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REVIEW

Economic evaluation of human papillomavirus vaccination in the Global South: a systematic review

Saba Abidi[1] · Satyanarayana Labani[2] · Aastha Singh[1] · Smita Asthana[2] · Puneeta Ajmera[1]

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Abstract

Objectives Many reviews have been conducted on the economic evaluation of the HPV vaccine in global north countries. But there is a dearth of such reviews in the Global South countries. Hence, this systematic review aims to summarize studies done in these countries.

Methods Four databases PubMed, Embase, Cochrane Library, and Google Scholar from 2009 to 2019 were searched for economic evaluations on HPV vaccination in the Global South countries. PRISMA guidelines were followed to include full-text articles. 40 original articles were shortlisted for full-text review.

Results Studies had varied models, assumptions, and results according to different scenarios. Most studies concluded HPV vaccination to be cost-effective under varied scenarios and vaccine cost was the most influential parameter affecting the sensitivity analyses, consequently incremental cost-effectiveness ratio. A wide range in the cost-effectiveness ratio was observed in the included studies due to different study settings, populations, and inconsistencies in modeling practices (variations in methodological approaches).

Conclusions This review suggests the introduction of HPV vaccination alone or in combination with screening according to different countries. The price of the vaccine should be economical and funds for the vaccine should be provided by public sector firms.

Keywords Cost-effectiveness · Economic evaluation · Global South · HPV vaccination · ICER

Introduction

Cervical cancer is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 6.6% of all female cancers. Approximately 90% of deaths from cervical cancer occurred in low- and middle-income countries (Vu et al. 2018). Most of the

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✉ Saba Abidi
saba.abidi91@gmail.com

Satyanarayana Labani
satyanarayanalabani@yahoo.com

Aastha Singh
aasthasingh777@gmail.com

Smita Asthana
smitasanjay97@yahoo.com

Puneeta Ajmera
puneeta_22@yahoo.com

1 Delhi Pharmaceutical Sciences and Research University, New Delhi, India

2 Indian Council of Medical Research – National Institute of Cancer Prevention and Research, Noida, Uttar Pradesh, India

countries in the Global South belong to low or middle-income countries and have got a high incidence of Cervical cancer. According to GLOBOCAN 2018, the top five countries of the high incidence of cervical cancer are part of the Global South (namely *Swaziland*, *Malawi*, *Zambia*, *Zimbabwe*, *Tanzania).*

The oncogenic strains of human papillomavirus (HPV) are responsible for cervical cancer globally (Burd 2003). World Health Organization (WHO) recommends HPV vaccination for girls in the age group 9–14 years.

There are three types of HPV vaccination available in the market in many countries across the world. They are bivalent, a quadrivalent, and a nonavalent vaccine. All three vaccines have been stated to have high efficacies for HPV 16 and 18, which, according to WHO, are responsible for more than half of the cases of cervical cancer globally. The WHO recommends that the cost-effectiveness of HPV vaccination is established before it is introduced in national vaccination programs. Though the HPV vaccine is costly in price as well as in administration, hence, it becomes even more crucial to assess the cost of the HPV vaccine to provide evidence-based research for its usage (Kim et al. 2008).

There have been many reviews, which have targeted both developed and developing Global North countries for the economic evaluation of HPV vaccination (Kim et al. 2008; Brisson et al. 2009; Kostaras et al. 2019; Fesenfeld et al. 2013; Silas et al. 2018). Global North countries represent economically developed countries that are technologically advanced and politically stable. While the Global South countries are agrarian-based, dependent economically, and politically on the Global North countries. There are many causes for these inequalities including the availability of natural resources; different levels of health and education; the nature of their economy; international trading policies and access to markets. Despite being several reviews done on HPV vaccination, there has been no systematic review of economic evaluations of HPV vaccination comprising of the entire global south countries. This study aims to guide decision-makers on the introduction of HPV vaccination in respective countries with its main focus on studies published in the Global South countries.

The objectives of this review are (1) to update and summarize the most recent studies conducted on the cost-effectiveness of HPV vaccination in the Global South countries (2) to identify the countries of the global south where the cost-effectiveness analysis of HPV vaccination has not been done. (3) to summarize various parameters and strategies affecting the cost-effectiveness of HPV vaccination, (4) to provide a supportive tool for decision-makers to include HPV vaccination in national vaccination programs (5) to summarize the most cost-effective strategies for implementation of the same.

Methods

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA), Fig. 1.

Search strategy and selection criteria

PubMed, Cochrane Library, Embase, and Google Scholar were searched for economic evaluations of HPV vaccination published from 2009 to October 2019 using a controlled vocabulary.

Search strategy: various combinations of the following terms were used.

"cost-effectiveness" OR "cost-effectiveness analysis" OR "cost–benefit analysis" OR "economic evaluation" OR "Cost-utility" AND "HPV vaccination" OR "vaccine" OR "human papillomavirus vaccine*" AND "*name of the country of Global South*" were used as MeSH terms.

The names of the global south countries were obtained from the UNDP, 2004 list of the global south countries.

Inclusion and exclusion criteria

Population and study design

Following characteristics were defined to include the studies,

(a) The primary studies targeting the HPV vaccination of girls and boys more than 9 years of age (b) studies targeting the Global South countries (c) an economic evaluation (cost-effectiveness/cost–benefit/cost-utility analysis) study (d) a health economic model is used to assess the cost-effectiveness (e) studies of catch-up vaccination against HPV (f) studies including cervical cancers and its precursors and genital warts as the diseases captured in the model. Studies targeting some specific populations like HIV+ people were excluded. The studies including non-cervical diseases as diseases captured in the study were excluded. Reviews, systematic reviews, conference papers, news items were also excluded.

Intervention

The bivalent vaccine against HPV types 16 and 18, quadrivalent against HPV types 6,11,16,18, and Nonavalent vaccine against HPV types 16/18/6/11/31/33/45/52/58. We defined vaccine schedule as one dose, two-dose, and three doses and booster dose if considered in the study.

Comparisons

(a) Two doses vs three doses of the same vaccine.

