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Review

Systematic review of cost-effectiveness studies of human papillomavirus (HPV) vaccination: 9-Valent vaccine, gender-neutral and multiple age cohort vaccination

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ABSTRACT

Background: The success of human papillomavirus (HPV) national immunization program depends on effective strategies in optimizing the uptake of HPV vaccine. Given the increasing number of economic evaluations, this review was conducted to update the economic evidence on HPV vaccination, by focusing on: (i) 9-valent vaccine compared to bi- or quadrivalent vaccine; (ii) gender-neutral vaccination compared to female only vaccination; and (iii) multiple age cohort immunization compared to single age cohort immunization.

Methods: Searches were performed until June 2016 using 4 databases: PubMed; Embase; Cochrane Library; and LILACS. The combined WHO, Drummond and CHEERS checklist were used to evaluate the quality of included studies.

Results: Thirty-four studies were included in the review and most of them were conducted in high-income countries. The inclusion of adolescent boys in vaccination program was found to be cost-effective if vaccine price and coverage was low. When coverage for female was above 75%, gender-neutral vaccination was less cost-effective than when targeting only girls aged 9–18 years. Current evidence does not show conclusive proof of greater cost-effectiveness of 9-valent vaccine compared to the older HPV vaccines as the price for 9-valent vaccine was still uncertain. Multicohort immunization strategy was cost-effective in the age range 9–14 years but the upper age limit at which vaccination was no longer cost-effective needs to be further investigated. Key influential parameters identified were duration of vaccine protection, vaccine price, coverage, and discounting rates.

Conclusions: These findings are expected to support policy-makers in making recommendations for HPV immunization programs on either switching to the 9-valent vaccine or inclusion of adolescent boys' vaccination or extending the age of vaccination.

Contents

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1. Introduction

Human papillomavirus (HPV) is the most common sexually-transmitted viral infection, which causes a range of conditions including cervical cancer and non-cervical HPV-attributable diseases such as genital warts, oropharyngeal, penile, vaginal and anogenital cancers [1]. Three HPV vaccines; a bivalent (Cervarix), a quadrivalent (Gardasil) and the new 9-valent vaccine (Gardasil-9) are currently licensed in the market for the prevention of HPV-related diseases. However, as of March 2017, only 71 countries (37% of all countries) have introduced HPV vaccines in their national immunization programs for girls and 11 countries (6%) for additional boys [2].

The first global recommendation on HPV vaccination was proposed by the WHO's SAGE (Strategic Advisory Group of Experts) on Immunization in October 2008 [3], whereby HPV vaccination was recommended in all girls aged 9–13 years old. This recommendation was then updated in April 2014 [4], with the emphasis to include extended 2-dose HPV immunization for girls aged 9–14 years, who were not immunocompromised. With the recent licensing of the 9-valent vaccine and the introduction of various HPV vaccination strategies, an update in the current recommendations of HPV vaccination is inevitable. Hence, this review was conducted to assist the WHO SAGE 2016 meeting in updating the economic evidence on HPV vaccination, with the focus on: (i) 9-valent vaccine compared to bi- or quadrivalent vaccine, (ii) gender-neutral immunization compared to female only immunization and (iii) multiple age cohort immunization compared to single age cohort immunization.

2. Materials and methods

2.1. Search strategy

Searches were performed till June 2016 using 4 databases: PubMed; EMBASE; Cochrane Library; and LILACS (Index of scientific and technical literature of Latin American and the Caribbean). Reference lists of relevant published studies and grey literature were also searched. This review was an extension of the previous work by Fesenfeld et al. [5] and thus, similar search strategy was adopted but modified to include all countries regardless of income levels. (See Appendix A for full search strategy).

2.2. Study selection

All identified studies were considered based on title and abstract, and included for further review if they evaluated either a 9-valent HPV vaccine or gender-neutral or multicohort immunization strategy. The included study must be a full economic evaluation considering both costs and outcomes. Reviews, editorials, and conference abstract were excluded. Studies which evaluated on a specific population (e.g. HIV positive patients, renal transplant patients and neonatal) were also excluded. No language restrictions were applied.

2.3. Data extraction & synthesis

Two reviewers (SSN and NC) independently reviewed the titles and abstract. Data from all eligible studies were extracted by the same two authors using a standardized data collection form. Supplementary appendices were referred to if insufficient information was obtained from the main text. Studies were categorized based on three themes: (i) 9-valent HPV vaccine compared to bi- or quadrivalent vaccine, (ii) gender-neutral vaccination compared to female only vaccination and (iii) multiple age cohort immunization compared to single age cohort immunization. The income levels for each country were determined based on the World Bank classification [6]. Gross domestic product (GDP) per capita in United States Dollars (US$) of 2016 was obtained from the World Bank [7]. To compare results across studies, we presented raw study-reported incremental cost-effectiveness ratios (ICERs) and standardized cost-effectiveness. Standardized cost-effectiveness was based on

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Table 1
General characteristics of the included studies.

Author year	Location (Setting)	Income category	Intervention (Comparator)	No. of doses	Diseases captured	EE type	Type of model	Perspective	Time horizon	Discount rate	Sensitivity analysis	Most sensitive parameter
9-valent vaccine versus Bi- or quadrivalent HPV vaccine												
Boiron et al. [17]	Austria	HIC	9 V gender-neutral (4V gender-neutral)	9 V: 2 4 V: 2	CC, CIN, GW, AGC, OC, RRP	CUA	Dynamic	P	100 years	3%	One-way	Vaccine price, Discount rate, Duration of protection
Brisson et al. [18]	United States	HIC	9 V gender-neutral (4V gender-neutral)	9 V: 3 4 V: 3	CC, GW, AGC, OC	CUA	Dynamic	S	70 years	3%	One-way	Vaccine price
Chesson et al. [20]	United States	HIC	9 V gender-neutral (4V gender-neutral)	9 V: 3 4 V: 3	CC, CIN, GW, AGC, OC, RRP,	CUA	Dynamic	S	100 years	3%	One-way, Multi-way (Best-worst case)	Time horizon
Chesson et al. [19]	United States	HIC	[a]Additional 9 V (4V)	9 V: 3 4 V: 3	CC, GW, AGC, OC, RRP	CUA	Dynamic	S	100 years	3%	One-way, Multi-way (Best-worst case)	Vaccine price
Drolet et al. [15]	Canada	HIC	9 V (4V)	9 V: 3 4 V: 3	CC, GW, AGC, OC	CUA	Static	S	70 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection, Vaccine efficacy, Vaccine price
Kiatpongsan et al. [16]	Kenya & Uganda	LMIC	9 V (4V & 2 V)	9 V: 3 4 V: 3 2 V: 3	CC	CEA	Dynamic	HCP	NS	3%	One-way, Multi-way (Best-worst case)	Discount rate
Gender-neutral HPV immunization versus female-only HPV immunization												
Bresse et al. [21]	Austria	HIC	4 V gender-neutral (4V female)	4 V: 3	CC, CIN, GW, AGC, OC, RRP	CUA	Dynamic	P	100 years	C: 3% B: 3%	One-way	Discount rate
Chesson et al. [22]	United States	HIC	4 V gender-neutral (4V female)	4 V: 3	CC, CIN, GW, AGC, OC, RRP	CUA	Dynamic	S	100 years	NS	One-way, PSA	Vaccine efficacy, Vaccine price
Elbasha et al. [24]	United States	HIC	4 V gender-neutral (4V female)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	100 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection, Vaccine coverage, Discount rate
Elbasha et al. [23]	United States	HIC	4 V gender-neutral (4V female)	4 V: 3	CC, CIN, GW, AGC, OC, RRP	CUA	Dynamic	NS	100 years	3%	Multi-way (Best-worst case) PSA	Vaccine efficacy
Haeussler et al. [25]	Italy	HIC	4 V gender-neutral (4V female)	4 V: 3	CC, CIN, GW, AGC, OC	CUA	Dynamic	NS	55 years	C: 3% B: 3%	PSA	Vaccine efficacy, Discount rate
Insinga et al. [26]	Mexico	UMIC	4 V gender-neutral (4V female)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	100 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection, Vaccine coverage
Jit et al. [27]	United Kingdom	HIC	4 V gender-neutral (4V female)	4 V: 3	CC, GW, AGC, OC,	CUA	Dynamic	HCP	100 years	C: 3.5% B: 3.5%	One-way	Duration of protection
Kim et al. [28]	Brazil	UMIC	4 V gender-neutral (4V female)	4 V: 3	CC, CIN	CEA	Dynamic	S	NS	3%	One-way	Vaccine price, Vaccine coverage
Kim et al. [29]	United States	HIC	4 V gender-neutral (4V female)	4 V: 3	CC, CIN, GW, AGC, OC, RRP	CUA	Dynamic	S	100 years	C:3% B: 3%	One-way	Vaccine coverage, Vaccine efficacy
Laprise et al. [30]	Canada	HIC	4 V gender-neutral (4V female)	4 V: 2	CC, CIN, GW, AGC, OC	CUA	Dynamic	P	70 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Vaccine price
Olsen et al. [31]	Denmark	HIC	4 V gender-neutral (4V female)	4 V: 2 & 3	CC, CIN, GW, AGC, OC	CUA & CEA	Dynamic	HCP	62 years	C: 3% B: 3%	One-way, PSA	Discount rate, Vaccine price
Sharma et al. [32]	Vietnam	LMIC	4 V gender-neutral (4V female)	4 V: 3	CC. CIN, GW	CUA	Dynamic	S	100 years	C: 3% B: 3%	One-way	Vaccine coverage, Vaccine price
Taira et al. [49]	United States	HIC	2 V gender-neutral (2V female)	2 V: 3	CC	CUA	Dynamic	NS	NS	NS	One-way	Vaccine penetration, Discount rate
Zechmesiter et al. [34]	Austria	HIC	4 V gender-neutral (4V female)	NS	CC, CIN	CEA	Dynamic	P & S	52 years	5%	One-way, Multi-way (Best-worst case)	Vaccine price, Discount rate
Multiple age cohort HPV immunization versus single age HPV immunization												
Bogaards et al. [47]	Netherlands	HIC	17 yrs F 19 yrs F 21 yrs F 23 yrs F 25 yrs 17–25 yrs (No vaccination)	4 V:3	CC, CIN	CUA	Dynamic	S	NS	C: 4% B: 1.5%	One-way, Multi-way (Best-worst case)	Vaccine price, Discount rate

