngeal and vulval cancers and anogenital warts.	To examine the cost-effectiveness of adding boys to a girls-only program in New Zealand.
26	Drolet et al., 2021[37]	LMIC: India, Vietnam, Uganda, And Nigeria	Cervical cancer.	To identify optimal HPV vaccination strategies in the context of elimination of cervical cancer, vaccine shortage, and resource constraints.

Note:

HPV-related cancers (RRP: recurrent respiratory papillomatosis, CIN: Cervical intraepithelial neoplasia, VIN: Vulvar intraepithelial neoplasia, VAIN: Vaginal intraepithelial neoplasia); HPV vaccination program (GNV: Gender-neutral vaccination, FOV: Female only vaccination, GOV: Girls only vaccination); HPV vaccine (2-valent (2vHPV): Bivalent vaccine, 4-valent (4vHPV): Quadrivalent vaccine, 9-valent (9vHPV): Nonvalent vaccine).

ISSN 3025-5198

Table 2. Methodological aspects and the base-case parameters

No	Authors, publication year	Method	Perspective	Time horizon	Vaccine type	Vaccine price	Age target	Population	Coverage	Disc. rate (utility)	Disc. rate (cost)	Health outcome
1	Chanthavilay et al., 2016[12]	Compartment model	Public health care system	100 years	NS	NS	10 y.o girls and boys	NS	70%	3%	3%	DALY
2	Kitano, 2022[13]	Decision tree model	Individual	Lifetime	Nonavalent	$260.20/ dose.	12 y.o boys	100,000	NS	3%	3%	QALY
3	Cheung et al., 2023[14]	Transmission dynamic model	Health care system	100 years	Nonavalent	$212.65/ dose.	12 y.o boys, 10-12 y.o girls, catch up 13-18 y.o boys and girls	3,961,200 females; 3,375,400 males	70%	NS	NS	QALY
4	Wahab et al., 2023[15]	Compartmental model	Health care system	100 years	Bivalent, Nonavalent	$102.5/ dose (bivalent), $313.3/ dose (nonavalent).	13 y.o boys	25,000 males; 25,000 females	80%	1.5%; 3%	1.5%; 3%	QALY
5	Laprise et al., 2014[16]	Transmission dynamic model	Health care system	70 years	Quadrivalent	$119/ dose.	9 y.o girls and boys	NS	80%	3%	3%	QALY
6	Brisson et al., 2015[17]	Transmission-dynamic model	Societal	70 years	Quadrivalent, Nonavalent	$202.62 (quadrivalent); $220.78 (nonavalent).	9 y.o girls and boys	NS	NS	3%	3%	QALY
7	Graham et al., 2015[18]	Markov state-transition model	Payer (Government)	Lifetime	Quadrivalent	NS	12 y.o boys	192,940 boys	50-85%	5%	5%	QALY
8	Chesson et al., 2018[19]	Deterministic, dynamic model	Health care system	100 years	Quadrivalent	$633.4/ 3 dose	12-21 y.o males	NS	NS	3%	3%	QALY
9	Chesson et al., 2020[20]	Dynamic mathematical model	Health care system	100 years	Quadrivalent	$633.4/ 3 dose	12-45 y.o boys	NS	NS	3%	3%	QALY
10	Choi et al., 2022[21]	Markov state transition model	Health care system	Lifetime	NS	$506.25/ dose	9 y.o girls and boys	2,068,473 males; 1,986,805 females	48.7% males; 53.7% females	3%	3%	QALY
11	Wolff et al., 2018[22]	Dynamic compartmental model, Markov multi-state model	Health care system	100 years	NS	NS	10-12 y.o girls and boys	NS	80%	3%	3%	QALY
12	Burger et al., 2014[23]	Transmission dynamic model	Societal	Lifetime	Quadrivalent	$105/ dose	12 y.o girls and boys	30	79% (2 dose); 71% (3 dose)	4%	4%	QALY

