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Cost Effectiveness of Human Papillomavirus Vaccination for Men Who have Sex with Men; Reviewing the Available Evidence

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Abstract

Background Men who have sex with men require special attention for human papillomavirus vaccination given elevated infection risks and the development of, in particular, anal cancer.

Objective Our purpose was to review the cost effectiveness of human papillomavirus vaccination for both currently vaccine-eligible and non-eligible individuals, particularly the men-who-have-sex-with-men population, and synthesize the available evidence.

Methods We systematically searched for published articles in two main databases (PubMed and EMBASE). Screening and data extraction were performed by two independent reviewers. The risk of bias was assessed using a validated instrument (Bias in Economic Evaluation, ECOBIAS). Methodological aspects, study results, and sensitivity analyses were extracted and synthesized to generate a consistent overview of the cost effectiveness of human papillomavirus vaccination in the men-who-have-sex-with-men population.

Results From 770 identified articles, four met the inclusion criteria. Across the studies, human papillomavirus vaccination showed incremental cost-effectiveness ratios ranging from dominant to US\$96,146 and US\$14,000 to US\$18,200 for tertiary prevention and primary prevention, respectively. The incremental cost-effectiveness ratio seemed most sensitive to vaccine efficacy, vaccine costs, and the incidence of anal cancer in the selected target populations.

Conclusion This review presents the human papillomavirus vaccine, both as a primary and adjuvant (tertiary) vaccination, as a potentially cost-effective strategy for preventing mainly—but not limited to only—anal cancer in men-who-have-sex-with-men populations.

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Key Points for Decision Makers

All the health economic studies included in this review considered human papillomavirus vaccination for men-who-have-sex-with-men to be cost effective or even cost saving.

The specific target population and the exact setting for the intervention varied between the studies identified.

Cost-effectiveness results were sensitive to vaccine efficacy, vaccine cost, and the incidence of anal cancer.

There is a need for additional robust data and further studies for more countries.

1 Introduction

Human papillomavirus (HPV) belongs to a group of DNA viruses [1]. Human papillomavirus concerns one of the most widely recognized, sexually transmitted viral infections [2]. Based on their specific properties, HPV infections may result in anogenital warts (condyloma acuminata) [3] or cancers of the anogenital tract, i.e., anal and penile, and their precursor stages [2]. High-risk oncogenic HPV types (such as types 16 and 18) predispose to the development of cancers of the cervix, vulva, vagina, urethra, penis, anus, and oropharynx whereas low-risk types (such as types 6 and 11) are associated with warts [4–8].

Human papillomavirus causes considerable disease burden in both women and men [9]. Men who have sex with men (MSM) are at a particularly higher risk of HPV infections and related illnesses such as genital warts and anal cancer, as compared with heterosexual men [10]. A study revealed that the prevalence of HPV infection among MSM is higher compared with men having sex with women [11–13]. Consistently, the incidence of anal cancer is substantially higher in MSM [14–18]. The burden is even more in HIV-positive MSM. A systematic review estimated that the annual anal cancer incidence in HIV-negative MSM was 5 per 100,000 per year while it was 46 per 100,000 per year in HIV-positive MSM [18].

There are currently three commercially available HPV vaccines, a bivalent, a quadravalent, and a nonavalent vaccine, with the first two reflecting the ‘older’ products. The bivalent vaccine (Cervarix[®] manufactured by GlaxoSmithKline) protects against HPV types 16 and 18 and the quadravalent vaccine (Gardasil[®], manufactured by

Merck & Co.) provides protection against four types of HPV (6, 11, 16, and 18). The 9-valent vaccine (Gardasil 9[®] also manufactured by Merck & Co.) is designed to target five more HPV types (31, 33, 45, 52, and 58) in addition to the four HPV types included in the quadravalent one [19]. It has been documented that HPV vaccines are effective in preventing HPV infection and related diseases in men [20, 21].

