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Modeling Preventative Strategies against HPV-Related Disease in Developed Countries

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Abstract

Over the last five years, prophylactic vaccination against Human Papillomavirus (HPV) in pre-adolescent females has been introduced in most developed countries, supported by modeled evaluations which have almost universally found vaccination of pre-adolescent females to be cost-effective. Studies to date suggest that vaccination of pre-adolescent males may also be cost-effective at a cost per vaccinated individual ~US\$400–500 if vaccination coverage in females cannot be increased above ~50%; but if it is possible, increasing coverage in females appears to be a better return on investment. Comparative evaluation of the quadrivalent (HPV16,18,6,11) and bivalent (HPV16,18) vaccines centers around the potential tradeoff between protection against anogenital warts and vaccine-specific levels of cross-protection against infections not targeted by the vaccines. Future evaluations will also need to consider the cost-effectiveness of a next generation nonavalent vaccine designed to protect against ~90% of cervical cancers. The timing of the effect of vaccination on cervical screening programs will be country-specific and will depend on vaccination catch-up age range and coverage and the age at which screening starts. Initial evaluations suggest that if screening remains unchanged it will be less cost-effective in vaccinated compared to unvaccinated women but, in the context of current vaccines, will remain an important prevention method. Comprehensive evaluation of new approaches to screening will need to consider the population-level effects of vaccination over time. New screening strategies of particular interest include delaying the start age of screening, increasing the screening interval and switching to primary HPV screening. Future evaluations of screening will also need to focus on the effects of disparities in screening and vaccination uptake, the potential effects of vaccination on screening participation, and the effects of imperfect compliance with screening recommendations.

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Keywords

HPV; Intraepithelial neoplasia; Uterine cervical neoplasms; Vulvar; vaginal; anal; oral cavity and oropharyngeal cancer; Anogenital warts; Recurrent Respiratory Papillomatosis; Vaccines; Mathematical models; Cervical cancer screening; Cost-effectiveness analysis; Developed countries

1. Introduction

Infection with oncogenic types of the sexually transmitted human papillomavirus (HPV) has been associated with cancers in several anatomic sites in both males and females, including cancers of the anogenital area (cervix, vulva, vagina, anus and penis) and head and neck (oral and oropharyngeal cancers). In total, it has been estimated that oncogenic HPV infection accounted for around 610,000 cancer cases globally in 2008; of these, the majority were in less developed regions, due to limited access to organized cervical screening programs, but ~120,000 occurred in developed regions.(1) Overall, an estimated 530,000 cervical cancers and 80,000 cases of non-cervical HPV-related cancers were diagnosed worldwide during 2008, including up to 39,000 cancers among men.(1) 'Low risk' HPV types 6 and 11 are also implicated in the development of anogenital warts and recurrent respiratory papillomatosis (RRP). HPV vaccination of young females for the prevention of cervical cancer has now been introduced in many developed countries. Because vaccine-conferred protection against a particular HPV type has been shown to be effective only prior to exposure, HPV vaccines are targeted to pre-adolescents or young girls generally before the initiation of sexual activity, but are designed to protect against cervical cancer, which peaks in women aged 45 years and above.(2) As a consequence, the majority of the health gains for cervical cancer prevention are likely to be observed several decades after implementation. In addition to enabling predictions several decades into the future, modeling allows extrapolation of the individual-level efficacy of HPV vaccination to the population level. Mathematical models have therefore played a key role in the evaluation of HPV vaccination, because they enable long term predictions of health and economic benefits that are informative in policy decisions.

A previous review of the HPV vaccination modeling literature, conducted in 2008, concluded that vaccination of pre-adolescent females had been consistently found to be cost-effective, even in the context of established cervical cancer screening practices, provided that high efficacy and long duration of vaccine-conferred protection were assumed,(3) and a subsequent review reached a similar conclusion.(4) At the time of the 2008 review, the analyses had been conducted mainly for North America (with six identified) and a few evaluations had been conducted in other developed countries. More recently, a large number of new evaluations for female HPV vaccination in developed countries throughout Europe and the Asia-Pacific region have been published. At the same time, several related issues have become of immediate policy relevance, which can be considered in three broad categories.

Firstly, there are a number of uncertainties about the cost-effectiveness of extending the appropriate target population for vaccination, particularly the inclusion of pre-adolescent males in vaccination programs. The estimated absolute numbers of preventable HPV-related cancers in males is considerably lower than that in females, because of the high and unique burden of disease associated with cervical cancer, even in the context of existing cervical screening regimes in many developed countries. The HPV-attributable fraction at cancer sites relevant to males has been estimated at 13–56% for oropharyngeal cancers (depending on geographical area), 50% for penile cancers, and 88% for anal cancers.(1) Vaccination has

been shown to be effective in preventing persistent type-specific infection, external genital lesions, and anal intraepithelial neoplasia in males,(5, 6) and vaccination of males also potentially affects transmission to females and to other males. HPV vaccines have been licensed for use in males in several countries and routine vaccination of males has now been recommended in at least two developed countries. In October 2011, the US CDC's Advisory Committee on Immunization Practices (ACIP) recommended routine HPV vaccination of 11–12 year old boys, with catch-up vaccination up to age 21,(7) and in November 2011, Australia's Pharmaceutical Benefits Advisory Committee recommended routine vaccination of 12–13 year old boys with catch-up to age 14–15.(8) The routine inclusion of young males in HPV vaccination programs is also likely to become an imminent policy consideration in other developed countries.

Secondly, an important set of policy questions concerns the choice of vaccine. Two prophylactic vaccines are currently available – the quadrivalent HPV 16,18,6 and 11 vaccine (Gardasil,® Merck&Co., Whitehouse Station, NJ USA) and the bivalent HPV 16 and 18 vaccine (Cervarix®, GlaxoSmithKline Biologicals, Rixensart, Belgium). The inclusion of HPV types 16 and 18 in both vaccines implies that they will ultimately prevent ~70% of cervical cancers in vaccinated women.(9) However, the relative cost-effectiveness of the two vaccines in a particular setting depends on a complex trade-off between vaccine price, the inclusion in the quadrivalent vaccine of protection against anogenital warts (caused by HPV types 6 and 11) and potentially differing levels and duration of cross-protection against oncogenic types not targeted by the vaccines. Furthermore, second generation nonavalent vaccines, expected to protect against approximately 90% of cervical cancers, are now in Phase 3 trials(10) and the incremental cost-effectiveness of these vaccines compared to bivalent or quadrivalent vaccines will require evaluation in settings which have already implemented vaccination programs.