13	Jiménez et al., 2015[24]	Deterministic, dynamic model	Health care and societal	100 years	Quadrivalent	$246/ dose.	12 y.o girls and boys	NS	82%	2-4%	2-4%	QALY
14	Boiron et al., 2016[25]	Transmission dynamic model	Payer (Public tenders)	100 years	Quadrivalent, Nonavalent	$198.7/ dose (quadrivalent)	9 y.o girls and boys	8,507,786 people	60% girls; 40% boys	3%	3%	HRQoL
15	Mennini et al., 2017[26]	Transmission dynamic model	National health service	100 years	Quadrivalent, Nonavalent	$155.3/ dose	12 y.o girls and boys	NS	70%	3%	3%	QALY
16	Qendri et al., 2017[27]	Transmission dynamic model	Health care system	Lifetime	Bivalent	$114/ 2 dose.	12 y.o girls and boys	200,000	60% girls, 40% boys	3%	3%	LY
17	Datta et al., 2019[28]	Dynamic model	Societal	100 years	Bivalent, Quadrivalent, Nonavalent	$16.8/ dose	12 y.o girls and boys	50,000 individuals	76-90%	1.5%; 3.5%	1.5% ; 3.5%	QALY
18	Qendri et al., 2020[29]	Bayesian synthesis framework	Health care system	Lifetime	Bivalent, Quadrivalent, Nonavalent	Average $69.6/ dose	Girls and boys	100,000 girls, 100,000 boys	80%	1.5%; 3%; 5%	1.5% ; 3%; 5%	QALY
19	Simons et al., 2020[30]	Static Markov model	Health care system	Lifetime	AS04-HPV-16/18 vaccine	$205.4/ 2 dose.	12 y.o boys	100,000	30%	1.5%; 4%	1.5% ; 4%	QALY
20	Majed et al., 2021[31]	Transmission dynamic model	NS	100 years	Nonavalent	$162.3/ dose.	11–14 y.o	NS	26.2%; 60%	4%	4%	DALY
21	Portnoy et al., 2021[32]	Multi-modelling approach (dynamic model)	Societal	Lifetime	Bivalent, Nonavalent	$54.60/ dose	12 y.o girls and boys	NS	89-90%	4%	4%	QALY
22	Daniels et al., 2022[33]	Transmission dynamic model	NS	100 years	Nonavalent	$71.43/ dose.	12-13 y.o girls and boys	31,532,900 males; 32,572,800 females	89%	3.5%	3.5%	QALY
23	Linertová et al., 2022[34]	Dynamic model	Health care system	NS	Quadrivalent, Nonavalent	$110.99 - $33.32/ dose (2-valent/4-valent); $55.50/ dose (9-valent)	12 y.o girls and boy	245,693 girls; 262,266 boys	70.20%	3%	3%	QALY
24	Blakely et al., 2014[35]	Markov macro-simulation model	Health care system	Lifetime	Quadrivalent	$119.50/ dose (ministry of health); $19/ dose (GAVI).	12 y.o girls and boys	NS	(1) 56% ; (2) 73%; (3) 93%	3%	3%	QALY
25	Pearson et al., 2014[36]	Markov macro-simulation model	Health care system	NS	Quadrivalent	$79.92/ dose.	12-13 y.o girls and boys	NS	73%	3%	3%	QALY
26	Drolet et al., 2021[37]	Transmission dynamic model	Health care system	100 years	Nonavalent	$5.72 and $9.32/ dose	9–14 y.o girls and boys	100,000	80%	3%	3%	QALY, LY

The Commission recommends that if the ICER is less than one to three times the per capita gross domestic product (GDP) of a country, an intervention should be considered a cost-effective strategy. Therefore, country-specific economic classification and GDP in 2023 were collected from a currency converter and inflation calculator. The economic information, including vaccine price, ICER, and CET from each study, was updated to 2023 and converted to United States dollars (US$) using the country-specific inflation rate. We excluded studies with the following characteristics because they did not mention or were accessible: abstract only and/or not free full text; chapter book; review; consist of comment, debate, discussion, and presentation.

Result

Our search identified 120 articles from the PubMed database and 186 articles from the ScienceDirect database. After removing 10 duplicated articles, we screened the remaining 296 articles based on their titles and abstracts. During the screening process, 135 articles were excluded, of which 117 were published before 2013, 3 were not written in English or Indonesian, 25 provided abstracts only and/or did not provide free access to the full text, 18 were book chapters, 36 were mentioned in reviews (literature or systematic), 12 were comments, consensus, debates, discussions, or presentations, and 41 were not pharmacoeconomic studies.

Forty-four articles were assessed for eligibility criteria, of which 3 articles only mentioned cost or economic burden, 13 articles did not mention the male population in the HPV vaccination program, and 2 articles did not focus on HPV vaccination as the main topic of the study. Ultimately, 26 articles were included in this study.

1. Study characteristics

In this review, 26 studies were included from five different continents: four studies from Asia[12–15], six studies from America[16–21], 13 studies from Europe[22-34], two studies from Oceania[35,36] and just one study from Asia-Africa[37]. Two different studies performed Quality Adjusted Life Years (QALYs) as the main study outcome, using Cost Utility Analysis (CUA) and Cost Effectiveness Analysis (CEA). HPV-related cancers that were prevented in the articles were cervical cancer only[12,32,37], head and neck cancer (HNC) only[18,21], cervical and anogenital cancer[24], HNC and anogenital cancer[30]. Approximately 19 studies showed all HPV-related cancers are preventable, consisting of cervical cancer, HNC, and anogenital cancer (Table 1).

2. Study design

Since the clinical outcomes of HPV vaccination, such as reductions in HPV-related cancer incidence and mortality, are difficult to obtain from clinical trials, a mathematical model is commonly used in the cost-effectiveness analysis of HPV vaccination for boys. All of the studies implemented a modelling approach. Around 16 studies used the transmission dynamic model; five studies used Markov models; three studies used compartment models; one study used a decision tree; and one study used a mathematical model.

In health-economic studies, study perspective plays an important role as it not only influences the data required in the analysis but also the conclusion generated from the studies. Various perspectives were implemented in the studies performed, including individual[13], societal (n = 4), payer (n = 2), and combination health care system and societal[24]. Most of the studies (16 studies) used a health care system perspective (Table 2). Unfortunately, two studies did not mention these perspectives.

To obtain a complete description of the cost-effectiveness of HPV vaccination, the implementation of a lifetime horizon is as important as the cost and effectiveness of HPV vaccination. This is because the reduction in cancer incidence and mortality won't become apparent until several decades after the vaccination. Most studies (13 studies) included in this review modelled a 100-year time horizon for their studies, and nine studies included a lifetime horizon. However, there were two studies that modelled a 70-year time horizon[16,17] and two studies did not mention the time horizon, respectively. Most studies evaluated the quadrivalent HPV vaccine (4-valent, n = 8), five studies examined the nonavalent HPV vaccine (9-valent), and only one study examined the bivalent HPV vaccine (2-valent). Six studies compared two vaccine types.

