SUMMARY OF EVIDENCE

HUMAN PAPILLOMA VIRUS (HPV) VACCINATION: AN UPDATED SYSTEMATIC REVIEW OF COST-EFFECTIVENESS ANALYSES [1]

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KEY FINDINGS

Question 1: What is the cost-effectiveness of 9-valent vaccine versus bi- or quadrivalent vaccine?

Studies that compared the cost-effectiveness of switching from bi- or quadrivalent vaccine to 9-valent vaccine in adolescent females were scarce. The 9-valent vaccine price per dose and the cross-protection provided by HPV vaccine types highly influence the cost-effectiveness analyses. As the price for 9-valent vaccine remain unknown especially in LMIC, the cost-effectiveness of immunization with 9-valent HPV vaccine is still uncertain and more economic evaluations are still needed to understand the true value for money of 9-valent HPV immunization.

Question 2: What is the cost-effectiveness of gender-neutral HPV immunization versus female-only immunization?

Almost half of the studies showed that gender-neutral immunization was cost-effective. Vaccine coverage and price play a crucial role in influencing the cost-effectiveness analyses especially in LMIC. If female vaccine coverage is greater than approximately 70-80%, the incremental effectiveness is diminished and gender-neutral immunization that includes adolescent boys become less cost-effective than routine vaccination of adolescent girls only. Several existing economic studies fail to account for the broader benefits of HPV vaccination especially among male population such as penile and anal cancers, genital warts and oropharyngeal cancer. Exclusion of these HPV-related male benefits could results in underestimation of the real value of gender-neutral immunization. As such, more cost-effectiveness evidence for gender-neutral immunization are still needed to understand its monetary benefits especially in LMIC.

Question 3: What is the cost-effectiveness of immunization of multiple age cohorts with defined age range vs single age cohort immunization only?

Most studies reported that immunization targeting multiple age cohorts were cost-effective due to wider primary protection and more rapid herd effects. However, the extend of immunization age needs to be interpreted cautiously as several studies analyzed the cost-effectiveness of HPV immunization in a single age range only and did not compare in the next age range gradually. The incremental cost-effectiveness for each additional age cohort of girls and women aged ≥15 years is expected to decline gradually as more girls and women would have already become sexually active. Above age 15 years, the upper age limit at which HPV immunization stop being cost-effective depends on the country context. Duration of vaccine protection and vaccine price influences the cost-effectiveness of targeting multiple age cohort immunization. If duration of vaccine protection is reduced to a minimum of 10 years, the cost-effectiveness ratio increases and is only cost-effective in the broader age range of immunization, 12-24 years old. Hence, further economic evidences on immunization based on multiple age cohorts are still required especially in LMIC and also in determining the most cost-effective age limit of HPV vaccination.

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ABSTRACT

BACKGROUND

The first global recommendations on HPV vaccination were made by WHO's SAGE in October 2008. These recommendations were reviewed again in April 2014, with emphasis to include the extended 2-dose HPV immunization for girls aged 9-14 years, who are not immunocompromised. As new evidences on the novel 9-valent vaccine, on male immunization and on multiple age cohort immunization emerged, updated new recommendations are deemed necessary.

OBJECTIVES

To systematically review and update the evidence for cost-effectiveness analyses of HPV immunization on: (i) 9-valent vaccine versus bi- or quadrivalent vaccine, (ii) gender-neutral HPV immunization versus girls-only immunization and (iii) immunization of multiple age cohorts with defined age range versus single age cohort immunization only.

METHODS

Searches were conducted in the following databases: MEDLINE (PubMed), EMBASE (OVID), Cochrane Library and LILCAS for HPV economic evaluation studies published from inception to Jun 2016. Literature search was performed using the broad combined search strings of ('hpv OR papilloma* OR cervi*) AND (vaccine* OR vaccinated OR vaccination OR vaccinated OR immune*) AND (cost OR cost-effective* OR cost-utility* OR cost-benefit*) AND (analysis OR "economic evaluation*") AND cervical cancer. To be included, studies must be a full economic evaluation of HPV immunization. No language restrictions were applied. Editorials, reviews and publications with abstract only without a full paper were excluded. Items extracted included study assumptions, methodology, parameters and results. To facilitate inter-country comparisons, local currencies were converted to US$ of 1st January of the base year and were then inflated to US $ 2015 using the US$ Consumer Price Index for all urban consumer.

