**Cost-effectiveness of HPV vaccination: a review of modelling approaches**

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**Abstract:**

Background: A large number of economic evaluations have been published that assess alternative possible HPV vaccination strategies. Understanding differences in the modelling methodologies used in these studies is important to assess the accuracy, comparability and generalisability of their results.

Objectives: The aim of this review was to identify published economic models of HPV vaccination programmes, and understand how characteristics of these studies vary by geographical area, date of publication and the policy question being addressed.

Methods: Literature searches were performed in Medline, Embase, Econlit, The Health Economic Evaluations Database and The NHS Economic Evaluation Database. From the 1,189 unique studies retrieved, 65 studies were included for data extraction based on a priori eligibility criteria. Two authors independently reviewed these articles to determine eligibility for the final review. Data were analysed in the selected studies, focussing on six key structural or methodological themes covering different aspects of the model(s) used that may influence cost-effectiveness results.

Results: More recently published studies tend to model a larger number of HPV strains, and include a larger number of HPV-associated diseases. Studies published in Europe and North America also tend to include a larger number of diseases, as well as being more likely to incorporate the impact of herd-immunity, and use more realistic assumptions around vaccine efficacy and coverage. Studies based on previous models often do not include sufficiently robust justifications as to the applicability of the adapted model to the new context.

Conclusions: The considerable between-study heterogeneity in economic evaluations of HPV vaccination programmes makes comparisons between studies difficult, as observed differences in cost-effectiveness may be driven by differences in methodology as well as by variation in funding and

delivery models and estimates of model parameters. Studies should not only consistently report all simplifying assumptions made, but also the estimated impact of these assumptions on the cost-effectiveness results.

**Summary:**

- There is considerable variety in methodology between economic evaluations of HPV vaccination strategies conducted in different settings and populations.
- Different implementation decisions may therefore result not from actual differences in effectiveness/cost-effectiveness between settings, but simply from differences in methodology.
- Inequitable differences in implementation of HPV vaccination strategies between jurisdictions may be exacerbated by factors such as paucity of data in countries outside of Europe and North America.

## Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted viruses, with up to 80% of the population infected at some point during their lives [1]. It is a cause of cervical cancer, as well as being associated with genital warts, oropharyngeal cancer and a number of other anogenital cancers [2]. The global burden of illness from HPV associated diseases is high, with approximately 530,000 new cases of cervical cancer and 275,000 deaths from the disease reported during the year 2008 [3].

Three vaccines are now licensed for the prevention of HPV infection. Cervarix is a bivalent vaccine that targets HPV types 16 and 18, which are estimated to be responsible for around 70% of worldwide cases of cervical cancer [4]. Gardasil is a quadrivalent vaccine that protects against HPV types 6, 11, 16 and 18, with types 6 and 11 associated with many cases of anogenital warts and recurrent respiratory papillomatosis [5]. Gardasil 9, a nonavalent vaccine which protects against the four strains listed above, and additionally types 31, 33, 45, 52 and 58, was approved by the U.S. Food and Drug Administration (FDA) in December 2014 [6]. Additionally, the bivalent and quadrivalent vaccines have shown some levels of cross protection against HPV types not included in the vaccine [7].

Many countries around the world now implement large-scale HPV vaccination programmes [8]. However, due to the range of potential vaccination strategies, the specific details of the implemented programmes vary considerably between countries. The most common vaccination programme implemented is of adolescent girls [8], although there are a wide range of vaccination ages used. Some countries have also considered vaccination of adolescent boys [9], adult women [10], and specific high risk subgroups (e.g. men who have sex with men [11]). In addition, the vaccines available differ in licensed indication, efficacy, levels of cross-protection and long term immunogenicity [12], as well as price and the required number of doses.

Due to the young age at which individuals are generally vaccinated, the sexually transmitted nature of HPV and the considerably later age at which many HPV-related clinical events (e.g. cervical cancer) occur, there is a long delay between vaccination and the prevention of clinical events. In addition, HPV vaccination has the potential to impact not just clinical outcomes but also the suitability, relevance and cost-effectiveness of other health programmes (e.g. cervical screening). These factors have led to the use of economic modelling to inform integrated HPV prevention policies, given the limitations associated with using clinical trial or short-term observational data alone in informing these decisions. However, the models used vary considerably, for example in terms of their structural frameworks (including in terms of how their input parameters are related and how the clinical events and health states of interest are characterised), in the strains of HPV and types of HPV associated diseases included, the modelling approach applied, and in the assumptions made regarding vaccine characteristics such as efficacy, coverage and duration of protection. Much of the variation between models can be attributed to progress in the area of HPV prevention. Both the availability of vaccines covering increasing numbers of strains of HPV (bivalent, followed by quadrivalent and nonavalent), as well as evidence of cross-protection to non-vaccine HPV types, have tended to increase the numbers of strains of HPV modelled. While immunity to HPV is type-specific, the high degree of homology between some vaccine types with non-vaccine types has led to a certain amount of cross-protection: the clinical manifestation of this cross-protective effect is a greater than expected reduction of cervical intraepithelial neoplasia (CIN). Similarly, as the evidence base linking HPV to increasing numbers of anogenital cancers has grown, so has the number of diseases modelled.

A number of recent systematic reviews have assessed cost-effectiveness models of HPV vaccination programmes [9,13,14,15,16,17]. However, the purpose of these reviews has tended to relate more to the synthesis of evidence on the cost-effectiveness of vaccination in a particular policy context, rather than to providing a more general understanding of the methods used in the modelling of HPV vaccination programmes across policy contexts. The modelling methodology used, however, affects

both the generalisability of the results produced, as well as the comparability of different studies addressing the same or similar questions, which may produce very different results depending on the type of analysis undertaken. As such, an understanding of the range of methods used in analysing the cost-effectiveness of HPV vaccination across policy contexts, as well as the reasons why different methods are selected in different situations, is required in order to appreciate where the results of any individual study sit in the context of similar studies.

To address this issue, a broad systematic literature review was conducted, with the goal of identifying and summarising all economic models that have been produced to evaluate HPV vaccination programmes. Variation in the types of methods used with respect to publication date, geographical region and in light of the specific policy question being asked were explored. Finally, the direction in which different methods might be expected to influence model results was assessed, considering the impact this has on how these results should be used to inform decision making.