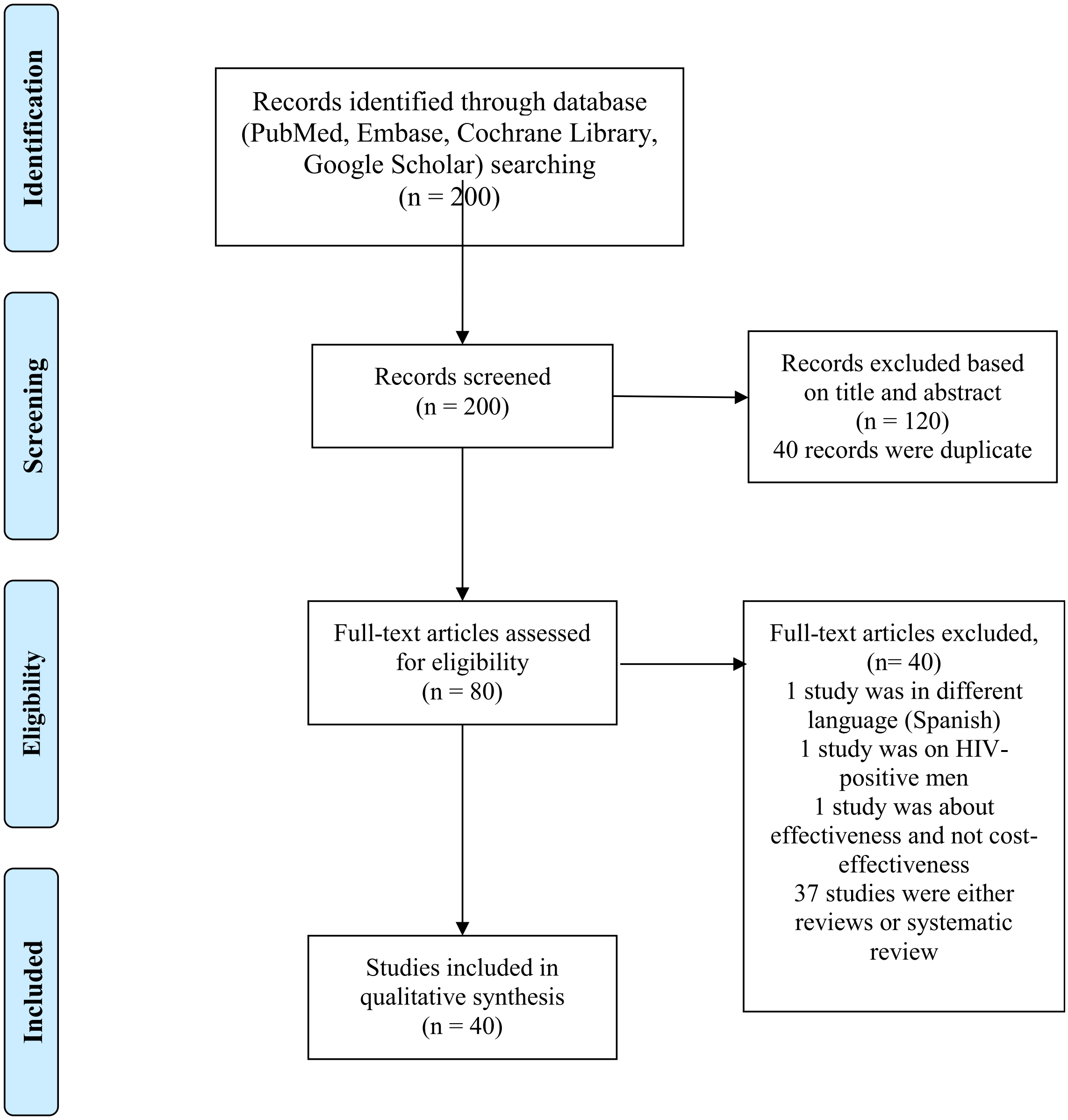

Fig. 1 Flowchart of study selection process through preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for the systematic review of the economic evaluation of human papillomavirus vaccination in the Global South

(b) Comparison between bivalent and quadrivalent vaccine.
(c) Comparison between the introduction of HPV vaccination and doing nothing
(d) Comparison between the introduction of HPV vaccination and current screening practice
(e) Comparison of combined strategy (HPV vaccination and current screening practice) with vaccination alone and screening alone.
(f) Comparison between the HPV vaccination program of girls with/without boy vaccination program.
(g) Comparison between the HPV vaccination program of girls with/without catch-up component.

Outcomes

Reduction in cancer incidence

Health economic outcomes in terms of DALYs (disability-adjusted life years), QALYs (quality-adjusted life years), YLS (years of life saved).

Incremental cost-effectiveness ratio (ICERs) were used to ascertain the cost-effectiveness of a particular intervention. ICERs were in terms of Cost/QALY, Cost/DALY, Cost/YLS.

“Data extraction”

After searching the databases for the number of articles found, one reviewer (AS) conducted the searches and excluded titles that were ineligible, e.g., duplicates, Global

North country, news items. Then, two reviewers (SA and AS) independently screened the titles and abstracts of the remaining records. Systematic reviews, reviews, conference papers were excluded. Two independent reviewers read the full text of potentially eligible records and decided to include them. Any disputes or differences were resolved by discussion or by a third reviewer (SL). Drummond's checklist which is used to assess the quality of the economic evaluations was then used to check the quality of papers (Drummond et al. 1997).

After the selection of the records for full-text review, relevant data were extracted according to a pre-designed template, which included authors, years of publication, country, a period of the model run, the mathematical model used, vaccine price, schedule, discount rate, age of vaccination, catch-up or booster included, strategies compared, outcome measures, vaccination coverage, vaccine efficacy, screening coverage and type of screening, sensitivity analysis conducted, economic outcomes: ICERs: [cost/QALY (quality-adjusted life years), cost/DALY (disability-adjusted life years) and cost per life years gained/saved (LYS/YLG)] for all the included strategies were extracted and compared. The affiliation was determined by the institutional affiliation of the first author. The funding source of a study was determined by any support directly received for the study stated in the acknowledgment or declarations.

