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HPV vaccination for boys? A systematic review of economic studies

Vaccinazione anti-HPV anche per i maschi? Una revisione sistematica degli studi farmaco-economici

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Abstract

Introduction. HPV vaccination is recommended in many countries, including Italy, for girls in their twelfth year of age. In some countries, the goal of vaccination coverage has not been reached, and extension to boys has thus been debated.

Objective. Aim of this study is to perform a systematic review of pharmaco-economic studies considering the extension of HPV vaccination to boys.

Methods. An electronic literature search was performed on Pubmed to identify studies published from 2005 to 2015 in English and Italian. Four search strategies were used, including the terms «HPV», «boys», «vaccination», «economic evaluation», «cost effectiveness», and «epidemiological impact». Screening of titles, abstracts, and full texts was conducted, and economical evaluation of the extension of HPV vaccination to males was considered a criteria of inclusion. A total of 289 articles were identified. Only 15 articles were finally considered pertinent.

Results. The extension of HPV vaccination to boys was cost-effective or potentially cost-effective in 53% and 7% of the studies, respectively. Six studies did not positively evaluate the implementation of this intervention. However, taking into account both the new two-dose vaccination schedule available for all subjects ≤13 years, and the dramatic reduction in the price of vaccines in the last few years, the advantages of universal vaccination are more consistent.

Conclusion. The extension of HPV vaccination to boys is therefore foreseen to become increasingly implemented in the near future.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 51-58)

Key words: HPV, boys, cost-effectiveness

Riassunto

Introduzione. La vaccinazione anti-HPV è raccomandata in molti Paesi, tra cui l'Italia, alle ragazze nel dodicesimo anno di vita. In diverse nazioni l'obiettivo di copertura vaccinale non è stato raggiunto e l'estensione ai maschi è in discussione.

Obiettivo. Scopo dello studio è stato quello di effettuare una revisione sistematica degli studi farmaco-economici che valutano l'estensione della vaccinazione anti-HPV ai maschi.

Metodi. E' stata condotta una ricerca sugli studi pubblicati dal 2005 al 2015 in inglese e italiano su Pubmed, utilizzando 4 stringhe di ricerca che includevano i termini «HPV», «boys», «vaccination», «economic evaluation», «cost effectiveness», «epidemiological impact». Gli articoli sono stati inizialmente selezionati se nel titolo, nell'abstract e nel testo esaminavano a livello economico l'estensione della vaccinazione anti-HPV ai maschi. Sono stati individuati 289 articoli: solo 15 sono stati ritenuti infine pertinenti.

Risultati. L'estensione della vaccinazione anti-HPV ai maschi risulta costo-efficace o potenzialmente costo-efficace rispettivamente nel 53% e nel 7% degli studi. Sei articoli, in base alle loro assunzioni, non valutano positivamente l'implementazione di tale intervento. Tuttavia, considerando la nuova schedula vaccinale a due dosi disponibile per tutti i soggetti di età ≤13 anni e la notevole riduzione del prezzo del vaccino intervenuta negli ultimi anni, si rende necessario aggiornare tali valutazioni utilizzando i nuovi dati di input.

Conclusioni. L'estensione della vaccinazione anti-HPV anche ai maschi sembra essere un intervento destinato a sempre più ampia applicazione nel prossimo futuro.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 51-58)

Parole chiave: HPV, maschi, costo-efficacia

INTRODUCTION

Infection due to high-risk *Human papillomavirus* (HPV) is the main cause of cervical cancer in women.[1,2] Usually, HPV infections are cleared quickly within 1-2 years. Persistence of an oncogenic HPV infection is the first step towards cervical precancerous lesions and, more rarely, cervical cancer.[3] The public health impact of HPV infections is more evident in women; however, high-risk HPVs are also responsible for other significant cancers like ano-genital and head-and-neck cancers, not necessarily correlated to female gender.[4,5] In USA, during 2004-2008, 33,369 HPV-associated cancers (with a rate amounting to 10.8 cases per 100,000) were notified annually: 12,080 cases were among males (8.1 per 100,000) and 21,290 among females (13.2 per 100,000), according to data from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results program.[6] Cervical cancer was the most frequently notified, with about 11,967 cases per year, immediately followed by oropharyngeal cancer, with 11,726 cases per year. Furthermore, 2,370 head-and-neck cancers were registered among females and 9,356 among males. Particularly, the rate of head-and-neck cancers among males was four times higher than that among females (6.2 *versus* 1.4 per 100,000). Finally, anal cancer was more common among females (1.8 per 100,000) than among males (1.2 per 100,000).[6]

Two vaccines, the bivalent HPV-16/18 and the quadrivalent HPV-16/18/6/11, are currently available and recommended for protection against HPV infection. The main goal of current vaccination programs is the prevention of cervical cancer in females by reducing infections and precancerous lesions caused by high-risk HPV types in naïve girls. A cross-protective efficacy against four oncogenic non-vaccine HPV types (HPV 33/31/45/51) was reported for the bivalent HPV 16/18 vaccine, while the quadrivalent HPV 16/18/6/11 vaccine, in addition to the same cross protection, especially against HPV 33 and 31, also protects directly against genital warts caused by the low-risk HPV 6 and 11.[7-10]

HPV vaccination is usually recommended for 12-year-old girls. However, in many countries the goal of vaccination coverage (>70-80%) has not been reached in the target cohorts. In Italy, vaccination coverage with the complete schedule was 71% for the 1997-2000 girl cohorts in 2014, with wide regional variability, and did not show the expected increase in the last invited cohorts.[11] HPV vaccination coverage of girls was also lower than expected in other European countries.[12]

In order to improve the impact of HPV vaccination (reducing HPV transmission and, consequently, incidence of infections, disease, and cancer in females through herd immunity and reduction of HPV infections in males), some countries with low vaccination coverage for the main target population (e.g., USA, with 49% of adolescent girls with at least the first of three HPV doses in 2010) have recently extended HPV vaccination offer to boys in a universal immunization program.[13,14]

Universal HPV immunization, including boy cohorts, could determine benefits by direct boys' immunization, but also by indirect protection of unvaccinated girls.