## Methods

*Protocol*

The aim of this review was to identify and compare modelling methodologies used in the economic evaluation of HPV vaccination programmes. As such, the primary aim was to identify as many economic models of HPV vaccination programmes as possible and breadth of coverage was given priority. Literature searches were carried out in Medline, Embase, Econlit, The Health Economic Evaluations Database (HEED) and The NHS Economic Evaluation Database (NHS EED), looking for any economic evaluations which compared the impact of different HPV vaccination strategies. The search was conducted on April 10th 2015 and covered the period of each database since its inception. Full details of the search strategy and search terms used can be found in Appendix A of the online supplementary material.

Following literature searches and removal of duplicates, all titles and abstracts were screened independently by two separate reviewers (JP, BP). If either reviewer selected a title and abstract for inclusion, then it was included at this stage and the full report obtained. All full reports selected for inclusion were initially screened independently by two separate reviewers (JP, BP) and consensus sought on whether or not the report met the review's inclusion criteria. Where consensus on inclusion was not achieved a third senior reviewer (SP) made a final decision on the full report. Reports were then divided equally between the two main reviewers (JP, BP) and data extracted independently according to a pre-specified data extraction template (Appendix B of the online supplementary material), with data for 10% of extracted studies cross-checked by the other reviewer to ensure consistency in extraction. Reference lists within included studies were also searched for additional potentially relevant studies.

Full details of the review process from titles and abstracts through to final reports are shown in Figure 1. The inclusion and exclusion criteria for the selection of full reports were as follows:

*Inclusion criteria*

- Published study (including study published online) and;
- Original (previously unpublished in a peer-reviewed journal) decision-analytic model comparing different vaccination strategies for HPV (with or without screening strategies) or HPV vaccination (with or without screening strategies) versus no vaccination/screening only.

*Exclusion criteria*

- Not an original decision-analytic model – adapted version of a published model where no changes were made to the structural framework of the original model (A – see below);
- Conference abstract;
- Previous systematic review (B – see below);
- Published in a language for which an interpreter was unavailable;
- Model only compared different cervical cancer screening strategies and did not include at least one HPV vaccination strategy; or
- Model based on hypothetical rather than actual HPV vaccine(s).

Studies were excluded from the review if they contained an adaptation of a previously published model, rather than a new model (see A, above). This was defined as a decision-analytic model that had the same essential structural framework as a previous model and differed only in terms of values of parameter inputs. Previous systematic literature reviews were also excluded from this review (see B, above). However, the reference lists of studies included in each review identified was searched for any additional relevant studies not captured by our original search. The full list of previous systematic reviews searched is given in Appendix C of the online supplementary material.

*Analysis*

Following data extraction from all identified studies the data were analysed, focussing on six key structural or methodological themes covering different aspects of the model(s) used and that may influence cost-effectiveness results. These were:

- Strain(s) of HPV included in the model;
- HPV-associated diseases included in the model;
- Type of economic evaluation (cost-benefit, cost-utility etc.), and the primary outcome measure used;
- Model complexity (or mathematical sophistication) – including assumptions made around vaccine coverage, efficacy, duration of protection etc.
- Cost perspective and currency applied; and
- Discount rates/time horizon applied.

An assessment was made of how these different model aspects have changed over time, as well as how they vary by geographical area and the policy question being addressed. Finally, where there was evidence of clear methodological heterogeneity between different studies, a qualitative assessment was made as to the expected impact of this heterogeneity on the conclusions drawn from the different studies, and how this affects the comparability of studies using different methods.

## Results

The full search, across all five databases, identified 1,639 studies, of which 1,189 remained after the removal of duplicates. The full screening process is detailed in figure 1, with 65 studies included in the final review for full data extraction (Appendix B of the online supplementary material). A further 50 studies were identified but excluded from full data extraction as each was based on a pre-existing model. These studies are, however, also listed in Appendix B of the online supplementary material, categorised by the model on which they are based. A summary of the characteristics of the studies included in the review is given in table 1. Results are presented both for the 65 studies fully extracted, and the complete sample of 115 studies (inclusive of the 50 further studies excluded from full data extraction).

Detailed information on the characteristics of the 65 studies included in this systematic review is provided in Appendix B of the online supplementary material. The majority of the studies identified modelled populations in either North America or Europe (57%, 37/65), and the number of studies published has been increasing over time (12 between 2005 and 2008, rising to 37 between 2009 and 2012). The majority of studies considered vaccination of girls (78%, 51/65), compared vaccination versus no vaccination (91%, 59/65), and only considered health outcomes in females (82%, 53/65). There was considerable heterogeneity in the numbers of strains and diseases included in the models, as well as in the estimates of vaccine efficacy, coverage, and whether or not secondary cases and/or herd immunity were included in the models.

The results of the models identified varied widely, both between and often within models, given the frequent use of wide-ranging sensitivity and scenario analyses. Between models, results varied due to the different decision problems addressed, the type of economic evaluation conducted, the inclusion/exclusion of different model features (such as herd immunity) and the values of individual model parameters. The results of the 'base case' analysis for each study (where a single 'base case' was identified) are described in detail in Appendix B of the online supplementary material.

*Strains of HPV included in model*

When considering which HPV strain types were included in the various models, three broad classes of model were identified. In the first, only strains 16 and 18 were modelled, meaning that the impact of events caused by other strains (e.g. genital warts) would not be captured. The second class of models included strains 6, 11, 16 and 18 (including, therefore, the impact of genital warts), and the third class included these four strains, as well as a larger number of other cancer-associated strain types. There were also a small number of models where differing strains were grouped together (e.g. one strain representing all high-risk strain types).