MAIN RESULTS

28 studies were included in the review, among which 2 studies analyzed the cost-effectiveness of 9-valent vaccine versus bi- or quadrivalent vaccine [1, 2], 14 studies conducted the cost-effectiveness analyses of gender-neutral HPV immunization versus female-only immunization [3-16] and 15 studies evaluated the cost-effectiveness of immunization of multiple age cohorts [6, 8, 9, 17-28]. 3 studies analyzed both the cost-effectiveness of gender-neutral and multiple age cohort immunization [6, 8, 9].

Question 1: What is the cost-effectiveness of 9-valent vaccine versus bi- or quadrivalent vaccine?

For Kiatpongsan et al. study, in the base-case analysis without herd effects incorporation, with overlap between unidentifiable HPV types and multiple infections with vaccine-targeted HPV types and 37.4% cross protection against non-vaccine types, vaccination with 9-valent vaccine was very cost-effective (below CEA threshold of 1XGDP) if the added cost of 9-valent vaccine per course (3 doses) did not exceed I$9.7 (US$11.74) and I$8.3 (US$10) in Kenya and Uganda respectively [2]. For Drolet et al. study, vaccination with 9-valent vaccine was also very cost-effective (below CAD$ 40,000/QALY-gained) if the additional cost of 9-valent vaccine per dose did not exceed CAD$24 (US$22.56) [1]. In Kiatpongsan et al. study, when the overlap of unidentifiable HPV types from no to full benefits to prevent cervical cancer and the cross-protective effects were varied, the additional cost of 9-valent vaccine per course ranged from I$6.8 – I$14.5 (US$8.2 – US$17.4) in Kenya and I$5.8 – I$12.5 (US$5.5 – US$11.8) in Uganda [2]. In Drolet et al. study, the additional cost of 9-valent vaccine per dose varied from CAD$8 to CAD$37 (US$9.6 – US$44) when the vaccine coverage, duration of protection and vaccine efficacy were varied [1].

Question 2: What is the cost-effectiveness of gender-neutral HPV immunization versus female-only immunization?

The vaccination strategy of including boys and girls were cost-effective in 7 studies : 5 studies from HIC [3-5, 7, 13], 1 study from UMIC [10] and 1 study from LMIC [14]. Among the 7 studies, 3 studies reported that gender-neutral immunization was only cost-effective when vaccine coverage is ≤75% [4, 10, 14]. Cervical cancer, genital warts and non-cervical HPV-related cancer (anal/penile/vaginal/vulvar/oropharyngeal cancer) were captured in 5 of the cost-effective studies [3-5, 7, 13]. Cost-effectiveness analyses were sensitive to vaccine coverage [4, 6, 8, 10, 12-14], vaccine price [4, 5, 7, 10, 12-16], duration of vaccine protection [3, 5, 6, 8, 9, 11, 12] and discount rate [4, 7, 9, 13, 15, 16]. Increasing vaccine price will increase the cost-effectiveness ratio. A Brazil study showed that when vaccine price was increased from US$12/dose to US$134/dose, gender-neutral immunization was no longer cost-effective even when vaccine coverage was decreased to 25% [10]. The second most influential parameter reported was vaccine coverage especially in LMIC. When vaccine coverage was high, the additional benefits from including boys into immunization program were minimal as high vaccine coverage can prevent most cervical cancers in female and genital warts in both sexes. A Brazil study found that when vaccine coverage was increased to 90%, gender-neutral immunization was no longer cost-effective despite 58% reduction in vaccine price [10]. Results were sensitive to the health benefits captured by HPV vaccination too especially in male population. The Denmark study showed that gender-neutral immunization was no longer cost-effective when HPV-related male benefits of genital warts and head or neck cancer protection were excluded [13]

Question 3: What is the cost-effectiveness of immunization of multiple age cohorts with defined age range versus single age cohort immunization only?