(*continued on next page*)

Table 1 (*continued*)

Author year	Location (Setting)	Income category	Intervention (Comparator)	No. of doses	Diseases captured	EE type	Type of model	Perspective	Time horizon	Discount rate	Sensitivity analysis	Most sensitive parameter
Dasbach et al. [35]	United Kingdom	HIC	12–14 yrs F 12–17 yrs F 12–24 yrs F (12 yrs F)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	100 years	C: 3.5% B: 3.5%	One-way, Multi-way (Best-worst case)	Duration of protection, Health utilities
Dasbach et al. [36]	Taiwan	HIC	12–24 yrs F (No vaccination)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	100 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection
Dasbach et al. [37]	Norway	HIC	12–24 yrs F (12 yrs F)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	100 years	C: 3.5% B: 3.5%	One-way, Multi-way (Best-worst case)	Duration of protection
Dasbach et al. [38]	Hungary	HIC	12–24 yrs F (12 yrs F)	4 V: 3	CC, CIN, GW	CUA	Dynamic	P (Insurer)	100 years	C: 5% B: 5%	One-way, Multi-way (Best-worst case)	Duration of protection
Elbasha et al. [24]	United States	HIC	12 yrs F + 12–24 yrs F 12yrs F & M + 12–24 yrs F 12 yrs F & M + 12–24 yrs F & M (12 yrs F)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	100 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection, Vaccine coverage, Discount rate
Elbasha et al. [39]	United States	HIC	12–14 yrs F 12–17 yrs F 12–19 yrs F 12–24 yrs F (12 yrs F)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	NS	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection, Vaccine price, Vaccine coverage
Favato et al. [48]	Italy	HIC	12–15 yrs F 12–18 yrs F 12–25 yrs F (12 yrs F)	4 V: 3	CC, CIN, GW	CUA	Static (Markov)	NS	90 years	C: 3% B: 1.5%	PSA	Duration of protection
Insinga et al. [26]	Mexico	UMIC	12 yrs F + 12–24 yrs F 12yrs F & M + 12–24 yrs F 12 yrs F & M + 12–24 yrs F & M (12 yrs F)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	100 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection, Vaccine coverage
Jit et al. [27]	United Kingdom	HIC	12–14 yrs F 12–16 yrs F 12–18 yrs F 12–25 yrs F (12 yrs F)	4 V: 3	CC, GW, AGC, OC,	CUA	Dynamic	HCP	100 years	C: 3.5% B: 3.5%	One-way	Duration of protection
Kawai et al. [40]	Brazil	UMIC	12–26 yrs F (12 yrs F)	4 V: 3	CC, CIN, GW	CUA	Dynamic	HCP	100 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection, Vaccine price, Discount rate
Liu et al. [41]	China	UMIC	12–25 yrs F (12 yrs F)	2 V: 3	CC, CIN	CUA	Static (Markov)	P	NS	C: 3% B: 3%	NS	NS
Tully et al. [42]	Canada	HIC	School-based 12–18 yrs F Clinic-based 12–18 yrs F (12 yrs F)	2 V: 3	CC, CIN	CUA	Dynamic	MOH	80 years	C: 3% B: 3%	One-way, PSA	Vaccine Price, Vaccine coverage
Turner et al. [43]	United Kingdom	HIC	12–17 yrs F 12–19 yrs F 12–24 yrs F 12–29 yrs F 12–24 yrs F (12 yrs F)	2 V: 3	CC, CIN	CUA	Dynamic	HCP	100 years	C: 3.5% B: 3.5%	One-way, Multi-way (Best-worst case)	Vaccine price, Duration of protection

Usher et al. [44]	Ireland	HIC	12–15 yrs F 12–17 yrs F 12–19 yrs F 12–26 yrs F (12 yrs F)	4 V: 3	CC, CIN	CEA	Dynamic	P	70 years	C: 3.5% B: 3.5%	One-way, PSA	Discount rate, Vaccine price, Vaccine coverage
Westra et al. [45]	Netherlands	HIC	12–16 yrs F 12–18 yrs F 12–25 yrs F (12 yrs F)	4 V: 3	CC, CIN	CUA	Static (Markov)	NS	NS	C: 4% B: 1.5%	One-way, PSA	Vaccine price, Duration of protection
Yamabe et al. [46]	Japan	HIC	12–24 yrs F (No vaccination)	4 V: 3	CC, CIN, GW	CUA	Dynamic	P	100 years	C: 3% B: 3%	One-way, Multi-way (Best-worst case)	Duration of protection

LMIC = Low-middle income country; UMIC = Upper-middle income country; HIC = High-income country; F: Female; M: Male; CUC = Catch-up campaign; CC = Cervical cancer; AGC = Anogenital cancer other than cervical cancer (Anal, vaginal, vulvar and penile cancer); OC: Oropharyngeal cancer; CIN = Cervical interstitial neoplasia; GW = Genital warts; RRP: Recurrent respiratory papillomatoses; CUA = Cost-utility analysis; CEA = Cost-effectiveness analysis; MOH: Ministry of Health; *HCP: Healthcare Provider*; *S* = Societal; P = Payer; *NS* = Not stated; PSA = Probabilistic sensitivity analysis.

[a] Additional 9 V: 9 V HPV vaccination to female aged 13–19 years who had previously completed a 3dose 4 V HPV vaccination.

the principle adapted from WHO's Commission on Macroeconomic and Health pervasive threshold [8,9], whereby ICER which was lower than 1 time of GDP per capita was interpreted as 'very cost-effective' intervention and ICER which was lower than 3 times of GDP per capita as 'cost-effective' intervention. On the contrary, if ICER was equal or more than 3 times of GDP per capita, the intervention was 'not cost-effective'. However, for studies that reported their own local threshold, the original author's interpretation of cost-effectiveness was retained because this threshold was presumed to have better local relevance than threshold based on GDP per capita [8,9].