There does not appear to be any clear relationship between the country for which the analysis was conducted and the numbers of strains included in the model (Table 2), but there does appear to be a trend over time towards the inclusion of larger numbers of strains (Table 3). More than four strains were included in no models prior to 2005, 8% of models published between 2005 and 2008, 16% between 2009 and 2010, 24% between 2011 and 2012 and 33% after 2012. The trend towards including greater numbers of strains is likely a reflection of both the development of vaccines covering greater numbers of HPV types (bivalent, quadrivalent, nonavalent) as well as evidence for cross-protection against non-vaccine HPV types. A further consideration relates to the availability of data (both on the prevalence of these additional strains and on the link between infection and risk of disease). Hence, in addition to the development of more valent vaccines and the increasing integration of vaccination and screening policies, part of shift towards inclusion of a greater number of strains may also be related to improvements in data collection for these additional strains. The net impact of this is that more recent analyses, incorporating a larger number of strains, are likely to show vaccination to be more cost-effective than older analyses incorporating fewer strains (as more vaccine

preventable disease is being modelled), even if there have been no changes in the dynamics of the disease, and therefore the actual impact of the introduction of the programme remains the same. It is simply that, depending upon assumed etiologic fractions and effectiveness against disease endpoints, more of the health benefits are now being captured by the models.

*HPV-associated diseases included in model*

Associated with, but distinct from, the number of strains included in the model, is the number of HPV associated diseases modelled in the economic evaluation. The inclusion of a larger number of diseases would be expected, in the absence of other changes, to result in vaccination appearing more cost-effective, as there will be more vaccine preventable disease included in the analysis. Again, three broad classes of model were identified: 1) Only cervical cancer or cervical intra-epithelial neoplasia (CIN) and cervical cancer are included in the model), 2) Cervical cancer, CIN and genital warts are included as events, and 3) A broader range of health outcomes are considered, usually including other anogenital cancers, oropharyngeal cancer and/or recurrent respiratory papillomatosis.

Models of North American and European populations are more likely to include a wider range of diseases than those from the rest of the world, with 88% (7/8) of the models including a broad range of health outcomes coming from these two regions (Table 2). 75% (6/8) of these models have also been published since 2012 (with none prior to 2008), indicating that there is a trend towards the inclusion of a broader range of health outcomes in more recent analyses (Table 3). This may partly be due to increasing knowledge of the role of HPV in the pathogenesis of health outcomes other than cervical cancers. Finally, evaluations that assessed the impact of vaccinating both boys and girls were more likely to include a broader range of outcomes (50%, 4/8) than those which only considered vaccinating girls (6%, 3/54), though this finding may be related to time, since the majority of evaluations considering vaccination of both boys and girls have been conducted in more recent years (Table 4).

The net result of this is that more recent evaluations, those conducted in North America and Europe, and those considering vaccination of both boys and girls (as opposed to vaccination of girls alone), are likely to produce more favourable cost-effectiveness estimates than other evaluations, due to the inclusion of a broader range of vaccine preventable diseases (having accounted for other methodological considerations, such as variations in strains included and vaccine coverage; Appendix B of the online supplementary material).

*Type of economic evaluation*

The type of economic evaluation conducted has implications for the comparability of the study results and, therefore, for the extent to which the study results can be interpreted in the context of similar studies. Results of studies using the same evaluation methodology and primary outcome measure (e.g. cost-utility analyses using quality-adjusted life years (QALYs)) can be compared directly, although results from studies with similar primary outcome measures such as cost-utility analyses using disability-adjusted life years (DALYs), cost-effectiveness analyses using life years and even cost-benefit analyses using monetary measures of benefit may retain a more limited comparative interpretation. Cost-consequence approaches, given the range of disparate outcomes considered, present the most problems when considering comparison of the results with those of other studies.

Of the studies included in the review, the majority (74%, 48/65) were cost-utility analyses using QALYs (Table 5). A large majority of studies conducted in North America (100%, 14/14) and Europe (83%, 19/23) used QALYs, whilst cost-effectiveness analyses were more commonly found in studies modelling populations in South/Central America and Africa (40%, 4/10). These differences may represent either differences in the information required by decision making bodies in the different

jurisdictions, or a lack of utility tariffs available for countries in some areas, meaning that the measurement of QALYs may not have been a practical option.

*Model complexity (or mathematical sophistication)*

While all models are a simplification of a complex reality, the extent of this simplification and the existence of any patterns in model simplification over time and geography are of interest. More complex cost-effectiveness models of HPV vaccination would typically include the effects of cross-protection, herd immunity and would model multiple diseases, all of which will likely have a positive impact on the cost-effectiveness of vaccination. However, they may also contain more realistic assumptions regarding vaccine efficacy, coverage and duration of protection, rather than making potentially over-optimistic assumptions of 100% coverage, 100% efficacy and lifetime protection, all of which would tend to decrease the cost-effectiveness of vaccination. Of course, the aggregate effect of these factors on cost-effectiveness will depend on the relative influence of these factors within the model, which in turn will depend on the model structure. While alternative model structures limit the systematic comparisons that can be drawn, it is possible to observe historical and geographical trends in those parameters governing complexity and that is the approach taken by this section, focussing on herd immunity, cross-protection and vaccine efficacy, coverage and duration.

The majority of studies (69%, 45/65) did not include the effects of herd immunity. However, of the North American studies, 8 of 14 did include the effects of herd immunity. Similarly, the majority of studies did not include the impact of cross-protection on non-vaccine type strains (68%, 44/65). This effect was largely consistent across time and geographical region. A large number treated vaccine efficacy as 100% in the base case (26%, 17/65), effectively ignoring the potential impact of less than perfect vaccine efficacy in the model. A further 54% (35/65) of studies assumed vaccine efficacy of 90-99%. Considering North American studies, only 1 of 14 used a vaccine efficacy of 100%, with 11 of 14 using a vaccine efficacy between 90 and 99%. Levels of vaccine coverage were more evenly spread, with a peak at 100% coverage (15 out of 65 studies) but with 17/65 and 14/65 using vaccine coverages of 80-89% and 70-79%, respectively. This effect was largely consistent over time, although of Asian studies, 6 of 11 assumed a vaccine coverage of 100%. Considering duration of protection offered by vaccination, the majority (85%, 55/65) of studies assumed a lifetime duration. This was largely consistent over time and geography, although of the 10 studies not using lifetime duration (2 of which did not state the duration used at all), 4 were European and 3 were North American. These results are summarised in Tables 5 and 6.

Some heterogeneity in methodology and parameter values is to be expected between different countries. For example, differences in estimated vaccine coverage, based on the demographics of those countries and the type of vaccination programme under consideration, would be expected between different countries. However, when comparing the results between different studies, it is important to be aware of systematic differences in methodology that may lead to differences in outcomes. The discussion sections of many of the included studies simply report different estimates of cost-effectiveness from a number of other studies, without considering whether the methodologies and parameter values of the different studies are sufficiently similar to allow for meaningful comparison (i.e. differences in cost-effectiveness represent true differences between populations, and are not merely artefacts of the modelling methodology used).