Therefore, while clinical benefits of adding vaccination to boys has been clearly demonstrated, the most debated issue is the cost-effectiveness profile of universal vaccination. In the last ECDC guidance on the introduction of HPV vaccination in European Union countries, universal HPV immunization programs including boys were considered too expensive compared to the potential benefits. This was in accordance with several original studies and review articles on the economic impact of HPV vaccination already published at the time the guidance was issued.[12]

The aim of the present study was to perform an updated systematic review on economic studies related to the extension of HPV vaccination to boys, considering also the more recent indications (like the reduction to a 2-dose vaccination schedule for subjects aged <14 years) and the reduced vaccine costs.

MATERIALS AND METHODS

Search strategy

A systematic review of economic studies considering HPV vaccination and strategies including boys was performed. PubMed was searched for articles and reviews pertaining to cost-effectiveness evaluation of HPV vaccination.

A search was made for the following headings: «HPV», «boys», «vaccination», «economic evaluation», «cost effectiveness», «epidemiological impact». Four search strategies were adopted:

- search strategy 1: «vaccin*» AND («human papillomavirus» [MeSH] OR «HPV») AND («ICER» OR «cost effectiv*» OR «economic evaluation» OR «model*») AND («male» OR «males» OR «boy*» OR «men»)» – only free open access results;
- search strategy 2: «HPV vaccination AND («economic evaluation» OR «cost effectiveness») AND («male» OR «men» OR «boys»)»;
- search strategy 3: «(«HPV vaccination» OR «human papillomavirus vaccine») AND («economic evaluation» OR «cost effectiveness» OR «pharmacoeconomics» OR «modelling» OR «cost-utility analysis» OR «incremental cost-effectiveness ratio» OR «cost-benefit» OR «epidemiological impact» OR «economic impact» OR «mathematical model») AND («male» OR «men» OR «boys»)»;
- search strategy 4: «HPV vaccination AND («economic evaluation» OR «cost effectiveness» OR «pharmacoeconomics» OR «modelling» OR «cost-utility analysis» OR «incremental cost-effectiveness ratio» OR «cost-benefit» OR «epidemiological impact» OR «economic impact» OR «mathematical model») AND («male» OR «men» OR «boys») NOT women».

The identified articles were compared in order to exclude duplicate studies. Articles were selected if first in the title, then in the abstract, and finally in the text they evaluated the economic extension of HPV vaccination to boys. A general research on Pubmed was also conducted in order to increase the review sensitivity. In addition, a research of published reviews was performed in order to identify other articles and compare their outcomes. Figure 1 shows the flow diagram of the literature search.

Inclusion criteria

The economic studies searched for were original articles in English or Italian, published between 2005 and 2015, evaluating the