Thirdly, because most developed countries have long-established cervical screening programs (or high levels of opportunistic screening), future evaluations will need to explicitly account for the ongoing interaction between screening and vaccination, in order to predict the impact of vaccination on existing screening programs as new vaccinated cohorts reach screening age, and to assess the cost-effectiveness of new screening strategies in populations of mixed vaccination status.

The objective of the current chapter is to provide an updated review of the literature on modeled evaluations of the cost-effectiveness of HPV vaccination in developed countries, to provide an overview of current areas of consensus, and to discuss some of the emerging challenges in evaluating male vaccination, the choice of vaccine type, and the interaction between screening and vaccination. The chapter focuses on countries with already established organized screening programs or high levels of opportunistic screening in North America, Western Europe and the Asia-Pacific. However, because many Central and Eastern European countries are currently considering implementing organized screening programs, the scope of the review was also extended to include this region and thus to encompass a recent set of evaluations for Central and Eastern Europe (Berkhof, Vaccine, this issue(11)).

2. Overview of mathematical models for decision making

A comprehensive approach to the evaluation of cervical cancer preventative strategies raises a number of technical challenges. These include accurate modeling of HPV transmission within a population, the natural history of progression to cervical pre-neoplastic and neoplastic disease and other HPV-associated cancers, the efficacy of vaccination against different HPV types, screening test performance for various screening and triage test

technologies, diagnostic and treatment processes, and screening and vaccination uptake. Models of HPV-related disease prevention can be conceptually categorized into several interacting components, as follows (i) HPV infection, transmission and vaccination; (ii) natural history of cervical precancerous disease, invasive cervical cancer, anogenital warts and other HPV-related conditions; and (iii) cervical screening. Figure 1 presents a broad conceptual schema for a comprehensive model of HPV disease prevention which is designed to guide the broad structure of future models.

Models may be either *static* or *dynamic*. A commonly used static implementation is the *Markov cohort model* - in their simplest form, cohort models simulate a single birth cohort of people through their lives. In cohort models of HPV-related disease, the probability of incident infection is usually modeled as being dependent on age, but age-specific infection does not change over time. Therefore, such models can only be used to estimate the direct effects of vaccination on vaccinated groups and they cannot capture the changing effect of vaccination over time in reducing the probability of HPV exposure in unvaccinated groups, which is known as *herd immunity*. As a result, cohort models tend to underestimate the overall effectiveness of HPV vaccination. In order to capture the effects of herd immunity, *dynamic models* are required, in which HPV transmission in the population is directly simulated. In a dynamic model, the probability of being infected with HPV depends on the number of sexual partners (usually modeled as being dependent on age and sexual behavior), the probability of a new partner being infected, and the probability of HPV being transmitted from an infected to uninfected partner.

A cost-effectiveness assessment involves calculating the long-term costs and effects of a particular intervention in relation to a comparator strategy, which generally reflects existing practice. The primary outcomes of interest are the predicted change in life years saved (LYS) or quality-adjusted life years (QALYs) saved and the lifetime costs associated with each prevention strategy; these are used to calculate incremental cost-effectiveness ratios (ICER) for competing strategies. The cost per QALY saved takes the quality of life decrements (or *disutilities*) associated with some health states into account. The cost per QALY or LYS may be compared to a willingness-to-pay threshold (which varies from country to country) to determine if an intervention is cost-effective.

It should be noted that cost-effectiveness evaluations are designed to assist in population level decision-making at a government or policy-maker perspective. They assist decision-makers in allocating health care resources effectively. However, the results of cost-effectiveness analyses are not designed to directly inform individual decision-making in situations where elective uptake of HPV vaccine is being considered (for example, in women over 26 years). In these situations, the regulatory approved indications for use, the individual's perspective, and the outcome of their interaction with a medical professional will all play a key role in the decision to be vaccinated.

The Supplementary Material provides more detail on implementation, structure, cost-effectiveness calculations, and calibration, validation and sensitivity analysis for current models of HPV-related disease.

3. Cost-effectiveness of HPV vaccination of females

The implementation of HPV vaccination programs for pre-adolescent females has been supported by setting-specific evaluations of the cost-effectiveness of routine vaccination of pre-adolescents and of catch-up programs in young females. A systematic review was performed of peer-reviewed studies evaluating the cost-effectiveness of vaccination of pre-adolescent females in the context of existing levels and mechanisms of cervical screening in developed countries. PubMed was used as the search database and the final search was

performed on 1st March 2012 (One study not indexed on PubMed, identified via further searching for published evaluations in specific countries in which HPV vaccination has been implemented, was also included in the review(12)). Detailed search terms used are given as notes to Supplementary Table I. A total of 299 potentially eligible studies were identified via abstract review from the initial PubMed search; 40 studies were found to be eligible. Data were initially extracted from each of the studies by one of the authors (KC); this process was independently repeated by a second co-author (HC) and also by two further reviewers (see Acknowledgments). Discrepancies in extracted data were resolved by review and discussion.

The first evaluations published were primarily in the setting of North America. However, 26 evaluations for European countries have now been published (excluding Central and Eastern Europe), most of these since 2008. Prior to 2012, 4 evaluations for Central and Eastern European countries had been performed. A new evaluation of the cost-effectiveness of HPV vaccination in 21 Central and Eastern European countries has recently been reported; this incorporated detailed evaluations of combined screening and vaccination alternatives for 3 countries - Slovenia, Poland and the Republic of Georgia (Berkhof, Vaccine, this issue(11)). Several evaluations (7) have also been performed for developed countries in the Asia-Pacific region (Supplementary Table I).