*Cost perspective and currency*

Cost perspective is expected to impact primarily upon costs of different screening strategies, as for example travelling to screening appointments incurs costs, both in terms of travel expenses and time off work. As such, the effect of adopting a societal as opposed to a health service perspective would be expected to make vaccination more cost-effective relative to screening-only strategies.

The majority of studies (71%, 46/65) adopted a health service perspective for costs, with the remainder taking a societal perspective and typically including elements such as loss of earnings due to illness and expenses incurred travelling to screening appointments. This effect was broadly consistent over time and geography, with the exception of Asian studies, where 55% (6/11) of studies adopted a societal costing perspective (Table 5).

The majority of studies (65%, 42/65) expressed costs in terms of their local currency, with the next most common currency used being US Dollars (by countries for which US Dollars were not the local currency), with 16/65 studies using US Dollars. Although the reporting of studies from different countries in a widely-used currency, such as US Dollars, may facilitate comparisons of the cost-effectiveness of different vaccination strategies, this approach harbours a number of methodological caveats, outlined in the ISPOR Good Practices Task Force on Transferability of Economic Evaluations Across Jurisdictions [18]. Considering geography, US Dollars were well represented across regions, most so in South and Central American studies where 5/7 studies used US Dollars. None of the 10 South/Central American and African studies expressed costs in terms of their local currencies (Table 5).

*Differential discount rates and time horizon*

Studies adopting differential discount rates with costs discounted at a higher rate than outcomes, effectively increase the relative weight applied to outcomes vs costs in the cost-effectiveness calculation, and hence, *ceteris paribus*, HPV vaccination strategies would be expected to appear more cost-effective. Most of the studies reviewed (75%, 49/65) used equal discount rates for costs and outcomes (Table 5). Of the 65 included studies, 11 discounted costs at a higher rate than outcomes and of these, 9 were European studies (5 Dutch, 2 Belgian, 1 French and 1 Italian study). Different discount rates in different countries are to be expected given the different guidelines specified by reimbursement bodies in those countries, but again it is important to consider the impact of these differing assumptions when comparing studies from different settings. Specifically, a result that a vaccination strategy is cost-effective in one country but not another may partly depend on a priori choices for discount rates, as well as on other methodological factors such as between-country differences in cost and effectiveness of the vaccination strategy and the value of the cost-effectiveness threshold applied to the primary health outcome of interest.

Some studies considered a model time horizon of one year, at the point at which the model reaches a steady state. The appropriateness of this approach is questionable as in reality the journey to the steady state is the path that is taken following implementation – to effectively ignore this period and jump forward to the point of steady state ignores the process by which a steady state is achieved (which may not be for a considerable number of years into the future). Furthermore, changes in the healthcare landscape over time cannot be foreseen and so this adds further uncertainty to the model results, which effectively assume the current landscape remains constant until the steady state is reached. The majority of studies (72%, 47/65) used a lifetime or >75 year time horizon (for the initial vaccinated cohort).

*Studies based on previous models*

In addition to the 65 unique models discussed above, an additional 50 studies were identified that met the criteria for inclusion in the review, with the exception that they involved modifications of pre-existing models, rather than development of de novo models (Appendix B of the online supplementary material). Modifications of pre-existing models offer some benefits, including an expanded knowledge base for evaluating the face validity and cross validity of model structural frameworks [19]. Some of the additional 50 studies represented situations where the authors of the initial study then published a number of additional studies, modelling different decision problems but

using the same model framework, whilst others were new groups of authors building models, but basing them heavily on previously published work.

Noticeably, studies based on previous models contained considerably less detail on the assumptions made in the model, and less justification of those assumptions than studies containing a de novo model. This lack of detail may be justified if the decision problem being modelled is very similar to that of the initial study, as the justification for these assumptions from the initial study should remain valid. However, if the model has been applied to a considerably different situation, it is important that sufficient justification is given as to the legitimacy of applying the same model structure in a new context. In particular, there are a small number of models on which a large number of later studies have been based (e.g. 8 additional studies based on Elbasha et al, 2007 [20] and 8 based on Goldie et al [21], 2007), meaning that any over-simplifications made in the original model, such as the restriction of HPV associated diseases modelled in the economic evaluation by Goldie et al [21] to CIN and cervical cancer, are likely to be perpetuated through all subsequent iterations. A robust justification was not always given as to why these were the most relevant models to modify for the new context(s), as opposed to any of the other possible models that could have been chosen for adaptation.

*Impact of simplifying assumptions*

As has been seen above, there is considerable heterogeneity in model structure and parameterisation between different studies, even in models addressing very similar questions. Since it is unlikely that it will be possible to reduce this level of heterogeneity in the foreseeable future (often, even when assumptions differ, it is not possible to regard one as being more correct than another, they are merely different), it is important to consider the impact of these differing assumptions when comparing cost-effectiveness estimates from different models. Table 7 lists those aspects of model structure for which considerable heterogeneity was identified in this review, together with the expected impact, *ceteris paribus*, on the cost-effectiveness of vaccination (versus no vaccination/screening only) of these differing structural/parameter choices.

## Discussion

This review has identified considerable heterogeneity in the methodologies used in models to assess the cost-effectiveness of HPV vaccination programmes, even when those studies address the same decision problem. Although the heterogeneities may be explained in part by the focus of our review on original decision-analytic models, with the exclusion of adapted models, they generate difficulties in comparing the results of different studies. For example, it may be difficult to ascertain whether differences in conclusions between studies represent true differences in the cost-effectiveness of vaccination between different populations and/or interventions, or are simply artefacts of the particular structural or methodological assumptions used in given models. There is also the potential for systematic bias to be present in the conclusions reached by different studies, if there are systematic differences in the methodology employed to address different types of policy question.