Moreover, there were two studies that compared three different HPV vaccines: the bivalent, quadrivalent, and nonavalent versions. One study used the HPV vaccine model type, and three studies did not mention the HPV vaccine that was examined.

The mentioned vaccine price ranges from 1 to 3 doses. The range of vaccine prices is wide enough, starting from $5.72 to $506.25 per dose (based on US$ in 2023). Most of the studies modelled age targets following WHO recommendations (9–14 years old), both girls and boys. However, three studies examined the catch-up and/or extension of the model (13–18 years[14], 12-21 years[19], and 12-45 years[20]). On the other hand, vaccine coverage varied from 40-90% in many countries based on the vaccination program.

ISSN 3025-5198

Table 3. Clinical and economic outcomes of health economic studies of HPC vaccine

No	Authors, publication year	Current vaccination program	Intervention/ scenario	ICER (USD, 2023)	CET (USD, 2023)	Conclusion
1	Chanthavilay et al., 2016[12]	5th grade schoolgirls vaccination program	Including boys in the current vaccination program. (1) 10 years old girls + boys; (2) 10 years old girls + boys + catch-up girls aged 11–25 years old; (3) 10 years old girls + boys + catch-up girls and boys aged 11–25 years old; (4) 10 years old girls + boys + catch-up girls aged 11–75 years old; (5) 10 years old girls + boys + catch-up girls and boys aged 11–75 years old.	Dominated (high cost but lower effectiveness) in (1) - (4) scenario; $220,158.4/DALY in (5)	GDP per capita: $6,307.	Adding a vaccination program for 10-year-old boys was not found to be cost-effective unless a short time simulation (30 years or less) was considered, along with a catch-up vaccination component for both males and females
2	Kitano, 2022[13]	HPV vaccination for girls	Vaccination for boys.	$13,889.5 (3-dose) and $89,736 (2-dose).	NS	Male HPV vaccination program may not be cost-effective compared to the female one; 2 dose program more cost-effective than 3 dose programs.
3	Cheung et al., 2023[14]	School-based vaccination program for girls	(1) GNV (boys and girls); (2) GNV + catch up program compared to girls only.	$37,077/ QALY (1); $26,378 HKD/QALY (2).	$58,446.60 (1x GDP per capita).	The model results highlight the value of a routine GNV program among 12-year-olds to reduce the burden of HPV-related diseases in Hong Kong.
4	Wahab et al., 2023[15]	School-based HPV vaccination program for females	(1) Female-only vs gender-neutral (bivalent); (2) female-only vs gender-neutral (nonavalent) in schools.	3% disc. rate: $42,449.4/ QALY (1); $119,754.4/ QALY (2). 1.5% disc. rate: $15,837.5/ QALY (1); $47,513/ QALY (2).	$37,496/QALY.	Moving to gender-neutral vaccination program using bivalent vaccine may be cost-effective, compared with nonavalent vaccine prices. Gender-neutral vaccination program was not cost-effective in 3% discount rate.
5	Laprise et al., 2014[16]	HPV vaccination for girls	(1) 2 dose girls & boys vs 2 dose girls-only vaccination; (2) 3 dose girls & boys vs 3 dose girls only or 2 dose girls & boys vaccination.	$120,833.6/ QALY, $140,892.7/ QALY, $189,839.3/ QALY for (1) and 20, 25, 30 years protection; >$1,4M/ QALY, $238,745.4/ QALY, $234,137/ QALY for (2) and 20, 25 years, and lifetime protection.	$56,062/QALY.	Two-dose girls & boys HPV vaccination was unlikely to be cost-effective unless the cost per dose for boys was substantially lower than the cost for girls.
6	Brisson et al., 2015[17]	HPV vaccination for girls	Including boys in the current vaccination program, (1) 4-valent GNV vs no vaccination; (2) 9-valent GNV vs 9-valent girls vaccination/ 4-valent boys vaccination.	$10,200.7 (1); $195,909.4 (no cross protection) and $43,457.8 (with cross protection) (2)	NS	GNV was cost-effective when using 4-valent vaccine. Switching to a 9-valent gender-neutral HPV vaccination program was likely to be cost-saving if the additional cost/dose of the 9-valent was less than $18.
7	Graham et al., 2015[18]	HPV vaccination for girls	Vaccination in boys compared with no vaccination.	$2,693.7 (99% vaccine efficacy and 70% uptake); $1,696 (50% vaccine efficacy and 50% uptake).	NS	HPV vaccination for boys aged 12 years may be a cost-effective strategy for the prevention of OPC in Canada.