"Risk of bias assessment"

Generally, three types of bias may occur in an economic evaluation, viz. bias related to structure, data, and inconsistency. As a final step, the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) checklist was used to evaluate any bias in this study. This checklist is widely used in planning and analyzing an economic evaluation and includes a total of 22 biases, of which 14 are specific for model-based economic studies (Haider et al. 2019). We assessed based on these criteria: study perspective, description of the comparator, time horizon, description of discounting of cost and outcome, description of the model and with figures of the model provided, clear reporting of the study population, reporting ICER and its unit, sensitivity analysis, and disclosure of funding sources and any conflict of interest.

"Currency conversions"

Unit costs were converted into 2019 international dollars (I$) to facilitate inter-country comparisons. Purchasing power parity conversions provided by the United Nations Statistics Division were used (International Monetary Fund 2020). Local currencies were first converted into I$ using the stated year of currency conversion, or (if not available) base year for prices, or (if neither available) article publication year. Costs in I$ were then inflated to 2019 values using the US$ Consumer Price Index for all urban consumers (CPI-U) since the US$ by definition has the same inflation rate as the I$ (Consumer price index United States 2020).

Results

Titles and abstracts of 200 published articles were searched (see Fig. 1). The search yielded 40 economic evaluations of HPV vaccination in the Global South Countries. The key characteristics of the articles are shown in Fig. 2 and discussed below.

Study characteristics

Single or multi-country

There were four multi-country studies. The most extensive were two studies covering 48 sub-Saharan African Countries and 20 EMENA (Extended Middle East and North Africa) Countries, respectively. Such multi-country studies facilitate access to economic analyses in settings, which may lack resources for such analyses.

"Regions, funding and authorship" (Fesenfeld et al. 2013)

Single-country studies largely focused on upper-middle-income countries of WPRO (Regional office for western pacific) and PAHO (Pan American health organization) (see Fig. 3). In contrast, there were twelve single-country studies for lower-middle-income countries, three for low-income countries, and only one for a high-income country, i.e., (Chile) (Gomez et al. 2014). Most of the studies were funded by the private manufacturers, this depicts that the studies on HPV vaccination are not the point of focus of the national decision-makers. The Bill and Melinda Gates Foundation was the sole or joint funder of 9 of the reviewed studies, while a further 15 studies were funded by either of the two HPV vaccine manufacturers (MSD or GSK). Two studies (Minh et al. 2017; Yaghoubi et al. 2018) were funded by WHO and one was funded by World Bank (Praditsitthikorn et al. 2011).

"Comparators" (Sinisgalli et al. 2015)

Almost all (34) studies investigated the cost-effectiveness of introducing HPV vaccination to girls aged 13 or younger. Four studies looked at vaccinating 15-year-old girls or above while one study (Liu et al. 2016) explored the impact of varying the age range from 12 to 55 years, another study estimated the cost-effectiveness of vaccinating girls between 10 and 14 years. All studies investigated vaccination either as an addition to existing screening programs or (more commonly) to opportunistic preventive programs or none at all. Most studies (Gomez et al. 2014)

Countries Covered	Single Country (36); Multi Country (4)
Income Level	Low (3); Lower Middle (11); Upper Middle (22); Mixed (3); ↓ High (1)
Region	PAHO (10); WPRO (13); SEARO (6); AFRO (6); EMRO (3); Multiple (2)
Threshold	<1 GDP/capita (32); ↓ (3) <3 GDP/Capita (3); Not clear (5)
Discount rate	3% / 3.50 (32); 5%/6% (5); NM (3)
Vaccine Duration	Lifelong (26); ↓ 10-30 yrs(1); ↓ 100 yrs(1); varied (2); Not clear (10)
Outcome Included	Cervical Cancer (13); Cervical Cancer + Precursor (18); Cervical Cancer + Precursor + GW (9)
Type of Screening	Pap/Cytology only (12); VIA/Pap + DNA (7); Pap + VIA (4); ↓ Pap or VILLI (1); VIA only (3); NM (3); NA (10)
Sensitivity Analysis	Univariate (20); Multivariate (4); Both (16)
Type of Model	Dynamic (5); Static (20); Mathematical (3); Markov (7); CERVIVAC (3); MCSM (1); CM (1)

AFRO- Regional Office for Africa, CM- Compartmental model, EMRO- Eastern Mediterranean Regional Office, GW- Genital warts, MCSM- Monte Carlo simulation model, NA- Not Applicable, NM- Not Mentioned, PAHO- Pan American Health Organization, PAP- Papanicolaou, SEARO- South-East Asia Regional Office, VIA- Visual Inspections with Acetic Acid, VILI- Visual Inspections with Lugol's iodine, WPRO- Western Pacific Regional Office.

Fig. 2 Categorization of the studies included in the systematic review of human papillomavirus vaccine in the Global South according to different characteristics

