

## Human papilloma virus vaccination – a systematic review of cost-effectiveness analyses

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### ABSTRACT

**Aim** To evaluate circumstances and prerequisites of cost effectiveness of human papilloma virus (HPV) vaccination.

**Methods** A comprehensive search of multiple electronic databases for studies on cost effectiveness of HPV vaccination published before September 28, 2013 was done. Only original cost effectiveness analyses published in the English language were eligible.

**Results** Over 64 countries around the world were included in cost effectiveness analyses of HPV vaccination. A total of 57 studies were reviewed. Most of the studies concluded that HPV vaccination was cost effective. Prerequisite for cost effectiveness of HPV vaccination is the vaccination of preadolescent female population. Mean value of incremental cost effectiveness ratio (ICER) was I\$ (International Dollars) 28399, median I\$ 15600. Values of ICER ranged from I\$ 100 to I\$ 455100. Variable study methodology was used within reviewed studies, which makes comparability between studies difficult.

**Conclusion** Despite the heterogeneity and aforementioned limitations, most of the studies generally concluded that HPV vaccination of preadolescent females is cost effective, particularly in settings without organized screening programs. An inclusion of males in the vaccination programs is not considered to be cost-effective.

**Key words:** sexually transmitted diseases, economic evaluation, cervical cancer, screening, prevention.

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### Original submission:

06 October 2013;

### Revised submission:

08 October 2013;

### Accepted:

19 October 2013.

SEEHSJ 2013; 3(2):159-168

## INTRODUCTION

Cervical cancer is the second most common cancer in women. About 250,000 deaths due to cervical cancer occur annually, with over 80% of them in low and middle income countries (LMICs) (1). This situation can partly be a consequence of lack of organized cervical cancer screening programs in LMICS (2). However, even when screening programs are present, there are often issues with screening coverage, accuracy and treatment availability (2,3).

It was proved that infection with oncogenic human papilloma virus (HPV) types causes cervical cancer and a number of non-cervical cancers (4). For example, it was estimated that HPV causes at least 80% of anal cancers and at least 40–60% of vulvar, vaginal and penile cancers (5).

Infection with HPV is one of the world's most common sexually transmitted infections, and has been associated with a number of cervical and non-cervical diseases, including cancer (6). Prophylactic HPV vaccines available since late 2000's offer a promising way to prevent cervical cancer and other HPV related cancers both in the developed and in the developing countries (7). The HPV vaccination represents complementary option to screening in cervical cancer prevention (8). The WHO recommends that the cost-effectiveness of HPV vaccination is determined before it is offered as part of national vaccination programs (5).

The cost-effectiveness threshold commonly used is country's per capita gross domestic product (GDP) based on a report by the Commission on Macroeconomics and Health (7,9). The WHO threshold is divided into 3 groups: highly cost-effective (less than a GDP per capita), cost-effective (1-3 times GDP per capita), and non-cost-effective (more than 3 times GDP per capita). These thresholds are commonly used in cost-effectiveness studies but they do not always reflect affordability (7,9).

Studies on cost-effectiveness of HPV have been done in many developing and developed countries. These analyses are mostly based on mathematical model construction, with model inputs calibrated in the context of the environment in which the study is performed (7).

Cost effectiveness analyses serve as argument for implementation of health interventions for the decision makers in order to effectively allocate constrained resources (10). Data on cost effectiveness of HPV vaccination in Bosnia and Herzegovina and surrounding countries are lacking.

In this study we wanted to analyze published results of cost-effectiveness analyses of HPV vaccination in the context of methodology used within the studies.

Published studies on cost effectiveness of HPV vaccination suggest that vaccination against HPV can be used and can be cost effective (8). We wanted to explore in which circumstances it is cost effective.

The aim of our study was to evaluate when HPV vaccination is cost effective and to evaluate circumstances and prerequisites for cost effectiveness of HPV vaccination using an analysis of available published studies on cost effectiveness of HPV in order to summarize their results and cost effectiveness ratios, and explain the value of the results in context of the country, in which the cost effectiveness analysis was done and to compare inter-study designs.