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8	Chesson et al., 2018[19]	HPV vaccination for girls	Comparison scenario: 9vHPV program for females aged 12 through 26 years and males aged 12 through 21 years; Expanded scenario: 9vHPV program for ages 12 through 26 years for all sexes.	$16,600/ QALY (comparison scenario); $228,800/ QALY (expanded scenario) vs no vaccination	NS	The cost-effectiveness ratios were not so favorable as to make a strong economic case for recommending expanding male vaccination (12 - 26 years old).
9	Chesson et al., 2020[20]	HPV vaccination for girls	Mid-adult vaccination strategy: people aged 12 through 45 years with 9vHPV; Comparison strategy: females aged 12 through 26 years and males aged 12 through 21 years.	Mid-adult vaccination strategy: $11,163.6; Comparison strategy: $792,737.	NS	Mid-adult vaccination is much less cost-effective than the comparison strategy of routine vaccination for all adolescents at ages 11 to 12 years and catch-up vaccination for women through age 26 years and all men through age 21 years.
10	Choi et al., 2022[21]	HPV vaccination for girls and boys	Increasing HPV vaccination uptake rate to 80% for both sexes.	$102,355.7/ QALY	WTP: $176,597.2/QALY.	Expanding HPV vaccination rates would likely provide a cost-effective way to reduce the OPC incidence, particularly among males.
11	Wolff et al., 2018[22]	HPV vaccination for girls	Sex-neutral vaccination program compared vaccination program for girls.	$57,085.6 (societal); $60,943 (healthcare).	$74,646.5.	The cost-effectiveness of a sex-neutral program is highly dependent on the price of the vaccine, the lower the price the more favorable it is to also vaccinate boys.
12	Burger et al., 2014[23]	HPV vaccination for girls	Gender-neutral vaccination program.	$83,981/ QALY	$115,980.6/ QALY	Increasing coverage in girls was uniformly more effective and cost-effective than expanding vaccination coverage to boys and should be considered a priority.
13	Jiménez et al., 2015[24]	HPV vaccination for girls	Including boys in the current vaccination program vs girls on vaccination program.	$395,231.2/QALY (healthcare); $359,184.8/ QALY (societal).	WTP: $55,216.4 - $441,731.4/ QALY.	Lower price per vaccine (under NNO550/ dose) and increasing coverage among girls to 92% reduced the ICER value and become cost effective.
14	Boiron et al., 2016[25]	HPV vaccination for girls (quadrivalent)	9-valent and 4-valent vaccine for girls and boys associated with current cervical cancer screening.	$25,600.7/QALY	WHO: $62,285.16	The present study demonstrated that the switch from Gardasil® to the nonavalent universal vaccination in Austria can bring substantial incremental public health benefits and would constitute a cost-effective intervention.
15	Mennini et al., 2017[26]	HPV vaccination for both boys and girls (quadrivalent)	(1) Universal vaccination 9-valent vs 4-valent; (2) universal vaccination 9-valent vs girls vaccination 4-valent.	$15,620.6/QALY (1); $20,215.7/ QALY (2)	$37,323.3 - $59,717.2	The vaccination of girls only and universal vaccination with the nine-valent vaccine were cost-effective strategies compared with the vaccination of girls with the bivalent or the quadrivalent vaccine.
16	Qendri et al., 2017[27]	HPV vaccination for girls	Sex-neutral vaccination to girls-only vaccination.	$3,758.5/LY girls only program vs no vaccination; $15,997/LY expanding vaccinating boys vs girls only.	GDP per capita: $70,054.	Uptake among girls was more efficient for reducing the total burden than switching to a sex-neutral program. Sex-neutral program had a favorable cost-effective profile even if coverage among girls improves.

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17	Datta et al., 2019[28]	HPV vaccination for girls	Historical vaccination, followed by selecting 85% of 12-year old girls and 85% of 12-year old boys to start vaccinated (2017); Historical vaccination, followed by selecting 42.5% of 12-year old girls and 42.5% of 12-year old boys at the start vaccinated (2017); Vaccinating 60% of 12-year old girls and 60% of 12-year old boys from 2008 onwards, no historical vaccination.	ICER based on vaccine price: Girls and boys, cost-effective in 3.5% disc. rate; Girls and boys, bivalent ($61.20), quadrivalent ($75), nonavalent ($78.7) in 1.5% disc. rate compared girls only vaccination.	$33,570.4/ QALY	Vaccinating girls is extremely cost-effective compared with no vaccination, vaccinating both sexes is less so. Adding boys to an already successful girls-only program has a low cost-effectiveness.
18	Qendri et al., 2020[29]	HPV vaccination for girls; HPV vaccination program including boys	Including boys in the current vaccination program (on several countries).	Austria $18,636.3; Belgium $15,771.4; Croatia $79,352.8; Estonia $83,113; Italy $34,049.3; Latvia $19,636.6; Netherlands $6,512.2; Poland $15,901.4; Slovenia $19,097.6; Spain $37,957.2; Sweden $17,628.5.	Average $44,788 - $59,717.2.	At uniform 80% uptake, a favorable cost-effectiveness profile was retained for most of the countries investigated (Austria, Belgium, Italy, Latvia, the Netherlands, Spain, and Sweden).
19	Simons et al., 2020[30]	HPV vaccination for girls	Gender-neutral vaccination program compared to a girls-only program.	$25,747.6/ QALY (boys only); $10,510.7/ QALY (gender neutral).	WTP: $31,632.8 (100% HPV vaccination boys effective); $28,757 (94% HPV vaccination boys effective).	Vaccination of boys, additional to girls, will prevent a relevant number of cancers in both boys and girls. Based on the current Dutch situation vaccination of HPV in boys is likely cost-effective.
20	Majed et al., 2021[31]	HPV vaccination for girls (nonavalent, 2 dose); catch-up for 15–19-years-old girls	Gender-neutral vaccination program compared to a girls-only program.	$34,465.4/QALY in genital warts; $21,133.2/QALY in HPV-related cancers; $56,230.6/QALY anogenital cancers uptake 60% vaccination boys; $34,338.8 anogenital cancers uptake 21.2% vaccination boys	1-3x GDP per capita ($52,879 - $158,637.2).	GNV has a significant impact in terms of public health benefits and may be considered cost-effective compared with GOV at low and high coverage rates.
21	Portnoy et al., 2021[32]	HPV vaccination for girls	Vaccination of boys and girls with 9vHPV vs vaccination of boys and girls with 2vHPV.	$211,744.4	WTP: $57,445.2/ QALY; GDP per capita: $99,179.	A potential switch to 9vHPV may lead to greater benefits, but does not affect elimination timing and may not be cost-effective unless the additional cost of 9vHPV is substantially reduced.
22	Daniels et al., 2022[33]	HPV vaccination for girls and boys (nonavalent)	Switching 2-dose to 1-dose 9vHPV vaccine.	NS	WTP: $31,605.2/ QALY.	Adoption of 1-dose 9vHPV vaccination program resulted in more vaccine preventable HPV-related cancer and disease cases in males and females, also had a low probability of being cost-effective compared to the 2-dose program.