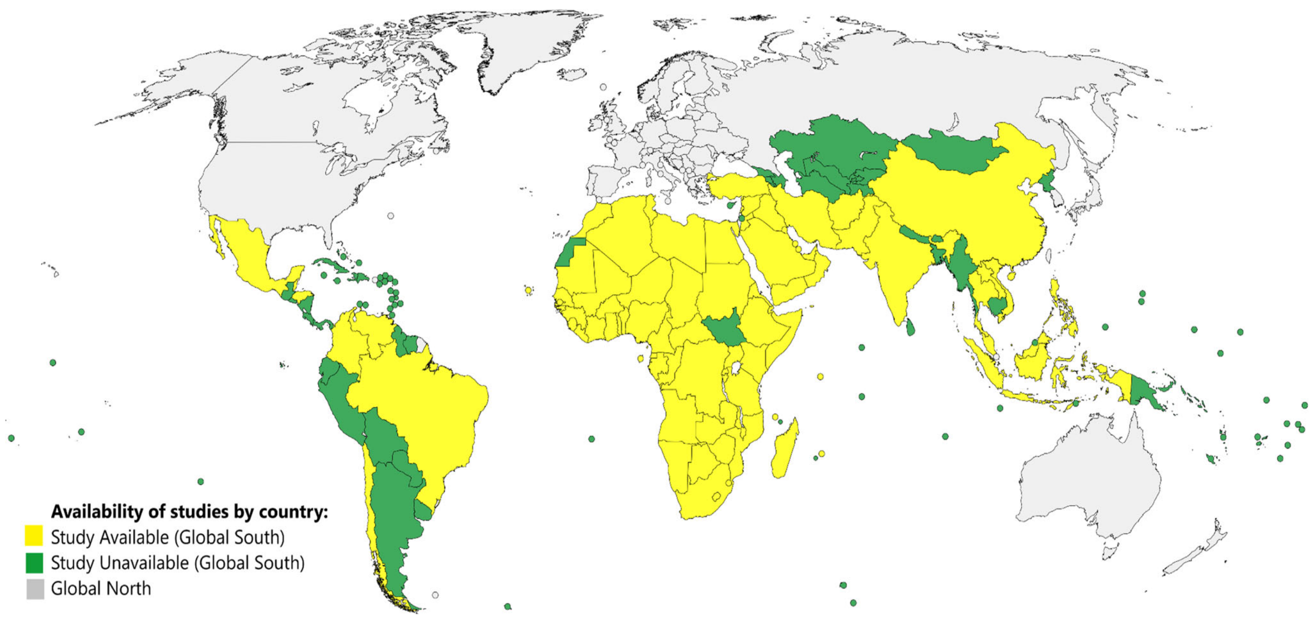

Fig. 3 Map representing the countries of the Global South and the Global North. Also, it depicts those countries of the Global South whose economic evaluations of human papilloma virus vaccine were available and unavailable. Available studies of the Global South were included in this systematic review

also considered a range of vaccination and screening options to find the most cost-effective combination. Different screening methods were examined, including conventional cytology alone, and various combinations of visual inspection, HPV DNA testing, and conventional cytology. Only one study looked at the cost-effectiveness of expanding vaccination to boys as well as girls (Chanthavilay et al. 2016a, b).

"Thresholds for the cost-effectiveness of interventions" (Marseille et al. 2015)

There is no universal criterion that defines a threshold cost-effectiveness ratio, below which an intervention would be considered cost-effective (Campos et al. 2012).

The WHO recommended the cost-effectiveness threshold was used in most of the studies. This shows the need for estimation of local thresholds because the conditions and the situations are different in various countries. So, generalizing this threshold for every country is questionable. Almost all (32) studies used either national GDP (gross domestic product) per capita or three times GDP per capita as the cost-effectiveness threshold, as proposed by the WHO (Sharma et al. 2011). This may reflect the lack of local thresholds for decision-making; however, it is unclear if this GDP-based threshold reflects societal willingness to pay for additional health gains and if the national budgets can afford the new healthcare interventions (Sinanovic et al. 2009). Only one study (Kawai et al. 2012) used a threshold based on local guidelines. Interestingly, three studies (Kiatpongsan and Kim 2014; Liu et al. 2016; Li et al. 2015) used higher thresholds based on GDP per capita or more than three times GDP per capita (Khatibi et al. 2014). Five studies did not state their cost-effectiveness threshold.

"Decision Models used" (Sinisgalli et al. 2015)

Bibliographic search shows that several types of decision models have been used by systematic reviews to synthesize evidence and to address research questions. Decision models can improve the value of systematic reviews by adding a formal structure that can extrapolate the evidence to explore additional outcomes pertinent to decision-makers. These are categorized into a Markov model, a micro-simulation model, dynamic models, and discrete event simulation models. Most (27) studies used Markov models which relate that the probability of being infected in a certain period of time does not change as a consequence of vaccination and so indirect (herd) protection for non-vaccinated individuals is not taken into account (Mo et al. 2017). Static models are recommended for estimating the cost-effectiveness of routine vaccination of young girls only, and not of catch-up or male vaccination (Mo et al. 2017). Of the remaining studies, five were dynamic models (which include disease transmission effects), three followed some mathematical models whose name was not specified, and three followed established CERVIVAC model, one study followed the Monte Carlo simulation model (Levin et al. 2015) and one study used compartmental model (Tracy et al. 2014).

"Vaccine Dosage" (D'Addario et al. 2017; Fesenfeld et al. 2013)

Most of the studies (20) focused on three doses of HPV vaccines. No study considered just the one dose vaccination. Two studies considered one dose and two-dose vaccine. Six studies compared two doses and the three-dose vaccine. Another six studies focused only on two doses of the HPV vaccine. Three studies included all, one, two, and three doses of vaccine. Three studies did not mention the dose of the HPV vaccine included.

The study conducted in Malaysia identified the two-dose HPV vaccination more protective than the three-dose vaccine (Aljunid et al. 2016). The countries which just introduced the HPV vaccination even one-dose vaccination results in cost-savings compared with no HPV vaccination (Burger et al. 2018). In Mexico, the three-dose strategy was found to be very cost-effective (Reynales-shigematsu et al. 2009). In contrast to the above statements, three-dose HPV vaccination was found to be not cost-effective in Iran because of the high vaccine price (Yaghoubi et al. 2018).

"Vaccine Coverage" (Fesenfeld et al. 2013)

Almost all studies assumed that three-dose vaccine coverage would be 70% or greater. Eight studies assumed the coverage as 100%. Several studies assumed the variability in the coverage of the vaccine. It was observed that the changes in the coverage directly affect the total cost of vaccination. As most of the models did not include herd immunity or cross-protection, so it was necessary to assume the maximum coverage of vaccine for better results. As the coverage will increase, the investment for HPV vaccine capacity building of health systems and outreach services will also increase.