National HPV vaccination programs targeting girls between 9 and 14 years of age are in place in many countries. However, only a few countries such as Australia, USA, and Canada recommended a sex-neutral vaccination program [22–24]. In particular, in settings where vaccine coverage among girls is poor, adding boys to the vaccination program can introduce beneficial herd effects for unvaccinated women and obviously directly protect male individuals. In settings with high vaccination coverage among girls, male individuals would potentially benefit from herd immunity and it appears that the addition of boys to a vaccination program might not be cost effective [25]. Furthermore, as the risk of anal cancer in the MSM population is substantially elevated, targeted HPV vaccination of MSM is recommended to provide direct protection against HPV-associated cancers, and anogenital warts [26, 27]. Additionally, HPV vaccines offer considerable protection against recurrent high-grade squamous intraepithelial lesions in this specific group [12, 13]. Therefore, in this specific context, the vaccine seems to provide both primary (against infection) as well as tertiary (against advanced disease) prevention.

The importance of cost effectiveness is increasing within the context of evidence-based decision-making processes. This review aims to analyze the cost effectiveness of HPV vaccination with the objective of primary and tertiary prevention among current vaccine-eligible and not eligible MSM, respectively.

2 Methods

2.1 Search Strategy

A systematic search was conducted using PubMed and EMBASE databases on 17 January, 2017. We used the following search terms: “economics”, “cost effectiveness analysis”, “economic evaluation”, “pharmacoeconomics”, “papillomavirus vaccines”, “human papillomavirus vaccines”, “HPV vaccines”, “men who have sex with men”, “MSM”, “homosexuality”, “male”, “boy”, and “men”. Full details of the search strategy are available in the “Appendix”.

2.2 Study Selection

The search results were imported into Mendeley Desktop and duplicates removed. Then, titles and abstracts of the search results were screened independently by two reviewers (DS and AW) to identify relevant articles. The full texts of potentially relevant articles were then assessed for eligibility. Studies investigating the cost effectiveness of targeted HPV vaccination of MSM were included. Reviews, editorials, letters, and articles not in English were also excluded. Discrepancies among the reviewers were resolved by discussions and consensus.

2.3 Data Extraction

The data were extracted by DS and AW independently, using a data abstraction template created in Microsoft Excel[®]. The data were cross-checked by the same two authors for accuracy and consistency. The following data were extracted from each article: author(s), publication year, setting (country/location of the economic evaluation), the intervention and comparator(s) considered, type of model used, perspective, time horizon, discount rate for costs and effects, cost and cost items for intervention and comparator groups, incremental cost-effectiveness ratio (ICER), and type and outcome of sensitivity analysis performed. To provide comparable calculations, all the monetary values were transformed into 2016 US\$ using inflation rates and purchasing power parities from the World Bank database [28, 29].

2.4 Risk-of-Bias Assessment

The risk of bias of the included studies was assessed by using the Bias in Economic Evaluation (ECOBias) checklist, consisting of 22 items specifically intended for model-based studies [30]. This checklist is divided into two parts: an overall checklist for bias in the economic evaluation (part A) and a part considering bias in the model-specific aspects of the economic evaluation. In particular, the latter part (part B) covers potential bias related to structure, model specification and time horizon considered, data, and internal consistency.

3 Results

3.1 Literature Search

A total of 770 articles were initially found. Upon removal of duplicates, 612 articles remained and were screened. Of these 598 articles were excluded owing to the following reasons: not a health economic study (272 articles), not on

MSM (84 articles), descriptive/observational study only (126 articles), review paper (70 articles), report only (31 articles), conference abstract (five articles), correspondence (seven articles), and studies not on HPV infection (three articles). Furthermore, of the remaining 14 articles eligible for full-text screening, ten were subsequently still excluded as they were not on vaccination in MSM populations. Finally, four articles were included in this review (Fig. 1).

3.2 Study Characteristics

All four studies considered vaccination strategies using the quadrivalent vaccine and targeting a different sub-population of MSM, defined by HIV status and age. Three studies originated from USA (US\$27,28,30) and one from the UK [29]. Notably, two studies from Deshmukh et al. considered the vaccination as a tertiary prevention strategy for both HIV-positive and HIV-negative MSM who had already developed high-grade squamous intraepithelial lesions [31, 32] while two other studies evaluated the impact of vaccination as a primary prevention of infection [33, 34]. Only one study considered genito-urinary medicine clinics as the delivery of the vaccination [34]. All studies used a lifetime time horizon. Most (75%) of the studies were conducted from the perspective of the healthcare provider [31, 32, 34] and used Markov models [31–33]. Only one study implemented a dynamic transition model [34]. With regard to the discount rate for both costs and health effects, all studies from USA implemented a 3% discount rate [31–33] while the study from the UK implemented a 3.5% discount rate [34]. Anal cancer was considered in all studies. In addition, some studies also investigated anogenital warts [33, 34] and other HPV-related cancers including penile, oropharyngeal, oral cavity, and laryngeal cancers [34] (Table 1).