Affiliation was determined based on the first listed institutional affiliation of the first author. Funding sources were determined by any support for the study stated in the declarations or acknowledgements. If any co-authors worked for a vaccine company, this would be considered as a funding source even though it was addressed as a conflict of interest. Included studies were appraised for quality by applying the WHO guidance [10], Drummond's checklist [11] and the CHEERS statement [12]. They were assessed based on specific methodological and reporting practices of economic evaluation studies such as identification of study questions; expression of the study perspective, time horizon and discount rate; justification of model used for data analysis; assumptions behind the calculation of costs and outcomes; presenting of ICERS; sensitivity analysis; justification of study conclusion as well as the disclosure of funding sources.

2.4. Currency conversions

To facilitate inter-country comparisons, local currencies were initially converted to US$ of 1st January of the base year [13] and were then inflated to 2016 US$ using the US$ Consumer Price Index for all urban consumers (CPI-U) [14]. Costs in I$ were inflated directly to 2016 US$ [14] as I$ is a theoretical currency which represents what can be purchased in a country with one US$ and hence, has the same inflation rate as the US$. Vaccine price per dose were also converted to US$ of 1st January of the base year [13] and were then inflated to US$ 2016 using the CPI-U [14].

3. Study characteristics

The initial search yielded 1280 articles, of which 238 duplicates were removed. After screening by title and abstract, 254 articles were selected for full-text review. Of those, 34 articles were included in the final review (see Table 1). Studies were excluded for the following reasons: conference abstract (n = 51), reviews or editorial papers (n = 13), not full economic evaluations (n = 8) or addressing HPV vaccination strategy not of interest (n = 148) such as 2-doses versus 3-doses regimen (n = 2), vaccination versus no vaccination or screening only (n = 108), quadrivalent versus bivalent vaccine (n = 11), varying discounting rates (n = 3) and others (n = 24). The process of electronic searching is presented in the PRISMA flow diagram in Fig. 1. Fig. 2 demonstrates the income-level setting of the included studies.

3.1. Comparators and study questions

Six studies evaluated the cost-effectiveness of 9-valent vaccine compared to bi- or quadrivalent HPV vaccines [15–20]. The cost-effectiveness of gender-neutral vaccination were compared in fourteen studies [21–34]. Seventeen studies [24,26,27,35–48] explored the economic impact of multiple age cohort immunization, whereby three studies extended their cost-effectiveness analyses by including both gender in the multicohort immunization strategy [24,26,27] (see Table 2).

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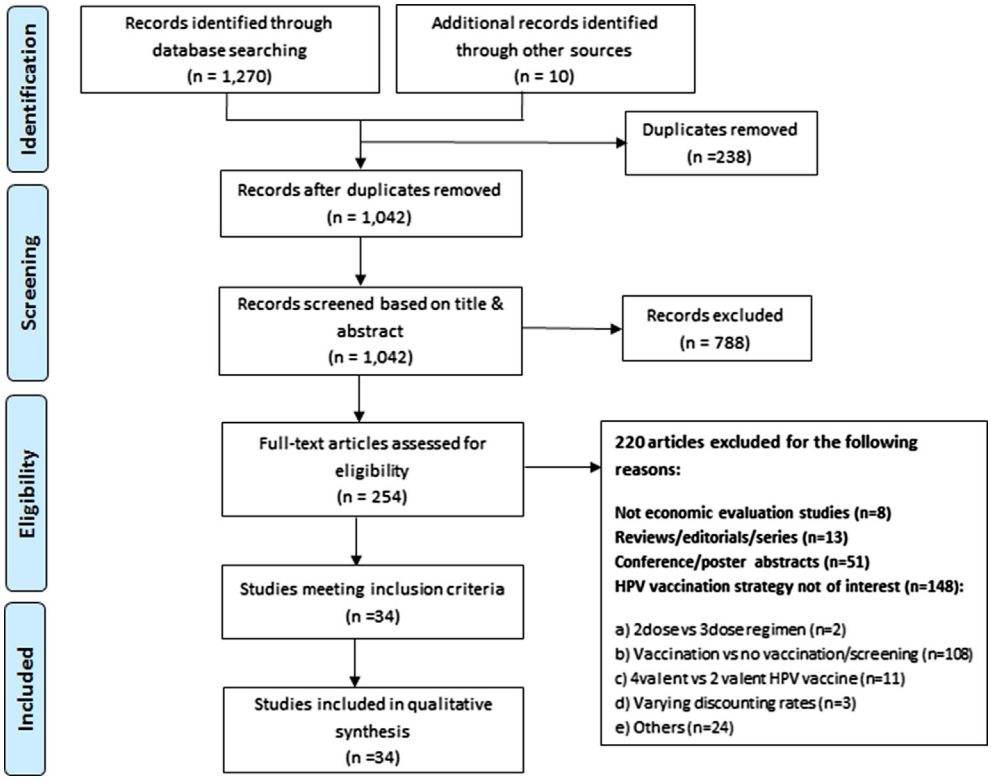

Fig. 1. PRISMA Flow diagram describing study selection process.

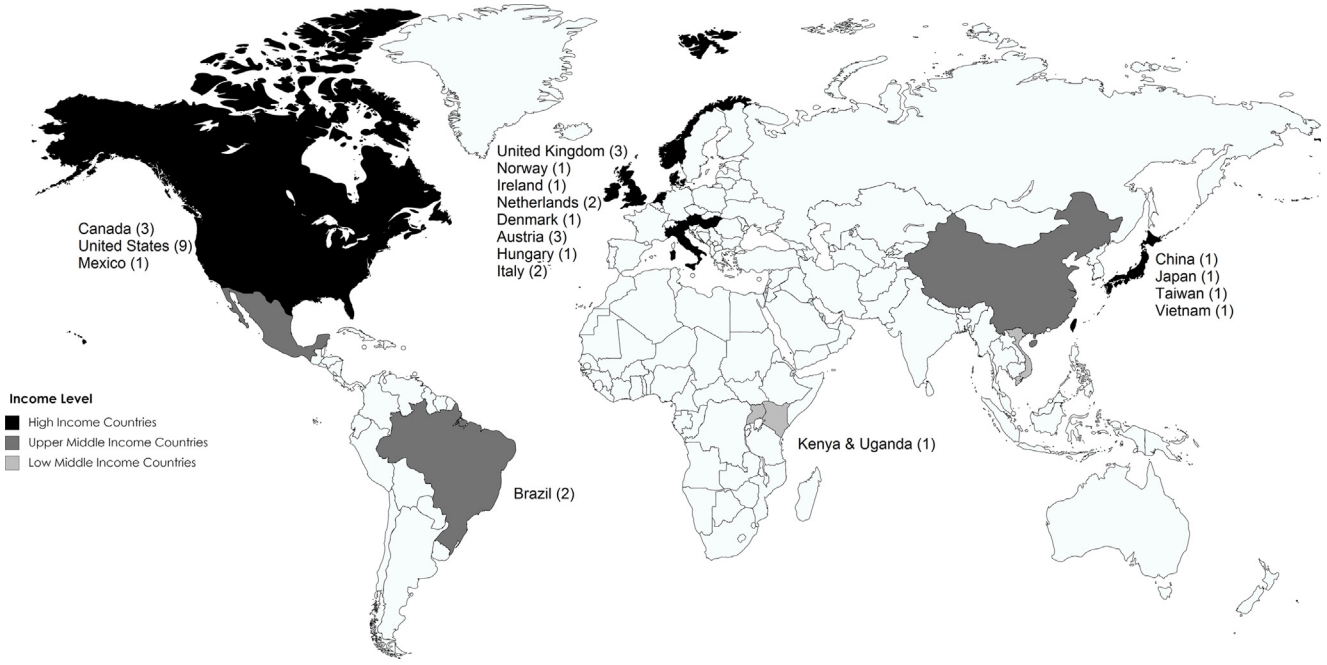

Fig. 2. Availability of studies by country. Text shows country-specific studies, with the number of such studies in parentheses.

