REPORT OF THE PLAGIARISM CHECK

THE REPORT CERTIFIES THAT THE ATTACHED WORK

09. Cost Effectiveness of Human Papillomavirus Vaccination for Men Who have Sex with Men

WAS CHECKED WITH THE PLAGIARISM PREVENTION SERVICE PLAGRAMME.COM

AND HAS:

SIMILARITY

5%

RISK OF THE PLAGIARISM

9%

PARAPHRASE

0%

IMPROPER CITATIONS

0%

File name: 03. Manuscript CEA of HPV Vaccine MSM Responses Plagramme.docx

File checked: 2018-09-17
Report generated: 2018-09-17
Cost-effectiveness of HPV vaccination for Men-who-have- Sex-with-Men (MSM); reviewing the available evidence

Abstract

**Background** Men-who-have-Sex-with-Men (MSM) require special attention for HPV vaccination given their elevated risks of infection and anal cancer, in particular.

**Objective** Our purpose was to review the cost-effectiveness of HPV vaccination for both vaccine-eligible and non-eligible individuals, particularly the MSM 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 (ECOBIAS). Methodological aspects, study results and the sensitivity analyses were extracted and synthesized to generate a consistent overview of the cost-effectiveness of HPV vaccination in the MSM population.

**Results** Of 770 identified articles, four met the inclusion criteria. Across the studies, HPV vaccination showed ICERs ranging from dominant to USD 96,146 and USD 14,000 to USD 18,200 for tertiary prevention and primary prevention, respectively. The ICER seemed most sensitive to vaccine efficacy, vaccine costs and the incidence of anal cancer in the selected target populations.

**Conclusion** This review presents the HPV vaccine, both as a primary and adjuvant (tertiary) vaccination, as a potentially cost-effective strategy, mainly – but not only – for preventing anal cancer in MSM populations.

**Key points for decision-makers**

- All the health economic studies included in this review considered HPV vaccination for Men-who-have-Sex-with-Men as 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 robust additional data and further studies for more countries.
Introduction

Human papillomavirus (HPV) belongs to a group of DNA viruses (1). HPV concerns one of the most widely recognized sexually transmitted viral infections (2). Depending on their specific properties, HPV infections can 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 ones (such as types 6 and 11) are associated with warts (4–8).

HPV causes considerable disease burden in both women and men (9). Men-who-have-Sex-with-Men (MSM) are at particularly higher risk of HPV infections and related illnesses, such as genital warts and anal cancer, compared to heterosexual men (10). A study revealed that the prevalence of HPV infection among MSM is higher compared to men who have sex with women (11–13). Consistently, the incidence of anal cancer is substantially higher in MSM (14–18). The burden is even greater 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 nonavalent vaccine, with the first two representing 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 nonavalent 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 targeted by the quadravalent vaccine (19). It has been documented that HPV vaccines are effective in preventing HPV infection and related diseases in men (20, 21).

National HPV vaccination programmes targeting girls aged 9 to 14 years are in place in many countries. However, only few countries such as Australia, the USA and Canada recommend gender-neutral vaccination programmes (22–24). Where vaccine coverage in girls is poor, in particular, the inclusion of boys in the vaccination programme can bring about beneficial herd effects for unvaccinated girls and obviously directly protects boys. Where vaccination coverage is high for girls, boys potentially already benefit from herd immunity and it would appear that the addition of boys to a vaccination programme might not offer very good value for money (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). HPV vaccines also offer considerable protection against recurrent HSIL lesions in this specific group (12,13). In this specific context the vaccine therefore seems to provide both primary (against infection) and tertiary (against advanced disease) prevention.

The importance of cost-effectiveness is increasing in the context of evidence-based decision-making processes. This review aims to analyse the cost-effectiveness of HPV vaccination targeting primary and tertiary prevention, in current vaccine-eligible and vaccine-ineligible MSM respectively.
Methods

Search strategy


Study selection

The search results were imported into Mendeley Desktop and duplicates were removed. The titles and abstracts of (onlinelibrary.wiley.com) the search results were screened independently by two reviewers (DS and AW) to identify relevant articles. The full texts of potentially relevant articles were (www.health.gov.on.ca) then assessed for eligibility. Studies investigating the cost-effectiveness of the targeted HPV vaccination of MSM were included. Reviews, editorials, letters and articles not in English were excluded. Disagreement among the reviewers was resolved by discussion.