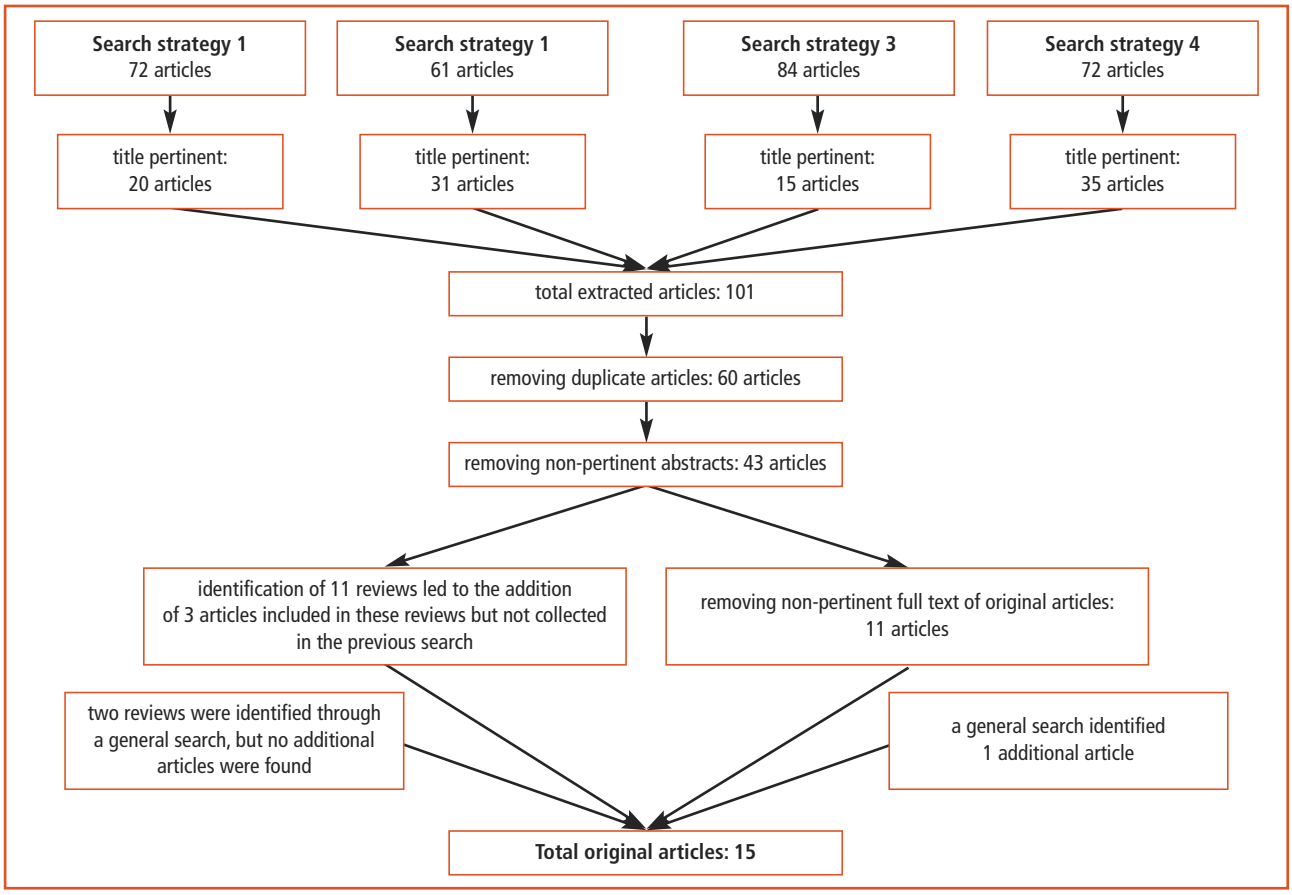

Figure 1. Flow diagram of the literature search and studies included or excluded in the review.
Figura 1. Diagramma di flusso della ricerca di letteratura e studi inclusi od esclusi nella review.

cost-effectiveness of the extension of HPV vaccination to boy cohorts compared with female-only adolescent immunization (standard target population for vaccination). All articles were assessed for methodological quality and data extraction was performed by 4 reviewers. In case of doubt, the topic was discussed together by all authors.

Data extraction

A table including the main relevant data of each study (authors, year of publication, country, period of analysis, mathematical model used, vaccine, price per dose and schedule, discounted rate, population, age of vaccination and catch-up, comparator, clinical outcomes considered, vaccine efficacy, duration of protection, assumptions on vaccination coverage, screening status, sensitivity analysis, economic outcomes – cost/QALY, cost/LYG – and other outcomes and conclusions) was created.

RESULTS

A total of 289 articles were identified: 246 articles were excluded because inconsistent with the research topic in the title or in the abstract, and as a consequence of duplicate removal. After assessment of the remaining 43 full-text articles, 11 were eventually considered suitable for inclusion in the present review because the other 32 articles did not focus on economic evaluation. In addition, 11 reviews were identified which allowed for the identification of three more articles not collected through the applied search strategies. Finally, another article identified through general search in PubMed was included. Other two reviews were found through general search, but no additional articles were retrieved. A total of 15 original economic studies were examined (table 1).

All studies were published in the period 2007-2015; most of them referred to high-income countries (USA, UK, Australia, etc.), while two articles referred to middle-income countries (Mexico[17] and Brazil[16]).

The bivalent vaccine was analyzed in three studies[16,18,21] while the quadrivalent vaccine (HPV 6/11/16/18) was analyzed in the other 12 studies. Age at vaccination ranged from 9 to 26 years, but immunization was more frequently administrated in the twelfth year of age. Some studies also considered a program of catch up for females and/or males aged 12-25 year in addition to universal vaccination. All studies took into account a three-dose schedule, except Laprise et al., which also considered a two-dose schedule.[26] Vaccine cost ranged between EUR 110-139 and USD 59-133. Vaccination coverage rate considered in the studies varied between 20% (Chesson et al.,[24] resulting in USD 23,600/QALY) and 90% (Kim et al.,[16] resulting in I$ 136,910/QALY).

According to WHO recommendations, a health intervention is considered cost-effective when cost/quality adjusted life