3.2. Country, funding, and authorship

Among all included studies, majority studies (28/34) were conducted in high income countries [15,17–25,27,29–31,33–39,42–48], four studies in upper-middle income countries [26,28,40,41] and two studies in low-middle income countries [16,32]. Majority studies (21/34) were funded by vaccine manufacturers (e.g. Merck, Sharp & Dome; Sanofi Pasteur MSD and GlaxoSmith Kline) [17,21, 23–27,30,31,35–42,45–48] while elven studies were funded by not-for-profit funders [15,16,18,19,28,29,32–34,43,44]. The remaining two studies [20,22] did not specify their funding sources. Twenty studies were first authored by investigators based in the countries being studied [15,19,20,22–24,27,29–31,33,34,39, 41–47] and most studies were first authored by investigators in

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Table 2
Summary of results of the included studies.

Author year	Vaccine efficacy	Vaccine coverage	Duration of vaccine protection	Herd effect	Currency, year	Conversion factor to US$ 2016	Vaccine price/dose (US$ 2015)	Unit	QALY-gained per patient	GDP per capita (US$ 2016)	Threshold used	ICER (US$ 2015)	Conclusion	Study funder
9-Valent HPV vaccine versus bi- or quadrivalent HPV vaccine														
Boiron et al. [17]	16/18 transient infections: F:76–96% M: 41–62% 16/18 persistent infections[a]: 98% CIN: 97.9–100%	F: 60% M: 40%	Lifelong	Y	€ 2016	1.09	4 V: €110 (US $119.90) 9 V: €135 (US $147.15)	€/ QALY	NS	44,767.35	€30,000 (US$32,700)	Cost-saving at vaccine prince up to €113 & cost-effective up to a price of €153	Cost-effective up to a price of $166.77, compared to 4 V vaccine at a price of $119.90	Sanofi Pasteur MSD
Brisson et al. [18]	6/11/16/18 persistent infections: 95%	NS	Lifelong	Y	$ 2010	1.19	4 V: $145 (US $172.55) 9 V: $158 (US $188.02)	$/ QALY	0.148	48,373.88	NS	Cost-saving regardless of cross-protection assumptions	Cost-saving if additional cost of 9 V is less than $13	CDC, Canadian Research Chair Program
Chesson et al. [20]	95%	F: 25.8% M: 11.7%	Lifelong	Y	$ 2013	1.03	4 V: $145 (US $149.35) 9 V: $158 (US $162.74)	$/ QALY	0.96–0.147	52,787.03	NS	Cost-saving regardless of cross-protection assumptions (<$0)	Cost-saving	NS
Chesson et al. [19]	95%	F: 46% M: 25%	Lifelong	Y	$ 2013	1.03	4 V: $145 (US $149.35) 9 V: $158 (US $162.74	$/ QALY	0.00390	52,787.03	$100,000 (US$103,000)	$108,200 (US$111,446)	Not cost-effective	CDC, Canada Research Chair Program, Canadian Institute for Health Research
Drolet et al. [15]	95%	80%	20 years	Y	CAD$ 2014	0.95	CAD$ 95 (US$ 90.25)	CAD $/ QALY	0.000337	50,440.44	GDP per capita	$12,203 (US$ 11,593)	Very cost-effective if additional cost of 9 V vaccine per dose is ≤ $22.80	Canadian Research Chair Program
Kiatpongsan et al. [16]	100%	100%	Lifelong	N	I$ 2015	1.01	NS	I$/ LYG	NS	Kenya: 1,349.97 Uganda: 674.05	GDP per capita	NS	Very cost-effective if additional cost of 9 V vaccine per course ≤ $9.8 in Kenya & ≤ $8.4 in Uganda	Bill & Melinda Gates Foundation
Gender-neutral HPV immunization versus female-only HPV immunization														
Bresse et al. [21]	6/11/16/18 transient infections: F: 76–96% M: 41–57% 6/11/16/18 persistent infections: F: 98% M: 78–96% CIN: 97–100% Genital warts: F: 98–100% M: 84–90%	65%	Lifelong	Y	€ 2010	1.56	€110 (US$ 171.6)	€/ QALY	NS	46,858.04	NS	€10,333 (US$ 16,120)	Very cost-effective	Sanofi Pasteur MSD
Chesson et al. [22]	6/11/16/18 persistent infections: F: 95% M: 90%	20–75%	Lifelong	N	$ 2010	1.09	$300-$360 (US$ 327–392.40)	$/ QALY	NS	48,373.88	$100,000 (US$ 109,000)	20% VC: $23,600 (US$ 25,724) 30% VC: $41,400 (US$ 45,126) 75% VC:	Cost-effective if VC < 75%	NS

(*continued on next page*)

Table 2 (*continued*)

Author year	Vaccine efficacy	Vaccine coverage	Duration of vaccine protection	Herd effect	Currency, year	Conversion factor to US$ 2016	Vaccine price/dose (US$ 2015)	Unit	QALY-gained per patient	GDP per capita (US$ 2016)	Threshold used	ICER (US$ 2015)	Conclusion	Study funder
Elbasha et al. [24]	6/11/16/18 transient infections: 90% 6/11/16/18 persistent infections: 100%	12 yrs: 0–70% in first 5 yrs & remain at 70% 12–24 yrs: 0–50% in fist 5 yrs & reduce to 0% after 5 yrs	Lifelong	Y	$ 2005	1.24	NS	$/ QALY	0.00149	44,307.92	NS	$184,300 ($200,887) Dominated	Not cost-effective	Merck
Elbasha et al. [23]	76–96%	50–90%	Lifelong	Y	$ 2008	1.12	NS	$/ QALY	NS	48,401.43	$50,000-$100,000 (US$ 56,000- US$ 112,000)	$25,700-$69,000 (US $28,784-US$77,280)	Cost-effective	Merck
Haeussler et al. [25]	NS	NS	Lifelong	Y	€ 2015	1.23	€40-€104 (US $49.20-US $127.92)	€/ QALY	0.00027	30,171.74	€25,000–€40,000 (US$30,750–US $49,200)	€11,600 (US$ 14,268)	Cost-effective	Sanofi Pasteur MSD
Insinga et al. [26]	6/11/16/18 transient infections: 90% CIN: 95.2% Genital warts: 98.9%	12 yrs: 0–70% in first 5 yrs & remains at 70% 12–24 yrs: 0–50% in first 5 yrs & reduce to 0% after 5 yrs	Lifelong	Y	$ 2015	1.01	$80 (U$80.8)	$/ QALY	0.00282	9,152.87	3 X GDP per capita	Dominated	Not cost-effective	Merck
Jit et al. [27]	100%	80%	20 years	Y	£ 2006	2.05	£80.50 (US $165.03)	£/ QALY	NS	44,252.32	£ 30,000 (US $61,500)	£172,892 (US$ 354,429)	Not cost-effective	GSK
Kim et al. [28]	NS	25–90%	Lifelong	Y	I$ 2007	1.17	I$12 (US $14.04)	I$/ YLS	NS	7,313.56	GDP per capita	25% VC: I$810 (US$947.70) 50% VC: I$1740 (US$2,035.80) 75% VC: I$2180 (US$2,550.60) 90% VC: I$18,650 (US $21,820.50)	Very cost-effective if VC < 75%	National Cancer Institute, Bill Melinda Gates Foundation
Kim et al. [29]	6/11/16/18 transient infections: F: 100% M: 85% 6/11/16/18 persistent infections: F: 100% M: 90%	75%	Lifelong	Y	$ 2006	1.19	$120 (US $142.80)	$/ QALY	NS	46,437.07	$50,000-$100,000 (US$59,500-US $119,000)	$290,290 ($345,445)	Not cost-effective	National Cancer Institute, Bill Melinda Gates Foundation
Laprise et al. [30]	6/11/16/18 persistent infections: 95%	80%	20 years	Y	CAD$ 2010	1.04	CAD$85 (US $88.40)	CAD $/ QALY	0.000039	47,447.48	GDP per capita	CAD$89,662 ($93,248)	Cost-effective	GSK, Merck
Olsen et al. [31]	100%	85%	Lifelong	Y	€ 2012	1.36	€123 (US $167.28)	€/ LYG €/ QALY	NS	58,507.50	€50,000 (US $68,000)	LYG: €40,615 (US$55,236) QALY: €41,636 (US $56,625)	Cost-effective	Sanofi Pasteur MSD
Sharma et al. [32]	16/18 persistent infections: F: 100% M: 85%	25–90%	Lifelong	Y	I$ 2008	1.12	I$5 (US$5.6)	I$/ QALY	NS	1,164.61	GDP per capita	25% VC: I$734 (US$822) 50% VC: I$930 (US$1042) 75% VC: I$1364 (US$1528) 90% VC: I$2064 (US$2312)	Very cost-effective if VC < 50% Cost-effective if VC 75–90%	Bill & Melinda Gates Foundation
Taira et al. [49]	16/18 persistent infections:	70%	10 years (a booster dose	Y	$ 2004	1.28	$100 (US $128)	$/ QALY	0.21	41,921.81	NS	$442,039 (US$565,809)	Not cost-effective	Stanford School of Medicine Medical Scholar Award