3.1 Summary of methods and findings for evaluations of vaccination of pre-adolescent females

Supplementary Table I summarizes some of the key assumptions and findings of studies evaluating the cost-effectiveness of HPV vaccination for pre-adolescent females in developed countries. The majority of the evaluations used Markov cohort models. Many only considered outcomes related to cervical cancer, although several also considered anogenital warts in females. A few evaluations, conducted mainly in North America and the UK, considered a broader range of outcomes, such as other HPV-related cancers in females, (13–15) RRP, (14, 15) or outcomes in males (via the effects of herd immunity); these evaluations tended to use more complex dynamic transmission models or ‘hybrid’ approaches using both dynamic and static model components. The assumed cost per vaccinated individual (CVI - which is generally assumed to include the cost of 3 doses of the vaccine, and may also include other costs such as vaccine wastage, freight, supplies and administration) varied from \$360–500 in evaluations for North America conducted from 2008; from €232–480 in Europe; and from £235–282 in the UK. Most studies assumed 100% completion of the 3-dose vaccination course among those who had the initial dose, and assumed efficacy against vaccine type-specific infection in HPV-naïve women of 90–100%. The baseline assumption for most evaluations was that the vaccine conferred a lifetime duration of protection, but because duration of protection has been identified as one of the most important assumptions underlying estimates of cost-effectiveness(16–18) most evaluations considered the impact of waning protection, with 10 and 20 years being the most common periods considered. In the majority of evaluations, it was assumed that screening would remain unchanged in the context of vaccination; screening was modeled at varying levels of complexity, with some studies modeling screening according to recommendations, and others taking some account of the observed participation rates or compliance to recommendations (Supplementary Table I).

In accordance with local guidelines for health economic evaluation, various discount rates and associated willingness-to-pay thresholds were used and there were also differences in whether a societal or health services perspective was adopted for the evaluation. This variation means that the absolute values for cost-effectiveness ratios cannot be compared, except for evaluations performed within the same country at approximately the same time. However, all except one evaluation (discussed below) found that vaccination of pre-

adolescent girls against HPV would be cost-effective when compared to the appropriate local willingness-to-pay threshold.

In several countries, including the USA, Canada, the UK, Ireland, Belgium, France, Italy, and The Netherlands, multiple evaluations by different groups have been reported. Although consistently less than the willingness-to-pay threshold, the absolute value of the estimated incremental cost-effectiveness ratio in different evaluations for the same country varied considerably in some cases, for example in the US,(13, 15, 19) Italy (20, 21) and Ireland. (22, 23) In the UK, the estimated cost-effectiveness ratio has been variously reported as £6,000,(24) £21,000 (25) and £24,000.(26) In a more recent evaluation the cost-effectiveness ratio varied between £12,000–41,000, depending on which vaccine-included types, outcomes, and level of cross-protection were modeled.(14) In The Netherlands, three evaluations concluded that vaccination of pre-adolescent girls would be cost-effective, albeit with a cost-effectiveness ratio close to the willingness-to-pay threshold (27–29) but another reached the opposite conclusion.(30) All used static models, and considered only HPV 16 and 18-related outcomes, but the differences were largely explained by the choice of alternative discount rates used in the study with outlying results.(31–34) The inclusion of other outcomes related to non-cervical HPV-related cancers also improved the estimated cost-effectiveness in this model.(35)

Since organized cervical screening is not yet established (or has only been recently established) in the majority of countries in Central and Eastern Europe, it is difficult to directly compare the findings for the cost-effectiveness of female HPV vaccination in these countries to those for developed countries with long-established screening programs. However, a recent evaluation reporting cost-effectiveness for 21 countries (Berkhof, Vaccine, this issue(11)) concluded that vaccination of 12 year old females is very cost-effective if the CVI is \$100 (2005 international dollars), and in 16 countries vaccination remained very cost-effective at a CVI of \$300.

Overall, the cost-effectiveness ratio for the vaccination of pre-adolescent girls was sensitive to the duration of vaccine-conferred protection, and the associated need to consider booster injections.(15, 20, 25, 28, 36–38) However, in general terms, if a long duration of vaccine protection is assumed, the final decision on cost-effectiveness appears remarkably insensitive to the type of model used (static or dynamic), the outcomes included, or the cost per vaccinated individual (within a feasible range). There appears to be a considerable 'margin of error' in the evaluation of this policy question; since in many evaluations, even those considering only cervical cancer outcomes, the absolute value of the cost-effectiveness ratio was considerably lower than the willingness-to-pay threshold. This robustness of the findings to model structure and outcomes underpins the development of simplified models, which attempt to capture broad outcomes but may not explicitly model precancerous disease or cervical screening, for rapid evaluation of the cost-effectiveness of female vaccination in pre-adolescents. Considerable caution is recommended in the use of simplified models because they may not capture the full range of costs and outcomes of interest, but some initial validation of simplified approaches has been performed in specific settings (13, 26, 39). A major issue in the use of such models is that they may assume that rates of cervical cancer incidence and mortality will be stable in the absence of the vaccination intervention. However, since ongoing decline in cancer rates after the introduction of cervical screening is common, trends in cancer rates in the country of interest should be examined and the assumption of stability carefully justified. Simplified models at this time seem most appropriately used for addressing the specific policy question of the cost-effectiveness of vaccination of young females prior to HPV exposure; it is less likely that simplified models will lead to reliable results for more equivocal questions such as age of catch-up vaccination and male vaccination.