"Vaccine Efficacy" (Sinisgalli et al. 2015)

Studies used a variety of methods to represent vaccine efficacy. Seven studies assumed 100% efficacy against HPV types 16 and 18, some studies assumed lower figures ranging between 90% and 98%. Five studies assumed the efficacy against 16 and 18 less than 90%. Only one study (Gomez et al. 2014) assumed that the vaccines would provide some cross-protection against non-vaccine type infections, while six others took a different approach of using an overall figure against any HPV infection (or cervical cancer) rather than stratifying the model into different types. Some studies also compared the effectiveness of bivalent and quadrivalent vaccines. One such study showed the same results for both bivalent and quadrivalent (Bardach et al. 2017). As far as the only quadrivalent vaccine is concerned, it was found by a study in Brazil, that quadrivalent HPV female vaccination can be a cost-effective public health intervention and it can substantially reduce the burden of cervical diseases and genital warts in Brazil (Kawai et al. 2012). In contrast to this, the quadrivalent HPV vaccine was found not cost-effective in Iran based on the base-case parameters' values (Khatibi et al. 2014). Another limitation of most of the studies is that there is a lack of data on sexual behaviors. Sexual behaviors can be varied across different countries. HPV is the most sexually transmitted agent, and it is strongly affected by herd immunity. For example, the herd immunity benefits projected for Uganda cannot be generalized for all the countries (Burger et al. 2018). The impact of vaccination on other HPV-related diseases that are attributable to HPV 16/18 including anal cancer, vulvar and vaginal cancer, and oro-pharyngeal and oral cancer was not considered and it must have underestimated the benefits of the vaccine (Chanthavilay et al. 2016a, b; Ekwunife and Lhachimi 2017). The reduction in the above-mentioned cancers should also be incorporated to accurately evaluate the cost-effectiveness of the HPV vaccine.

"Vaccine duration" (Gervais et al. 2017)

Almost all studies assumed lifelong vaccine protection (26) or did not discuss the duration of protection assumed (Burger et al. 2018). In contrast to studies assuming lifelong protection (Burger et al. 2018; Li et al. 2015), only two studies examined scenarios with waning protection or the need for a booster dose.

"Vaccine administration cost" (Haider et al. 2019)

Only eight studies stated the programmatic costs either as vaccine delivery cost or vaccine administration cost. There was no uniformity between the delivery and programmatic cost among different countries. It varied according to the local system and structure.

"Discount rate and perspective" (Sinisgalli et al. 2015)

All studies used a very long-time horizon (such as lifetime or 70–100 years) to capture outcomes such as cervical cancer that take place decades after initial HPV infection. Costs and benefits were usually discounted at 3% per year in the base case, as recommended in guidelines on economic evaluations of immunization programs. Studies were split between those taking a healthcare provider perspective in the base case and others taking a societal perspective (and hence incorporating costs to patients and their families as well).

Study results

See Table 1.

"Vaccination of girls" (Fesenfeld et al. 2013)

All but one (Kawai et al. 2012) of the reviewed studies examining adolescent female HPV vaccination concluded that this is likely to be cost-effective within at least part of the vaccine price range explored. Hence the studies' numerical ICERs (which estimate the cost needed to gain a QALY or year of life) are more informative in differentiating between studies than their overall conclusions. Six studies did not mention the ICERs for their assumptions (Aljunid et al. 2016; Bardach et al. 2017; Germar et al. 2017; Kiatpongsan and Kim 2014; Kriekinge et al. 2018; Liu et al. 2016). Though they compared the ICER with a threshold but did not mention the cost. Some mentioned the cost-effectiveness in terms of QALYs or DALYs. There is a clear trend of increasing ICERs both with increasing country GDP per capita and with increasing CVG (cost per vaccinated girl).

"Vaccination of boys" (Ben Hadj Yahia et al. 2015)

Only one study (Chanthavilay et al. 2016a, b) considered the strategy of vaccinating boys along with girls. But this study also considered the catch-up vaccination for girls. The addition of the vaccination of the boys to the routine vaccination and catch-up vaccination in girls age 11–25 years leads to a very slight addition of benefits with a further reduction in cervical cancers by 3.4%. As a result, adding this component is less effective than a girl vaccination along with a catch-up vaccination component for 11–25-year-old women, which results in a further reduction of 8.9% in the number of cancers. Hence, vaccination was found to be less cost-effective as compared to vaccination of girls (Chanthavilay et al. 2016a, b)

"Catch-up vaccination" (Sinisgalli et al. 2015)

Six studies have included the catch-up vaccination in their model. All the studies concluded that the combined strategy of routine vaccination and catch-up vaccination was more cost-effective when compared to the vaccination only (Kawai et al. 2012; Kim et al. 2013a, b; Liu et al. 2016). Vaccinating 10-year-old girls with a catch-up program component for 11–25-year-old women is the most attractive option for Lao PDR in 100 years (Chanthavilay et al. 2016a, b). Another study found that the combined strategy of routine vaccination and catch-up was more cost-effective when compared with routine vaccination alone (Kawai et al. 2012).

"Role of vaccine prices" (Haider et al. 2019)

Almost half of the studies turned out to be very sensitive to the cost of the vaccines. HPV vaccination was found to be cost-effective in almost all of the studies which assumed the vaccine cost of GAVI (Global Alliance for vaccine and immunization) eligible country, i.e., US$5 per dose.

Other papers also have mentioned threshold (ceiling price) for vaccine costs. A study done in Uganda and Kenya stated that for the nonavalent vaccine to be cost-effective according to the threshold of GDP per capita, the

Table 1 Vaccine characteristics and economic outcomes of the studies included in the systematic review of Human Papillomavirus vaccine in the Global South