## METHODS

In this study the Meta-analyses-PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were followed (11).

All the studies dealing with cost effectiveness of the HPV vaccination published in literature in English were eligible. Systematic reviews, letters to editors and studies that were not country specific were excluded from the study, since these do not represent economic analyses.

A comprehensive search strategy across multiple databases was taken to identify studies that dealt with HPV vaccine cost-effectiveness. The following electronic databases were searched: Cochrane Library, Cochrane Central Register of Controlled trials, EMBASE, Ovid MEDLINE, Pub Med, Dissertation Abstract International, ProQuest Research Library.

No date restrictions were made. Databases

were last searched on September 28, 2013.

The key words included: HPV, vaccine, vaccination, cost effectiveness, and HPV vaccination.

Two reviewers independently read the articles that were included in the systematic review and discrepancies were resolved by consensus.

All studies that dealt with HPV cost effectiveness were screened, but only original country specific studies were included in the systematic review. Data were extracted on predefined auditing forms to allow for clarity, completeness and quality. Studies were screened for the author, year of publication, intervention, comparator, cost-effectiveness ratio, type of model used, type of sensitivity analysis performed, discount factor and funding source.

The principal summary measure was incremental cost effectiveness ratio that reflects cost per quality adjusted life year (QALY) saved by the vaccination.

The results of cost-effectiveness studies were compiled in a table, which represents an easily accessible means of comparing.

The risk of bias across the studies existed in the sense of publication bias and selective reporting within studies.

Since cost effectiveness analyses (CEAs) included in this study originated from different countries with different currencies and were done in various points in time, in order to make the results comparable, we converted all non-US currencies to International Dollars (I\$) by using relevant year purchasing power parities and inflating the results to 2013 US Dollars (12). This is a theoretical currency, which represents what can be bought in a country with one US dollar. In practice, it corresponds to US dollar.

However, changes in the costs of interventions and associated benefits consubstantially alter their cost per QALY or life year gained over time (13).

## RESULTS

A total of 749 studies was screened, out of which 547 remained after removing duplicates, 58 were eligible and a total of 57 was included in the study.

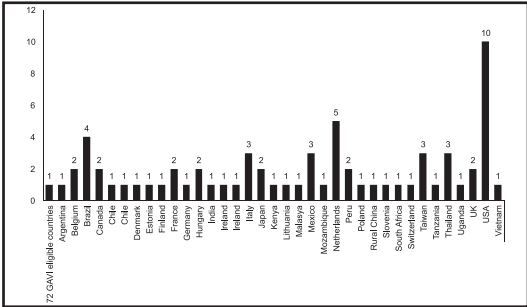
A total of 57 studies from more than 64 countries has been analyzed (Table 1).

**Table 1. Results of studies on cost effectiveness of HPV vaccination in the world**

Year	Country	Incremental cost effectiveness ratio (ICER) in I\$ 2013/ QALY. f- I\$/SLY (Saved Life Years)
2013 Fonseca et al. (30)	Brazil	900
2013 Brisson et al. (33)	Canada	15600 20200
2013 Uuskula et al. (34)	Estonia	6700
2013 Luttjeboer et al. (24)	Netherlands	7900 12500
2013 Demarteau et al. (35)	Belgium	23500 58000
2012 Goldie et al. (60)	Peru	500f 1400f
2012 Voko et al. (36)	Hungary	28000
2012 Vanni et al. (31)	Brazil	300 455
2012 Schobert et al. (37, 77)	Germany	5600 14500
2012 Favato et al. (38, 77)	Italy	17200
2012 Termrungruanglert et al. (63,77)	Thailand	5400
2011 Bogaards et al. (25,77)	Netherlands	31400
2011 Praditsithikorn et al. (64,77)	Thailand	900 20200 22800
2011 Westra et al. (26,77)	Netherlands	23800 27200 52700
2011 Chesson et al. (14,77)	USA	111300 2200
2012 Yamamoto et al. (39,77)	Japan	98200
2010 Kim et al. (15,77)	SAD	17200
2011, Demeartau el al. (40,77)	France	15200
2010 Obradovic et al. (41,77)	Slovenia	36500 28400
2010 Olsen and Jepsen (42,77)	Denmark	4700 3000
2010 Liu et al. (61,77)	Taiwan	15200
2010 Dasbach et al. (43,77)	Hungary	15200 14200
2010 La Torre et al. (44,77)	Italy	28400
2009 Kim et al. (22,77)	USA	445100
2010 Dee and Howell al. (45,77)	Ireland	45600
2009 de Kook et al. (27,77)	Netherlands	82000
2009 Sinanovic et al. (62,77)	South Africa	16200 1300
2009 Annemans et al. (46,77)	Belgium	15200 41500 21300
2009 Elsbasha et al. (17,77)	USA	13200
2009 Coupe et al. (28,77)	Netherlands	3900
2009 Mennini et al. (47,77)	Italy	15200
2008 Kim et al. (18,77)	USA	50600