Author year/ country	Model/ period of analysis	Vaccine used/ vaccine cost/ schedule	Disc. rate	Model population	Morbidities	Vaccination age/ catch up	Comparator	Vaccine efficacy	Duration of protection
Elbasha 2007[15] USA	dynamic 100 y	HPV 6/11/16/18 USD 360 (2005) 3 doses	3%	cohort based on US population	CIN 2/3 CC, GW	12 y no CU or 12-24 y F&M	F only	90%	lifelong
Kim 2007[16] Brazil	dynamic n.a.	HPV 16/18 I$ 25-400 (2000) 3 doses	3%	cohort based on Brazillian population associated only)	age-specific cancer incidence rates (HPV16-18	12 y n.a.	F only *vs* F&M	100%	lifelong
Insinga 2007[17] Mexico	dynamic 62 y	HPV 6/11/16/18 USD 240 3 doses	3%	cohort based on Mexican population	CIN 2/3 CC, GW	12 y no or CU 12-24 for F&M	F only F only + CU for F F&M + CU for F	90%	lifelong
Kulasingam 2007[18] Australia	Markov n.a.	HPV 16/18 AUD 115/dose (2005) 3 doses	5%	cohort based on Australian population	all HPV 16/18 associated diseases	12 y no	screening only	100%	lifelong
Jit 2008[19] UK	dynamic 100 y	HPV 6/11/16/18 GBP 60-80.50/dose (2006-2007) 3 doses	3.5%	cohorts based on UK population	CIN, CC, GW HPV-related	12-25 y no	F only + CU 12-25 y	100% *vs* vaccine type HPV infection	lifelong 10 y
Kim 2009[20] USA	hybrid/dynamic n.a.	HPV 6/11/16/18 USD 120/dose (2006) 3 doses	3%	cohort based on US population	all HPV-related diseases	12 y n.a.	F only	*vs* infection: F 100% M 85% *vs* disease F 100% M 90%	lifelong
Zechmeister 2009[21] Austria	dynamic 52 y	HPV 16/18 EUR 100/dose (2007) 3 doses	5%	cohort based on international epidemiological data	CC, CIN 1/3	12 y no	F only	90%	lifelong (booster at 10y)
Olsen 2010[22] Denmark	dynamic 62 y	HPV 6/11/16/18 EUR 415 (2007) 3 doses	3%	heterosexual	CC, CIN 1/3, GW	12 y scenario CU for F to 15-26 y	F+CU to 15 y *vs* F+CU to 26 y	100%	n.a.
Elbasha 2010[23] USA	dynamic n.a.	HPV 6/11/16/18 USD 400 (2008) 3 doses	3%	cohort based on US population	CC, ANA, VAG, VUL,PEN, H&N, CIN 1-3, GW, RRP	9-26 y no	F only	90%	lifelong
Chesson 2011[24] USA	hybrid 100 y	HPV 6/11/16/18 USD 116/dose (2008) 3 doses	3%	cohort based on USA population	GW, CC, VAG, VUL, ANA, PEN, ORPH	F 12-26 y M 12 y annual CU for F 13-26 y	F only increased coverage in F	F: 95% M: 90%	lifelong
Pearson 2014[25] New Zealand	Markov n.a.	HPV 6/11/16/18 USD 59/dose (2011) 3 doses	3%	cohort based on New Zealand and Australia population	CIN 1/3, GW, CC, ANA, VUL, ORPH	12 y no	F only	99%	20 y
Laprise 2014[26] Canada	dynamic 70 y	HPV 6/11/16/18 CAD 85/dose (2010) 2/3 doses	3%	cohort based on Canadian population	GW, CC, VUL, VAG, ANA, PEN, ORPH	9 y CU 14 y	F only	2-dose: 90% 3-dose: 95%	2-dose: 10-30 y 3-dose: 20 y-lifelong
Burger 2014[27] Norway	dynamic lifetime	HPV 6/11/16/18 USD 75/dose (2010) 3 doses	4%	cohort based on Norwegian population	GW, CC, VUL, VAG, ANA, PEN, ORPH	12 y n.a.	F only	F: 100% M: 90%	lifelong
Bresse 2014[28] Austria	dynamic 100 y	HPV 6/11/16/18 EUR 120/dose (2012) 3 doses	3%	cohort based on Austrian population	GW, CC, VUL, VAG, ANA, PEN, ORPH	9 y no	no vaccination	F: 76-100% M: 41-96%	lifelong 20 y
Olsen 2015[29] Denmark	dynamic 62 y	HPV 6/11/16/18 EUR 417 (2008) 3 doses	3%	heterosexual	GW, CIN, CC, ANA, VAG, VUL, PEN, H&N	12 y n.a.	F only	100%	lifelong

F: female, M: male; Y: years; CC: cervical cancer; GW: genital warts; VAG;: vaginal cancer; VUL: vulvar cancer; ANA: anal cancer; PEN: penil cancer; H&N: head and neck cancer; ORPH: oropharynx cancer; RRP: re

Table 1. Cost-effectiveness studies on HPV vaccination including boys. / **Tabella 1.** Studi di costo-efficacia sulla vaccinazione anti-HPV nei maschi.