	90%		administered after 10 years)											
Zechmesiter et al. [34]	90%	65%	10 years (a booster dose administered after 10 years)	Y	€ 2007	1.54	€110 (US $169.40)	€/ LYG	0.0004	46,855.77	NS	P: €311,000 (US$478,940) S: €299,000 (US$460,460)	Not cost-effective	MOH
Multiple age cohort HPV immunization versus single cohort HPV immunization														
Bogaards et al. [47]	16/18 persistent infections: 100%	50%	NS	Y	€ 2010	1.56	€125 (US$195)	€/ QALY	0.0032–0.0347	50,338.26	€20,000 (US$31,200)	17 yrs €25,535 (US$39,835) 19 yrs €36,235 (US$56,527) 21 yrs €60,147 (US$93,829) 23 yrs €81,439 (US$127,045) 25 yrs €107,796 (US$168,162) 17–25 yrs €48,433 (US$75,556)	17–25 yrs immunization is not cost-effective	GSK
Dasbach et al. [35]	6/11/16/18 transient infections: 90% CIN: 95.2% Genital Warts: 98.9%	12 yrs: 80% 12–14 yrs: 40% 12–17 yrs: 30% 12–24 yrs: 25%	Lifelong	Y	£ 2006	2.10	£75 (US $157.50)	£/ QALY	0.00026–0.0049	44,252.32	NS	12–14 yrs: £5882 (US $12,353) 12–17 yrs: £5971 (US $12,539) 12–24 yrs: £11,412 (US $23,965)	12–24 yrs immunization is very cost-effective	Merck
Dasbach et al. [36]	6/11/16/18 transient infections: 90% CIN: 95.2% Genital Warts: 98.9%	12 yrs: 0–85% in first 5 yrs & remains at 85% 12–24 yrs: 0–50% in first 5 yrs & reduce to 0% after 5 yrs	Lifelong	Y	NT$ 2006	0.03	NS	NT$/ QALY	0.00239	29,500	GDP per capita	NT$ 410,477 (US$12,314)	12–24 yrs immunization is very cost-effective	Merck
Dasbach et al. [37]	6/11/16/18 transient infections: 90% CIN: 95.2% Genital Warts: 98.9%	12 yrs: 0–90% in first 5 yrs & remains at 90% 12–24 yrs: 0–90% in first 5 yrs & reduce to 0% after 5 yrs	Lifelong	Y	NOK 2006	0.18	NS	NOK/ QALY	0.00245	74,114.70	NOK500,000 (US90,000)	NOK63,294 (US$11,393)	12–24 yrs immunization is cost-effective	Merck
Dasbach et al. [38]	6/11/16/18 transient infections: 90% CIN: 95.2% Genital Warts: 98.9%	12yrs: 0–85% in first 5 yrs 12–24 yrs: 0–10% in first 5 yrs	Lifelong	Y	€ 2010	1.56	NS	€/ QALY	0.00039	13,092.23	GDP per capita	€10,646 (US$16,608)	12–24 yrs immunization is cost-effective	Merck
Elbasha et al. [24]	6/11/16/18 transient infections: 90% 6/11/16/18 persistent infections:	12 yrs: 0–70% in first 5 yrs & remains at 70% 12–24 yrs: 0–50% in first 5 yrs & reduce to 0% after 5 yrs	Lifelong	Y	$ 2005	1.24	NS	$/ QALY	0.00016 – 0.00045	44,307.92	NS	12yrs F + 12–24 yrs F: $4666 (US$5786) 12 yrs F & M + 12–24 yrs F: $41,802 (US$51,834) 12 yrs F & M + 12–24 yrs F & M: $45,056 (US$55,869)	12–24 yrs F immunization in addition to 12yrs F is very cost-effective 12–24 yrs F with or without M in addition to gender-neutral 12 yrs immunization is cost-effective	Merck

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Table 2 (*continued*)

Author year	Vaccine efficacy	Vaccine coverage	Duration of vaccine protection	Herd effect	Currency, year	Conversion factor to US$ 2016	Vaccine price/dose (US$ 2015)	Unit	QALY-gained per patient	GDP per capita (US$ 2016)	Threshold used	ICER (US$ 2015)	Conclusion	Study funder
Elbasha et al. [39]	100% 6/11/16/18 transient infections: 90% CIN: 95.2% Genital Warts: 98.9%	12 yrs: 0–70% in first 5 yrs & remains at 70% 12–14/17/19/24 yrs: 0–50% in first 5 yrs & reduce to 0%	Lifelong	Y	$ 2005	1.24	NS	$/ QALY	0.00028 – 0.00047	44,307.92	NS	12–14 yrs: Weakly Dominated 12–17 yrs: $3115 (US $3863) 12–19 yrs: $3512 (US $4355) 12–24 yrs: $10,986 (US $13,623)	12–24 yrs immunization is very cost-effective	Merck
Favato et al. [48]	100%	84.7%	Lifelong	N	€ 2008	1.64	€69 (US $113.16)	€/ QALY	NS	40,640.18	€30,000–€ 45,000 (US$49,200-US$73,800)	12–16 yrs: €12,013 (US$19,701) 12–18 yrs: €13,232 (US$21,700) 12–25 yrs: €15,890 (US$26,060)	12–25 yrs immunization is cost-effective	Sanofi Pasteur MSD
Insinga et al. [26]	6/11/16/18 transient infections: 90% CIN: 95.2% Genital warts: 98.9%	12 yrs: 0–70% in first 5 yrs & remain at 70% 12–24 yrs: 0–50% in fist 5 yrs & reduce to 0% after 5 yrs	Lifelong	Y	$ 2005	1.24	$80 (US $99.20)	$/ QALY	0.0009–0.00371	9,152.87	3 X GDP per capita	12yrs F + 12–24 yrs F: $3048 (US$3780) 12 yrs F & M + 12–24 yrs F: $16,663 (US$20,662) 12 yrs F & M + 12–24 yrs F & M: $16,702 (US$20,710)	12–24 yrs F immunization in addition to 12yrs F is very cost-effective 12–24 yrs F with or without M in addition to gender-neutral 12 yrs immunization is cost-effective	Merck
Jit et al. [27]	100%	80%	20 years	Y	£ 2006	2.05	£80.50 (US $165)	£/ QALY	NS	44,252.32	£30,000 (US $61,500)	12–14 yrs: £18,856 (US $38,655) 12–16 yrs: £16,417 (US $33,655) 12–18 yrs: £11,856 (US $24,305) 12–25 yrs: £128,032 (US $260,453)	12–18 yrs immunization is cost-effective	GSK
Kawai et al. [40]	76–96%	85–90%	Lifelong	Y	$ 2011	1.08	$15.15 (US $16.36)	$/ QALY	0.00238	13,167.47	GDP per capita	12–26 yrs: $450 (US$486)	12–26 yrs immunization is very cost-effective	Merck
Liu et al. [41]	6/11/16/18 persistent infections: 93.2% (CC) CIN: 50.3–64.9%	70%	NS	N	CNY 2013	0.16	CNY633 (US $101.28)	CNY/ QALY	NS	7,077.77	3XGDP per capita	<CNY120,000 (< US$19,200)	12–25 yrs immunization is cost-effective	GSK
Tully et al. [42]	16/18 persistent infections: greater than90% CIN: 54%	School-based:80% Clinic-based: 40%	Lifelong	Y	CAD$ 2010	1.04	CAD$90 (US $93.60)	CAD $/ QALY	School-based: 0.0034 Clinic-based: 0.0026	47,447.48	CAD$50,000 (US$52,000)	School-based: CAD$6361 (US$6615) Clinic-based: CAD$8260 (US$8590)	School-based & clinic-based 12–18 yrs immunization is cost-effective	GSK
Turner et al. [43]	16/18 persistent infections: 100%	NS	Lifelong	Y	£ 2013	1.68	£20 (US $33.60)	£/ QALY	NS	42,724.07	£30,000 (US $50,400)	*In the presence of protection to non-naïve women* 12–17 yrs: £1627 (US $2733) 12–19 yrs: £10,433 (US $17,527) 12–24 yrs: £16,557 (US $27,816) 12–29 yrs: £33,897 (US $56,947) 12–34 yrs: £50,125 (US $84,210) *In the absence of protection to non-naïve women* 12–17 yrs: £1801 (US$3026)	12–24 yrs immunization is cost-effective in the presence of protection to non-naïve women. 12–19 yrs immunization was cost-effective in the absence of protection to non-naïve women.	European Community 7th Framework Program