Most of the studies compared multiple age cohort immunization in female aged ≥ 12 to the routine vaccination of 12-year-old female alone except for 2 studies which compared to no vaccination strategy [18, 28]. Therefore, these 2 studies are likely to over-estimate the cost-effectiveness of age cohort immunization. Targeting HPV immunization in female aged 12 up to 24 or 25 or 26 years were found to be cost-effective in eight studies [6, 8, 18-20, 22, 23, 28]. When HPV immunization

was extended in several age range cohorts, a UK study found that HPV immunization up to age 18 years only was cost-effective [9]. Conversely, an Ireland study found that the cost-effectiveness of HPV immunization was limited up to age 15 years only. 3 studies that compared age cohort immunization in the next age range gradually reported that HPV vaccination until the age 24/25 years were cost-effective. Turner et al. found that HPV immunization up to age 24 years was only cost-effective in the presence of protection to non-naïve women if vaccine price was below £20 (US$33.18) [25]. 2 studies concluded that the most effective strategy was HPV immunization in age cohort of 12-24 years, covering both females and males [6, 8]. Tully et al. showed that both school-based and clinic-based immunization up to age 18 years were cost-effective, in which school-based had a lower ICER than the clinic-based immunization [24]. The most influential parameters were duration of vaccine protection [6, 8, 9, 17-22, 25, 27, 28] and vaccine price [20-22, 24-27]. Decreasing the duration of vaccine protection increased the cost-effectiveness ratio for immunization in multiple age cohorts. For example, in a Taiwan study, when duration of vaccine protection is reduced from lifelong to 10 years, the ICER for multiple age cohort strategy increased by 3.6-fold relative to the reference case and was no longer cost-effective [18]. Interestingly, when duration of vaccine protection was limited to 10 years, HPV immunization was only cost-effective in broader age range (12-24 years) as HPV immunization sustained-benefits can only be achieved by targeting a broader age group of vaccination[17]. Results were sensitive to vaccine price too. A study in Netherlands found that when vaccine price was reduced by 38%, ICER for immunization in multiple age cohorts became highly cost-effective and was below the lower range of CEA threshold [27]. 3 studies showed that cost-effectiveness analyses were not sensitive much to changes of vaccine coverage [9, 19, 21]. When vaccine coverage increased, both the cost of vaccination and reduction in diseases concomitantly increased too and as such, did not result in significant changes in the cost per QALY-gained.

IMPLICATIONS & CONCLUSIONS

Price for 9-valent vaccine is still unknown especially in LMIC and hence, cost-effectiveness of immunization with 9-valent HPV vaccine remains uncertain. Therefore, more cost-effectiveness evidences are still needed to understand the true value for money of 9-valent HPV immunization among young girls.

Gender-neutral immunization could be cost-effective depending on the study parameters and country context especially on vaccine coverage, vaccine price and the consideration of HPV-related male benefits.

Immunization of multiple age cohorts is generally cost-effective. However, the extend of immunization age needs to be interpreted cautiously as several studies analyzed the age cohort immunization in a single age range only and did not compare in the next age range gradually. The cost-effectiveness of multiple age cohort immunization is dependent on the duration of vaccine protection and vaccine price. Nevertheless, more cost-effectiveness evidences on both gender-neutral and multiple age cohort immunizations are still required especially in LMIC and also in defining the most cost-effective age limit for HPV immunization.

SUMMARY OF FINDINGS: Cost-effectiveness of 9-valent vaccine versus bi- or quadrivalent vaccine

First Author, year (Country)	Country Income based on World bank classification	HPV Vaccine Type (3 doses)	Age of vaccination	HPV-related benefits captured in study	Type of model	Perspective	Cost included	Vaccine Efficacy	Vaccine coverage	Currency year	Duration of vaccine protection	Sensitivity analysis	Cost-effectiveness measure	QALY/LYG gained per patient	Cost-effectiveness Threshold (US$2015)	ICER (US $2015)	Cost-effectiveness based on study threshold
Kiatpongsan, 2014 (Kenya & Uganda)	LMIC	4V & 2V (3 doses)	12 years	Cervical cancer	Static model (Mathematical)	Societal	Direct medical costs	100%	100%	2005 I$	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best	LYG	NS	1-3XGDP GDP Kenya: I$ 1,470 (US$ 1,779) GDP Uganda: I$1,077 (US$ 1,292)	NS	9-valent vaccine is cost effective If additional 9-valent vaccine price/course (3 doses) < I$9.7 (US$11.74) and I$8.3 (US$10)
Drolet, 2014 (Canada)	HIC	4V (3 doses)	10 years	Cervical cancer, Genital wart, non-cervical cancer HPV-related diseases	Dynamic transmission model	Healthcare payer	Direct medical costs	95%	80%	2014 CAD$	20 years	One-way sensitivity analysis	QALY	0.000337	1XGDP GDP: CAD$ 40,000 (US$37,600)	$12,203	9-valent vaccine is cost-effective if additional cost of 9-valent vaccine/dose <CAD$24 (US$22.56)