	Coverage	Screening status	Sensitivity analysis			Outcome cost/QALY cost/LYG	Other outcomes and conclusions
			natural history	vaccine parameters	economic parameters		
	70%	current	n.a.	one-way	one-way	Vaccination F&M: dominated Vaccination F&M + CU 12–24 y for F: USD 41,803 ICER of most effective strategy (F&M12+CU F&M): USD 45,056/QALY	Quadrivalent vaccine can substantially reduce genital warts, CIN, and cervical cancer
	25-90%	n.d.	multi variate	multi variate	multi variate	The ratio for vaccinating both girls and boys increased from I$ 810/LYG to I$8,650/LYG, as coverage increased	Adding boys to a vaccination programme may not be cost-effective in Brazil, unless the cost per vaccinated person is well below I$50, coverage in girls is well below 50% and could not be increased.
	70%	current	one-way	one-way	one-way	Vaccination F&M: dominated compared to F only. Vaccination F&M+CU for F: incremental USD 16,663/QALY compared to vaccinating F+CU for F Further incremental USD 16,702/QALY if CU for F&M	The most clinically effective strategy was vaccination of 12-year-old females and males combined with a temporary female and male 12-24-year-old catch-up program
	80%	current	no	one-way	one-way	AUD 33,644 compared to no vaccination program	In a setting with effective screening program, vaccinating boys is likely to be cost-effective when the morbidity of the screening program is taken into account (QALY), but not when only mortality associated with CC is considered (LYG).
	80%	current	multi variate	one-way	multi variate	Incremental GBP 113,846 if 10 years' vaccine protection is assumed Incremental GBP 172,892 if 20 y vaccine protection is assumed Incremental GBP 520,255 if lifetime vaccine protection is assumed	Adding boys is unlikely to be cost-effective, even if vaccination results in lifelong protection. This is because at 80% coverage it is likely that most HPV 16-18 related CC along with many cases of GW (in both sexes) will be prevented. Therefore the additional benefits from vaccination of boys are few.
	75%	current	multi variate	multi variate	multi variate	Indipendently from clinical outcomes considered, universal vaccination is not cost-effective (cost/QALY: USD 290,290 - 90,870)	Our results suggest that if vaccine coverage and efficacy are high among preadolescent girls (12 years), then including boys in an HPV vaccination program is unlikely to provide good value for resources compared vwith vaccinating girls only.
	65%	biannual screening	one-way	one-way	one-way	The additional vaccination of boys increases the ICER to EUR 311,000/LYG and EUR 299,000/LYG in a public care perspective or a societal one, respectively	Vaccinating boys may not be cost-effective without reducing the vaccine price.
	70%	current	multi variate	multi variate	multi variate	As scenario (12-year-old F and M vaccination at 70% coverage rate) ICER: EUR 18,677/QALY	HPV type 6-11-16-18 were estimated to be eliminated after 50 years of vaccination.
	75%	current	no	one-way	one-way	USD 25,700 if vaccination protects against all HPV-6/11/16/18 associated diseases USD 69,000 if it only protects against diseases currently in the vaccine indication	Adding quadrivalent vaccination to M 9-26 years potentially has substantial public health and economic benefits. The inclusion of M would further reduce HPV-related morbidity and is cost-effective at commonly cited thresholds.
	25-30-75%	current	multi variate	multi variate	multi variate	The incremental cost per QALY gained was was USD 23,600 in the lower female coverage scenario (20% coverage at 12 years) USD 184,300 in the higher female coverage scenario (75% coverage at 12 years)	HPV vaccination of M might potentially be cost-effective, if F coverage is low and if all potential health benefits are included. In the long term, adding M to vaccination reduces HPV-related CC in the three coverage scenarios.
	45-56% / 73%	current, but cost excluded	no	efficacy and coverage considered as independent variables	one-way	Vaccination of M to achieve the current coverage for F would not be cost-effective, at USD 61,400/QALY gained compared to the current F-only program An intensified F-only program would give USD 17,400/QALY gained Adding M to this program was also notcost-effective (USD 128,000/QALY)	Vaccination of boys was not found to be cost-effective, even with very low vaccine or program administration costs. In order for vaccination of males to become cost-effective in New Zealand, the vaccine would need to be supplied at very low prices and administration costs would need to be minimized.
	80%	current	multi variate	multi variate	multi variate	Vaccinating boys with 2 or 3 doses was not cost-effective (always above USD 100,000/QALY)	The price for M would need to be reduced by more than half to make a 2-dose F&M strategy cost-effective *vs* 3-dose F-only. Adding M to an HPV vaccination program would extend benefits to MSM, who do not benefit from the herd effects of F-only vaccination.
	71%	current	multi variate	multi variate	multi variate	USD 81,700/QALY considering only cancer for F&M USD 60,100/QALY when considering all HPV-related conditions	At the anticipated tender price, expanding the HPV vaccination program to boys may be cost-effective. Increasing coverage in F is uniformly more effective and cost-effective and should be considered a priority.
	65%	current	one-way	one-way	one-way	Cost-effective with base case analysis of EUR 26,701/QALY gained for CC only, EUR 15,820/QALY also including VAG,VUL and GW, EUR 10,033/QALY also considering ANA, PEN, ORPH	Decrease in infections (about -70% in F + M) reducing HPV 16/18-related cancers in both sexes. An increase of vaccine coverage among F + M from 65% to 80% would accelerate and increase the reduction in the prevalence of HPV 16/18-related infections by 10 and 14 points in F and M, respectively.
	85% (and 70%)	current: F 23-64 y every 3-5 y	one-way	multi variate	multi variate	Vaccination of F and M *vs* vaccination of F only: ICER: EUR 28,031/QALY (2-dose regimen) ICER: EUR 41,636/QALY (3-dose regimen)	Extension of the current HPV program in Denmark to include boys and girls is a cost-effective preventive intervention.

ecurrent respiratory papillomatosis; CU catch up; AUD: Australian dollars; CAD: Canadian dollars; EUR: Euros; GBP: British pounds; I$: International dollars; USD: US dollars