3.3 Base-Case Results

The costs and health outcomes related to HPV vaccination for MSM are presented in Table 2. The currency year used in the studies ranged from 2006 to 2014; however, as mentioned, all being updated to 2016 US\$. Direct medical costs, including treatment costs for the HPV-related outcomes considered were included. Quality-adjusted life-years (QALYs) were evaluated in all studies included [31–34], while incidence and mortality related to anal cancer were presented in three studies [31, 32, 34] and one study [32], respectively. Although HPV vaccination for MSM was the main question addressed in all included studies, there were differences in the specific and exact base-case analysis chosen.

Three studies specifically presented the values of discounted costs and utilities/QALYs for the individual

Fig. 1 PRISMA flow diagram for articles selection in the study. *HPV* human papillomavirus, *MSM* men who have sex with men

options investigated in their analysis [31, 32, 34], while one study (Kim et al.) only presented the ICERs for the various scenarios covering different ages and exposures to HPV type 6, 11, 16, and 18 infections [33]. Studies evaluating HPV vaccine for primary prevention showed that the ICER lies below US\$20,000 [33, 34] while two studies from Deshmukh et al., investigating tertiary prevention through (adjuvant) vaccination, showed varying results with the ICER at US\$96,000 or even negative for HIV-negative and HIV-positive MSM, respectively [31, 32]. Two studies showed that HPV vaccination for the MSM population, aiming to reduce the burden associated with anal cancer, would be a cost-effective strategy according to the suggested thresholds for USA and the UK of US\$50,000/QALYs and £20,000/QALYs (US\$29,000/QALYs), respectively [33, 34].

3.4 Sensitivity Analysis

A sensitivity analysis is performed to evaluate the robustness of the study results considering methodological, structural, heterogeneity, and parameter uncertainty (Table 3). A deterministic and/or one-way sensitivity analysis was performed by all studies included in this review [31–34]. Most of the studies also performed a probabilistic sensitivity analysis using Bayesian statistical decision theory to optimize the decision in relation to uncertainty in the data [31, 32, 34]. Based on the findings from a one-way sensitivity analysis, the cost effectiveness

of MSM HPV vaccination was found to be sensitive to vaccine efficacy, vaccine costs, and the incidence on anal cancer.

3.5 Risk-of-Bias Assessment

According to part A of the ECOBIAS checklist (Table 4), there were some aspects that have been performed well, such as using the comparator reflecting current practice (no vaccination for MSM), providing sufficient detail for the costs and ICER, applying recommended discount rates, and seemingly disclosing any sponsors related to the studies performed. However, there were several potential types of bias, according to the ECOBIAS checklist in the studies included in this review because most of the studies did not implement the societal perspective in their studies [31, 32, 34], did not use input parameters, particularly cost and outcomes, that being collected continuously (longitudinal data) [31–34], did not mention nor present a fully detailed cost calculation [31, 32, 34], and did not use any specific pre-specified protocol while doing the study [31–34]. Various aspects of uncertainty were partially evaluated (mostly related to parameter uncertainty and heterogeneity) in the studies included [31–34].

In part B, the first category of model-specific aspects of bias reflects bias related to structure, covering structural assumptions, treatment comparator, types of the model, and time horizon. Because two authors only developed one model in their study, potential bias could possibly occur

Table 1 Study characteristics

References	Country setting	Vaccination objective	Target population	Type of intervention	Comparator	Type of economic evaluation	Perspective, time horizon	Type of model	Discount rate (%)		Cancer types	
									Cost	Effects		
Deshmukh et al. [32]	USA	Tertiary (adjuvant)	HIV-negative MSM aged ≥ 27 years	Quadrivalent after treatment for HGAIN	No vaccination after treatment for HGAIN	CEA	Healthcare, lifetime	Markov	3	3	Anal	
Lin et al. [34]	UK	Primary prevention	Aged 16–40 years	Quadrivalent vaccine for MSM	No vaccination for MSM	CEA	Healthcare provider, 100 years	Dynamic	3.50	3.50	Anogenital warts, anal, penile, oropharyngeal, oral cavity, and laryngeal cancers	
Deshmukh et al. [31]	USA	Tertiary (adjuvant)	HIV-positive MSM aged ≥ 27 years	Quadrivalent after treatment for HGAIN	No vaccination after treatment for HGAIN	CEA	Healthcare, lifetime	Markov	3	3	Anal	
Kim et al. [33]	USA	Primary prevention	MSM aged 12 years	Vaccination (12, 20, and 26 years)	No vaccination	CEA	NS, lifetime	Markov	3	3	Anal (and genital warts)	