**HIC: high income countries, UMIC: upper-middle income countries, LMIC: low-middle income countries, NS: Not specified, Non-cervical cancer HPV related benefits: Anal, vaginal/vulvar, penile, oropharyngeal or head and neck cancer*

SUMMARY OF FINDINGS: Cost-effectiveness of gender-neutral immunization vs. female-only immunization

First Author, year (Country)	Country Income based on World bank classification	HPV Vaccine Type	Age of gender-neutral vaccination in study	HPV-related benefits captured in study	Type of model	Perspective	Cost included	Vaccine Efficacy	Vaccine coverage	Currency year	Vaccine price/ dose (US $2015)	Duration of vaccine protection	Sensitivity analysis	Cost-effectiveness measure	QALY/LYG gained per patient	Cost-effectiveness Threshold (US$2015)	ICER (US $2015)	Cost-effectiveness based on study threshold
Zechmeister, 2009 (Austria)	HIC	4V	12 years	Cervical cancer, CIN	Dynamic transmission model	Payer & Societal	Direct medical cost, indirect cost	90%	65%	2007 €	€ 110 ($166)	10 years (with booster dose)	One-way sensitivity analysis & Multivariate Analysis (Worst-best case)	LYG	0.0004	NS	Payer: € 311,000 ($468,055) Society: € 299,000 ($449,995)	Not cost-effective
Kim, 2007 (Brazil)	UMIC	4V	12 years	Cervical cancer, CIN	Dynamic transmission model	Societal	Direct medical cost, indirect cost	NS	25%-90%	2007 I$	I$ 12 ($14)	Lifelong	One-way sensitivity analysis	LYS	NS	1-3xGDP GDP: I$8600 ($9,804)	25% coverage: $923 50% coverage: $1,984 75% coverage: $2,485 90% coverage: $21,261	Cost-effective if vaccine coverage <75%
Jit, 2008 (United Kingdom)	HIC	4V	12 years	Cervical cancer, Genital Warts, Non-cervical cancer HPV-related diseases	Dynamic transmission model	Healthcare provider	Direct medical costs	100%	80%	2006 £	£ 80.50 ($163)	20 years	One-way sensitivity analysis	QALY	NS	£ 30,000 ($60,900)	£172,892 ($350,970)	Not cost-effective
Haeussler, 2015 (Italy)	HIC	4V	12 years	Cervical Cancer, CIN, Genital Warts, Non-cervical cancer HPV related diseases	Dynamic transmission model	Not specified	Direct medical costs	NS	NS	2015 €	€ 40 - € 104 ($48-$126)	Lifelong	Multivariate analysis (PSA0	QALY	0.00027	€25,000 - €40,000 ($30,250 - $48,400)	€ 11,600 ($14,036)	Cost-effective
Bresse,2014 (Austria)	HIC	4V	9 years	Cervical Cancer, CIN, Genital Warts, Non-cervical cancer HPV related diseases	Dynamic transmission model	Societal	Direct medical costs	Male: 40-90% Female: 76-100%	65%	2010 €	€ 110 ($172)	Lifelong	One-way sensitivity analysis	QALY	NS	NS	€10,333 ($16,129)	Cost-effective
Chesson, 2011 (United States)	HIC	4V	12-26 years	Cervical Cancer, CIN, Genital Warts, Non-cervical cancer HPV related diseases, RPP	Static (Markov Model) *Herd effects included	Societal	Direct medical costs	Female: 95% Male: 90%	20-75%	2011 $	$300-$360 ($315-$378)	Lifelong	One-way sensitivity analysis, Multivariate Analysis (PSA)	QALY	NS	$100,000 ($105,000)	20% vaccine coverage: $23,600 ($24,780) 30% vaccine coverage: $41,400 ($43,470) 75% vaccine coverage: $184,300 ($193,515)	Cost-effective if vaccine coverage <75%
Insinga, 2007 (Mexico)	UMIC	4V	12 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical costs	90%	70%	2005 $	$80 ($97)	Lifelong	One-way sensitivity analysis, Multivariate analysis (Worst-best	QALY	0.00282	1-3XGDP GDP: $10,000 ($12,100)	Gender-neutral immunization cost $39,637,487 ($47,961,359) more compared	Gender-neutral immunization strategy DOMINATED