23	Linertová et al., 2022[34]	HPV vaccination for girls	Gender-neutral vs girls-only program (9-valent and 4-valent vaccine).	$37,787/QALY	WTP: $27,752.24/QALY.	The gender-neutral 9-valent HPV vaccination in Spain offers more benefits than any other modeled strategy, although in the conservative base case it was not cost-effective.
24	Blakely et al., 2014[35]	HPV vaccination for girls	(1) 'as implemented' HPV vaccination program of girls; (2) modification to school-only program; (3) new mandatory law requiring active opting-out of vaccination; compared to no vaccination.	$23,900/ QALY (2) vs no vaccination; $32,784/ QALY (3) vs no vaccination; $36,696.5/ QALY (2) vs (1); $129,548/ QALY (3) vs (2).	WTP: $17,978/QALY; GDP/ capita: $42,301.	A more intensive school-only vaccination program (girls and boys) seemed cost effective compared with no vaccination and established program HPV vaccination (girls only).
25	Pearson et al., 2014[36]	HPV vaccination for girls	(1) Adding boys to girls vaccination program; (2) adding boys to school-based delivery in girls; all 3 dose.	$83,172.34/ QALY (1); $173,388.59/QALY (2).	WTP: $40,096	Adding boys to the girls-only HPV vaccination program was highly unlikely to be cost-effective. To become cost-effective, vaccine would need to be supplied at very low prices and administration costs would need to be minimized.
26	Drolet et al., 2021[37]	HPV vaccination for girls	Including boys in the current vaccination program.	Using cost vaccine 1 and 2: India ($6,884, $8,552.3); Vietnam ($5,750.5, $7,161.3); Uganda ($920, $1,337.6); Nigeria ($5,334, $6,635.5) vs girls only.	GDP per capita (India: $8,771; Vietnam: $8,423; Uganda: $2,317; and Nigeria: $7,285.7)	All LMIC countries were cost effective if they want to add vaccination for boys to the existing vaccination program.

Table 4. Sensitivity analysis of health economic studies of HPV vaccination

No	Authors, publication year	Sensitivity analysis	Sensitive parameter
1	Chanthavilay et al., 2016[12]	One-way sensitivity analysis	Coverage, vaccine cost, discount rate, cervical cancer incidence, duration of vaccine protection, and vaccine efficacy
2	Kitano, 2022[13]	One-way sensitivity analysis	vaccine dose
3	Cheung et al., 2023[14]	One-way sensitivity analysis	Vaccination rate
4	Wahab et al., 2023[15]	One-way sensitivity analysis	Cancer survival, risk ratio (RR)
5	Laprise et al., 2014[16]	One-and multi-way sensitivity analysis.	Vaccine cost, coverage
6	Brisson et al., 2015[17]	One-way sensitivity analysis	Vaccine cost
7	Graham et al., 2015[18]	One-way sensitivity analysis	Vaccine uptake rate, infection rate, and survival probability
8	Chesson et al., 2018[19]	One-way sensitivity analysis, probabilistic sensitivity analysis	Vaccine cost
9	Chesson et al., 2020[20]	One-way sensitivity analysis, probabilistic sensitivity analysis	Utility, coverage
10	Choi et al., 2022[21]	One-way sensitivity analysis, probabilistic sensitivity analysis	Coverage rate
11	Wolff et al., 2018[22]	Deterministic sensitivity analysis	Vaccine price, vaccination coverage
12	Burger et al., 2014[23]	One-and multi-way sensitivity analysis.	Vaccine price, discount rate, vaccination coverage
13	Jiménez et al., 2015[24]	One-way sensitivity analysis, probabilistic sensitivity analysis	Vaccine per dose
14	Boiron et al., 2016[25]	One-way sensitivity analysis	Discount rate, duration of protection
15	Mennini et al., 2017[26]	One-way sensitivity analysis	Discount rate, duration of protection
16	Qendri et al., 2017[27]	One-way sensitivity analysis	Vaccine uptake rate
17	Datta et al., 2019[28]	NS	NS
18	Qendri et al., 2020[29]	One-way sensitivity analysis	Vaccine cost
19	Simons et al., 2020[30]	One-way sensitivity analysis, probabilistic sensitivity analysis	Cancer prevention
20	Majed et al., 2021[31]	Deterministic sensitivity analysis	Duration of protection, discount rate
21	Portnoy et al., 2021[32]	NS	NS
22	Daniels et al., 2022[33]	One-way sensitivity analysis, probabilistic sensitivity analysis	NS
23	Linertová et al., 2022[34]	Probabilistic sensitivity analysis	Vaccine price
24	Blakely et al., 2014[35]	One-way sensitivity analysis; probabilistic sensitivity analysis (cost-effectiveness plane).	Vaccination cost, genital warts incidence rate and disability weight, coverage
25	Pearson et al., 2014[36]	One-way sensitivity analysis	Vaccine and administration cost
26	Drolet et al., 2021[37]	One-way sensitivity analysis	Vaccine dose