No.	References	Age at vaccination	Dosage	Vaccine cost	Coverage	Vaccine efficacy versus HPV 16/18	Type of sensitivity analysis	GDP per capita (2019)	ICER (vaccination)	ICER (I$ 2019)
1	Aguilar et al. (2015)	F 11 years	1d, 2d, 3d	US$ 13.45 per dose	1d: 100% 2d: 99% 3d: 95% Booster: 95%	94.30%	One way	US$ 2522.20	Government: US$ 926 Societal: US$ 843	Government: I$ 1966.18 Societal: I$ 1789.95
2	Aljunid et al. (2016	F 13 years	2d, 3d	MYR 134	100%	98%	One way	US$ 11,614.20	NM	NM
3	Aponte-González et al. (2013)	F 12 years	2d, 3d	2v: 214 (133-487) 4v: 188 (157-282)	80% (50-100%)	2v and 4v: 90%	One way, probabilistic	2 dose- US$ 6856.80 3 dose- US$ 20,571.51	4v:24,241 USD/DALY 2v: 28,765 USD/DALY	Quadrivalent: I$42,490 Bivalent: I$ 50,419.92
4	Bardach et al. (2017)	F 11 years	2d, 3d	2v: 8.5 US$ 4v:13.79 US$	95%	98%	One way multi way: probabilistic, deterministic	US$ 10,976.10	2v and 4v: Cost saving	2v & 4v: Cost saving
5	Burger et al. (2018)	F 9 years	1d, 2d	US$ 4.50 per dose	70%	80%	One way	I$1636.97	2d - 1932$	I$ 6691.16
6	Campos* et al. (2012)	F 9 years	1d, 2d, 3d	varied from 0.55$ to 54.25$	70%	1d- 30% 2d- 90% 3d-100%	One way	Kenya (I$1651.21) Mozambique (I$888.51) Tanzania (I$1310.86) Uganda (I$1209.76)	Kenya: 160-1440/YLS Mozambique: 80-750/YLS Tanzania: CS- 440/YLS Uganda: 20—490/YLS	Kenya: I$414.01-3726.15 Mozambique: I$151.17-1417.23 Tanzania: I$1380.46 Uganda: I$60.54-1483.33
7	Chanthavilay et al. (2016a, b)	F-10 years M-10y	3d	5I$ (GAVI price)	70% (30-80%)	100%	One way, two-way: deterministic	I$5157.02	6334 I$ per cancer prevented 550 I$/DALY	I$ 6764.27 I$ 587.36
8	Chanthavilay et al. (2016a, b)	F 10 years	3d	4.5 I$	70%	100%	One way; probabilistic	I$5157.02	6555/ca reduction 557/DALY averted	I$ 7010.42 I$ 595.70
9	Ekwunife and Lhachimi (2017)	F 9 years	2d	4. 5 to 13 $ (4.5- gavi price)	50 and 90%	90%	One way, two way: probabilistic	US$ 3367.66	At vaccine cost $5, ICER = 7897, CS + NV	I$ 25,495.49
10	Ezat and Aljunid (2010a, b)	F 15 years	NM	RM 300- 400	95%	NM	One way	US$ 8040.50	ICER for one QALYs saved was RM 35347	I$ 94,131.59

Table 1 (continued)

No.	References	Age at vaccination	Dosage	Vaccine cost	Coverage	Vaccine efficacy versus HPV 16/18	Type of sensitivity analysis	GDP per capita (2019)	ICER (vaccination)	ICER (I$ 2019)
11	Ezat and Aljunid (2010a, b)	F 15 years	NM	RM 100-200 per dose	96%	NM	One way	US$ 11,614.20	RM 515.3 per QALYs saved.	I$ 1372.28
12	Fonseca et al. (2013)	F 12 years	3d	150 US$	70%	NM	One way	US$ 13,220.06	Vaccine + booster = 1650/QALY, Vaccine +CS (3 times) = 825/QALY. Vaccine + CS (10 times)-1275/QALY	I$ 4153.11 I$ 1258.52 I$ 1944.98
13	Germar et al. (2017)	F 13 years	1d, 2d	1000 PHP per dose	100%	98%	One way and probabilistic	US$ 2932.46	NM	NM
14	Gomez[#] et al(2014)	F 11 years	2d, 3d	20 US$	95%	2v:98% 4v: 98%	Two way: probabilistic	US$ 15,422.40	147 US dollars per LYS (2 V + CS)	I$ 253.03
15	Guerrero et al. (2015)	F 11/12/13 years	3d	3d- 2376 boster = 800 (19 USD)	low = 20%, high = 80%	74%	One way, two way: probabilistic	US$ 3057.04	ICER of Php 33,126 (783 USD) per QALY.	I$ 2001.14
16	Kawai et al. (2012)	F 12 years	3d	1d- 15.15US$ 3d- 45.45US$	85%	76–96%	One way	US$ 12,030.24	Vaccination: US$219/QALY 253US$/YLS Vaccination +catch-up (12–26): 450 Us$/QALY 503/YLS	Vaccination: I$ 322.42/QALY Vaccination +catch-up: I$ 662.52
17	Khatibi et al. (2014)	F 15 years	3d	4v- 265.5 euro per dose	70%	100%	One way	US$ 6275.68	439,000,000 Iranian Rial rate	I$ 57,686.90
18	Kiatpongsan* and Kim(2014)	F 9 years	3d	Kenya-9.7$ Uganda–8.3$	100%	100%	One way and two way	Kenya- I$ 1651.21 Uganda- I$ 1209.76	NM	NM
19	Kim* et al. (2013a, b)	F 12 years	3d	0.55- 26.75 I$	70%	100%	One way	I$ 1255.91	Uganda: CS- 3700 I$ South Africa: CS- 4900 I$	Uganda: I$ 4076.18 South Africa: I$ 5398.19
20	Kim* et al. (2013a, b)	F 12 years	3d	0.55–100 I$	70%	100%	Univariate	Varies	At 25 $- varied I$300 (Pakistan)- I$7800/DALY averted Egypt	I$330.50 (Pakistan)-I$8593.04/DALY averted Egypt

Table 1 (continued)