**Table 1. Results of studies on cost effectiveness analyses of HPV vaccination in the world (continued)**

2008 Dasbach et al. (50,77)	Taiwan	14200 15200
2008 Bergeron et al. (48,77)	France	12200 20300
2008 Chesson et al. (19,77)	USA	6400
2008 Szucs et al. (49,77)	Switzerland	24300
2008 Dasbach et al. (77,78)	UK	12200
2007 Elsbasha et al. (20,77)	USA	49600
2009 Anonychuk et al. (51)	Canada	19900 to 33700
2008 Kulasingam et al. (52)	UK	34700
2008 Goldhaber-Fiebert et al. (21)	USA	43900
2009 Kim et al. (16)	USA	12430 to 289300
2004 Goldie et al. (23)	USA	24600
	Kenya	2200
2012Campos et al. (59)	Mozambique	1300
	Tanzania	800
	Uganda	1100
2011 Canfell et al. (71)	Rural China	Cost effective
2009 Colantonio et al. (32)	Argentina, Brazil, Chile, Mexico, and Peru	Cost effective (<3xGDP per capita)
2008 Diaz et al (66)	India	Cost effective (<3xGDP per capita)
2011 Sharma et al. (69)	Thailand	Very cost effective (<1xGDP per capita)
2010 Ezat et al.(58,79)	Malasya	Screening more cost effective (800); Combined 2200
2008 Goldie et al. (70)	72 GAVI eligible countries	Cost effective; Provided high coverage of young adolescent girls is feasible, and vaccine costs are lowered
2007 Insinga et al.(57)	Mexico	3300 17500
2013 Yamabe et al. (53)	Japan	2200
2007 Kim et al. (29)	Brazil	600f 20200f
2008 Kim et al. (67)	Vietnam	
2009 Reynales-Shigematsu et al. (68)	Mexico	100f 17000f
2010 Vanagas et al. (54)	Lithuania	1500f 19800f
	Chile,	21100
	Finland,	21500
2008 et al. (55)	Ireland,	27900
	Poland	36400
	Taiwan	9000



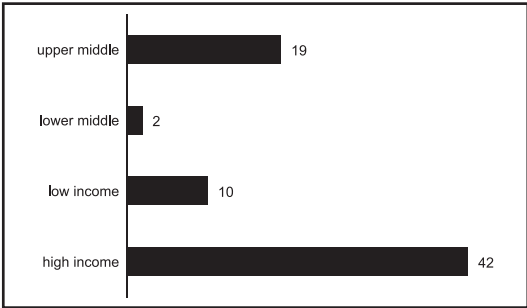
**Figure 1. The number of studies per country in which cost effectiveness of HPV was analyzed**

The highest number of studies was done in the United States of America (14–23), in the Netherlands, five (24–28), and Brazil, four (29–32) (Figure 1). Most of the studies were done in countries with high income (14–16,16–21,23–28,32–55) (Figure 2).