Lastly, the discount rate is an important consideration in health economic studies, especially when modelling is used and longtime horizons are considered. The majority of studies (17 studies) used a 3% discount rate. However, there are also studies that used different discount rates, such as 1.5%, 2%, 3.5%, 4%, and 5% (Table 2).

3. Study design

In all trials, the health outcome was Quality-Adjusted Life Years (QALYs) and/or Life Years (LYs). The health economic studies primarily provide the ICER, which illustrates the cost-effectiveness of a new HPV vaccination program intervention in comparison to a repeat intervention. All studies demonstrated the cost-effectiveness of implementing HPV vaccination for girls (Table 3). Most of the studies involved intervention, including boys, in the recurrent vaccination of girls. In those studies, boys population was included in school-based programs or gender-neutral vaccinations. In addition, another intervention or scenario was used: catch-up programs for girls and boys were examined in three studies, comparing the vaccine type (6 studies) and the vaccine dose (2 studies).

For high-income countries such as Singapore and European countries (Canada, Italy, the UK, Austria, Belgium, Spain, and the Netherlands), the cost-effectiveness threshold was officially set in each country (7 studies). However, the other study used willingness to pay (WTP) as the cost-effectiveness threshold (8 studies). In addition, other countries that did not set a threshold used 1-3 times the World Health Organization (WHO) recommended gross domestic product (GDP) per capita (6 studies). Unfortunately, five studies did not mention the threshold.

The Cost-Effectiveness Threshold (CET) may influence the cost-effectiveness of HPV vaccination in a country. Based on the review, sixteen out of twenty-six articles concluded that including boys in the HPV vaccination program was cost-effective compared to the current program. HPV vaccination may be cost-effective if only the price of the vaccine is reduced, as shown in studies from Canada, New Zealand, and Norway[16,24,36]. A review of European countries showed that a new intervention could be cost-effective in 80% of cases in Austria, Belgium, Italy, Latvia, the Netherlands, Spain, and Sweden[29]. Meanwhile, a study from Singapore found that HPV vaccination for boys was not cost-effective using a 3% discount rate[15].

4. **Sensitivity analysis**

As the mathematical model has been widely used in health economic studies, there have been several issues regarding the model uncertainty. Therefore, sensitivity analysis is needed to compensate for the uncertainties. There are two main types of sensitivity analysis: univariate sensitivity analysis (or one-way sensitivity analysis) and probabilistic sensitivity analysis (PSA). Univariate sensitivity analysis can identify the most influential parameters of the model conclusion. PSA determines whether the intervention is cost-effective based on a country's willingness to pay.

Twenty-six studies used a variety of sensitivity analysis methods. Most studies used only one-way sensitivity analysis to address uncertainty and assess the robustness of the results in the health economic study (12 studies); one study used only probabilistic sensitivity analysis; and two studies used only deterministic sensitivity analysis. Meanwhile, two studies used a combination of one-way and multi-way sensitivity analysis; seven studies combined one-way sensitivity analysis and probabilistic sensitivity analysis; and two studies did not mention sensitivity analysis (Table 4). Several parameters, including vaccine cost, vaccine coverage, duration of protection, and discount rate, affected the ICER generated from the included studies.

Discussion

Since its launch by the WHO in 2006, the HPV vaccine has been administered to girls aged 9–14 in many countries worldwide. Initially, the vaccine aimed to prevent or reduce the incidence of cervical cancer. However, recent studies have shown that it is also effective in reducing the incidence of all HPV-related cancers. Some countries have started to expand their HPV vaccination programs to include boys, both in school-based and gender-neutral vaccination programs. A cost-effectiveness study can help decision-makers determine whether adding HPV vaccination for boys will result in greater health and economic benefits within an acceptable budget. Our study found that expanding the HPV vaccination program to include boys is a cost-effective strategy for preventing HPV-related cancer and reducing incidence and mortality rates. These results were observed in both developed countries (Europe, the US, and Hong Kong) and developing countries (India, Vietnam, Uganda, and Nigeria).

To maintain a cost-effective ratio below the threshold, certain parameters become sensitive. Lower vaccine prices, wider coverage for girls, and longer vaccine protection duration were important considerations when implementing HPV vaccination for boys. These parameters were also influenced by the type of vaccine used, which can impact efficacy and price.