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											12–19 yrs: £16,769 (US $28,172) 12–24 yrs: £34,839 (US $58,530) 12–29 yrs: £105,637 (US $177,470) 12–34 yrs: £254,191 (US$427,041)		
Usher et al. [44]	CIN: 95% 16/18 persistent infections: 95%	School-based: 80% Clinic-based: 30% 100%	Lifelong	Y	€ 2008	1.64	€100 (US $164)	€/ LYG	NS	61,257.90	NS	12–15 yrs €52,968 (US$86,868)	Health Information & Quality Authority
Westra et al. [45]			Lifelong	N	€ 2011	1.44	€105 (US $151.20)	€/ QALY	NS	53,540.61	€20,000–€ 50,000 (US $28,800–US $72,000)	12–16 yrs: €22,500 (US $32,400) 12–18 yrs: €23,500 (US $33,840) 12–25 yrs: €26,900 (US $38,736)	12–15 yrs immunization is cost-effective 12–25 yrs immunization is cost-effective	GSK
Yamabe et al. [46]	6/11/16/18 transient infections: 90% CIN: 95.2% Genital warts: 98.9%	12 yrs: 0–80% in first 5 yrs & remain at 80% 12–24 yrs: 0–50% in first 5 years & reduce to 0% after 5 yrs	Lifelong	Y	¥ 2013	0.01	¥36,000 (US$360)	¥/ QALY	0.00365–0.00508	40,454.45	GDP per capita	¥1,205,800 (US$12,058)	12–24 yrs immunization is very cost-effective	Merck

Y = Yes; N = No; NS = Not stated; QALY = Quality adjusted life year; YLS = Years of life saved; LYG = Life year gained; F = Female; M = Male; VC = vaccine coverage; P = Payer; S = Society; MOH = Ministry of Health.
[a] HPV 6/11/16/18 persistent infections are associated with diseases such as cervical, penile, vaginal, vulvar, and anal cancers, as well as non-genital cancers of the oropharynx.

high income countries. Such findings reflect that low and middle-income countries are still lacking in technical capacity and funding to conduct their own economic evaluations [33].

3.3. Type of economic analysis

Twenty-nine studies performed cost-utility analyses (CUA) with quality-adjusted life year (QALY) outcome [15,17–27,29,30,32,33,35–43,45–48] while four studies [16,28,34,44] adopted cost-effectiveness (CEA) approach with life-year gained (LYG) or years life saved (YLS) as outcome measures. One study performed both cost-effectiveness and cost-utility analyses [31].

3.4. Type of model

Thirty studies [16–40,42–44,46,47] adopted dynamic transmission model which captured indirect protection from HPV vaccination into their analyses. The remaining four studies [15,41,45,48] used static model which did not include herd immunity into their models. Therefore, the benefits of HPV vaccination from this model especially in adolescent boys and older age groups may be underestimated. However, one study [45] explained that the use of static model for multicohort immunization was justified at that time as the benefits of herd immunity were likely to be limited because vaccine coverage in older age groups was low and HPV transmission was more likely to occur in an age-dependent fashion [45].

3.5. Cost-effectiveness thresholds

A cost-effectiveness threshold of either one or three times GDP per capita was used in eleven studies [15,16,26,28,30,32,36,38,40,41,46]. This may reflect the lack of local thresholds for decision-making especially in lower income countries. Conversely, fourteen studies [17,19,22,23,25,27,29,31,37,42,43,45,47,48] adopted their own local thresholds while the remaining nine studies [18,20,21,24,33–35,39,44] did not define their cost-effectiveness thresholds.

3.6. Perspective

Eleven studies undertook analysis from healthcare provider perspective [16,24,26,27,31,35–37,39,40,43] and seven studies by payer perspective [17,21,30,38,41,44,46]. Nine studies [15,18–20,22,28,29,32,47] utilized societal perspective, which incorporated both direct and indirect medical costs (e.g. transportation, patient's time, sickness leave and productivity loss). One study [42] used the Ministry of Health perspective and another study [34] adopted both societal and payer perspective. The adoption of several perspectives allows the comparison of economic impact with and without incorporating indirect costs. The remaining five studies [23,25,33,45,48] did not specify the perspective adopted in their modelling.

3.7. Vaccine coverage

The assumption on HPV vaccination coverage is crucial in influencing the potential impact of HPV vaccines on HPV-related disease. Most studies assumed a vaccination coverage rate above 60% and a compliance rate of 80–100% with the full series of three doses. Three studies [17,19,20] categorized the coverage based on gender, with higher vaccination coverage assumed for females (25–60%) than males (11–40%). For comparison of multicohort immunization, seven studies [24,26,36–39,46] assumed that up to 70–90% of 12-year-olds received the 3-dose vaccine, with the coverage increased linearly from 0% up to 70–90% during the first 5 years of the vaccination program and remained at 70–90% thereafter. In contrast, the vaccine coverage for additional catch-up

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cohorts increased linearly from 0% up to 10–90% during the first 5 years but was removed after 5 years. One study ranged the coverage according to the age of vaccination, whereby vaccination coverage decreased with increasing age of vaccination [35]. Two studies categorized the coverage based on delivery, either as school-based or clinic based [42,44].

3.8. Vaccine efficacy

Most models assumed vaccine characteristics of 90–100% efficacy against transient HPV 6/11/16/18 infections, consistent with the currently available data from controlled clinical trials of HPV vaccines. The prophylactic efficacy of the vaccine against persistent HPV 6/11/16/18 infections, HPV-related cervical intraepithelial neoplasia (CIN) and genital warts were mostly assumed to be 90–100%, 95.2% and 98.9% respectively. However, for comparison of gender-neutral vaccination strategy, several studies [21,22,28,32] assumed the efficacy of vaccine against both transient and persistent infections to be differently among gender, with lower vaccine efficacy in male (41–85%) than in female (76–100%).

3.9. Duration of vaccine protection

Majority studies (27/34) assumed lifelong vaccine protection while five studies assumed a shorter duration of protection, of either 10 years [34,49] or 20 years [15,27,30]. The remaining two studies [41,48] did not specify the duration of vaccine protection.

3.10. Other methodological choices (time horizon, discount rate)

In terms of time horizon, most studies (27/34) projected outcomes over 50 to 100 years to capture diseases such as cervical cancer which only occurred years after initial HPV infection [15,17–27,29–32,34–38,40,42–44,46,48]. The remaining seven studies [16,28,39,41,45,47,49] did not specify their time horizon. Most studies (22/34) applied fixed discounting rates of 3% to costs and benefits [15–21,23–26,28–32,36,39–42,46]. Five studies applied 3.5% [27,35,37,43,44] while two studies used 5% [34,38]. Three studies [45,47,48] used differential discounting (4% or 3% for costs and 1.5% for benefits) to account for the growing value of health benefits in the future [50]. The remaining two studies did not specify the discounting rate adopted in their economic evaluations [22,49].

3.11. Sensitivity analyses

Among all included studies, 33 studies [15–32,34–40,42–49] conducted sensitivity analyses. Of these, eight studies performed one-way sensitivity analysis [17,18,21,27–29,32,49], seventeen studies [15,16,19,20,24,26,30,34–40,43,46,47] performed both one- and multi-way sensitivity analysis and five studies [22,31,42,44,45] performed one-way and probabilistic sensitivity analysis. The remaining one study [23] performed multi-way and probabilistic sensitivity analysis while the other two studies [25,48] conducted probabilistic sensitivity analysis only.