CEA cost-effectiveness analysis, HGAIN high-grade anal intraepithelial neoplasia, HIV human immunodeficiency syndrome, MSM men who have sex with men, NS not specified

because the outcome generated from the model could not be compared with another model from the same natural history of the disease. The treatment comparator bias seemed optimally avoided because there were no current HPV vaccination strategies for the MSM population. With regard to the model-type bias, only one study (Lin et al.) used a dynamic model that comprehensively described the transmission of HPV infection in the population. Furthermore, another consequence, including HPV-related cancers particularly in the MSM population, was also explained. Finally, bias related to a potentially limited time horizon was avoided because all the studies investigated the impact of HPV vaccination using a lifetime horizon.

There were several potential biases related to the data used in the model because whereas all authors used data from well-designed studies, the justification on the process of deciding which data to include was lacking. Although the probabilities were adopted from well-established sources, the transformation process to align data with the model was not always clearly explained in the articles. The effectiveness of the vaccine used in the model was not derived from a meta-analysis but from single randomized clinical trials or non-concurrent cohort studies. Limited scope bias was also likely only partially avoided because all of the studies only evaluated the parameter and methodological uncertainty but not structural bias and heterogeneity. All studies seemingly avoided bias related to the quality-of-life weights and non-transparent data incorporation as the QALYs were derived from justifiable sources and all data used in the model were clearly presented.

Internal consistency reflects an important factor to yield a good mathematical model for economic evaluation. In this review, only one study (Kim et al.) tested the model before they used it for the main study [33]. This testing process was achieved by incorporating several different sets of parameter inputs and comparing the results with each other for consistency or comparing the output of the model with actual epidemiological data.

4 Discussion

Human papillomavirus vaccination is widely known as one of the main strategies to prevent HPV-related cancers. While universal vaccination programs for girls are common in many countries [35–37], with potential indirect herd immunity benefits to heterosexual boys, the MSM population remains fully unprotected [9, 16, 38]. The scarce number of studies and settings identified, four studies exploring three different scenarios of vaccination for MSM populations, shows that HPV vaccination for MSM populations can potentially be a cost-effective

Table 2 Cost and health characteristics of human papillomavirus (HPV) vaccination for men who have sex with men (MSM) studies

References	Year of currency	Cost component	Health outcome	Base case	Incremental		ICER	Authors' conclusions
					Costs (US\$)	Effects		
Deshmukh et al. [32]	2010	Anal cancer treatment cost, HGAIN treatment cost, vaccination cost	Incidence, mortality, and QALYs	Vaccination for HIV-negative MSM aged 27 years who have been diagnosed and treated for HGAIN	1615	0.0168	96,146	Vaccinating HIV-negative MSM treated for HGAIN decreases the lifetime risk of anal cancer and is likely to be a cost-effective intervention
Lin et al. [34]	2014	Vaccination cost, HPV-related healthcare cost	Incidence, QALYs	Quadrivalent vaccine for MSM aged 16–40 years	14.4M	1020	14,118	Quadrivalent HPV vaccination of MSM is a cost-effective method for reducing the burden of HPV-related disease in MSM
Deshmukh et al. [31]	2014	Cancer-related cost, HGAIN treatment cost, vaccination cost, HIV-related care cost	Incidence, QALYs	Quadrivalent HPV vaccination in HIV-positive MSM aged 27 years who have been diagnosed and treated for HGAIN	– 425	0.16	Dominant	Vaccination for HIV-positive MSM is cost saving
Kim et al. [33]	2006	Direct medical costs of diagnosis and treatment of anal cancer and genital warts	QALYs	50% vaccination coverage and 90% vaccine efficacy, HPV vaccination of MSM at age 12 years			18,209	HPV vaccination of MSM is likely to be a cost-effective intervention for the prevention of genital warts and anal cancer