These studies widely use the transmission dynamic model, also known as the dynamic model, which can describe changes over time and handle uncertainties like recurrence. It can also model non-linear relationships between parameters, making it more representative of real conditions in a country. Additionally, most studies employ a healthcare system perspective. This passage describes the cost burden of implementing vaccination programs, including vaccine costs, administration costs, and health worker expenses. If adding boys to the vaccination program is not cost-effective, healthcare providers can propose a health policy in collaboration with the government to consider the program.

A lifetime horizon is necessary for the cost-effectiveness analysis of HPV vaccination as a prevention strategy for HPV-related cancer. However, most studies have used a time horizon of 100 years, while some have used 70 years. Although the predetermined time horizon did not significantly affect the ICER value, it still provides reasonable results. Both time horizons describe the conditions of the next 70 and 100 years, assuming the population has died after reaching its life expectancy.

The presented systematic review has certain limitations. It only considers the expansion of HPV vaccination programs in boys, which typically begins at ages 9–14, similar to girls. The study did not include adolescent boys, men, or men who have sexual relations with men (MSM). Additionally, the study collected data from various countries, excluding developing countries like Indonesia that have not implemented vaccination programs for boys. Further research is necessary to examine the cost-effectiveness of vaccinating male populations of different ages, with a focus on low- and middle-income countries (LMICs).

Conclusions

Expanding HPV vaccination to boys is considered a cost-effective solution for preventing HPV-related cancers, based on studies conducted in many countries. It is recommended to conduct an economic evaluation to estimate the cost-effectiveness of HPV vaccination as a prevention method for HPV-related cancers in low- and middle-income countries like Indonesia. We suggest expanding the HPV vaccination target to boys with a lower-priced vaccine and increasing vaccination coverage to initiate the study.

Acknowledgment

This study was conducted as a part of thesis' requirement for the Master in Pharmacy Management Program at the Faculty of Pharmacy, Universitas Gadjah Mada.

Author Contribution

Study design	:	DTS
Data analysis	:	DTS
Manuscript writing	:	DTS, DE, MJP
Thesis Supervisor	:	DE, MJP

Competing Interests

The author has disclosed that there are no competing interests or personal relationships that could have influenced the work reported in this study.

Abbreviation

CEA	:	Cost-effectiveness analysis
CET	:	Cost-effectiveness treshold
CUA	:	Cost-utility analysis
DALY	:	Disability-adjusted life year
FDA	:	U.S. Food and Drug Administration
GDP	:	Gross Domestic Product
HPV	:	Human Papillomavirus
ICER	:	Incremental cost-effectiveness ratio
LMICs	:	Low- and middle-income countries
MSM	:	Men who have sex with men
PSA	:	Probability Sensitivity Analysis
QALY	:	Quality-adjusted life year
WHO	:	World Health Organization
WTP	:	Willingness to Pay

References

1. WHO. Human Papillomavirus (HPV). *World Health Organization* https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/human-papillomavirus (2023).
2. Prigge, E. S., von Knebel Doeberitz, M. & Reuschenbach, M. Clinical relevance and implications of HPV-induced neoplasia in different anatomical locations. *Mutat. Res. - Rev. Mutat. Res.* **772**, 51–66 (2017).
3. National Cancer Institute. HPV and Cancer. *National Cancer Institute* https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-and-cancer#:~:text=HPV can cause six types,and cases of genital warts. (2019).
4. Sung, H. *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA. Cancer J. Clin.* **71**, 209–249 (2021).
5. Chen, S. *et al.* Estimates and Projections of the Global Economic Cost of 29 Cancers in 204 Countries and Territories from 2020 to 2050. *JAMA Oncol.* **9**, 465–472 (2023).
6. American Cancer Society. The Economic Burden of Cancer. *The Cancer Atlas* (2019).
7. Jemal, A. *et al.* Global Cancer Statistics. *CA Cancer J Clin* **61**, 69–90 (2011).
8. Demarteau, N., Tang, C. H., Chen, H. C., Chen, C. J. & Van Kriekinge, G. Cost-effectiveness analysis of the bivalent compared with the quadrivalent human papillomavirus vaccines