Authors	Year	Number of evaluated articles (year range)	Main conclusions
Newall et al.[30]	2007	4 (2003-2004)	The additional vaccination of boys was found to be unttractive under most plausible scenarios.
Kim et al.[31]	2008	6 (2004-2007)	Vaccination of boys is unlikely to be cost-effective if reasonable levels of coverage are achieved in girls Increasing vaccine coverage of girls is always more cost-effective than extending coverage to boys.
Brisson et al.[32]	2009	12 (2003-2008)	If vaccine coverage is high in girls, including boys in a vaccination program will not be cost-effective.
Marra et al.[33]	2009	13 (2003-2008)	The cost effectiveness of a male and female vaccination program is generally not cost-effective compared with female-only vaccination.
Jeurissen et al.[34]	2009	11 (2003-2008)	Vaccinating boys is not cost-effective.
Garland et al.[35]	2010	5 (2002-2009)	Inclusion of males in an HPV vaccination program is likely to have significant health and economic benefits. Comprehensive cost–benefit analyses are needed to determine the efficacy of these programs in the overall population.
Seto et al.[36]	2012	29 (2007-2010)	It appears that the addition of boys to a vaccination program generally exceeds traditional cost-effectiveness thresholds. The MSM population represents a potential additional target for routine HPV vaccination.
Low et al.[37]	2012	18 (2000-2010)	Models currently show that vaccination strategies with high female coverage enjoy the same benefits with greater savings than strategies that include males. Benefits of vaccinating males often do not warrant the high cost when considering only prevention of cervical cancer. Authors suspect that once adequate adequate cost-effectiveness modelling of HPV-related morbidities in males is completed, data will support vaccination in men at that time.
Canfell et al.[38]	2012	3 (2009-2011)	Although the inclusion of males in HPV vaccination programs can be cost-effective in some circumstances, increasing coverage in males is unlikely to be associated with a more attractive cost-effectiveness ratio than increasing coverage in females, if this can be achieved.
ECDC[12]	2012	11 (2004-2011)	Universal HPV vaccination may not be cost-effective. The cost-effectiveness can be re-assessed if vaccination costs are significantly reduced in the future, especially if regimens of less than 3 vaccine doses are proven to be just as efficacious as the current standard vaccination protocols.
Jiang et al.[39]	2013	9 (2004-2011)	More favourable cost-effectiveness appeared when all HPV-related disease outcomes were considered, a suboptimal vaccine coverage among girls, and/or lower vaccine prices were assumed.
Fasenfeld et al.[40]	2013	25 (2007-2012)	Two study considering vaccination in males, contrasting conclusions due to different assumptions (GW included, higher threshold and lower vaccine efficacy in the favourable study).
Marsh et al.[41]	2014	8 (2004-2011)	Current studies of the cost-effectiveness of universal HPV vaccination suffer from a number of limitations. Decisions to invest in universal HPV vaccination need to be based on a complete assessment of the value that it generates. This is not provided by existing economic evaluations.

Table 2. Reviews of cost-effectiveness studies on HPV vaccination including boys. / **Tabella 2.** Review di studi di costo-efficacia sulla vaccinazione anti-HPV nei maschi.

year (QALY) is less than 1 out of 3 times the Gross Domestic Product (GDP) per capita and very cost-effective if less than one GDP per capita. Therefore, the cost-effectiveness threshold is related to the specific economic background of each country. Based on this assumption, 8 studies (53%) considered adding boys to the female vaccination program a cost-effective intervention, with a cost/QALY ranging from EUR 10,033 (Bresse et al.,[28] assuming a 65% coverage) to USD 81,700 (Burger et al.,[27] assuming a 71% coverage). Chesson et al. considered adding boys to the vaccination program to be cost-effective under some assumptions: universal vaccination is cost-effective if immunization coverage in girls is less than 30%, but with a vaccine price of USD 116 per dose ($23,600/QALY).[24]

On the other hand, 6 studies (40%) indicated that universal vaccination is not cost-effective. Among these studies, Laprise et al. showed that a two-dose vaccination series for girls and boys compared to a three-dose series with girls-only vaccination would become cost-effective if the vaccine price for boys were reduced by more than half.[26] Zechmeister et al. suggested that vaccinating boys with 3 doses of bivalent vaccine may not be cost-effective without reducing the vaccine price (price considered: EUR 110 per dose) and when the economic evaluation is limited to only direct benefits related to cervical carcinoma prevention.[21] In the analysis performed by Kim et al., universal vaccination did not turn out to be cost-effective for prevention of HPV 16 and 18 related cancers in a limited-resource setting unless the cost of vaccination is well below USD 50 and vaccine coverage in girls is well below 50%, with no possible increase.[16] Pearson et al. admitted that vaccination of boys may become cost-effective only if a very low vaccine price (about USD 30) and lower program administration costs are achieved in the future.[25] The high vaccination coverage rate for girls (80%) assumed in Jit et al. was bound to determine the lack of cost-effectiveness of male vaccination.[19] Finally, like others, in a study performed by Kim et al. considering a cost per vaccine dose of USD 120, which is far higher than the current cost, boys' vaccination was not economically favourable.[20]

Table 2 shows the 13 reviews identified through the literature search. The oldest reviews concluded that universal vaccination was not cost-effective compared to female-only vaccination or increasing coverage among girls.[30-34] The most recent reviews, instead, suggested that adding boys could become cost-effective in the future if vaccine costs are reduced, if coverage among girls does not increase, and if all HPV-related disease are taken into account.[12,39,41] These statements are in agreement with the findings of our review.

DISCUSSION AND CONCLUSIONS

The previous published reviews showed that the cost-effectiveness of universal vaccination with the old parameters was controversial and generally unfavourable.