													case)				to female only immunization with lower QALY-gained.	
Kim, 2009 (United States)	HIC	4V	12 years	Cervical Cancer, CIN, Genital Warts, Non-cervical cancer HPV related diseases, RPP	Dynamic transmission model	Societal	Direct medical cost, indirect costs	Female: 100% Male: 85%	75%	2006 $	$120 ($142)	Lifelong	One-way sensitivity analysis	QALY	NS	$50,000 to $100,00 ($ 59,000 - $118,000)	$290,290 ($342,542)	Not cost-effective
Laprise, 2014 (Canada)	HIC	4V	12 years	Cervical Cancer, CIN, Genital Warts, Non-cervical cancer HPV related diseases	Dynamic transmission model	Payer	Direct medical cost	95%	80%	2010 CAD$	CAD $85 ($87)	20 years	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.000039	1XGDP GDP: CAD $40,000 ($41,040)	CAD $86,214 ($88,456)	Not cost-effective
Olsen, 2015 (Denmark)	HIC	4V	12 years	Cervical Cancer, CIN, Genital Warts, Non-cervical cancer HPV related diseases	Dynamic transmission model	Healthcare	Direct medical cost	100%	85%	2012 €	€123 ($164)	Lifelong	One-way sensitivity analysis, Multivariate analysis PSA	QALY & LYG	NS	€ 50000 ($66,750)	QALY: €41,636 ($55,584) LYG: €40,615 ($54,221)	Not cost-effective
Sharma, 2016 (Vietnam)	LMIC	4V	11 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Societal	Direct medical cost, indirect cost	Female: 100% Male: 85%	25-90%	2008 I$	I$5 ($5.5)	Lifelong	One-way sensitivity analysis	QALY	NS	1xGDP: GDP: I$2,800 ($3,080)	25% coverage: I$73 ($807) 50% coverage: I$930 ($1,023) 75% coverage I$1,364 ($1,500) 90% coverage: I$2,064 ($2,270)	Cost-effective if vaccine coverage is <75%
Taira,2004 (United States)	HIC	2V	12 years	Cervical cancer, CIN	Dynamic Transmission model	NS	NS	90%	70%	2004 $	$100 ($125)	10 years (with booster dose)	One-way sensitivity analysis	QALY	0.21	NS	$442,039 ($552,549)	Cost-effective
Elbasha, 2010 (United States)	HIC	4V	12 years	Cervical Cancer, CIN, Genital Warts, Non-cervical cancer HPV related diseases, RPP	Dynamic transmission model	NS	Direct medical cost	76-96%	76-96%	2008 $	NS	NS	Multivariate analysis (PSA)	QALY	NS	$50,000 - $100,000 ($55,000-$110,000)	$25,700 - $ 69,00 ($28,270 -$ 75,900)	Cost-effective

**HIC: high income countries, UMIC: upper-middle income countries, LMIC: low-middle income countries, NS: Not specified, CIN: cervical interstitial neoplasia, Non-cervical cancer HPV related benefits: Anal, vaginal/vulvar, penile, oropharyngeal or head and neck cancer, RPP: recurrent respiratory papillomatosis, PSA: probabilistic sensitivity analysis*

SUMMARY OF FINDINGS: Cost-effectiveness of immunization of multiple age cohorts with defined age range versus single age cohort immunization only