in Taiwan. *Value Heal.* **15**, 622–631 (2012).
9. CDC. Human Papillomavirus (HPV) Vaccination: What Everyone Should Know. *Center for Disease Control and Prevention* https://www.cdc.gov/vaccines/vpd/hpv/public/index.html (2021).
10. Ding, W. *et al.* The lifetime cost estimation of human papillomavirus-related diseases in China: A modeling study. *J. Transl. Intern. Med.* **9**, 200–211 (2021).
11. De Kok, I. M. C. M., Habbema, J. D. F., Van Rosmalen, J. & Van Ballegooijen, M. Would the effect of HPV vaccination on non-cervical HPV-positive cancers make the difference for its cost-effectiveness? *Eur. J. Cancer* **47**, 428–435 (2011).
12. Chanthavilay, P. *et al.* The economic evaluation of human papillomavirus vaccination strategies against cervical cancer in women in Lao PDR: A mathematical modelling approach. *BMC Health Serv. Res.* **16**, 1–10 (2016).
13. Kitano, T. Risk–Benefit Analysis of the 9-Valent HPV Vaccination for Adolescent Boys from an Individual Perspective. *Japanese Journal of Infectious Diseases* vol. 75 114–120 at https://doi.org/10.7883/yoken.JJID.2021.367 (2022).
14. Cheung, T. H. *et al.* Health impact and cost-effectiveness of implementing gender-neutral vaccination with the 9-valent HPV vaccine in Hong Kong. *Hum. Vaccines Immunother.* **19**, (2023).
15. Wahab, M. T., Tan, R. K. J., Cook, A. R. & Prem, K. Impact of including boys in the national school-based human papillomavirus vaccination programme in Singapore: A modelling-based cost-effectiveness analysis. *Vaccine* **41**, 1934–1942 (2023).
16. Laprise, J. F. *et al.* Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: A transmission-dynamic modelling study. *Vaccine* **32**, 5845–5853 (2014).
17. Brisson, M. *et al.* Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States. *J. Natl. Cancer Inst.* **108**, 1–9 (2016).
18. Graham, D. M. *et al.* A cost-effectiveness analysis of human papillomavirus vaccination of boys for the prevention of oropharyngeal cancer. *Cancer* **121**, 1785–1792 (2015).
19. Chesson, H. W., Meites, E., Ekwueme, D. U., Saraiya, M. & Markowitz, L. E. Cost-effectiveness of nonavalent HPV vaccination among males aged 22 through 26 years in the United States. *Vaccine* **36**, 4362–4368 (2018).
20. Chesson, H. W., Meites, E., Ekwueme, D. U., Saraiya, M. & Markowitz, L. E. Cost-effectiveness of HPV vaccination for adults through age 45 years in the United States: Estimates from a simplified transmission model. *Vaccine* **38**, 8032–8039 (2020).
21. Choi, S. E. *et al.* Increasing HPV vaccination coverage to prevent oropharyngeal cancer: A cost-effectiveness analysis. *Tumour Virus Res.* **13**, 200234 (2022).
22. Wolff, E. *et al.* Cost-effectiveness of sex-neutral HPV-vaccination in Sweden, accounting for herd-immunity and sexual behaviour. *Vaccine* **36**, 5160–5165 (2018).
23. Burger, E. A., Sy, S., Nygård, M., Kristiansen, I. S. & Kim, J. J. Prevention of HPV-related cancers in Norway: Cost-effectiveness of expanding the HPV vaccination program to include pre-adolescent boys. *PLoS One* **9**, (2014).
24. Jimenez, J. E. *et al.* Surgical factors associated with patient-reported quality of life outcomes after free flap reconstruction of the oral cavity. *Oral Oncol.* **123**, 105574 (2021).
25. Boiron, L., Joura, E., Largeron, N., Prager, B. & Uhart, M. Estimating the cost-effectiveness profile of a universal vaccination programme with a nine-valent HPV vaccine in Austria. *BMC Infect. Dis.* **16**, 1–15 (2016).
26. Mennini, F. S. *et al.* Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. *Cost Eff. Resour. Alloc.* **15**, 1–14 (2017).
27. Qendri, V., Bogaards, J. A. & Berkhof, J. Health and economic impact of a tender-based, sex-neutral human papillomavirus 16/18 vaccination program in the Netherlands. *J. Infect. Dis.* **216**, 210–219 (2017).
28. Datta, S. *et al.* Assessing the cost-effectiveness of HPV vaccination strategies for adolescent girls and boys in the UK. *BMC Infect. Dis.* **19**, 1–16 (2019).
29. Qendri, V. *et al.* The cost-effectiveness profile of sex-neutral HPV immunisation in European tender-based settings: a model-based assessment. *Lancet Public Heal.* **5**, e592–e603 (2020).
30. Simons, J. J. M., Vida, N., Westra, T. A. & Postma, M. J. Cost-effectiveness analysis of a gender-neutral human papillomavirus vaccination program in the Netherlands. *Vaccine* **38**, 4687–4694 (2020).
31. Majed, L. *et al.* Public health impact and cost-effectiveness of a nine-valent gender-neutral HPV vaccination program in France. *Vaccine* **39**, 438–446 (2021).
32. Portnoy, A. *et al.* Impact and cost-effectiveness of strategies to accelerate cervical cancer elimination: A model-based analysis. *Prev. Med. (Baltim).* **144**, 106276 (2021).
33. Daniels, V. *et al.* Modeling the health and economic implications of adopting a 1-dose 9-valent human papillomavirus vaccination regimen in a high-income country setting: An analysis in the United Kingdom. *Vaccine* **40**, 2173–2183 (2022).

34. Linertová, R., Guirado-Fuentes, C., Mar-Medina, J. & Teljeur, C. Cost-effectiveness and epidemiological impact of gender-neutral HPV vaccination in Spain. *Hum. Vaccines Immunother.* **18**, (2022).
35. Blakely, T. *et al.* Cost-effectiveness and equity impacts of three HPV vaccination programmes for school-aged girls in New Zealand. *Vaccine* **32**, 2645–2656 (2014).
36. Pearson, A. L. *et al.* Is expanding HPV vaccination programs to include school-aged boys likely to be value-for-money: A cost-utility analysis in a country with an existing school-girl program. *BMC Infect. Dis.* **14**, (2014).
37. Drolet, M. *et al.* Optimal human papillomavirus vaccination strategies to prevent cervical cancer in low-income and middle-income countries in the context of limited resources: a mathematical modelling analysis. *Lancet Infect. Dis.* **21**, 1598–1610 (2021).