In particular, certain factors are predictive of the presence of certain model features, with more recent studies, those conducted in North America and Europe, and those looking at vaccination programmes including boys as well as girls tending to incorporate features such as a larger number of strains and diseases, as well as explicit models of disease transmission (enabling the benefits due to herd immunity to be captured). These features reflect developments in the field and their inclusion allows for a more realistic and accurate account of the benefits of vaccination, whilst also generally having a positive effect on the cost-effectiveness of vaccination versus no vaccination/screening only (there is an exception to this in the case of herd immunity and vaccinating boys, see Table 7). As such, models which do not incorporate these features, such as those conducted longer ago, in other parts of the world, and considering girl's vaccination only, are *ceteris paribus* at a disadvantage. This disadvantage relates purely to the conceptualisation of models and not to any differences in the benefits of vaccination – models which do not incorporate these features can be expected to produce cost-effectiveness estimates which systematically underestimate the true cost-effectiveness of vaccination. This has the potential to produce inequitable differences in implementation decisions between countries, which would not be the case if a consistent methodology were used. For example, given the data limitations present in developing countries, it is likely that a smaller range of diseases will be included in these models. This is likely to lead to estimates of health and economic outcomes that underestimate the true cost-effectiveness of vaccination, although this has to be counter-balanced by the effects of absence of cervical screening programmes in many developing countries which in turn results in a proportionately greater burden of cervical cancer on HPV-preventable disease.

Since there is unlikely to be any prospect of standardising the modelling methodologies used in evaluating different HPV vaccination programmes, it is therefore important that the impact of these differences be specifically considered, both when drawing conclusions from a single model and when comparing between different analyses. In particular, when a pre-existing model is adapted to address a new decision problem, the justification for the assumptions used should be just as rigorous as in the original modelling application, to ensure the model is appropriate for the new context. Secondly, since all models will inevitably contain simplifying assumptions, the impact of those simplifications on potential cost-effectiveness (specifically, in which direction those simplifications might be expected to impact cost-effectiveness, and how they might compare with other studies in the same area) should be explicitly discussed for each set of cost-effectiveness results generated. The most accurate predictions of cost-effectiveness can be expected to come from those models that reflect current understanding and so contain the full range of strains and diseases (i.e. including the effects of cross protection to non-vaccine HPV types and all diseases which have been causally linked to HPV), and where all model parameters (e.g. efficacy, coverage, cross-protection) are based on observed data. Therefore, any deviations from the most conceptually and scientifically up-to-date structure should be justified in each individual model, not merely based on precedent from other evaluations.

There have been many previous systematic reviews that have attempted to synthesise cost-effectiveness evidence for specific HPV policy decisions [9,13,14,15,16,17]. However, these reviews have regularly run into issues related to the lack of clarity around the specific methods used in individual studies, as well as a lack of justification for the choice of those methods in a given context. Improvements in the reporting and justification of methodological assumptions should lead to a greater ability to compare the results of different studies, both in the same context and between different situations, leading to a more robust evidence base being available to inform policy decisions.

In conclusion, there is considerable between-study heterogeneity in economic evaluations of HPV vaccination programmes which makes comparisons between studies difficult, as observed differences in cost-effectiveness may be driven by differences in methodology, as well as by variation in funding and delivery models and estimates of model parameters. Future studies should not only consistently report all simplifying assumptions made, but also the estimated impact of these assumptions on the cost-effectiveness results.

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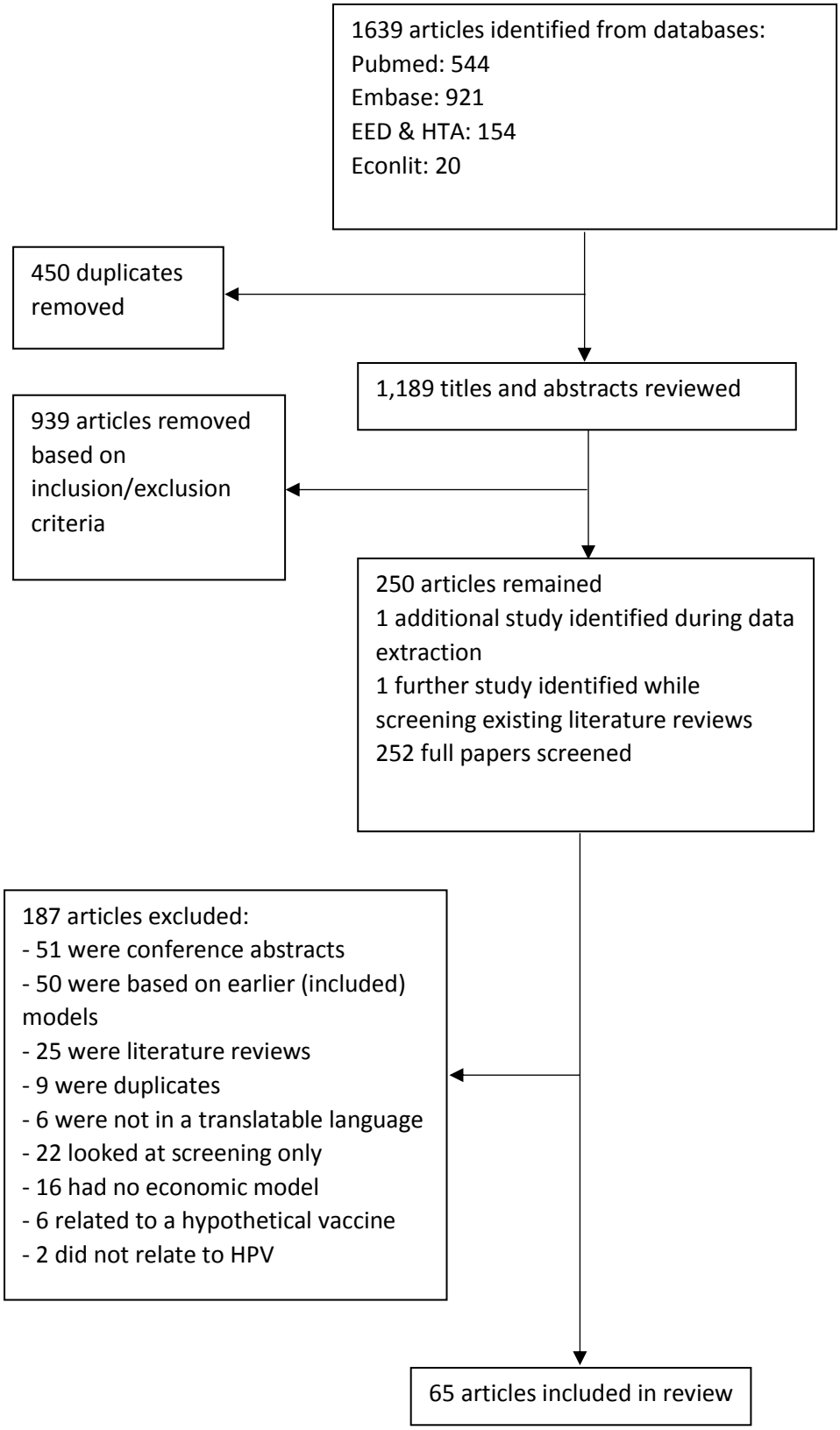
**Figure 1 – Systematic review flow chart**