The results of this review, instead, show that many studies have a favourable cost-effectiveness profile, while others indicate that it could be cost-effective only with a low vaccination coverage in girls and with lower vaccine costs. However, in the last years, vaccine cost has decreased greatly worldwide compared to the price assumed in the analyzed studies. For example, the current cost per dose is about EUR 35 in Italy: this parameter surely has a great effect on the total costs of a universal vaccination program. In addition, the European Medicine Agency (EMA) authorized a two-dose schedule for both vaccines when used in younger subjects (≤13 and ≤14 years for the quadrivalent and bivalent vaccines, respectively).[42] Indeed, considering the input parameters in studies not favourable to universal vaccination, and their conclusions, at the current price of EUR 35 per dose and a two-dose schedule instead of a three-dose regimen, results would become cost-effective in all studies (Laprise et al.,[26] Zechmeister et al.,[21] Jit et al.,[19] Kim et al.[20]), except Kim et al.[16] and Pearson et al.,[25] whose conclusions would remain unfavourable to universal adolescent vaccination strategy. If Chesson et al.[24] had considered a price per dose of USD 38.11 (about EUR 35) instead of 116, and a two-dose regimen, their conclusions would have been favourable, too. In the other studies, with updated parameters, the results would be even more favourable for universal vaccination. These two parameters (price and number of doses) are a crucial change for the economic sustainability of universal vaccination. Therefore, economic studies should be updated assuming more recent vaccination costs and immunization schedules, so that the cost-effectiveness profile of universal vaccination would most likely be significantly improved.

In addition, as reported by Marsh et al.,[41] all HPV-related clinical outcomes should be included in economic studies in order to obtain a more accurate cost-effectiveness profile. Lastly, new economic evaluation on HPV universal vaccination should also be performed considering the availability of a 9-valent HPV vaccine in the near future.

Therefore, many issues are still open and should be further analyzed. For example, no evaluation on universal immunization policies is available for the scenario where vaccine coverage is 70% (a value that Kim et al.[31] recognize as insufficient). However, compared to previous reviews, our findings show better results in the economic evaluation of adding boys to vaccination, especially with updated economic parameters (12 studies out of 15 would confirm cost-effectiveness).

A possible limitation of our review is the use of a single electronic database (PubMed). We cannot rule out the possibility that a few articles on the subject may have been missed.

In conclusion, a universal HPV vaccination program could greatly reduce the incidence of new HPV infections in the population, and is likely to be cost-effective and economically sustainable, considering current vaccine prices and the two-dose schedule. Taking into account that several recent epidemiological studies and reviews have highlighted that HPV-related diseases pose a substantial burden even on males, the extension of HPV vaccination to boys is highly desirable and should become a reality in many countries in the next few years

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References/Bibliografia

1. Munoz N, Bosch FX, de Sanjosé S, et al. The International Agency for Research on Cancer Multicenter Cervical Cancer Study Group: Epidemiologic Classification of *Human Papillomavirus* Types Associated with Cervical Cancer. *N Engl J Med* 2003;348:518-27.
2. Walboomers JM, Jacobs MV, Manos MM, et al. *Human papillomavirus* is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189: 12-19.
3. Dalstein V, Riethmuller D, Pretet JL, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. *Int J Cancer* 2003;106:396-403.
4. De Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;13:607-15.
5. Herrero R, Castellsague X, Pawlita M, et al. *Human papillomavirus* and oral cancer: the International Agency for Research on Cancer multicenter study. *JNCI* 2003;95:1772-83.
6. Centers for Disease Control and Prevention (CDC). *Human papillomavirus*-associated cancers – United States, 2004-2008. *MMWR* 2012;61:258-61.
7. Wheeler CM, Castellsague X, Garland SM, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol* 2012;13: 100-10.
8. Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol* 2012;13:89-99.
9. European Medicines Agency. *Gardasil*. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf
10. Agenzia Italiana del Farmaco (AIFA). *Gardasil*. https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_000737_037311_RCP.pdf&retry=0&sys=m0b1l3
11. Giambi C. *Stato di avanzamento della campagna vaccinale per l'HPV: dati di copertura vaccinale al 31/12/2014 – Rapporto semestrale*. Epidemiologia di malattie infettive del Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore Sanità. http://www.epicentro.iss.it/problemi/hpv/pdf/Aggiornamento_HPV_31122014.pdf
12. European Centre for Disease Prevention and Control. *Introduction of HPV vaccines in European Union countries – An update*. Stockholm, ECDC, 2012.
13. Centers for Disease Control and Prevention. Press briefing transcript: *ACIP recommends all 11-12 year-old males get vaccinated against HPV*. http://www.cdc.gov/media/releases/2011/t1025_hpv_12yroldvaccine.html
14. Recommendations on the use of quadrivalent *human papillomavirus* vaccine in males – Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* 2011;60:1705-708.
15. Elbasha EH, Dasbach EJ, Insinga RP. Model for Assessing *Human Papillomavirus* Vaccination Strategies. *Emerg Infect Dis* 2007;13: 28-41.
16. Kim JJ, Andres-Beck B, Goldie SJ. The value of including boys in an HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting. *Br J Cancer* 2007; 97:1322-28.
17. Insinga RP, Dasbach EJ, Elbasha EH, Puig A, Reynales-Shigematsu LM.