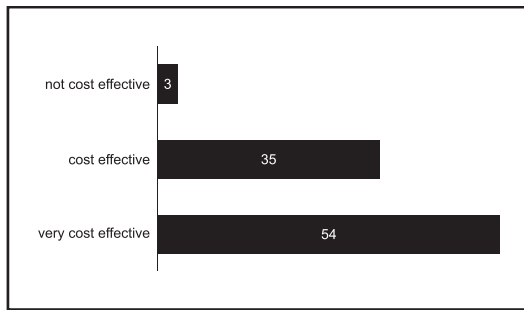
Mean value of incremental cost effectiveness ratio was I\$ 28399, median I\$ 15600. Values of ICER ranged from I\$ 100 to I\$ 455100.

Out of 92 reported cost effectiveness ratios, 54 (58.7%) were considered very cost effective, 35 (38%) were cost effective and only 3 (3.2%) were not cost effective (Figure 3) in the context of economic development of the country in which analysis was done.

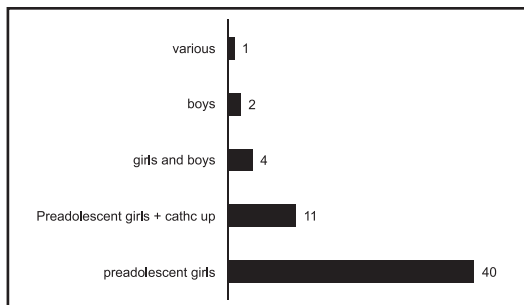
A total of 58 program options were analyzed (Figure 4) with majority (87.9%) analyzing vaccination of preadolescent girls, with (18.9%) or without (68.9%) catch up program. One study (56) analyzed various program options, and two (3.4%) analyzed male vaccination (15,29). Four (7 %) studies analyzed vaccination of both sexes (16,20,42,57). Vaccination including boys and older women (16) was not cost effective. Only a Malaysian study concluded that screening alone was more cost effective.



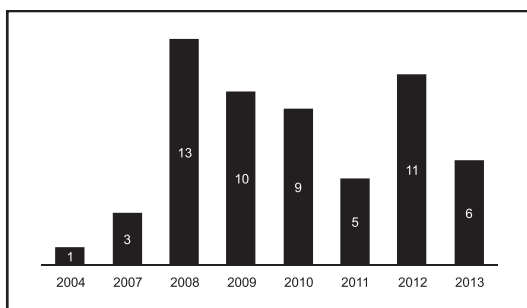
**Figure 2. The number of countries for which a cost effectiveness analysis of HPV vaccination was done as classified according to the World Bank**



**Figure 3. The structure of the results of cost effectiveness analyses in reviewed studies**



**Figure 4. The number of studies per different vaccination programs in reviewed cost effectiveness analyses**



**Figure 5. A trend of the number of studies on cost effectiveness of HPV vaccination conducted in the period between 2004 and 2013**

ve than preadolescent female vaccination (58). The number of studies on cost effectiveness of HPV vaccination peaked in the year 2008 and has shown a slight downward trend in the last 5 years (Figure 5).

Four (7%) out of 57 studies were multi-country studies (32, 55, 59, 60).

Most studies, 32 (56.1%) had compared HPV vaccination against some forms of cervical cancer screening program. A high number of studies, 16 (28%) compared HPV vaccination to no vaccination. There was only one study identified that compared bivalent and quadrivalent vaccine (33).

All studies were based on construction of de-

cision analytic model. Most of the studies used Markov cohort model (14–16,19,21,23–26,30,32,33,35,36,38–42,44–49,51–55,59,61–68), some of them used dynamic state transition model (16,20,29,31,33,34,37,43,50,53) and three (5,2 %) used Monte Carlo simulation model (16,60,69).

Only one study used primary epidemiologic data as a model input parameter (58). Two studies analyzed cost effectiveness of male vaccination alone (14, 15) and five analyzed vaccination of both sexes (29, 32, 42, 50, 57). One concluded that vaccinating boys could have benefit when low cervical cancer screening coverage is considered (57) and the other study concluded that an inclusion of boys in vaccination is not likely to be cost-effective (29).