Footnote to Figure 1: EED denotes Economic Evaluation Databases including The Health Economic Evaluations Database (HEED) and The NHS Economic Evaluation Database (NHS EED).

**Table 1 – Study characteristics.**

| | | Unique models (n=65) | All studies (n=115) |
|---|---|---|---|
| Country | North America | 14 | 23 |
| | South/Central America | 7 | 11 |
| | Europe | 23 | 43 |
| | Africa | 3 | 6 |
| | Asia | 11 | 20 |
| | Other/multiple regions | 7 | 12 |
| Year of publication | Pre 2005 | 2 | 2 |
| | 2005-2008 | 12 | 25 |
| | 2009-2012 | 37 | 58 |
| | Post 2012 | 14 | 30 |
| Vaccinated population (primary analysis) | Girls | 51 | 92 |
| | Girls and boys | 8 | 16 |
| | MSM | 2 | 2 |
| | Adult women | 4 | 5 |
| Vaccination decision (primary analysis) | Vaccination versus no vaccination | 59 | 104 |
| | Comparing different vaccines | 3 | 6 |
| | Comparing number of vaccine doses | 0 | 1 |
| | Age of vaccination | 3 | 4 |
| Disease transmission model | Disease transmission explicitly modelled | 15 | 38 |
| | No disease transmission, but adjustment for herd immunity | 5 | 8 |
| | No herd immunity | 45 | 69 |
| Number of strains modelled | 16/18 | 23 | 42 |
| | 6/11/16/18 | 21 | 40 |
| | More than 4 strains | 13 | 23 |
| | Other | 8 | 10 |
| Health benefits included | Females only | 53 | 91 |
| | Males only | 2 | 2 |
| | Females and males | 10 | 22 |
| Diseases modelled | Cervical cancer/CIN only | 36 | 62 |
| | Cervical cancer/CIN and genital warts | 18 | 35 |
| | Anal cancer and genital warts | 2 | 2 |
| | RRP | 1 | 1 |

| | | | |
|---|---|---|---|
| | Broader range of outcomes | 8 | 15 |
| Vaccine efficacy (vaccine-specific types) | 100% | 17 | 34 |
| | 95-99% | 20 | 38 |
| | <95% | 21 | 32 |
| | Not stated | 7 | 11 |
| Vaccine coverage | 100% | 15 | 26 |
| | 90-99% | 5 | 12 |
| | 80-89% | 17 | 31 |
| | <80% | 20 | 37 |
| | N/A (Benefits/costs calculated per vaccinated person) | 6 | 6 |
| | Not stated | 2 | 3 |
| Type of economic analysis (QALY/DALY) | Cost-utility (QALYs) | 48 | 88 |
| | Cost-utility (DALYs) | 3 | 5 |
| | Cost-effectiveness | 10 | 18 |
| | Cost-benefit | 1 | 1 |
| | Cost-consequence | 3 | 3 |
| Time Horizon | Life (for initial vaccinated cohort) | 32 | 55 |
| | >75 years | 15 | 36 |
| | 50-75 years | 11 | 14 |
| | 30-50 years | 2 | 2 |
| | 1 year (at steady state) | 3 | 3 |
| | Not stated | 2 | 5 |
| Costing perspective | Health service | 46 | 80 |
| | Societal | 19 | 35 |
| Discount rates | Equal for costs and outcomes | 49 | 97 |
| | Higher for costs than outcomes | 11 | 13 |
| | No discounting | 3 | 3 |
| | Not stated | 2 | 2 |

MSM denotes men who have sex with men; CIN denotes cervical intraepithelial neoplasia; RRP denotes recurrent respiratory papillomatosis.

**Table 2 – Disease model characteristics (by geographical area)**

| | North America | South/Central America | Europe | Africa | Asia | Other/Multiple |
|---|---|---|---|---|---|---|
| **Disease transmission** | | | | | | |
| Disease transmission modelled | 6 | 2 | 5 | 1 | 1 | 0 |
| Disease transmission not modelled | 8 | 5 | 18 | 2 | 10 | 7 |
| **Strains modelled** | | | | | | |
| 16/18 | 3 | 2 | 8 | 2 | 4 | 3 |
| 6/11/16/18 | 5 | 1 | 8 | 0 | 3 | 2 |
| More than 4 strains | 2 | 1 | 6 | 1 | 2 | 1 |
| Other | 4 | 3 | 1 | 0 | 2 | 1 |
| **Diseases modelled** | | | | | | |
| CIN/cervical cancer only | 4 | 5 | 11 | 3 | 6 | 6 |
| CIN/cervical cancer and genital warts | 3 | 2 | 9 | 0 | 5 | 0 |
| Broader range of outcomes | 4 | 0 | 3 | 0 | 0 | 1 |
| Other | 3 | 0 | 0 | 0 | 0 | 0 |

CIN denotes cervical intraepithelial neoplasia .

**Table 3 – Disease model characteristics (by date of publication)**

| | Pre 2005 | 2005-2008 | 2009-2010 | 2011-2012 | Post 2012 |
|---|---|---|---|---|---|
| Disease transmission | | | | | |
| Disease transmission modelled | 1 | 3 | 3 | 3 | 5 |
| Disease transmission not modelled | 1 | 9 | 16 | 14 | 10 |
| Strains modelled | | | | | |
| 16/18 | 1 | 2 | 7 | 7 | 5 |
| 6/11/16/18 | 0 | 5 | 6 | 4 | 4 |
| More than 4 strains | 0 | 1 | 3 | 4 | 5 |
| Other | 1 | 4 | 3 | 2 | 1 |
| Diseases modelled | | | | | |
| CIN/cervical cancer only | 2 | 4 | 13 | 10 | 6 |
| CIN/cervical cancer and genital warts | 0 | 7 | 4 | 6 | 2 |
| Broader range of outcomes | 0 | 0 | 1 | 1 | 6 |
| Other | 0 | 1 | 1 | 0 | 1 |

CIN denotes cervical intraepithelial neoplasia.