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: authors, publication year, setting (country/location of the economic evaluation), the intervention and comparators considered, type of model used, perspective, time horizon under study, 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 obtain comparable calculations, all the monetary values were transformed into 2016 USD using inflation rates and purchasing power parities from the World Bank Database (28,29).

Risk of Bias Assessment

The risk of bias in the studies included was assessed using (www.salute.gov.it) the Bias in Economic Evaluation (ECOBIAS) checklist, consisting of 22 items specifically intended for model-based studies (30). This checklist is divided into two (www.salute.gov.it) 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. The latter part (part B) specifically covers potential bias related to structure, model specification and the time horizon under study, and data and internal consistency.
Results

Literature search

A total of 770 articles were found initially. Upon removal of duplicates, 612 articles remained and were screened. Of these, 598 articles were excluded for the following reasons: (www.karger.com) 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 (5 articles), correspondence (7 articles) and studies not on HPV infection (3 articles). Furthermore, of the remaining 14 articles eligible for full-text screening, 10 were excluded later as they were (www.karger.com) on vaccination in MSM populations. Therefore, 4 articles were ultimately included in this review (Figure 1).

FIGURE 1 HERE

Study characteristics

All four studies considered vaccination strategies using the quadrivalent vaccine targeting different MSM sub-populations, defined by HIV status and age. Three studies originated in the US (27,28,30) and one in the UK (29). Notably, two studies by Deshmukh et al. considered vaccination as a tertiary prevention strategy for both HIV-positive and HIV-negative MSM who had already developed HSIL (31,32), while two other studies evaluated the impact of vaccination as a primary infection prevention strategy (33,34). Only one study considered Genito-Urinary Medicine (GUM) clinics for the delivery of the vaccination (34). All the studies used a lifetime time horizon. Most (75%) of the studies were 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). As regards the discount rate for costs and health effects, all the studies from the US applied a 3% discount rate (31–33) while the study from the UK applied a 3.5% discount rate (34). Anal cancer was considered in all the studies. (www.salute.gov.it) 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).

TABLE 1 HERE

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 (www.salute.gov.it) ranged from 2006 to 2014; however, as mentioned, all were updated to 2016 USD. Direct medical costs, including treatment costs for the HPV-related outcomes considered were included. Quality Adjusted Life Years (QALYs) were evaluated in all the studies (www.salute.gov.it) included (31–34), while the 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 the studies (www.salute.gov.it) included, there were differences in the specific and exact base case analysis chosen.

TABLE 2 HERE
Three studies specifically presented the values of discounted costs and utilities/QALYs for the individual 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 exposure to HPV type 6, 11, 16 and 18 infections (33). Studies evaluating HPV vaccine for primary prevention showed that the ICER lies below USD 20,000 (33,34) while two studies from Desmukh et al., investigating tertiary prevention through primary or adjuvant vaccination, obtained varying results, with an ICER of USD 96,000 or even negative for HIV-negative and HIV-positive MSM, respectively (31,32). Two studies showed that HPV vaccination of the MSM population aiming to reduce the burden associated with anal cancer would be a cost-effective strategy at the suggested thresholds for the US and UK of USD 50,000/QALYs and GBP 20,000/QALYs (USD 29,000/QALYs), respectively (33,34).

**Sensitivity Analysis**

Sensitivity analysis is performed to evaluate the robustness of the study results considering their heterogeneity and the methodological, structural and parametric uncertainty (Table 3). Deterministic and/or one-way sensitivity analysis was performed by all studies included in this review (31–34). Most of the studies (www.salute.gov.it) also performed probabilistic sensitivity analysis (PSA) using Bayesian statistical decision theory to optimise the decision in relation to the uncertainty in the data (31,32,34). Based on the findings from the one-way sensitivity analysis, the cost-effectiveness of (aura.abdn.ac.uk) MSM HPV vaccination was found to be sensitive to vaccine efficacy, vaccine costs and the incidence of (www.salute.gov.it) anal cancer.