3.2 Catch-up vaccination and vaccination of older women

The modeling of catch-up vaccination is more complicated since catch-up cohorts are more likely to have prior exposure to HPV infection. Some evaluations have considered only the routine vaccination of pre-adolescent girls (or early adolescent girls prior to sexual debut) and others reported only on the combined cost-effectiveness of routine vaccination with catch-up versus routine vaccination,(39–41) but a few studies have reported upon the cost-effectiveness of incorporating progressively older age cohorts to the catch-up program.(15, 22, 24, 42–45) This latter method is the most rigorous approach to determining the appropriate age of catch-up vaccination. In broad terms, incorporating catch-up vaccination to older ages decreases the cost-effectiveness of female vaccination. However, the specific findings have not been consistent – some studies found the cost-effectiveness ratio became unfavorable over age 15 years,(22) others over age 18–21 years,(15, 44) or age 26 years.(24, 42, 45) These differences are likely to result from complex interactions of a multitude of factors including differences in model types and specification, and differences in country-specific factors such as vaccine price. One study on vaccination of 17–25 year-old females in The Netherlands found that vaccination would be cost-effective if the local vaccine price was reduced by 50%.(46) Another evaluation looked specifically at the role of HPV vaccination in women older than 26 years (the upper age limit for most catch-up vaccination programs) and found that the probability of vaccination being cost-effective for women aged 35 to 45 years in the USA was less than 5% in the context of 3-yearly screening.(47)

The validity of the conclusions about catch-up vaccination and vaccination of older women depends on assumptions made about exposure of each of the age cohorts to type-specific HPV infection, since vaccination against a particular HPV type has only been shown to be effective in women who are HPV DNA negative for that type. Furthermore, appropriate modeling of naturally-acquired immunity to infection strongly impacts the calculation of vaccine effectiveness in catch-up cohorts; if naturally-acquired immunity is not included in the model, then catch-up vaccination appears more cost-effective.(43) As the mechanisms of natural immunity are becoming better understood, models will need to be revised to adequately capture the interactions of vaccine-induced protection and naturally-acquired immunity. In the meantime, well-calibrated dynamic models should be equipped to simulate and explore various assumptions around naturally-acquired HPV infection,(48) especially when addressing the differential effects of catch-up vaccination.

4. Cost-effectiveness of inclusion of males in population-based vaccination programs

The inclusion of males in population-based HPV vaccination programs has potential benefits, including direct benefits to vaccinated males for protection against male HPV-related cancers and anogenital warts, and also indirect benefits to non-vaccinated female and male sexual partners via increased herd immunity.(49, 50) However, the return on investment of including males in existing vaccination programs will generally be lower than that of female vaccination for two reasons; firstly because the HPV-related burden of disease in males is lower than in females, but also because heterosexual males derive benefits from female-only vaccination via herd immunity, particularly if coverage in females is high.(49, 51, 52) In general terms, the cost-effectiveness of vaccinating males depends on a number of factors including the predicted herd immunity in heterosexual males derived from vaccinating females, and the proportion of all male HPV-related disease that are in men who have sex with men (MSM).

Using similar methods to those described in Section 3, we performed a systematic review of studies that evaluated the cost-effectiveness of HPV vaccination of pre-adolescent males as

an addition to pre-adolescent female vaccination (detailed search terms used are given as notes to Supplementary Table II). PubMed was used as the search database with the final search performed on 1st March 2012. We found that cost-effectiveness analyses of male vaccination that have been performed vary in which disease outcomes have been considered, and in their assumptions about coverage rates in females. Supplementary Table II shows a summary of the key methods, assumptions and findings of modeled evaluations of population-based male vaccination in developed countries. A total of seven comprehensive published evaluations were identified; four for the USA,(53–56) and three for European countries (the UK, Austria and Denmark).(44, 45, 57)

4.1 Summary of methods and findings for males

Cost-effectiveness analysis of male vaccination has thus far mainly involved dynamic transmission models, although one study used a simplified model of HPV transmission and then simulated outcomes in multiple cohorts.(55) Static cohort models are problematic in the evaluation of the incremental benefits of male vaccination in populations where female vaccination has already been implemented, because cohort models do not take into account herd immunity and thus tend to underestimate the effectiveness of female vaccination, which may lead to a more attractive cost-effectiveness ratio for male vaccination. The majority of evaluations considered vaccination of 12 year old males in relation to female-only vaccination, conducted in context of cervical screening, although the male vaccination scenario considered in one study included male catch-up from 9–26 years.(54) The assumed cost per vaccinated individual in the main cost-effectiveness analysis varied from \$400–\$500 in US studies and from €15–480 in European studies (see Section 5 for a discussion of the issue of the impact of vaccine price).

We identified four US studies, all reporting on results according to varying coverage scenarios in females; three of these also reported according to a range of outcomes, and Table 1 shows the incremental cost-effectiveness ratios as a function of these variables. As shown in Table 1, the estimated incremental cost-effectiveness ratio associated with vaccinating males increases with increasing coverage in females, and decreases with consideration of more health outcomes. If several of the outcomes for which the quadrivalent vaccine is approved by the US Food and Drug Administration (FDA) are included (cervical, vulval, vaginal cancers and anogenital warts), and coverage rates in females are lower than 50%, then male HPV vaccination would have a cost-effectiveness ratio in the range \$50,000–100,000;(54, 55) however, even if all potential HPV disease-related outcomes are considered, cost-effectiveness ratios are generally unfavorable if coverage in females is higher than 70%.(53, 55, 56) Consequently, an informal benchmark has emerged that inclusion of males in vaccination programs is less likely to be cost-effective when coverage in females is higher than 50%.(49) The recent recommendation to vaccinate young males in the US was in the context of comparatively low coverage in females overall, with 32% 3-dose completion among females aged 13–17 years in 2010.(58)

The cost-effectiveness of male vaccination is also sensitive to the assumed CVI.(53) Although the 50% female vaccination coverage threshold is a useful metric, there exists a threshold CVI at which vaccination of males is cost-effective, which will differ by setting because it will depend on the coverage rate achieved in females and other factors. In Australia, where coverage in females is comparatively high (i.e., 73% for 12–13 year old girls between 2007–9 (59)), after an initial rejection for public funding on grounds of cost-effectiveness, a recent re-evaluation was performed which resulted in a recommendation to extend vaccination to males. This specified ongoing administration to 12–13 year old males with a catch-up to 14–15 years,(8) but pricing and supply agreements, critical to implementation, have yet to be announced. Although the inclusion of males in HPV vaccination programs can be cost-effective in some circumstances, increasing coverage in

males is unlikely to be associated with a more attractive cost-effectiveness ratio than increasing coverage in females, if this can be achieved.(55, 60) For example, Chesson et al. found that increasing coverage of 12-year-old girls in the US would be more cost-effective than extending vaccination to males even if the increased female vaccination strategy incurred program costs of \$350 per additional girl vaccinated, roughly the cost of the three-dose series in the US.(55) In addition, the feasibility of achieving comparable coverage levels in males should be considered before male vaccination programs are implemented.