Most of the studies analyzed the cost effectiveness of HPV vaccination in high income and upper middle income countries (Figure 2). Only 2 (3.5%) studies analyzed the data for low income countries (59,70). Studies from upper middle income countries mostly compared cost effectiveness of vaccination with screening and screening alone (29–32, 50, 55, 57, 58, 60–64, 68, 69, 71).

Most analyses took the healthcare system perspective, 31 (54.3%) studies (14, 15, 17, 19, 20, 25, 26, 30, 31, 33, 35–38, 40–50, 50–52, 55, 61–63), further 11 (19.3%) studies took societal perspective (16,16,21,23,27,39,60,62,65,65–67,67,69), and two (3.5%) analyzed cost effectiveness from both perspectives (62,64), for the rest of the studies perspective of the analysis was not determined or not stated.

Sensitivity analyses were performed in all studies, among which 19 (33.3%) studies used multivariate sensitivity analysis (14, 16, 17, 19–21, 23, 26, 36, 38, 40, 41, 44, 50, 55, 64–66), 12 (63%) of which used probabilistic sensitivity analysis (14, 16, 20, 21, 26, 36, 38, 40, 41, 63, 64, 66).

It is important to point out the cost of vaccine as a very important factor that influences cost-effectiveness of vaccination program. For low income countries, the only acceptable cost is the total of \$5 per vaccinated girl. Vaccine prices varied widely within the studies, from \$2 in some of the Harvard studies (56, 66, 67,

69, 70, 72) to over \$150 in a Thai study (64).

## DISCUSSION

This review represents the synthesis of cost effectiveness analyses related to HPV vaccination and can be used by decision makers as a decision support instrument. Key conclusion of this study is that HPV vaccination could be, and it is cost effective, when applied to female population, mostly preadolescent, but also possibly with temporary catch up program until 26 years of age. Inclusion of males along with girls in the vaccination program appears to be more cost-effective if it is assumed that the vaccination coverage in females were low (73).

Only two studies came to the conclusion that male vaccination along with female would be the most effective strategy (42, 56). A study from Denmark conducted by Olsen and Jepsen (42) resulted in cost effectiveness ratio that is not cost effective (I\$56300 to I\$ 168700). Mexican study lead by Insinga (57) with ICER range from I\$9800 to I\$ 29300 suggests that vaccination of males could also be cost effective, especially when other non-cervical diseases are considered. The overall conclusion could be that there are not enough studies that consider cost effectiveness of males along with female vaccination to be able to make conclusions. Studies from the USA published by Kim et al., that analyzed various vaccination program scenarios where male vaccination also resulted in high ICERS that are considered not cost effective (13). Kim et al. (15) analyzed cost effectiveness of a special subgroup of male population, which is men having sex with men (MSM), who have an increased risk of anal cancer compared to general population. The study results with ICER between \$US 15 290 and \$US 19070 per QALY, which is below the cost effectiveness threshold, suggest that vaccination of this subgroup could be cost effective.

This is important because of significant public health burden caused by cervical cancer and other HPV related diseases on one hand and environment of resource constraints on the other (10). The WHO strongly suggests that cost effectiveness analyses precede the implementation of HPV vaccination programs (10).

The studies included in this review used different methodologies and had various assumptions but were consistent in the conclusion that preadolescent female vaccination is cost effective compared to screening alone. In countries with low resource setting the vaccine price was a decisive parameter of vaccination cost effectiveness (59, 66, 70, 71). In these circumstances HPV vaccination would be cost effective only under the assumption of the lowest price of vaccination. Otherwise, screening alone with prerequisite of higher screening coverage was shown to be more cost effective (58,59,66,70,71).

Effectiveness of vaccine depended on underlying incidence of HPV infection and proportion of the infected with HPV types 16 and 18, population age-structure and competing mortality (70).

The review supports extending vaccination to low income settings where vaccine prices are competitive, donor funding is available, cervical cancer burden is high and screening options are limited (8). In regions characterized by low income, low mortality and existing treatment coverage around 50%, expanding vaccination with or without combining it with screening appears to be cost-effective or very cost-effective (8, 70). Abandoning vaccination in favor of screening in a no-treatment scenario would not be cost-effective. Vaccination is usually the most cost-effective intervention (74). Penta or tri-annual PAP smears appear to be cost-effective, though when combined with HPV-DNA testing they are not cost-effective (74). In regions characterized by low income, high mortality and low vaccination levels, expanding vaccination with or without adding screening would be very cost-effective (8, 70). One-off PAP or VIA screening at the age of 40 are more cost-effective than other interventions though less effective overall (75).