**Table 4 – Disease model characteristics (by vaccinated population)**

| | Girls | Girls and boys | Adults |
|---|---|---|---|
| Disease transmission | | | |
| Disease transmission modelled | 7 | 7 | 1 |
| Disease transmission not modelled | 44 | 1 | 5 |
| Strains modelled | | | |
| 16/18 | 16 | 3 | 3 |
| 6/11/16/18 | 12 | 4 | 3 |
| More than 4 strains | 12 | 1 | 0 |
| Other | 11 | 0 | 0 |
| Diseases modelled | | | |
| CIN/cervical cancer only | 30 | 3 | 2 |
| CIN/cervical cancer and genital warts | 17 | 1 | 1 |
| Broader range of outcomes | 3 | 4 | 1 |
| Other | 1 | 0 | 2 |

CIN denotes cervical intraepithelial neoplasia.

**Table 5 – Economic model characteristics (by geographical area)**

| | North America | South/Central America | Europe | Africa | Asia | Other/Multiple |
|---|---|---|---|---|---|---|
| **Type of economic analysis** | | | | | | |
| Cost-utility (QALYs) | 14 | 4 | 19 | 1 | 7 | 3 |
| Cost-utility (DALYs) | 0 | 1 | 0 | 0 | 0 | 2 |
| Cost-effectiveness | 0 | 2 | 2 | 2 | 2 | 2 |
| Cost-consequence | 0 | 0 | 2 | 0 | 1 | 0 |
| Cost-benefit | 0 | 0 | 0 | 0 | 1 | 0 |
| **Herd immunity** | | | | | | |
| Herd immunity included | 8 | 2 | 7 | 1 | 1 | 1 |
| Herd immunity not included | 6 | 5 | 16 | 2 | 10 | 6 |
| **Cross-protection** | | | | | | |
| Cross-protection included | 5 | 3 | 6 | 1 | 4 | 2 |
| Cross-protection not included | 9 | 4 | 17 | 2 | 7 | 5 |
| **Vaccine efficacy** | | | | | | |
| 100% | 1 | 1 | 6 | 2 | 5 | 2 |
| 95-99% | 5 | 1 | 8 | 0 | 3 | 3 |
| 90-94% | 6 | 1 | 5 | 1 | 0 | 2 |
| 85-89% | 1 | 0 | 0 | 0 | 1 | 0 |
| <85% | 0 | 0 | 2 | 0 | 2 | 0 |
| Not stated | 1 | 4 | 2 | 0 | 0 | 0 |
| **Vaccine coverage** | | | | | | |
| 100% | 1 | 0 | 3 | 1 | 6 | 4 |
| 90-99% | 0 | 2 | 2 | 0 | 1 | 0 |
| 80-89% | 3 | 1 | 11 | 1 | 0 | 1 |
| 70-79% | 5 | 4 | 3 | 0 | 2 | 0 |
| 60-69% | 0 | 0 | 1 | 0 | 0 | 0 |
| <60% | 2 | 0 | 1 | 1 | 0 | 1 |
| N/A* | 2 | 0 | 2 | 0 | 1 | 1 |
| Not stated | 1 | 0 | 0 | 0 | 1 | 0 |
| **Duration of protection** | | | | | | |
| Lifetime | 11 | 6 | 18 | 3 | 11 | 6 |
| 30+ years | 1 | 0 | 1 | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 20-29 years | 2 | 0 | 2 | 0 | 0 | 1 |
| 10-19 years | 0 | 0 | 1 | 0 | 0 | 0 |
| Not stated | 0 | 1 | 1 | 0 | 0 | 0 |
| **Costing perspective** | | | | | | |
| Health service | 11 | 4 | 17 | 2 | 5 | 7 |
| Societal | 3 | 3 | 6 | 1 | 6 | 0 |
| **Currency** | | | | | | |
| Local | 13 | 0 | 18 | 0 | 7 | 4 |
| US Dollars | 1 | 5 | 3 | 1 | 4 | 2 |
| International Dollars | 0 | 2 | 0 | 2 | 0 | 1 |
| Euro | 0 | 0 | 2 | 0 | 0 | 0 |
| **Discount rates** | | | | | | |
| Equal for costs and outcomes | 13 | 7 | 12 | 3 | 9 | 5 |
| Higher for costs than outcomes | 0 | 0 | 9 | 0 | 1 | 1 |
| No discounting | 0 | 0 | 1 | 0 | 1 | 1 |
| Not stated | 1 | 0 | 1 | 0 | 0 | 0 |
| **Time horizon** | | | | | | |
| Life (for initial vaccinated cohort) | 6 | 2 | 13 | 2 | 5 | 4 |
| >75 years | 5 | 0 | 6 | 0 | 2 | 2 |
| 50-75 years | 2 | 3 | 3 | 1 | 2 | 0 |
| 30-49 years | 1 | 0 | 0 | 0 | 1 | 0 |
| 1 year (at steady state) | 0 | 0 | 1 | 0 | 1 | 1 |
| Not stated | 0 | 2 | 0 | 0 | 0 | 0 |

*(benefits/costs calculated per vaccinated person)