HGAIN high-grade anal intraepithelial neoplasia, *HIV* human immunodeficiency virus, *ICER* incremental cost-effectiveness ratio, *QALYs* quality-adjusted life-years

Table 3 Sensitivity analysis

References	Sensitivity analysis	Sensitive parameters
Deshmukh et al. [32]	Deterministic and probabilistic sensitivity analyses	The age at vaccination and treatment, the transition from HGAIN to anal cancer
Lin et al. [34]	Deterministic and probabilistic sensitivity analyses	Vaccine cost, the disutility around wart episodes, the duration and cost of anal cancer treatment
Deshmukh et al. [31]	Deterministic and probabilistic sensitivity analyses	Vaccine efficacy and the transition from HGAIN to anal cancer
Kim et al. [33]	Deterministic sensitivity analyses	Variations in anal cancer incidence, duration of vaccine protection, and HIV prevalence in MSM

HGAIN high-grade anal intraepithelial neoplasia, *HIV* human immunodeficiency virus, *MSM* men who have sex with men

strategy. In the models, the potentially favorable cost effectiveness is mainly owing to, but not limited to, anal cancer prevention [31–34]. This finding emphasizes the importance of expanding HPV vaccination policies for not only young-aged girls but also to other target populations such as MSM. Of course, the result of this review should be considered alongside other practical implementation considerations. Notably, in settings where vaccination for adolescent boys is considered not feasible [39], targeting

MSM individuals aged 15–64 years could be considered acceptable [31, 32, 34].

From this review, we found that generally we can divide the studies into two groups: those targeting primary prevention and those targeting tertiary prevention using the HPV vaccine. Primary prevention aims to prevent the incidence of primarily anal cancer in the population at risk, particularly MSM. Primary prevention is aimed at avoiding the infection per se, while tertiary prevention specifically

Table 4 Risk-of-bias assessment according to the Bias in Economic Evaluation (ECOBias) checklist

Type of bias	Deshmukh et al. [32]	Justification	Lin et al. [34]	Justification	Deshmukh et al. [31]	Justification	Kim et al. [33]	Justification
Part A: overall checklist for ECOBIAS								
Narrow perspective bias	No	No justification	No	No justification	No	No justification	Unclear	Did not mention the perspective
Inefficient comparator bias	Yes	Compared to current practice, which is no vaccination	Yes	Compared to current practice, which is no vaccination	Yes	Compared to current practice, which is no vaccination	Yes	Compared to current practice, which is no vaccination
Cost measurement omission bias	Yes	According to the perspective	Yes	According to the perspective	Yes	According to the perspective	Unclear	Did not mention the perspective
Intermittent data collection bias	No	The resources (both cost and clinical outcomes) were not measured continuously	No	The resources (both cost and clinical outcomes) were not measured continuously	No	The resources (both cost and clinical outcomes) were not measured continuously	No	The resources (both cost and clinical outcomes) were not measured continuously
Invalid valuation bias	No	The price calculation was not presented in a detailed manner	No	The price calculation was not presented in a detailed manner	No	The price calculation was not presented in a detailed manner	No	The price calculation was not presented in a detailed manner
Ordinal ICER bias	Yes		Unclear		Yes		Yes	
Double-counting bias	Unclear		Unclear		Unclear		Unclear	
Inappropriate discounting bias	Yes		Yes		Yes		Yes	
Limited sensitivity analysis bias	Partly	Only parameter and methodological uncertainty have been considered	Partly	Only parameter and methodological uncertainty have been considered	Partly	Only parameter and methodological uncertainty have been considered	Partly	Only parameter and methodological uncertainty have been considered
Sponsor bias	Yes		Yes		Yes		Yes	
Reporting and dissemination bias	NA		NA		NA		NA	
Part B: model-specific aspects of ECOBIAS								
(I) Bias related to structure								
Structure assumptions bias	Partly	Author directly uses one specific model	Partly	Author directly uses one specific model	Partly	Author directly uses one specific model	Partly	Author directly uses one specific model
No treatment comparator bias	Yes		Yes		Yes		Yes	
Wrong model bias	Yes		Yes		Yes		Yes	