4.2 Vaccination of men who have sex with men

HPV vaccination of males has the potential to directly benefit men who have sex with men (MSM). MSM, particularly those who are HIV-positive, may be at a disproportionately higher risk of anal cancer.(61, 62) There are no current recommendations to screen for anal cancer in high risk groups, and so primary prevention with HPV vaccination is an attractive possibility. Targeted vaccination of MSM would depend on willingness to disclose exposure to receptive anal intercourse, and models need to account for the possibility of prior exposure to HPV in this group. Kim(63) found that targeted vaccination of MSM in the US could be cost-effective up to age 26 years under varied assumptions of HPV exposure, anal cancer rates, and HIV prevalence. The specific findings were dependent on the assumed proportion of MSM still susceptible to incident infection with vaccine-included types at the time of vaccination. Because the evidence on HPV in MSM is less certain and variable across settings, and because this evaluation used a static rather than dynamic model, these results should be viewed as preliminary and not generalizable to other settings. The models of population-based male vaccination reported to date (Supplementary Table II) do not explicitly include MSM in their analysis, and therefore may underestimate the cost-effectiveness of including males in vaccination programs. However, including MSM in population models is complex because non-exclusive MSM may receive some benefits from female vaccination; and even exclusive MSM could theoretically benefit from reduced rates of infection in non-exclusive MSM in their network. In practice, sufficiently detailed population-level data for modeling behavior in non-exclusive MSM is very difficult to obtain. A pragmatic alternative is to perform sensitivity analysis where the most favorable assumptions are explored for male vaccination. For example, since much of the burden of HPV-related cancer in MSM is due to anal cancer, one such favorable assumption is that no anal cancers in the male population overall will be prevented as a result of female vaccination-induced herd immunity.(52) Such sensitivity analysis will assist in deriving a range of potential cost-effectiveness estimates for male vaccination which encompass the uncertainties in both heterosexual male and MSM behavior.

4.3 Future research on male HPV vaccination

The effect of the cost per vaccinated individual on the cost-effectiveness of male vaccination is a major issue for future research, and it is likely that threshold analysis on vaccine price in specific settings will be required. As the experience in Australia demonstrates, in countries with high levels of vaccination coverage in females, vaccine price is likely to play a major role. The CVI may also decrease as a result of the possible introduction of 2-dose, rather than 3-dose schedules.(64)

As discussed in Section 4.2, an area of uncertainty for future research includes the uncertainties related to the herd immunity derived from female-only vaccination.(50, 65) Another area of research will involve more detailed consideration of the uncertainties generated by the more limited data on vaccine efficacy for prevention of infection and cancer outcomes in men,(66) because the incremental effectiveness of male vaccination increases in the context of higher efficacy assumptions for male vaccination, or lower efficacy assumptions for female vaccination.(49, 52, 54) Another important challenge will

be specific modeling of genital-oral HPV transmission and consideration of potential increases in the HPV-attributable fraction of oropharyngeal cancers.(67) Finally, an important area of research concerns patterns of uptake between males and females. In situations where males who are vaccinated tend to be in the same social and behavioral groups as vaccinated females, the incremental benefits of male vaccination are likely to be lower.(68)

5. Vaccine Price

Vaccine prices to accredited large scale government vaccination programs are likely to have been set in many countries after competitive tender processes and perhaps also after subsequent negotiation with suppliers. The prices at which vaccine is supplied within such programs are not generally available in the public domain; however, it is thought that per-dose prices in some settings may be considerably lower than the ~US\$100 per dose initial list price, corresponding to a CVI of ~\$400–500, which has been the basis for the majority of published cost-effectiveness evaluations of vaccination (see Supplementary Table I and II).

Many of the published HPV modeling studies have evaluated the sensitivity of the cost-effectiveness estimates to assumptions regarding CVI. Predictably, the CVI is usually an important determinant of the cost-effectiveness of vaccination. For example, one study estimated that the cost per QALY gained by quadrivalent vaccination of 12-year-old girls was CAN\$20,500 when the CVI was CAN\$400, and that each decrease of CAN\$50 in the CVI would reduce the cost per QALY gained by about CAN\$3000.(69) As another example, the ICER for male HPV vaccination was estimated to vary from \$25,900 per QALY with a CVI of \$360 to \$52,500 per QALY with a CVI of \$600.(55) The relative impact of changes in the CVI on the ICER varies depending on a range of factors that influence the estimated magnitude of the vaccine impact on health outcomes, such as vaccine efficacy, duration of protection, the health outcomes included in the analysis, and the burden of disease in the absence of vaccination. Thus, the sensitivity of cost-effectiveness findings to changes in assumptions about CVI can vary across different countries as well as across different types of models.

A related issue is that of vaccine program fixed overheads and/or the potential for wastage due sunk costs associated with bulk pre-purchasing of vaccine. Few identified evaluations directly examined the effects of these factors as a function of the vaccine coverage rate. In the majority of the evaluations of pre-adolescent female vaccination, the cost per vaccinated individual was assumed to be independent of vaccination coverage. Under this assumption, cost-effectiveness has not varied greatly with coverage in most evaluations (although in dynamic models there is some variation which is driven by herd immunity effects at different coverage levels). If fixed overheads are considered, then vaccination of females is expected to become less cost-effective at lower coverage rates. One evaluation for Singapore found that if sunken costs are assumed for a cohort, then the ICER for a QALY gained at 20% coverage was (SGD)\$61,804 and \$67,631 for the quadrivalent and bivalent vaccine, but at 80% coverage this decreased to \$12,367 and \$13,973, respectively.(70) The interactive effect of vaccination coverage rates and program overheads and/or sunk costs on the cost-effectiveness of both female and male HPV vaccination remains an important consideration for future evaluations.

