Cost-effectiveness analyses of human papillomavirus vaccination

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With a human papillomavirus (HPV) vaccine soon to become available for widespread use, several studies have modelled the cost-effectiveness of vaccination. These pioneer studies are likely to be influential on the design of further analyses, and we have therefore summarised and critically reviewed the strengths and limitations of their methods and assumptions. Despite a lack of transparency in some key elements, the most influential assumptions were identified as relating to vaccine effectiveness, cervical screening, and model design. Although the studies suggest that the introduction of an HPV vaccine could be cost effective compared with current practice in the USA, there is still substantial uncertainty around key variables, and model validation seems insufficient. The desirability of vaccinating boys in addition to girls has been explored in only one study. Further refinements to model design and epidemiological variables of (type-specific) HPV disease progression, and expansions on the options for vaccine use, are required for policy making.

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Introduction

Worldwide, 500 000 new cases of cervical cancer are estimated to occur each year, resulting in 250 000 deaths.[1] In recent years, the link between human papillomavirus (HPV) and cervical cancer has been conclusively proven.[2] HPV is now thought to be a necessary but not sufficient cause of cervical cancer.[3] This type of necessary causal relation offers substantial scope for both primary and secondary prevention strategies.[4]

HPV is primarily spread through sexual contact,[5] and is associated with a wide range of diseases, including genital warts[6] and many forms of cancer.[7] Although several HPV types are defined as highly carcinogenic (known as high-risk or oncogenic types), those most commonly responsible for cervical cancer are HPV16 and HPV18.[8] Worldwide, HPV16 and HPV18 have been estimated to account for approximately 70% of cervical cancers.[9] The non-oncogenic types HPV6 and HPV11 are the main cause of condylomata acuminata (genital warts).

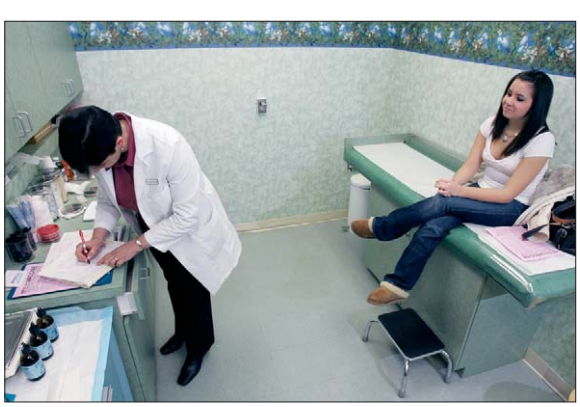
The incidence of cervical cancer differs between regions, particularly between high-income and low-income countries.[10] The variation is mainly a function of cytological screening efforts and the quality of the screening programmes. Through Papanicolaou screening, cervical cancer is largely preventable.[9] However, the precursors of cancer and ambiguous cytology results still represent a major burden to health-care systems.[9] In the USA, the costs of screening represent up to two-thirds of the direct economic burden of cervical HPV-related disease.[11]

To date the most promising prophylactic vaccines have been based on virus-like particles.[4] Currently, there are two vaccine candidates: a bivalent vaccine targeted at the oncogenic HPV16 and HPV18,[12] and a quadrivalent vaccine targeted at the oncogenic HPV types and the HPV types primarily responsible for genital warts (HPV6 and HPV11).[13] Both vaccines have been shown to be safe, immunogenic, and highly effective against type-specific persistent infection.[12,13] Several countries have licensed the quadrivalent vaccine.

Models of cost-effectiveness

Mathematical models can play an important role in our understanding of the effect of a new intervention, as well as identifying the best strategies for its introduction. In the context of HPV vaccination, an additional complexity is introduced by the existence of effective cytological screening programmes. Since there are more oncogenic HPV types than those targeted by current vaccine candidates, vaccination cannot yet replace screening in high-income countries, and must be assessed as a complementary measure. The maintenance of current screening programmes will also be vital to protect older cohorts of individuals who have not been vaccinated.

With an HPV vaccine likely to be commercially available in the near future (figure), several groups have attempted to predict the economic impact of options for vaccination. In many countries, cost-effectiveness of new vaccines must be shown as a pre-requisite for government-funded vaccination programmes. Although cost-effectiveness analyses are important for policy, there is a need for timely critical review, interpretation, and future guidance for studies tackling specific public-health issues. This need is greater when compatible interventions exist and industry-funded research prevails, as is the case for HPV.