Table 4 continued

Type of bias	Deshmukh et al. [32]	Justification	Lin et al. [34]	Justification	Deshmukh et al. [31]	Justification	Kim et al. [33]	Justification
Limited time horizon bias	Yes		Yes		Yes		Yes	
(II) Bias related to data								
Bias related to data identification	Partly	Well-designed studies but no justification	Partly	Well-designed studies but no justification	Partly	Well-designed studies but no justification	Partly	Well-designed studies but no justification
Bias related to baseline data	Unclear		Unclear		Unclear		Unclear	
Bias related to treatment effects	No	The treatment effects come from a non-concurrent cohort study	No	RCT	No	The treatment effects come from a non-concurrent cohort study	Unclear	Using assumption (exploration study)
Bias related to quality-of-life weights (utilities)	Yes	Using QALYs	Yes	Using QALYs	Yes	Using QALYs	Yes	The value is weighted by the average the of stage-specific utilities by stage distribution of disease
Non-transparent data incorporation bias	Yes		Yes		Yes		Yes	
Limited scope bias	Partly		Partly		Partly		Partly	
(III) Bias related to consistency								
Bias related to internal consistency	No	The model was not tested before use	No	The model was not tested before use	No	The model was not tested before use	Yes	The model estimation was compared with a reference

ICER incremental cost-effectiveness ratio, NA not applicable, QALYs quality-adjusted life-years, RCT randomized clinical trial

considers the impact of the HPV vaccine for MSM populations who have had high-grade anal intraepithelial neoplasia (HGAIN). While the results of primary prevention studies show favorable cost effectiveness, the outcomes from the tertiary prevention studies seem highly influenced by the HIV status of MSM. The findings do show however that cost effectiveness provides justification for decision makers to expand the current vaccination program for mostly young-aged girls to MSM populations [40].

One study may provide relatively strong evidence because the authors used a dynamic transmission model [34], which captured the dynamic interaction among individuals in the population and accounted for the impact of herd immunity within the MSM population itself [41–43]. Herd immunity is an important additional benefit from vaccination policies to societies and covers better the detailed impact of vaccination on clinical and economic issues. Although this study did not incorporate the herd effects of vaccination to bisexual men, the ICER found in this study (US\$20,461/QALY) was well below the willingness to pay for the UK (US\$30,000/QALY).

While adding HPV vaccination for young boys to girls' programs showed debatable cost effectiveness [44–46], expanding vaccination policies beyond the girls currently covered to all MSM populations in the society may be a favorable option as demonstrated by two different studies from Lin et al. and Kim et al. [33, 34]. Both studies showed that the ICER for this extension lies below the recommended threshold for the countries considered (UK and USA). Hence, HPV vaccination policies for MSM populations seem worth considering, in particular, as these individuals will not get the herd protection benefits from existing female vaccination policies.

Both studies from Deshmukh et al. [31, 32] analyzed vaccinations for MSM who already developed and were treated for HGAIN to reduce recurrent HGAIN and the development of anal cancer. Notably, previous evidence showed that a quadrivalent vaccine could potentially reduce both the recurrence and the development of anal cancer by almost 50% after the first treatment of HGAIN [20]. Both studies showed that the strategy was likely cost effective or even potentially cost saving for HIV-negative and HIV-positive MSM, respectively. These findings were considered beneficial for US decision makers should they want to expand the current vaccination strategies to both HIV-negative and HIV-positive MSM who obtained the first treatment of HGAIN in USA.

To optimally underpin the decision-making process with high-quality research, bias should be avoided in any study. According to the ECOBIAS checklist, consisting of two parts (overall bias in economic evaluation and model-specific aspects) [30], there were some potential biases that could potentially occur. Notably, some issues may exist in

the identified studies with regard to using the societal perspectives, using data that are collected continuously, checking for double counting, and registering the protocol of the study upfront. These biases are common in economic evaluations owing to some limitations that generally exist, including unclear, incomplete, or unnecessarily reporting of indirect cost data, limited time for data collection, and scarce data availability. Additionally, unlike economic evaluations conducted alongside clinical trials, upfront formal protocols for model-based economic evaluations are still rarely made.