Despite these issues, for female vaccination it appears that the majority of evaluations have been conservative with respect to vaccine price, assuming high CVIs which broadly correspond to the list price of the vaccine. Since the currently supplied vaccine prices in some settings may be considerably lower, this provides some reassurance that these

vaccination programs for pre-adolescent females are operating at attractive levels of cost-effectiveness. For male vaccination, threshold analyses for vaccine price are likely to be an important area for ongoing evaluation.

6. Choice of vaccine type

6.1 Bivalent versus quadrivalent vaccines

The quadrivalent vaccine has now been adopted for use in many developed countries; and the bivalent vaccine has been used in national programs in the UK, the Netherlands, Italy and in some autonomous regions of Spain (although the UK will use the quadrivalent vaccine in its national vaccination program from September 2012 (71)). In countries choosing to adopt only one vaccine, an important category of evaluation is the comparison of the relative cost-effectiveness of bivalent and quadrivalent vaccines. In general, such a comparison depends upon a complex trade-off between assumptions for the duration of direct protection, the extent and duration of cross-protection, and protection against anogenital warts and RRP. An obvious advantage of the quadrivalent vaccine is the additional benefits and cost-savings associated with protection against anogenital warts conferred by inclusion of HPV types 6 and 11. When potential differences in cross-protection or vaccine price trade-offs were not considered, a number of studies have found that the cost-effectiveness ratio for vaccination against HPV 16,18,6 and 11 is more favorable than for HPV 16 and 18 alone (Supplementary Table I).

In analyses of vaccine cost-effectiveness it is generally assumed, in the base case, that both vaccines will have very long duration or lifetime protection for vaccine-included types. Although reports of Phase 3 clinical trials have provided follow-up data for 10 years or less, a plateau in HPV16 antibody titers after several years of follow-up suggests that protection is likely to be sustained over the long term;(72) however, in the case of the quadrivalent vaccine it is not yet clear whether protection will be sustained in the long term for HPV18. The bivalent vaccine induces higher titers of serum neutralizing antibodies (73) and while the long term clinical implications are unknown, it is possible that this might eventually be associated with a longer duration of protection. Additionally, reports from the relevant Phase 3 trials for each vaccine suggest that the bivalent vaccine may be associated with an increased level of cross-protection against non-vaccine-included types(74, 75) but differences in analytic methods and follow-up times make it difficult to directly compare trial results. Duration of cross-protection is also a major area of uncertainty since cross-neutralizing antibody titers are substantially lower for types not included in the vaccine than for vaccine-included types.(76)

An analysis comparing two hypothetical, equivalently priced vaccines in three countries concluded that a bivalent vaccine becomes cost-effective if it provides a 22–44% higher level of cross-protection against non-vaccine-included types than a quadrivalent vaccine. (77) An analysis for Italy concluded that the costs savings for anogenital warts could potentially be offset by the additional savings in treatment costs for precancerous lesions and cervical cancer that arise from greater cross-protection by the bivalent vaccine.(78) However, if quality of life aspects are taken into account the quadrivalent vaccine may be more attractive due to the quality of life gains associated with prevention of anogenital warts.(70)

An alternative approach is to calculate the threshold cost at which the two vaccines have equivalent cost-effectiveness. Jit et al have performed analyses in the UK which considered a range of outcomes, duration of protection and cross-protection assumptions.(14, 44) and concluded that the bivalent vaccine would need to be £19–35 (approximately 22–41%) cheaper per dose to have equivalent cost-effectiveness to the quadrivalent vaccine, mainly

due to the lack of protection against anogenital warts. This finding is consistent with analyses for Ireland and Canada that the bivalent vaccine would need to be 22–26% cheaper, although these analyses considered only cervical cancer and anogenital warts outcomes.(23, 69) Taken together, these studies imply that although the price trade-off between vaccines is setting-specific, it is primarily driven by the burden of disease for anogenital warts, the relative costs of treatment for warts and precancerous lesions, and the associated quality of life impacts.

6.2 Nonavalent vaccines

Second generation nonavalent (nine-valent) vaccines are currently in clinical trials with results expected in 2012.(10) The nonavalent vaccine is expected to include HPV types 16/18/31/33/45/52/58, together implicated in approximately 90% of cervical cancers, in addition to types 6 and 11. It is not yet known what the duration and degree of protection will be for each of the included HPV types, or whether the current high levels of efficacy against HPV 16/18 will be maintained. An initial report of an evaluation of the comparative effectiveness of bivalent, quadrivalent and nonavalent vaccines estimated that the protection against cervical cancer, assuming 70% coverage, would be 78%, 73% and 84%, respectively.(79) Since HPV 16 is responsible for the majority of cancers at sites other than the cervix, the comparative effectiveness against other HPV-related cancers is expected to be very similar for all vaccines, provided that the efficacy and duration of protection against HPV 16 are comparable. This will considerably simplify the calculation of the comparative cost-effectiveness of second generation vaccines, since, to a first approximation, incremental effectiveness will be driven by further reductions in cervical precancerous lesions and invasive cervical cancer. It is likely that cost threshold analyses for bivalent or quadrivalent versus nonavalent vaccines will be required in different settings.