First Author, year (Country)	Country income based on World Bank classification	HPV vaccine type (Number of doses)	Age of routine vaccination female	Comparator (Age cohort of immunization)	Duration of multiple age cohort immunization	HPV-related benefits captured in study	Type of model	Perspective	Cost included	Vaccine Efficacy	Vaccine coverage	Currency year	Vaccine price/ dose (US $2015)	Duration of vaccine protection	Sensitivity analysis	Effectiveness measure	QALY gained / patient	Threshold used in study (US$2015)	ICER (US $2015)	Cost-effectiveness based on study threshold
Tully, 2012 (Canada)	HIC	2V (3 doses)	12 years	12 years F + School based 12-18 years 12 years F + Clinic based 12-18 years	3 years	Cervical cancer, CIN	Dynamic transmission Model	Ministry of Health	Direct medical cost	>90%	School based: 80% Clinic based: 40%	2010 CAD$	CAD $90 ($92.97)	Lifelong	One-way sensitivity analysis, Multivariate analysis (PSA)	QALY	School based CUF: 0.0034 Clinic based CUF: 0.0026	CAD $ 50,000 ($ 51,650)	School based: $ CAD 6,361 ($6,571) Clinic based: CAD $ 8,260 ($8,533)	School-based & clinic-based 12-18 years' immunization is cost-effective
Jit, 2008 (United Kingdom)	HIC	4V (3 doses)	12 years	12-14 years 12-16 years 12-18 years 12-25 years	2 years	Cervical cancer, CIN, Genital warts, Non-cervical cancer HPV-related diseases	Dynamic transmission model	Healthcare	Direct medical costs	100%	80%	2006 £	£ 80.50 ($163)	20 years	One-way sensitivity analysis	QALY	NS	£ 30,000 ($60,900)	CUF 12-14 years: £18,856 ($ 38,278) CUF 12-16 years: £16,417 ($33,327) CUF 12- 18 years: £11,856 ($24,068) CUF 12-25 years: £128,302 ($260,453)	12-18 years' immunization cost-effective
Elbasha, 2009 (United States)	HIC	4V (3 doses)	12 years	12-14 years 12-17 years 12-19 years 12-24 years	5 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical cost	90%	Base case: 0-70% in first 5 years then remain at 70% CUF: 0-50% first 5 years then 0% after 5 years	2005 $	NS	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.00028-0.00047	NS	CUF 12-17 years: $3115 ($3769) CUF 12-19 years: $3512 ($4,249) CUF 12-24 years $10,986 ($13,293)	12-24 years' immunization is cost-effective
Elbasha, 2007 (United States)	HIC	4V (3 doses)	12 years	12 years F + 12-24 years F 12 years F & M + 12-24 years F 12 years F & M + 12-24 years F & M	5 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical cost	90%	Base case: 0-70% in first 5 years then remain at 70% CUF: 0-50% first 5 years then 0% after 5 years	2005 $	NS	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.00016-0.00045	$50,000 ($60,000)	12 years F + CUF 12-24 years: $4,666 ($5,646) 12 years old F & M + CUF 12-24 years: $41,803 ($50,582) 12 years old F & M + CUU 12-24 years: $45,056 ($54,517)	12-24 years' female immunization is cost-effective but 12-24 years' gender-neutral immunization is the most effective strategy.

Dasbach, 2008 (Taiwan)	HIC	4V (3 doses)	12 years	12-24 years	5 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical cost	100%	Base case:0-85% in first 5 years then remain at 85% CUF: 0-50% first 5 years then 0% after 5 years	2006 NT$	NS	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.00239	1-3XGDP GDP: NT$ 512,000 ($18,432)	NT$ 410,477 ($14,777)	12-24 years' immunization is cost-effective
Dasbach, 2008 (Norway)	HIC	4V (3 doses)	12 years	12-24 years	5 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical cost	100%	Base case:0-90% in first 5 years then remain at 90% CUF: 0-90% first 5 years then 0% after 5 years	2006 NOK	NS	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.00245	NOK 500,00 ($87,500)	NOK 63,294 ($11,076)	12-24 years' immunization is cost-effective
Dasbach 2008 (United Kingdom)	HIC	4V (3 doses)	12 years	12-14 years 12-17 years 12-24 years	2 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical costs	90%	12 years: 80% 12-14 years: 40% 12-17 years: 30% 12-24 years: 25%	2006 £	£75 ($15)	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.00026-0.00498	1X3GDP	CUF 12-14 years: £5,882 ($11,940) CUF 12-17 years: £5,971 ($12,121) CUF 12-24 years: £11,412 (23,166)	12-24 years' immunization is cost-effective
Dasbach, 2010 (Hungary)	HIC	4V (3 doses)	12 years	12-24 years	5 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical cost	90%	Base case:85% CUF: 0-10% first 5 years then 0% after 5 years	2010 €	NS	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.00039	1X3GDP GDP: €12,098 ($18,897)	€ 10,646 ($16,629)	12-24 years' immunization is cost-effective
Insinga, 2007 (Mexico)	UMIC	4V (3 doses)	12 years	12 years F + 12-24 years f 12 years F & M + 12-24 years F 12 years F & M + 12-24 years F & M	5 years	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical costs	90%	Base case: 0-70% in first 5 years then remain at 70% CUF: 0-50% first 5 years then 0% after 5 years	2005 $	$80 ($96.8)	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.0009-0.00371	1X3GDP GDP:$10,000 ($12,100)	12 years F & CUF 12-24 years: $3,048 ($3,688) 12 years F & M + CUF 12-24 years: $16,663 ($20,162) 12 years F & M + CUU 12-24 years: $16,702 ($20,209)	12-24 years' female immunization is cost-effective but 12-24 years' gender-neutral immunization is the most effective strategy. .
Kawai, 2012 (Brazil)	UMIC	4V (3 doses)	12 years	12-26 years	NS	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical costs	67-96%	85%-90%	2011 $	$15.15 ($15.91)	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.00238	1X3GD GDP: $10,710 ($11,245)	$450 ($472.50)	12-26 years' immunization is cost-effective
Turner, 2013 (United Kingdom)	HIC	2V (3 doses)	12 years	12-17 years 12-19 years 12-24 years	NS	Cervical cancer, CIN, Genital warts	Dynamic transmission model	Healthcare	Direct medical cost	100%	NS	2013 £	£20 ($33)	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best	QALY	NS	£30,000 ($49,770)	CUF 12-17 years: £1,627 ($2,699) CUF 12-19 years old:	12-24 years' immunization is cost-effective in the presence of protection to non-naïve women if