No.	References	Age at vaccination	Dosage	Vaccine cost	Coverage	Vaccine efficacy versus HPV 16/18	Type of sensitivity analysis	GDP per capita (2019)	ICER (vaccination)	ICER (I$ 2019)
21	Kosen et al. 2017	F 11–12 years	2d	$25 per dose	nm	90% (CC) 95.2 (CIN) 98.9% (GW)	One way and multivariate	US$ 3713.02	Vaccination: $450/QALY Vaccination +catch-up: $390/QALY	Vaccination: I$ 1504.39 Vaccination +catch-up: I$1303.81
22	Kriekinge et al. (2018)	F 13 years	2d	69,412,000	100%	98%	One & two way: probabilistic	US$ 11,614.20	NM	NM
23	Levin et al. (2015)	F 12 years	3d	10US$	70%	NM	Univariate	US$ 9977.84	513I$	I$ 553.18
24	Liu et al. (2016)	12 to 55,	3d	3d- 1900 CNY	70%	93.2%	Univariate	US$ 19,361.76	NM	NM
25	Messoudi et al. (2019)	F 14 years	2d	US$10 per dose	70%	90%	One way and two-way	US$ 2924.01	Vaccine + CS 1295/YLS US$	I$ 3553.54
26	Minh et al. (2017)	F 11 years	3d	4.55US$ per dose (GAVI), 2v- 35.60US$ 4v- 55.80US$	95%	NM	Univariate	US$ 2620.99	At 4.55 US$- 780–1120 At list price: US$ 8000/DALY	I$ 24,728.23
27	Mo et al. (2017)	F 12 years	3d	2v/4v-403.23 9v-447.10 (US$)	20% (10–100%)	2v- 80.72% 4v- 81.51% 9v- 90.78%	Univariate	US$ 25,105.29	HPV4/9: 5400$/QALY HPV2: 5434/QALY	HPV4/9: I$ 10,850.50 HPV2: I$ 10,918.82
28	Novaes et al. (2015)	F 11 years	1d, 2d, 3d	$13.19	1d = 80% 2d = 60% 3d = 50%	1d- 48.4% 2d-48.4% 3d- 94.3%	Univariate, multivariate	1 GDP per capita (US$ 8757.06), 3 GDP per capita (US$ 26,272.25)	Government: 7663 US$/ DALY Health system:7412 US$/ DALY Society:7298 US$/DALY	Government: I$ 14,977.63 Health system: I$ 14,487.04 Society: I$ 14,264.22
29	Praditsitthikorn et al. (2011)	>15 years	3d	3d- Bt 15 000	100%	79%	Univariate	US$ 5663.57	Discount 3%: 1470000/QALY Thai Baht 5%: 502000/QALY 10%: 35554000	3%: I$ 135,365.04 5%: I$ 46,226.64 10%: I$ 3,273,992.40
30	Prinja et al. (2017)	F 11 years	2d	4.5 US$	70%	93%	Multivariate Probabilistic	US$ 2052.59	INR 1827 per QALY gained	I$ 88.94

Table 1 (continued)

No.	References	Age at vaccination	Dosage	Vaccine cost	Coverage	Vaccine efficacy versus HPV 16/18	Type of sensitivity analysis	GDP per capita (2019)	ICER (vaccination)	ICER (I$ 2019)
31	Reynales-shigematsu et al. (2009)	F12	3d	US$ 15	100%	95%	Univariate	I$ 7382.75	68 MXP (116 I$ 2011)	I$ 132.13
32	Setiawan 2016	F 12 years	3d	14.76 I$	76.60%	95%	Univariate, multivariate:	US$ 3716.43	1863/QALY	I$ 1992.43
33	Sharma et al. (2011)	F > 9 years	3d	10, 25, 50 $ per dose	80% (25 to 100%)	75%	Univariate	I$ 9226.65	10 I$- CS 25$- 350 50$- 1200	CS: I$ 11.39 I$ 28.48-398.68 I$ 56.95-1366.91
34	Sinanovic et al. (2009)	F 12 years	3d	US$360, booster-US$120	80% (60–100%)	90%	Univariate	US$ 6840.22	HCP:1460/QALY Societal: 1078/QALY	I$ 3355.34 I$ 2311.83
35	Termrungruanglert et al. (2012)	F 12 years	3d	3d- 6189 Thai baht per	100%	4v: 98%	Univariate	US$ 5584.91	160,649.50 baht/QALY	I$ 14,587.95
36	Tracy et al. (2014)	F 10–14 y	NM	I$5 per dose	0–90%	NC	Univariate	I$ 1296.18	1030 US$ (urban) 725 US$ (rural)	Urban: I$ 1112.56 Rural: I$ 783.11
37	Walwyn et al. (2015)	F 10 years	2d	US$ 13.79 per dose	95%	1d- 48.4% 2d- 48.4% 3d- 94.3%	Univariate	US$ 5170.56	US$ 429/DALY averted	I$ 804.51
38	Li et al. (2015)	F 12 years	2d	ZAR 595.39 per dose	100%	50.3% - 93.2%	One way, two-way probabilistic	US$ 4721.17	ICER: US$ 4 900 per LYS	I$ 12,084.65
39	Yaghoubi et al. (2018)	F 9 years	2d, 3d	2d-US$15.87, 3d-US $13.75	85%, 83%, and 80%	94.30%	One way, two-way deterministic	US$ 4863.93	Governmental: US $15,205 Societal: US $14,999	Governmental I$ 58,815.79 Societal: I$ 58,018.94

Table 1 (continued)

No.	References	Age at vaccination	Dosage	Vaccine cost	Coverage	Vaccine efficacy versus HPV 16/18	Type of sensitivity analysis	GDP per capita (2019)	ICER (vaccination)	ICER (I$ 2019)
40	Zhang et al. (2016)	F 12 years	3d	US$ 39	70%	50.3%-93.2%	One way, two way and probabilistic	US$ 7114.16	Urban: US$ 972 Rural: US$ 1804	Urban: I$ 1871.27 Rural: I$ 3472.74

All the studies mentioned in the table are single country studies except for those with asterisk sign. Those with asterisk sign aremulticountry studies

1d one dose, *2d* two dose, *3d* three dose, *2v* bivalent, *4v* quadrivalent, *9v* nonavalent, *CC* cervical cancer, *CS* current screening, *DALY* disability- adjusted life years, *GAVI* global alliance for vaccine and immunization, *GDP* gross domestic product, *I$* international dollar, *ICER* incremental cost-effectiveness ratio, *NC* not clear, *NM* not mentioned, *NV* national vaccination program, *QALY* quality-adjusted life years, *US$* United States Dollar, *YLS* years of life saved

additional cost for the vaccine should be capped at I$3.2 and I$2.8 in Kenya and Uganda, respectively, (Kiatpongsan and Kim 2014). A study conducted in 48 sub-Saharan countries, concluded that HPV vaccination was cost-saving when the cost per vaccinated girl was as low as I$5 ($0.55 per dose). For EMENA countries, HPV vaccination was cost saving when the vaccination was available at low costs (Kim et al. 2013a, b). Hence, the vaccine cost needs to be reduced to make it very cost-effective and affordable as well, in particular in poverty areas with high disease burden (Zhang et al. 2016).