**Table 6 – Economic model characteristics (by date of publication)**

| | Pre 2005 | 2005-2008 | 2009-2012 | Post 2012 |
|---|---|---|---|---|
| **Type of economic analysis** | | | | |
| Cost-utility (QALYs) | 2 | 9 | 27 | 10 |
| Cost-utility (DALYs) | 0 | 0 | 1 | 2 |
| Cost-effectiveness | 0 | 2 | 6 | 2 |
| Cost-consequence | 0 | 1 | 2 | 0 |
| Cost-benefit | 0 | 0 | 0 | 1 |
| **Herd immunity** | | | | |
| Herd immunity included | 1 | 3 | 10 | 6 |
| Herd immunity not included | 1 | 9 | 27 | 8 |
| **Cross-protection** | | | | |
| Cross-protection included | 1 | 4 | 11 | 5 |
| Cross-protection not included | 1 | 8 | 26 | 9 |
| **Vaccine efficacy** | | | | |
| 100% | 0 | 5 | 6 | 6 |
| 95-99% | 0 | 3 | 14 | 3 |
| 90-94% | 2 | 3 | 7 | 3 |
| 85-89% | 0 | 0 | 2 | 0 |
| <85% | 0 | 0 | 4 | 0 |
| Not stated | 0 | 1 | 4 | 2 |
| **Vaccine coverage** | | | | |
| 100% | 1 | 2 | 11 | 1 |
| 90-99% | 0 | 0 | 3 | 2 |
| 80-89% | 0 | 4 | 10 | 3 |
| 70-79% | 1 | 4 | 6 | 3 |
| 60-69% | 0 | 0 | 1 | 0 |
| <60% | 0 | 0 | 3 | 2 |
| N/A* | 0 | 2 | 2 | 2 |
| Not stated | 0 | 0 | 1 | 1 |
| **Duration of protection** | | | | |
| Lifetime | 1 | 10 | 32 | 12 |
| 30+ years | 0 | 0 | 2 | 0 |
| 20-29 years | 1 | 1 | 1 | 2 |
| 10-19 years | 0 | 0 | 1 | 0 |
| Not stated | 0 | 1 | 1 | 0 |
| **Costing perspective** | | | | |
| Health service | 1 | 9 | 27 | 9 |
| Societal | 1 | 3 | 10 | 5 |
| **Currency** | | | | |
| Local | 2 | 10 | 25 | 5 |

| | | | | |
|---|---|---|---|---|
| US Dollars | 0 | 0 | 9 | 7 |
| International Dollars | 0 | 2 | 1 | 2 |
| Euro | 0 | 0 | 2 | 0 |
| **Discount rates** | | | | |
| Equal for costs and outcomes | 2 | 9 | 25 | 13 |
| Higher for costs than outcomes | 0 | 2 | 8 | 1 |
| No discounting | 0 | 0 | 3 | 0 |
| Not stated | 0 | 1 | 1 | 0 |
| **Time horizon** | | | | |
| Life (for initial vaccinated cohort) | 2 | 6 | 16 | 8 |
| >75 years | 0 | 3 | 11 | 1 |
| 50-75 years | 0 | 1 | 5 | 5 |
| 30-49 years | 0 | 1 | 1 | 0 |
| 1 year (at steady state) | 0 | 0 | 3 | 0 |
| Not stated | 0 | 1 | 1 | 0 |

*(benefits/costs calculated per vaccinated person)

**Table 7 – Ceteris paribus impact of simplifying assumptions on cost-effectiveness**

| **Structural feature** | **Possible assumptions** | **Expected impact on cost-effectiveness of vaccination versus no vaccination/screening only** |
|---|---|---|
| Disease transmission/herd immunity | 1) Disease transmission explicitly modelled.<br>2) Disease transmission not modelled, but an adjustment made for herd immunity.<br>3) Health benefits considered for vaccinated individuals only. | Limiting the benefits of vaccination to only vaccinated individuals, and not considering the benefits of a reduced number of secondary cases, will result in vaccination appearing less cost-effective than if the full benefits of vaccination are considered (evaluations of this type are effectively a lower bound of the minimum possible benefit of vaccination). An exception to this is in the case of vaccinating boys, where the inclusion of herd immunity due to vaccinating girls would be expected to reduce the cost-effectiveness of vaccinating boys. |
| Number of HPV strains modelled | Modelling all HPV associated strains versus a restricted set of strains. | Modelling a larger number of HPV strains means a higher proportion of HPV associated disease will be included in the model, and hence vaccination will appear more cost-effective. However, the level of uncertainty in the model will also increase, due to the less robust data available for some HPV strains. |
| Health benefits included | Benefits included for only a subsection of the overall population versus benefits for the whole population. | Many models of HPV vaccination for adolescent girls only include health benefits in females, not males. However, vaccination would also be expected to provide health benefits in males due to reduced transmission, and hence the inclusion of these benefits will make vaccination appear more cost-effective. |
| Diseases modelled | Modelling all HPV associated diseases versus a restricted set of diseases. | Modelling a larger number of HPV associated diseases means the model will include a larger amount of vaccine preventable disease, hence making vaccination appear more cost-effective. However, the level of uncertainty in the model will also increase, due to the less robust data available for the link between HPV infection and some diseases. |
| Vaccine efficacy | Assuming 100% vaccine efficacy versus a data based estimate of vaccine efficacy. | An assumption of 100% vaccine efficacy will make vaccination appear more cost-effective than a more realistic, data based, assumption for efficacy |
| Vaccine coverage | Assuming 100% vaccine coverage versus a data based estimate of vaccine coverage. | An assumption of 100% vaccine coverage, in any population where disease transmission is modelled, will make vaccination appear more effective than a more realistic, data based, assumption for coverage, but the impact on cost-effectiveness is unclear (will depend on the model of disease transmission used). |
| Duration of protection | Assuming lifetime protection versus a limited duration of protection. | An assumption of lifetime protection will make vaccination appear more cost-effective than if protection is assumed to wane over time |
| Cross-protection | Inclusion/exclusion of cross-protection (impact of vaccine on non-vaccine type strains). | The inclusion of cross-protection will lead to vaccination appearing more cost-effective, as a higher proportion of disease in the model becomes vaccine preventable. |

Primary search databases since database inception: Medline, Embase, HEED, NHS EED, HTA database, EconLit

| Search | Search terms |
|---|---|
| 1 | HPV |
| 2 | Papillomavirus |
| 3 | Papilloma virus |
| 4 | 1 or 2 or 3 |
| 5 | Cost-effectiveness |
| 6 | Cost-utility |
| 7 | Cost-benefit |
| 8 | Economic evaluation |
| 9 | Economic model |
| 10 | 5 or 6 or 7 or 8 or 9 |
| 11 | Vaccin* |
| 12 | Immun* |
| 13 | 11 or 12 |
| Final | 4 and 10 and 13 |