Vaccine efficacy data used in health economic studies are generally never based on a formal meta-analysis. This limitation is possibly the result of the limited number of clinical trials or cohort studies on HPV vaccination in men [20], particularly in the MSM population because not all countries have specific healthcare services for this specific population. Another important consideration is that other types of prevention obviously exist, for example, using condoms as a means to prevent HPV infection and even other diseases. This has not been included in the studies reviewed. Such alternatives may prove to be cost effective to prevent anal cancer or other types of sexually transmitted infections.

Another important limitation of our review is the fact that studies come from two countries only, USA and the UK, which obviously does not necessarily represent the context for MSM populations in other developed countries, let alone developing countries. Notably, economic evaluations are often seen as highly country specific, being closely related to the healthcare system in place. Moreover, there may be additional cultural issues for MSMs, making the whole issue even more country-context specific. Studies for further countries are urgently needed as potentially expanding or introducing HPV vaccination policies to and for MSM populations can potentially bring relevant benefits and reduce the health and economic burden generated by HPV infection.

5 Concluding Remarks

Scant evidence identified in our review (reflecting on four studies, two countries, and three different scenarios) indicates that HPV vaccination for MSM populations may be considered cost effective or can even be cost saving. Cost effectiveness appeared particularly sensitive to vaccine efficacy and vaccine costs. Given the scarcity of the evidence, it is difficult to make a definite and strong conclusion. Further research is needed to provide stronger model inputs and evidence for more countries. Such country-specific studies on MSM populations will assist decision makers as to whether to expand or introduce HPV vaccination policies in their respective contexts.

Author contributions DS, AW, and MJ developed the research question and methodology, DS and AW performed the search term development, screening, and data extraction, and conducted the analysis. All authors contributed to the manuscript.

Compliance with Ethical Standards

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Data availability statement The data, particularly the included articles, that mainly support the findings of this review are publicly available.

Appendix

Search Terms for PubMed

("Economics"[Mesh] OR "Economic*" [tiab] OR "Cost-Benefit Analysis"[Mesh] OR "Cost Effectiveness Analysis"[tiab] OR "Cost-Effectiveness Analysis"[tiab] OR "Economic Evaluation*" [tiab] OR "Cost Utility Analysis"[tiab] OR "Cost-Utility Analyses"[tiab] OR "Cost Effectiveness"[tiab] OR "Cost-Benefit Analyses"[tiab] OR "Cost Benefit Analysis"[tiab] OR "Cost Benefit Analyses"[tiab] OR pharmacoeconomics OR Cost* [tiab] OR "Costs and Cost Analysis"[Mesh] OR "Costs and Cost Analysis"[tiab]) AND ("Papillomavirus Vaccines"[Mesh] OR "Papillomavirus Vaccines"[tiab] OR "Human Papillomavirus Vaccines"[tiab] OR "Human Papilloma Virus Vaccines"[tiab] OR "HPV Vaccines"[tiab] OR ("Papillomavirus"[tiab] OR "Human Papillomavirus"[tiab] OR "Human Papilloma Virus"[tiab] OR "HPV"[tiab]) AND ("vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab] OR "vaccinated"[tiab] OR vaccinations[tiab] OR "immunization"[tiab] OR immunizations[tiab] OR "immunisation"[tiab] OR immunisations[tiab] OR "immunized"[tiab] OR "immunised"[tiab]))).

Search Terms for EMBASE

('economics'/exp OR 'economic*' OR 'cost effectiveness analysis'/exp OR 'cost effectiveness analysis' OR 'economic evaluation'/exp OR 'economic evaluation' OR 'health economics'/exp OR 'health economics' 'pharmacoeconomics'/exp OR 'pharmacoeconomics' OR 'cost*'

OR 'cost benefit analysis' OR 'cost effectiveness analysis' OR 'cost minimization analysis' OR 'cost utility analysis' OR Cost*) AND ('Wart virus vaccine'/exp OR 'Wart virus vaccine' OR ('Papillomaviridae'/exp OR 'Wart virus'/exp OR 'Papillomavirus' OR 'Human Papillomavirus' OR 'Human Papilloma Virus' OR 'HPV') AND (vaccine OR vaccines OR vaccination OR vaccinated OR vaccinations OR immunization OR immunizations OR immunization OR immunisations OR immunized OR immunised))) AND ('men who have sex with men'/exp OR 'men who have sex with men' OR 'homosexual male'/exp OR homosexual* OR gay* OR boy* OR men OR man).

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