Cost-effectiveness of quadrivalent *human papillomavirus* (HPV) vaccination in Mexico: a transmission dynamic model-based evaluation. *Vaccine* 2007;22: 128-39.
18. Kulasingam S, Connelly L, Conway E, et al. A cost-effectiveness analysis of adding a *human papillomavirus* vaccine to the Australian National Cervical Cancer Screening Program. *Sex Health* 2007;4:165-75.
19. Jit M, Choi YH, Edmunds WJ. Economic evaluation of *human papillomavirus* vaccination in the United Kingdom. *BMJ* 2008; 337:a769.
20. Kim JJ, Goldie SJ. Cost-effectiveness analysis of including boys in a *human papillomavirus* vaccination programme in the United States. *BMJ* 2009; 339:b3884.
21. Zechmeister I, Blasio BF, Garnett G, Neilson AR, Siebert U. Cost-effectiveness analysis of *human papillomavirus*-vaccination programs to prevent cervical cancer in Austria. *Vaccine* 2009; 27: 5133-41.
22. Olsen J, Jepsen MR. *Human papillomavirus* transmission and cost-effectiveness of introducing quadrivalent HPV vaccination in Denmark. *Int J Technol Assess* 2010;26:183-91.
23. Elbasha H, Dasbach EJ. Impact of vaccinating boys and men against HPV in the United States. *Vaccine* 2010;28:6858-67.
24. Chesson HW, Ekwuemeb DU, Saraiyab M, Dunnea EF, Markowitz LE. The cost effectiveness of male HPV vaccination in the United States. *Vaccine* 2011; 29: 8443-50.
25. Pearson AL, Kvizhinadze G, Wilson N, Smith M, Canfell K, Blakely T. Is expanding HPV vaccination programs to include school-aged boys likely to be value-for-money: a cost-utility analysis in a country with an existing schoolgirl program. *BMC Infect Dis* 2014,14:3512014.
26. Laprise JF, Drolet M, Boily MC, et al. Comparing the cost-effectiveness of two- and three-dose schedules of *human papillomavirus* vaccination: a transmission-dynamic modelling study. *Vaccine* 2014;32:5845-53.
27. Burger EA, Sy S, Nyga rd M, Kristiansen IS, Kim JJ. Prevention of HPV-Related Cancers in Norway: Cost-Effectiveness of Expanding the HPV Vaccination Program to Include Pre-Adolescent Boys. *PLoS ONE* 2014;9:e89974. doi:10.1371/journal.pone.0089974
28. Bresse X, Goergen C, Prager B, Joura E. Universal vaccination with the quadrivalent HPV vaccine in Austria: Impact on virus circulation, public health and cost-effectiveness analysis. Expert Rev Pharmacoecon. *Outcomes Res* 2014; doi:10.1586/14737167.2014.881253
29. Olsen J, Jørgensen TR. Revisiting the cost-effectiveness of universal HPV-vaccination in Denmark accounting for all potentially vaccine preventable HPV-related diseases in males and females. *Cost Eff Resour Alloc* 2015;13:4. doi: 10.1186/s12962-015-0029-9
30. Newall AT, Beutels P, Wood JG, Edmunds WJ, MacIntyre CR. Cost-effectiveness analyses of *human papillomavirus* vaccination. *Lancet Infect Dis* 2007; 7: 289-96.
31. Kim JJ, Brisson M, Edmunds WJ, Goldie SJ. Modeling Cervical Cancer Prevention in Developed Countries. *Vaccine* 2008;26(Suppl10):K76-86. doi:10.1016/j.vaccine.2008.06.009.
32. Brisson M, Van de Velde N, Boily MC. Economic Evaluation of *Human Papillomavirus* Vaccination in Developed Countries. *Public Health Genomics* 2009; 12:343-51. doi: 10.1159/000214924
33. Marra F, Cloutier K, Oteng B, Marra C, Ogilvie G. Effectiveness and Cost Effectiveness of *Human Papillomavirus* Vaccine: a Systematic Review. *Pharmacoeconomics* 2009;27:128-47.
34. Jeurissen S, Makar A. Epidemiological and Economic Impact of *Human Papillomavirus* Vaccines. *Int J Gynecol Cancer* 2009;19:761-71.
35. Garland SM. Prevention strategies against *human papillomavirus* in males. *Gynecol Oncol* 2010;117:S20-S25.
36. Seto K, Marra F, Raymakers A, Marra CA. The cost effectiveness of *human papillomavirus* vaccines: a systematic review. *Drugs* 2012;72:715-43.
37. Low GM, Attiga YS, Garg G, Schlegal R, Gallicano GI. Can Male Vaccination Reduce the Burden of *Human Papillomavirus*-Related Disease in the United States? *Viral Immunol* 2012;25:174-86.
38. Canfell K, Chesson H, Kulasingam SL, Berkhof J, Diaz M, Kim JJ. Modeling preventive strategies against human papillomavirus-related disease in developed countries. *Vaccine* 2012; 30(Suppl 5): 157-67.
39. Jiang Y, Gauthier A, Postma M J, Ribassin-Majed L, Largeron N, Bresse X. A critical review of cost-effectiveness analyses of vaccinating males against *human papillomavirus. Hum Vaccine Immunother* 2013;9:2285-95.
40. Fesenfeld M, Hutubessy R, Jit M. Cost-effectiveness of *human papillomavirus* vaccination in low and middle income countries: a systematic review. *Vaccine* 2013;31:3786-804.
41. Marsh K, Chapman R, Baggaley RF, Largeron N, Bresse X. Mind the gaps: what's missing from current economic evaluations of universal HPV vaccination? *Vaccine* 2014;32:3732-39.
42. European Commission. *Community register of medicinal products for human use.* http://ec.europa.eu/health/documents/community-register/html/h357.htm http://ec.europa.eu/health/documents/community-register/html/h419.htm