				12-29 years 12-34 years										case)				£10,433($17,308) CUF 12-24 years old: £16,557 ($27,468) CUF 12-29 years old £33,897 ($56,235) CUF 12-34 years old £50,125 ($83,157)	vaccine price/dose is below £20 ($33.18).
Usher, 2008 (Ireland)	HIC	4V (3 doses)	12 years	12-15 years 12-17 years 12-19 years 12-26 years	1 year	Cervical cancer, CIN	Dynamic transmission model	Payer	Direct medical cost	95%	School based: 80% Clinic based: 30%	2008 €	€ 100 ($160)	Lifelong	One-way sensitivity analysis, Multivariate analysis (PSA)	LYG	NS	NS	CUF 12-15 years: €52,968 ($85,067)	12-15 years' immunization is cost-effective
Liu, 2016 (China)	UMIC	2V (3 doses)	12 years	12-25 years	NS	Cervical cancer, CIN	Static (Markov Model)	Payer	Direct medical cost	93.2%	70%	2013 CNY	CNY 633 ($103)	NS	One-way sensitivity analysis	QALY	NS	3XGDP GDP: CNY 125,723 ($20,518)	NS	12-25 years' immunization is cost-effective
Westra, 2011 (Netherlands)	HIC	4V (3 doses)	12 years	12- 16 years 12-18 years 12-25 years	NS	Cervical cancer, CIN	Static (Markov Model)	NS	NS	95%	100%	2011 €	€ 105 ($147)	Lifelong	One-way sensitivity analysis, Multivariate analysis (PSA)	QALY	NS	€20,000 - €50,000 ($28,120 - $70,300)	CUF 12-16 years: €22,500 ($31,635) CUF 12-18 years: €23,500 ($33,041) CUF 12-25 years: €26,900 ($37,821)	12-25 years' immunization is cost-effective
Yamabe, 2013 (Japan)	HIC	No vaccination	No vaccination	12-24 years	5 years	Cervical cancer, CIN, Genital warts	Dynamic Transmission model	Payer	Direct medical cost	90%	Base case: 0-80% in first 5 years then remain at 70% CUF: 0-50% first 5 years then 0% after 5 years	2013 ¥	¥36,000 ($421)	Lifelong	One-way sensitivity analysis, Multivariate analysis (worst-best case)	QALY	0.00365-0.00508	1X3GDP GDP: ¥ 3,758,000 ($44,081)	CUF 12-24 years: ¥ 1,205,800 ($14,108)	12-24 years' immunization is cost-effective

**HIC: high income countries, UMIC: upper-middle income countries, LMIC: low-middle income countries, NS: Not specified, CIN: cervical interstitial neoplasia, Non-cervical cancer HPV related benefits: Anal, vaginal/vulvar, penile, oropharyngeal or head and neck cancer, RPP: recurrent respiratory papillomatosis, PSA: probabilistic sensitivity analysis*

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