Another study conducted in Brazil suggested that the reduction of a number of doses would consequently reduce the costs of the vaccine program. Especially, this strategy can be used for low and middle-income countries where the cost of the HPV vaccine is still a challenge (Novaes et al. 2015). This highlights the importance of more comprehensive and comparative analysis for one, two, and three doses of the HPV vaccine.

The ICERs are directly proportional to the vaccine price. Several studies have used the varied costs of the vaccine and demonstrated the changes in the ICER. It was found that the ICERs increases proportionally as the vaccine cost increases.

"Vaccination and screening" (Gervais et al. 2017)

Several studies have also compared vaccination and screening and also studied the combined effects of the same. Many studies found that the combined strategy (vaccination and screening) was a cost-effective option and sometimes, even very cost-effective (Fonseca et al. 2013; Chanthavilay et al. 2016a, b; Ekwunife and Lhachimi 2017; Ezat and Aljunid 2010a, b; Gomez et al. 2014; Messoudi et al. 2019).

"Sensitivity analyses" (Laprise et al. 2014)

Most (20) of the studies performed univariate analyses. Univariate analysis just explores the effect of one variable on the incremental cost-effectiveness ratio. Multivariate analysis was performed by four studies and sixteen studies included both the univariate and multivariate analysis. The multivariate analysis allows the combined effect of combinations of parameters to be explored. Among the studies which used both analysis, 12 studies used probabilistic sensitivity, which is recommended for cost-effectiveness studies in high-income countries. Vaccine price was identified as a key influential parameter in all studies which was explored in the review. Other important parameters identified included the discount rate, vaccine and screening coverage, duration of protection, vaccine efficacy (against vaccine and non-vaccine types), target age, natural history parameters, cervical cancer incidence and mortality, screening test performance. Most importantly, vaccine cost, duration of protection, vaccine efficacy, and coverage affect the ICER the most.

Discussion

Summary of the main findings and interpretation

This review identified only 40 studies on economic evaluations of HPV vaccination in countries of the Global South despite being around 145 countries in the Global South (UNDP 2004). There are countries where the economic assessment of HPV vaccination has not been done despite the high incidence of cervical cancer, e.g., Swaziland and Malawi, according to GLOBOCAN 2018.

Notably, different countries have different healthcare systems, the healthcare delivery systems are not heterogeneous and costs are measured from different perspectives. So, for identifying the most cost-effective strategy these points of difference should be incorporated as well.

The review discovered that there is variability among all the studies regarding the model used, the perspective is taken, vaccine efficacy, cost, and coverage, comparators, duration of protection, discount rate, but, all the studies but two have determined that the HPV vaccination is cost-effective. Two studies of Iran (Khatibi et al. 2014; Yaghoubi et al. 2018) did not find the vaccine cost-effective as these studies assumed a very high price of the vaccine.

Most of the studies have used static models for economic evaluation, but the static model does not take into consideration the herd immunity, age distribution shifts, waning effects. So, it is not a good reflector of a disease. Moreover, HPV can be sexually transmitted, and hence herd immunity can play a very crucial role in the containment of the disease. Therefore, the dynamic model should be preferred when assessing the cost-effectiveness of HPV vaccination (Gervais et al. 2017).

There was inconsistency about the "sensitivity analysis" used in the studies and many determinants were identified which directly affect the sensitivity analysis such as Vaccine price, discount rate, duration of protection. Hence, to introduce the HPV vaccination in a country, the price of the vaccine should be economical and should be available at a discount rate of at least 3%, and the duration of the vaccine should be lifelong depending upon the dosage. The wide range in the cost-effectiveness ratio was observed in the included studies that could be due to different study settings, populations, and varied models.

When the routine vaccination was compared with the combined strategy of vaccination and screening for cervical cancer, many studies found that the combined strategy was more cost-effective than vaccination alone (Ekwunife and Lhachimi 2017; Ezat and Aljunid 2010a, b; Messoudi et al. 2019; Sharma et al. 2011; Mo et al. 2017).

Strengths, limitations, and future prospects

It is a novel attempt to review the cost-effectiveness analysis of HPV vaccination in the Global South countries. The most comprehensive tables were made to summarize maximum data which will enable the reader to have the information at one glance. Studies investigating all the aspects of the vaccine were included namely, comparison between two doses and three doses, the effect of catch-up vaccine, and vaccination of boys. The limitation of the review was to exclude studies that have non-cervical diseases as the disease's outcome which may underestimate the effectiveness of HPV vaccination. Therefore, in future studies having non-cervical diseases as disease outcomes that can affect the effectiveness of HPV vaccination may be carried out.

Conclusions

This review supports and suggests the introduction of HPV vaccination in all the countries irrespective of the preventive strategy opted by the countries against cervical cancer. Cost-effectiveness analysis can serve as a powerful tool to help the decision-makers in choosing the most effective intervention in the view of scarce healthcare resources. Vaccination strategies can be implemented differently in each country depending on their needs, infrastructure, and healthcare budget. Those countries, which already have a screening program against cervical cancer, the combined strategy of vaccination and screening, can be adopted for better health economic outcomes. To achieve the most cost-effective scenario, efficacy, dose, coverage, and duration of the vaccine should be taken into account, and the vaccine should be made available at a competitive or GAVI eligible price or the government should provide funds for its implementation in low and middle-income countries of the Global South.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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Informed consent Not applicable.

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