This analysis has several limitations. First of all, due to our search strategy, it is possible that some studies were omitted from the review, although a recent study has confirmed that MEDLINE is a superior source for reviews of economic evaluations (76).

Also, this review included only the literature in the English language. Studies of CEA of HPV

vaccination in other languages were not included, as well as studies from grey literature and studies that had different outcome measures.

This study did not include recently published articles (after 28 September 2013.).

Values of cost effectiveness ratios are not static and can change in time. This could happen with changes in medication costs or in treatment improvements (13).

Studies of cost effectiveness of HPV vaccination also have some limitations. First of all, inter-study comparability was made difficult because of wide variations in study design and methodology. Also, reported ICERS might change in time and follow the changes in health care costs and service delivery and also changes in time value of money. Results of most cost effectiveness analyses of HPV vaccination might have overestimated ICERs, since they generally disregard other non-cervical benefits of HPV vaccination such as genital warts, vaginal and vulvar precancerous and cancerous lesions, head and neck tumors, anal cancer and other (6). Further, many studies assume inappropriate cervical screening coverage and overestimate in case of low screening coverage and underestimate in case of too high

screening coverage assumption (6).

The cost effectiveness threshold is also an important issue, since there is no overall consensus about which threshold to take. Some studies used GDP threshold and some threshold of I\$ 50 000 per QALY (6). It is not certain that any of these reflect social willingness to pay and affordability in a specific country (7,8).

Despite the heterogeneity and aforementioned limitations, most of the studies generally conclude that HPV vaccination of preadolescent female is cost effective, particularly in the setting without organized screening programs. Inclusion of males in vaccination programs is not considered to be cost effective although vaccination of special male subgroups might be cost effective. Cost effectiveness studies done in low income regions also support the implementation of the vaccination as cost effective interventions under prerequisite of lower vaccine prices and presence of donor funding.

## FUNDING

No specific funding was received for this study.

## TRANSPARENCY DECLARATION

Competing interests: None to declare.

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## Vakcinacija protiv humanog papiloma virusa- Sistematski pregled analiza troškova i efektivnosti

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### SAŽETAK

**Cilj:** Procijeniti okolnosti i preduvjete troškovne efektivnosti vakcinacije protiv humanog papiloma virusa (HPV).

**Metode:** U istraživanju su sveobuhvatno pretražene multiple elektronske baze podataka o istraživanju troškovne efektivnosti HPV vakcinacije, objavljene prije 28. septembra 2013. godine. Samo originalne analize troškova objavljene na engleskom jeziku su bile podobne za analizu.

**Rezultati:** Analize troškova i efektivnosti su urađene u preko 64 zemlje svijeta. U analizu je uključeno ukupno 57 studija. Zaključak većine studija je troškovna efektivnost HPV vakcinacije. Preduvjet za isplativost HPV vakcinacije je vakcinacija preadolescentne ženske populacije. Srednja vrijednost inkrementalnog odnosa troškova i efektivnosti (ICER) bila je I\$ (internacionalnih dolara) 28399, medijana I\$ 15600. Vrijednosti ICER-a su se kretale u rasponu od I\$ 100 do I\$ 455100. U analiziranim studijama je korištena varijabilna metodologija, što je otežavalo usporedivost među studijama.

**Zaključak:** Unatoč heterogenosti i ograničenjima, u većini studija je zaključeno da je HPV vakcinacija preadolescentne ženske populacije isplativa, naročito u okruženju bez organiziranog programa odabira. Uključivanje i muškaraca u programe vakcinacije smatra se neisplativim sa aspekta troškova.

**Ključne riječi:** spolno prenosive bolesti, ekonomska evaluacija, rak grlića maternice, probir, prevencija.