TABLE 3 HERE

**Risk of Bias Assessment**

According to part A of the ECOBIAS checklist (Table 4), some aspects have been performed well, such as using comparators which reflect 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. On the other hand, several potential types of bias according to the ECOBIAS checklist were found in the studies (www.salute.gov.it) included in this review, since most did not include the societal perspective (31,32,34), did not use continuously collected input parameters (longitudinal data) (31–34), did not mention or present fully detailed cost calculations (31,32,34), and did not use any specific pre-specified protocols in their performance (31–34). Various aspects of sensitivity analysis were partially evaluated (mostly related to parameter uncertainty and heterogeneity) in the included studies (31–34).

TABLE 4 HERE

The first category of model-specific aspects of bias pertains to bias related to structure in part B, covering structural assumptions, treatment comparators, model types and time horizon. Since two authors only developed one model in their studies, potential bias could occur because the outcomes generated from this model could not be compared with another model developed from the same natural disease history. Treatment comparator bias seemed to have been optimally avoided since there were no
current HPV vaccination strategies for MSM population. With respect to (www.salute.gov.it) model type bias, only one study by Lin et al. used a dynamic model which could comprehensively describe the transmission of HPV infection in the population and further consequences, including HPV-related cancers particularly in the MSM population. Finally, bias related to a potentially limited time horizon appears to have been avoided since all the studies investigated the (eprints.glos.ac.uk) impact of HPV vaccination using a lifetime horizon.

Several biases related to the data used in the model potentially occurred: all the authors used data from well-designed studies, but they did not provide justification for their choice of data to be included. Although the probabilities were adopted from well-established sources, the transformation process for aligning the 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 meta-analysis but from single Randomized Clinical Trials (RCTs) or non-concurrent cohort studies only. Limited scope bias was also probably only partly avoided since the studies only evaluated the parameter and methodological uncertainty and not structural bias or heterogeneity. All the studies appear to have avoided bias related to the quality of life weights and non-transparent data incorporation as the QALYs were derived from justifiable sources and all the data used in the model were clearly presented.

Internal consistency is an important (eprints.glos.ac.uk) factor for obtaining a good mathematical model for economic evaluation. Only one study in this review (Kim et al.) tested the model before using it for the main study (33). This testing process was achieved by incorporating several different sets of parameter inputs and comparing the results (eprints.glos.ac.uk) with each other for consistency or comparing the model output with actual epidemiological data.

Discussion

HPV vaccination is widely known to be one of the main strategies for preventing HPV-related cancers. While universal vaccination programmes 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 scarcity of studies and settings identified – four studies exploring three different scenarios of vaccination for MSM populations – shows that HPV vaccination for MSM populations can be a cost-effective strategy. In the models considered, the potentially favourable cost-effectiveness is mainly due to anal cancer, but not limited to it (31–34). This finding emphasizes the importance of (eprints.glos.ac.uk) extending HPV vaccination policies beyond girls to include other target populations, such as MSM. Of course, the outcomes of this review should be considered alongside other practical implementation considerations. For instance, where implementing vaccination for adolescent boys is considered unfeasible (39), targeting 15- to 64-year-old MSM individuals might be considered acceptable (31,32,34).

We found in this review that we can generally divide the studies into two groups: those targeting primary and those targeting tertiary prevention using the HPV vaccine. Primary prevention aims to prevent the incidence of primarily anal cancer in the at-risk population, particularly MSM. Primary
prevention is aimed at avoiding the infection per se. While tertiary prevention specifically considers the impact of the HPV vaccine on MSM populations who have had HGAIN, and the results of (eprints.glos.ac.uk) primary prevention studies show favourable cost-effectiveness, the outcomes from the tertiary prevention studies seem highly influenced by the HIV status of the MSM. The findings do show, however, that cost effectiveness provides some justification for decision-makers to extend current vaccination programmes beyond girls to MSM populations (40).

One study could provide relatively strong evidence since 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 (eprints.glos.ac.uk) additional benefit of vaccination policies for defined social groups and covers the detailed impact of vaccination on clinical and economic issues more effectively. Although this study did not assess the herd effects of vaccination on bisexual men, the ICER found in this study (USD 20,461/QALY) was well below the willingness to pay in the UK (USD 30,000/QALY).