3.12. Quality of included studies

Table 3 showed the extent to which the reviewed studies conformed with the standards for reporting economic evaluations based on the WHO guidance [10], Drummond's checklist [11] and CHEERS statement [12]. All studies clearly identified the study question, intervention(s), and comparator(s). A relatively high proportion of studies reported their study perspectives (29/34; 85%), time horizon (28/34; 82%) and discounting rates (32/34; 94%). Most studies performed sensitivity analyses (33/34; 97%) to assess the robustness of their findings. Almost all studies also clearly described the measurements and the assumption behind the calculation costs (33/34, 97%). The choice of model used was justified in majority studies (31/34; 91%), as a high proportion of these studies adopted dynamic transmission model to capture herds immunity. The currency and price data were reported in most studies too (30/34; 88%). 31 (91%) out 34 studies disclosed their funding sources. However, only 19 studies (56%) reported the measurement of effectiveness from synthesis-based estimates, either through the combination of several randomized trials or the use of systematic reviews.

Table 3
Extent to which included studies met standard reporting recommendations.

Recommended aspects	Number of studies fulfilling	Percentage
Study question clearly stated	34/34	100%
Described intervention and comparator	34/34	100%
Measurement of effectiveness reported		
Single study-based estimates	8/34	24%
Synthesis-based estimates	19/34	56%
Assumption of costs and outcomes specified	33/34	97%
Currency and price data reported	30/34	88%
Choice of model justified	31/34	91%
Perspective specified	29/34	85%
Time horizon specified	28/34	82%
Discounting rates specified	32/34	94%
Calculated and reported ICER or cost-saving	33/34	97%
Sensitivity analysis performed	33/34	97%
Conclusions follow from the data reported	34/34	100%
Disclosed funding source(s)	31/34	91%

ICER = incremental cost-effectiveness ratio.

4. Study results

4.1. Vaccination of 9-valent HPV vaccine

Three studies [15–17] concluded that vaccination with 9-valent vaccine was likely to be cost-effective compared to current vaccines, at least within the price range explored. In HICs (e.g. Canada and Austria), vaccination with 9-valent vaccine was cost-effective if the additional cost of 9-valent vaccine compared to quadrivalent vaccine is less than US$23-US$47 while in LMICs (e.g. Kenya and Uganda), the additional cost of 9-valent vaccine must not exceed US$8.40-US$9.80. Two studies [18,20] concluded that switching to a 9-valent gender-neutral HPV vaccination was cost-saving regardless of the assumptions on cross-protection. However, one study [19] reported that providing additional 9-valent vaccination to females aged 13–18 years who had previously completed a series of HPV vaccine was not cost-effective because additional 9-valent vaccination incurred an extra cost of a full price 9-valent vaccine for each vaccinated person. In contrast, when a primary quadrivalent HPV program was completely switched to a primary 9-valent program instead, the additional cost incurred was the differences in cost between the 9-valent and quadrivalent vaccines only [19].

4.2. Vaccination of adolescent boys and girls (gender-neutral)

Eight studies [21–23,25,28,30–32] reported that vaccinating adolescent boys in addition to girls was cost-effective. However, two studies [22,28] further specified that this vaccination strategy was no longer cost-effective when vaccine coverage for female is above 75%. Majority of the cost-effective studies [21–23,25,30,31] comprehensively captured all HPV-related diseases including male-associated cancers such as penile and oropharyngeal cancer. Hence, the assumption of lower female vaccine coverage and the

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inclusion of male-associated HPV diseases would result in a more favourable conclusion for the gender-neutral HPV vaccination strategy.

4.3. Vaccination of multiple age cohort

Multicohort female vaccination strategy was cost-effective in the age range of 9–14 years old. However, the cut-off range where HPV vaccination was no longer cost-effective varied among studies and was more important in differentiating between studies than their overall conclusions. Nine studies [24,26,35–39,43,46] concluded that HPV vaccination was cost-effective until the age of 24, three studies [41,45,48] up to the age of 25 and one study [40] till the age of 26. However, it is important to address that two of these cost-effective studies [36,46] compared multicohort vaccination to no vaccination strategy instead of routine vaccination of female aged 12. Therefore, the ICERs for additional age cohort immunization in these studies were likely to be overestimated as fewer individuals were potentially vaccinated and their results should be interpreted cautiously. Two studies [24,26] also found that gender-neutral HPV vaccination up to age 24 years was cost-effective. A study in United Kingdom [43] concluded that HPV vaccination up to age 24 years was only cost-effective in the presence of protection to non-naïve women, demonstrating that the exclusion of vaccine protection among non-naïve women may underestimate the cost-effectiveness of vaccinating additional older age women. When HPV vaccination was compared in the next age range gradually, it was cost-effective till the age of 18 years only in two studies [27,42] and 15 years in one study [44]. A Canadian study [42] found that HPV vaccination till the age of 18 years was cost-effective irrespective of the delivery method, with school-based delivery had a lower ICER compared to clinic-based delivery. Among the seventeen studies, only one study [47] reported that multicohort vaccination (17–25 years) was not cost-effective unless vaccine price in Netherlands was reduced by 52%.

4.4. Key drivers of cost-effectiveness

Several key drivers of cost-effectiveness were identified in this review such as duration of vaccine protection, vaccine price, coverage, and discounting rate.

4.4.1. Duration of vaccine protection

The cost-effectiveness of HPV vaccination depends heavily on the duration of vaccine protection. To date, HPV vaccine protection in women has been shown to last for at least 9.4 years with bivalent vaccine [51] and at least 10 years with quadrivalent vaccine, with a trend of sustained protection up to 12 years of follow-up [52]. Therefore, most studies varied the duration of protection between 10 and 20 years in their sensitivity analyses. For example, when the duration of protection was reduced from lifelong to 10 years, the ICER increased by 3.6-fold relative to the reference case [36]. Additionally, when protection lasted for 10 years only, multicohort vaccination strategy was more likely to be cost-effective in a broader age range (e.g. 12–24 years) as the sustained-benefits in reducing HPV-related disease can only be achieved by targeting a wider age group in a shorter period [35,37].

4.4.2. Vaccine price

Vaccine price has also emerged as an important parameter in the cost-effectiveness analyses. The assumed vaccine prices ranged widely across studies, from below US$5.60 per dose in LMIC to US $360 per dose in HIC. A Brazilian study [28] demonstrated that when vaccine price increased from US$12 to US$135 per dose, vaccinating adolescent boys in addition to girls was no longer cost-effective even when vaccine coverage for female was minimized to 25%. Moreover, Westra et al. study [45] also showed that the ICER fall below the lower range of CEA threshold (≤€20,000/QALY) when vaccine price was reduced by 38% and multicohort vaccination strategy became very cost-effective.

4.4.3. Vaccine coverage

Another influential parameter that drives the cost-effectiveness of HPV vaccination is vaccine coverage. When vaccine coverage for female was above 70–80%, the benefits of gender-neutral vaccination became rather small as the additional health gains for female were almost negligible, while the total costs nearly doubled. Similar Brazilian study also reported that when female vaccine coverage was increased to 90%, vaccinating both genders was no longer cost-effective even up to a 58% reduction in vaccine price [28].

4.5. Discount rate

Discounting has a large impact on the cost-effectiveness analyses as the costs for HPV vaccination occur at present while the health and economic gains are only observed after many years. For instance, Olsen et al. [31] explored the undiscounted and discounted net present value of gender-neutral HPV vaccination. The authors showed that the ICER increased when the discount rate increased and vaccinating both genders was not cost-effective at a higher discount rate of 5%. In contrast, gender-neutral vaccination became more cost-effective (lower ICER) in an undiscounted analysis (0%) [31]. Thus, the valuation of future health outcomes for HPV vaccination is highly dependent on the discounting rates adopted.

5. Discussions

Our review revealed that majority studies were not from LMICs and the studies from LMICs were predominantly performed by investigators based in HICs. Hence, more LMICs studies conducted by investigators from these countries are warranted to increase the specificity and ownership of study results in influencing local decision making [53].