7. Interaction between HPV vaccination and cervical screening

7.1 Evaluation of the impact of vaccination on screening

It is expected to be several decades before HPV vaccination has a direct impact on rates of cervical cancer, but in some countries a relatively rapid impact on rates of detected high grade precancerous abnormalities in young women may occur. The timing of this effect will depend on several factors, including the start age of screening, the oldest age to which vaccination catch-up was conducted, and vaccination coverage in the catch-up phase. Table 2 shows some of the key parameters for selected countries. In England, several years are expected before there is any overlap in screened and vaccinated cohorts and so reductions in abnormalities will not be apparent for some years after vaccination.(80) In the US, the ages of screened and vaccinated cohorts overlap, but because coverage in young women is lower, it may be some time before a discernible impact on screening outcomes is detected (although it is possible that effects may be seen in subgroups with high uptake of both screening and vaccination). In Australia, vaccinated and screened cohorts have also overlapped from the inception of the vaccination program, but vaccination coverage is higher. Therefore, Australia is expected to be one of the first settings where the effects on screening will be observed, and a preliminary report already shows decreasing rates of screen-detected high grade abnormality rates in females under age 18 years.(81)

It will be important to model the interactive effects of screening and vaccination for several reasons. The first is to predict the timing and extent of the effect of decreasing abnormality rates in young women, which will be important for predicting specialist referral and treatment rates. Vaccination will also eventually have an impact on laboratory reporting standards for quality assurance, which are often based on detection rates for abnormalities within specific ranges. Secondly, the effect of vaccination on the cost-effectiveness of

existing cervical screening programs will require assessment as a basis for considering future changes to screening in the context of vaccination, including delaying the start age of screening, extending the screening interval, and switching to primary HPV screening. From a programmatic perspective, consistent screening recommendations across vaccinated and unvaccinated cohorts would considerably facilitate the organization of screening; but even under this assumption modeled evaluations of screening will need to consider the ongoing effect of new vaccinated cohorts entering screening programs. If HPV testing is used in the screening pathway, screening could also serve to monitor the impact of vaccination, and this will also potentially play a role in the evaluation of new strategies for screening.

7.2 Effect of disparities in screening and vaccination uptake and changes in screening behavior post-vaccination

The majority of cost-effectiveness evaluations of HPV vaccination have assumed that vaccine uptake will be homogenous across different subgroups in the population. However, vaccine uptake is likely to be associated with factors such as socio-economic status and sexual behavior, both of which have been also associated with participation in cervical screening. It has been demonstrated that the cost-effectiveness of combined strategies is less attractive if high risk groups are less likely to participate in both the screening and vaccination programs.⁽¹⁵⁾ Conversely, concerns have been raised about a potential decrease in screening participation among vaccinated women. A few modeled evaluations have examined this issue^(19, 82) which will be an important component of the ongoing evaluation of the impact of vaccination on screening. Going forward, linked data from vaccination and screening registers in some countries (such as Australia and the Nordic countries) will provide information enabling detailed characterization of screening behaviors in relation to vaccination status, although these data may be difficult to extrapolate to other settings.

7.3 Evaluation of changes to screening in context of vaccination

Over time, the vaccination of successive cohorts of girls will continually reduce the average lifetime risk of developing invasive cervical cancer in the population, and therefore existing screening practices will eventually become less cost-effective. This is particularly true for nonavalent vaccines which in the long term are expected to reduce the lifetime risk of cervical cancer to very low levels. Finding cost-effective screening approaches in vaccinated populations will require consideration of new strategies. In recent years, a large body of evidence from large randomized controlled trials on primary HPV DNA testing has emerged, and this has been shown to be potentially cost-effective in unvaccinated women, if an appropriate triage procedure is used in HPV positive women and if women are screened at appropriate ages.⁽⁸³⁾ New automated platforms for primary HPV testing should drive down test costs, which will be an important consideration in maintaining the cost-effectiveness of screening in vaccinated populations. Raising the start age of screening and increasing the screening interval are also important strategies for increasing the cost-effectiveness of either cytological or HPV-based screening in vaccinated women. Various options for the management of HPV positive women have been proposed, including cytological triage, genotyping (i.e. to detect whether types 16, 18 and/or 45 are present), and dual-stained cytology for over-expression of p16INK4a (p16) and Ki-67. Most of these future screening options have not yet been evaluated for cost-effectiveness in the context of HPV vaccination. For future cohorts offered access to nonavalent vaccines, initial work suggests that HPV screening would still remain cost-effective if it is conducted less frequently, potentially once or twice per lifetime.⁽⁸⁴⁾

One approach to cost-effectiveness evaluation is to consider cohorts of vaccinated and unvaccinated women separately. This approach to evaluation should help to identify

generalizable screening strategies that are appropriate across populations of mixed vaccination status. One US study found that 3-yearly screening with cytology and HPV triage in young women (<30–35 years) switching to HPV screening with cytology triage in older women is associated with an ICER of \$78,000/QALY in unvaccinated women which increased to >\$150,000 per QALY in vaccinated women; but in vaccinated women the ICER was reduced to \$41,000/QALY if the screening interval was increased to 5 years.(85) A study for Spain found that 5-yearly cytology screening with HPV triage testing in women aged 30–65 years was associated with an ICER of €6,000/LYS in unvaccinated and €24,000/LYS in vaccinated women, respectively.(86) Although these results suggest cytology may still be a useful screening approach in vaccinated women, the performance of cytology may change in the future, potentially due to cytopathology de-training effects and/or depletion of the more cytologically apparent HPV-16 related lesions in vaccinated populations;(2) and the potential effect of this on the cost-effectiveness of screening requires further work. Future evaluations will also need to consider the changing cost-effectiveness of screening strategies from a population-level perspective as vaccinated cohorts enter screening programs over time; full evaluation will involve consideration of the effect of herd immunity in reducing infections and their sequelae even in unvaccinated women.

The introduction of screening at longer intervals will pose substantial challenges to screening programs. The cost-effectiveness of HPV-based screening will be adversely impacted if women attend more frequently than at the recommended interval, and, conversely, loss to follow-up may worsen over longer re-screening intervals. Many countries organize screening on a reminder-based system; moving to proactive ‘call-and-recall’ systems could be evaluated as part of the consideration of HPV-based screening. The differing compliance associated with alternative methods of organizing screening has been shown to influence the effectiveness and cost-effectiveness of longer-interval approaches in modeled evaluations (87) and therefore the robustness of conclusions about the cost-effectiveness of HPV screening will need to be tested against various assumptions about the degree of over- and under-screening that will occur in different circumstances.