While the cost effectiveness of adding HPV vaccination for boys to existing programmes for girls is questionable (44–46), the extension of vaccination policies beyond the girls currently covered to include all MSM populations in society is recommended, as demonstrated by two different studies from Lin et al. and Kim et al. (33,34). Both studies showed that the (eprints.glos.ac.uk) ICER for this extension is below the recommended threshold for the countries considered (the UK and the US). Therefore, HPV vaccination policies for MSM populations seem worth considering, in particular as these individuals will not enjoy the herd protection benefits from existing female vaccination policies.

Both studies by Desmukh et al. (31,32) analysed vaccination for MSM who had already developed and received treatment for High-Grade Anal Intraepithelial Neoplasia (HGAIN) to reduce recurrent HGAIN and avert the development of anal cancer. Notably, previous evidence showed that a quadrivalent vaccine could reduce both the recurrence and the development of anal cancer by almost 50% after the first treatment for HGAIN (20). Both studies showed that the (eprints.glos.ac.uk) strategy was likely to be cost-effective or even potentially cost-saving for HIV-negative and HIV-positive MSM, respectively. These findings influenced US decision-makers considering the expansion of the current vaccination strategies to include both HIV-negative and HIV-positive MSM who had already received treatment for HGAIN in the US.

To underpin decision-making optimally 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), some biases may have occurred in the studies considered. There may be some issues, in particular, concerning societal perspectives and longitudinal data, checking for double counting and advance registration of the study protocol. These biases are common in economic evaluations due to some frequently occurring limitations, including unclear, incomplete or unnecessary reporting of indirect cost data, short data collection periods and scarce data availability. Moreover, unlike the economic evaluations conducted alongside clinical trials, formal protocols for model-based economic evaluations are still rarely designed in advance.
The vaccine efficacy data used in health economic studies is generally never based on a formal meta-analysis. This limitation could result from the small number of male HPV vaccination clinical trials or cohort studies (20), particularly for the MSM population, since not all countries have specific healthcare services for this specific population. Another important consideration is that there are obviously other types of prevention, such as using condoms to prevent HPV and other disease infection. This was not included in the studies reviewed. Such alternatives may prove cost-effective for preventing anal cancer or other types of sexually transmitted infections.

Another important limitation of our review is that the (bmcpublichealth.biomedcentral.com) studies are from two countries only, namely the US and the UK, which obviously do not necessarily reflect the context for MSM populations in other developed countries, let alone developing countries. Economic evaluations in particular are often regarded as highly country-specific, as they are closely related to the healthcare systems in place. The cultural context surrounding MSM may make the whole issue even more country-specific. Studies of other countries are urgently needed to establish whether the extension or introduction of HPV vaccination policies to MSM populations is beneficial and might reduce the health and economic burden generated by HPV infection.

Concluding remarks

The scarce evidence identified in our review, which covered four studies, two countries and three different scenarios, indicates that HPV vaccination for MSM populations might be cost-effective or even cost saving. Cost-effectiveness appeared particularly sensitive to vaccine efficacy and vaccine costs. Given the scarcity of the evidence, however, it is challenging to arrive at definite and strong conclusions at this stage. Further research is needed to provide stronger model inputs and evidence and extended evidence for more countries. Such country-specific studies of MSM populations will assist decision-makers considering the extension or introduction of HPV vaccination policies in their respective contexts.

References


17. Daling JR, Weiss NS, Klopfenstein LL, Cochran LE, Chow WH, Daifuku R. Correlates of homosexual


30. Adarkwah CC, van Gils PF, Hiligsmann M, Evers SMAA. Risk of bias in model-based economic


46. Prue G. Vaccinate boys as well as girls against HPV: it works, and it may be cost effective. BMJ. England; 2014 Jul;349:g4834.

Appendix

Search Term for PubMed


Search Term 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' OR 'medical economics'/exp)
economics' 'pharmacoeconomics'/exp OR 'pharmacoeconomics' OR 'cost*' OR 'cost benefit analysis' OR 'cost effectiveness analysis' OR 'cost minimization analysis' OR 'cost (www.publichealthontario.ca) 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 immunisation OR immunized))) AND ('men who have sex with men'/exp OR 'men who have sex with men' OR (www.opensocietyfoundations.org) 'homosexual male'/exp OR homosexual* OR gay* OR boy* OR men OR man)