The positive economic value of gender-neutral vaccination was confirmed by more than half of the included studies. However, when vaccine coverage for female is higher than 70–80%, most of the cervical cancers in female have been prevented and thereby, vaccinating additional boys is less favourable than targeting girls only due the higher costs involved without additional benefits gained for the female population. Thus, achieving high female vaccine coverage should remain as the main priority especially in lower income countries as it is more effective and less costly than vaccinating additional boys. It is also important to address that several studies failed to account the broader benefits of HPV vaccination in male population such as the prevention of penile, anal, and oropharyngeal cancers. Exclusion of these male-related diseases may underestimate the true value of gender-neutral vaccination strategy. Moreover, gender-neutral vaccination may also result in tangible benefits such as more rapid induction of herd protection for boys, indirect protection of unvaccinated women and direct protection of men who have sex with men. Therefore, this vaccination strategy should remain for consideration in immunization programs based on other factors too such as disease burden, sexual behaviour in a country (prevalence of homosexual in a community), equity, budget impact, and affordability.

Despite different methodologies and various assumptions, most studies were consistent in the conclusion that multiple age cohort vaccination was cost-effective. However, the upper age limit at

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which HPV vaccination was no longer cost-effective should be interpreted cautiously as several studies analysed the cost-effectiveness in a single age range only and did not compare in the next age range gradually, resulting in a possible overestimation on the cut-off age range. The duration of protection from vaccination has a great impact on the cost-effectiveness of multicohort vaccination, with most studies assuming life-long protection. At present, it is still unknown if model assumptions of life-long protection is validated as current evidence has only demonstrated vaccine protection in women to last up to at least 9–10 years with bi- or quadrivalent HPV vaccines [51,52]. Therefore, the use of ICERs based on the conservative estimate of 10-year protection may be more representative of real-life effectiveness rather than the use of ICER based on lifetime protection.

The cost-effectiveness of HPV vaccination is also contingent upon the levels of vaccine coverage, compliance, and vaccine price. Most models assumed a high level of vaccine coverage (approximately 70% of the target population assumed to receive the full series of three doses). However, not everyone who initiate the vaccination complete all three doses within the recommended time frame. Based on the CDC 2016 report [54], only 43% of females and 31.5% of males aged 13–17 years of age received all three recommended HPV doses. Therefore, the reported cost-effectiveness may underestimate the actual costs and the modelling benefits from herd immunity is only theoretical unless the coverage level increases in the target population. Additionally, it is also uncertain how non-compliance may subsequently affect the vaccine efficacy and duration of protection [55]. Assumptions about the HPV vaccine price also affects the modelling estimates on the cost-effectiveness of switching from bi- or quadrivalent vaccine to the new 9-valent vaccine. As the price for 9-valent vaccine is currently unknown especially in lower income countries, the cost-effectiveness of 9-valent vaccine is still uncertain and there is no conclusive evidence of greater cost-effectiveness than the older licensed HPV vaccines. In fact, HPV vaccination is only cost-effective under the assumption of the lowest price of 9-valent vaccine. Therefore, once the 9-valent vaccine price is confirmed including the support by GAVI vaccine-alliance, revaluation on the cost-effectiveness of 9-valent vaccine is warranted.

Another model assumptions that may impact the cost-effectiveness were the inclusion or exclusion of herd immunity effects based on the type of model adopted. Four studies [15,41,45,48] adopted the static model which did not capture herd immunity effects. Ideally, the cost-effectiveness analyses of HPV vaccination should adopt dynamic transmission model because economic evaluations for primary prevention strategy should be driven by societal benefits (e.g. indirect effects on people were not vaccinated) rather than individual needs [48]. Hence, the use of static model in these four studies may underestimate the benefits of vaccination. If a HPV vaccination strategy is shown to be cost-effective from a static model, it is expected to be even more cost-effective when dynamic effects are considered.

6. Limitations

This review has several limitations. The cost-effectiveness based on GDP based thresholds of 1–3 times of GDP per capita lacks country specificity and has little meaning for country-level decision making [8]. It is uncertain whether this threshold truly reflects the country's affordability or societal willingness to pay for additional health gains. Another limitation is the use of US$ Consumer Price Index (CPI) to inflate costs to US$ 2016 prices for all countries. Inflation rates vary substantially among countries and CPI may have overestimated inflation. Additionally, CPI is originally intended to measure the experience of people residing in urban areas and thus, it may not actually reflect the experience of entire population in a country especially those living in rural areas. Apart from economic standpoint, other factors should be considered for the national immunization program such as budget availability, political issues, cultural influences, and availability of healthcare workforces.

7. Conclusions

Current evidence does not show conclusive proof of greater cost-effectiveness of the new 9-valent vaccine compared to the older bi- or quadrivalent vaccine as the price for 9-valent vaccine is still unknown. The inclusion of adolescent male in HPV vaccination program is cost-effective if vaccine price or coverage for female is low and if the HPV-associated male diseases are placed into consideration too. Multiple age cohort vaccination strategy is likely to be cost-effective in the age range 9–14 years, but the upper age limit at which HPV vaccination is no longer cost-effective needs to be further evaluated. Vaccine coverage, price, duration of protection and discount rates are important parameters for consideration in the uptake of HPV vaccination. Nonetheless, our findings are expected to support policy-makers and healthcare providers in making recommendations for HPV national immunization programs on either switching to the new 9-valent vaccine or inclusion of adolescent boys' vaccination or extending the age of immunization, but it should not divert resources from vaccinating the primary target population of girls aged 12 years or from effective cervical cancer screening programs.

Conflict of interest

None.

Role of funding source

None.

Acknowledgement

None.

Appendix A. Search strategies

PubMed

#1 (hpv[Title] OR papilloma*[Title] OR cervi*[Title]) AND (vaccine* OR vaccinated OR vaccination OR vaccinated OR immune*) AND (cost[Title/Abstract] OR costs[Title/Abstract] OR cost-effective* OR cost-utility* OR cost-benefit*) AND (analysis OR "economic evaluation*") AND cervical cancer

OR

#2 (((cost-effectiveness analysis OR cost-benefit analysis OR cost-utility analysis OR economic evaluation) AND (cervical cancer) AND (vaccine OR vaccination) AND (human papillomavirus OR HPV))) OR ((hpv[Title] OR papilloma*[Title] OR cervi*[Title]) AND (vaccine* OR vaccinated OR vaccination OR vaccinated OR immune*) AND (cost[Title/Abstract] OR costs[Title/Abstract] OR cost-effective* OR cost-utility* OR cost-benefit*) AND (analysis OR "economic evaluation*") AND cervical cancer)

Embase

#1 (hpv OR papilloma* OR cervi*).ti. AND (vaccine* OR vaccinate OR vaccination OR vaccinated OR immuni*).af. AND (cost OR costs OR cost-effective* OR cost-utility* OR cost-benefit*).af. AND (analysis or "economic evaluation*"). af. AND cervical cancer.af.

OR

#2 ((Cost-effectiveness analysis or cost-benefit analysis or cost-utility analysis or economic evaluation) and cervical cancer and (vaccine or vaccination) and (human papillomavirus or HPV)).af.

Cochrane Library

#1 (hpv OR papilloma* OR cervi*):ti AND (vaccine* OR vaccinated OR vaccination OR vaccinated OR immune*) AND ((cost OR costs):ti OR (cost OR costs):ab OR cost-effective* OR cost-utility* OR cost-benefit*) AND (analysis or "economic evaluation*") AND (cervical cancer)

OR

#2 (cost-effectiveness analysis OR cost-benefit analysis OR cost-utility analysis OR economic evaluation) AND (cervical cancer) AND (vaccine OR vaccination) AND (human papillomavirus or HPV)

LILACS

#1 (hpv OR papilloma$ OR cervi$) AND (vaccine$ OR vaccinate OR vaccination OR vaccinated OR immuni$) AND (cost OR costs OR cost-effective$ OR cost-utility$ OR cost-benefit$) AND (analysis OR "economic evaluation$") AND cancer

OR

#2 (Cost-effectiveness analysis OR cost-benefit analysis OR cost-utility analysis OR economic evaluation) AND (cervical cancer) AND (vaccine OR vaccination) AND (human papillomavirus OR HPV) [Title words]

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