8. Conclusions

A number of evaluations of the vaccination of pre-adolescent females against HPV in developed countries have now been conducted, and these have almost universally found this intervention to be cost-effective, even in the context of existing screening programs. Although studies differ in their conclusions about the optimal age for catch-up vaccination, many found that catch-up becomes increasingly less cost-effective over the age of 18 years. The cost-effectiveness of vaccination of males has been evaluated in a few settings and the findings suggest that, at current vaccine prices, vaccination of males is more likely to be cost-effective if vaccine coverage in females is less than about 50%, but additional consideration should be given as to whether a meaningful level of coverage in males can be achieved. A correlate of this finding is that the threshold vaccine price at which vaccination of both sexes becomes cost-effective will differ by setting, because it will depend on coverage in females. However, investing health care resources to increase coverage in females, if this can be done effectively, is likely to be a better return on investment than extending coverage to males under any vaccine pricing conditions. A few studies evaluating the choice of vaccine type have also been conducted, suggesting that the vaccines would have comparable cost-effectiveness in developed countries if the bivalent vaccine were to be supplied at a 20–40% lower cost compared to the quadrivalent vaccine.

A major focus for future modeling research will be evaluating the effects of vaccination on screening programs. It will be important to evaluate changes to screening in an integrated fashion, considering the combined effects of changes in test technology, age range, and

screening interval in the context of vaccination. Although primary HPV testing holds promise as an effective and cost-effective strategy in vaccinated populations, it will require further evaluation at the population level, as vaccinated cohorts age and enter screening programs. It is not yet clear whether there will be generalizable conclusions for optimizing screening, or whether differences in vaccination coverage, timing, catch-up ages, disparities in vaccination uptake, screening compliance and the existing screening background will drive differing screening recommendations across settings. A new group of modeled evaluations will be needed to deal with these complex issues as the interacting effect of vaccination and screening unfolds in developed countries over the next decade.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- HPV vaccination of pre-adolescent girls is cost-effective.
- At US\$400–500 per individual, male vaccination may be cost-effective if female uptake is <50%.
- Cost-effectiveness of screening requires re-evaluation in vaccinated populations.
- Primary HPV screening is a promising strategy in partially vaccinated populations.

Figure 1. Model of HPV transmission and vaccination, the natural history of disease, disease outcomes and cervical screening: Schematic diagram to guide future implementations

(a) Type-specific vaccination and naturally-acquired immunity can be modeled. Both vaccine-induced and naturally-acquired immunity can be modeled as waning over time. If the duration of immunity to HPV infection is modeled as lifelong, individuals do not become susceptible to re-infections with the same HPV type. Although vaccine can be delivered on a population basis, only susceptible individuals can be effectively vaccinated with current generation prophylactic vaccines.

(b) Anogenital to oral HPV transmission has not generally been modeled explicitly in the evaluations conducted to date.

(c) Many models to date have used the histological CIN 1–3 designation to represent natural history states, but the natural history schematic depicted here is designed to guide future evaluations by reflecting the most current biological understanding of the natural history of HPV infection of the cervix (see Supplementary Material). However, this does not necessarily imply that there are no transitory states between infection and CIN3 that are relevant to modeling; rather that future models should attempt to capture the best current understanding of underlying biological processes.

(d) In practice, precancerous lesions should ideally be incorporated into models of HPV transmission since they are more likely to arise from persistent HPV infections.

(e) In the future, male vaccination may be implemented in conjunction with anal cancer screening and this will need to be reflected in comprehensive models.

Table 1

Incremental cost-effectiveness ratios of HPV vaccination of 12 year old males compared to female-only vaccination in the USA (\$/QALY saved)(53–55)^{a,b}

Vaccination coverage in females	<50%	50–70%	>70%
<i>Considering cervical cancer outcomes only</i>			
Kim et al 2009	-	>\$220,000	\$290,000
Elbasha et al 2010^c	\$195,000	-	-
Chesson et al 2011	\$69,000-\$122,000	-	\$741,000
<i>Considering cervical, vulval, vaginal cancers and anogenital wart outcomes^d</i>			
Kim et al 2009^e	-	-	\$208,000
Elbasha et al 2010^c	\$69,000	-	-
Chesson et al 2011^f	\$52,000-\$89,000	-	\$436,000
<i>Considering all potential HPV-related disease outcomes</i>			
Kim et al 2009^e	-	\$62,000	\$91,000
Elbasha et al 2010^c	\$26,000	-	-
Chesson et al 2011	\$24,000-\$41,000	-	\$184,000

^a Assumes high vaccine efficacy against new infections in both males (85%+) and females (90%+) and long duration of protection in both sexes (30 years to lifelong).

^b Although there is no official threshold for determining cost-effectiveness of public health interventions in the US, a threshold of \$50,000–100,000 per QALY is often cited.

^c Considers vaccination of males and females aged 12–26 years compared to female-only vaccination over the same age range.

^d The quadrivalent vaccine was also approved for the prevention of anal cancer and associated precancerous lesions due to HPV 6, 11, 16, and 18 in people ages 9 through 26 years in the USA, in December 2010.

^e Does not include anogenital warts.

^f Considers cervical outcomes and anogenital warts only; excludes vulval and vaginal cancers.

Key parameters determining the magnitude and timing of the interaction between HPV vaccination and cervical screening: Selected countries

Table 2

Country	Vaccination commencement	Catch-up upper age (years)	Estimated 3-dose vaccination coverage in females	Screening starting age (years)	Screening interval recommendation
USA ^a	2006 – 2007 ^b	26	32% in 13–17 year olds (58)	21(88)	3-yearly ages 21–65 years; or 5-yearly for women ages 30–65 years who want to lengthen the screening interval, using adjunctive cytology and HPV testing (88)
England ^c	2008	18	84% in 12–13 year olds; 48–84% in 13–18 year olds(89)	25	3-yearly ages 25–49 years; 5-yearly ages 50–64 years
Australia	2007	26	73% in 12–13 year olds; 30% in 20–26 year olds(59)	18–20(90)	2-yearly(90)

^aScreening recommendation cited are from the US Preventive Services Task Force (USPSTF), March 2012 – broadly similar recommendations were also released by the ACS/ASCCP in 2012.

^bApproved by FDA in 2006; Advisory Committee on Immunization Practices Recommendations published in 2007.

^cIt should be noted that the age of starting cervical screening in Scotland and Wales is currently lower than in England (20 vs. 25 years).