Mike Derer/AP/Empics

Figure: **Girl waits to be given a human papilloma virus vaccine from her paediatrician**

	Sanders and Taira[14] (2003)	Kulasingam and Myers[15] (2003)	Goldie et al[16] (2004)	Taira et al[17] (2004)
Main characteristics				
Model	State-transition Markov model	State-transition Markov model	State-transition Markov model	Hybrid (dynamic/Markov model)
Perspective	Direct medical costs (QOL)	Direct medical costs (time costs and QOL in sensitivity)	Societal (direct medical costs, time costs, and QOL)	Direct medical costs (QOL)
Benefits	QALY	LYS	QALY	QALY
Base-case assumptions				
Efficacy	75% against 13 high-risk types (causing 90% of cancers)	90% against 70% of high-risk HPV types	90% against HPV16/HPV18 infection (causing 65% of cancers)	90% against HPV16/HPV18 infection
Vaccine coverage in target groups	70% of 12-year-old girls	100% of 12-year-old girls	100% of 12-year-old girls	70% of 12-year-old girls only, or girls and boys
Estimated effective coverage*	47·3%	63·0%	58·5%	40·1%
Screening compliance (estimate used for comparison with current practice)	71% every 2 years (same)	100%	100% (5·2% never screened, 70·5% <1 year ago, 12·6% <2 years, 4·3% <3 years, 3·0% <5 years, 9·6% >5 years)	71% every 2 years (same)
Duration of protection	10 years (boosters every 10 years)	10 years	Lifelong	10 years (boosters every 10 years)
Results				
The most effective strategy compared with next best strategy†	..	Vaccination of girls at age 12 years combined with biennial screening starting at 24 years had an ICER of US$44 889 per LYS compared with triennial screening only starting at 18 years (using US$50 000 as the threshold)	Vaccination of girls at age 12 years combined with triennial screening starting at 25 years had an ICER of US$58 500 per QALY gained compared with vaccination and screening every 5 years starting at 21 years (using US$60 000 as threshold)	..
ICER compared with current practice	US$22 755 per QALY gained	..	US$24 300 per QALY gained	US$14 583 per QALY gained (girls only)
Main shortcomings				
Factors not taken into account	Herd immunity; possibility of vaccinating males; reactivation of latent infections; genital warts; changes in screening initiation age.	Herd immunity; possibility of vaccinating males; reactivation of latent infections; genital warts.	Herd immunity; possibility of vaccinating males; genital warts.	Genital warts; reactivation of latent infections; changes in screening initiation age.

ICER=incremental cost-effectiveness ratio. LYS=life-year saved. QALY=quality-adjusted life-year. QOL=quality of life. ..=not applicable. *Defined here as (vaccine coverage)×(vaccine efficacy against targeted types)×(proportion of cancer caused by these types). †The next best alternative to options including vaccination is not always current practice (ie, currently screening is not applied in the best way in many settings).

Table 1: **Summary of economic analyses of HPV vaccine introduction**

Through our literature search, we identified four studies that comprehensively modelled the economic impact of HPV vaccination, all of which were based in the USA.[14–17] Three of the studies used the same basic modelling design, a static Markov cohort model, which followed a hypothetical single cohort of girls.[14–16] Taira and colleagues[17] used a dynamic disease-transmission model of HPV infection, which informed their previous static natural history model.[14] An overview of the studies is shown in table 1. The studies calculated the incremental cost-effectiveness ratio (ICER) of vaccination compared with current practice in the USA,[14,16,17] or compared with the next best strategy.[15,16] To improve comparability, all costs (table 2) have been standardised to the nearest US$ (as of 2004) by use of consumer price indices. However, since the original prices were only 1 year apart, ICERs are presented as originally reported (US$ in 2001,[13,14,17] or US$ in 2002[16]) to allow readers to easily refer back to the original studies. We aim to explore the strengths and limitations of the methodological approaches of these studies, and their implications for policy.

Epidemiological assumptions

Two of the studies[14,15] adapted a previous model by Myers and colleagues[18] to simulate both high-risk and low-risk HPV types. Taira and colleagues[17] generated infection rates through the dynamic modelling process, and then incorporated these rates into the natural history model of Sanders and Taira.[14] Therefore, three studies adapted the same progression and screening model.[18] Kulasingam and Myers[15] gave no detail of progression rates, instead referring readers to previous studies.[18–20] Sanders and Taira[14] gave more detailed progression probabilities separated into high-risk and low-risk HPV types. However, the lack of type-specific progression rates for the relevant serotypes (which may have been because of a lack of existing data) is a major shortcoming in these studies. Goldie and colleagues[16] modelled high-risk and low-risk HPV types, although they did not state how the transition probabilities differ by HPV type. They also did not present base-case values, and instead gave ranges, thereby hindering comparability and reproducibility of the model. Taira and colleagues[17] modelled type-specific

HPV16 and HPV18 transition probabilities, but did not give these values. Overall, we found that comparison of transition probabilities (for both HPV incidence and disease progression) between studies was hampered by a lack of detailed data. The proportions and durations of progression into specific disease states are likely to be highly influential on the incremental cost-effectiveness of prevention strategies over time.

Some of the HPV infections detected in older women may be the result of previous infections that have become reactivated, rather than the result of new HPV exposures. Only Goldie and colleagues[16] examined the effect of reactivation of latent infections. They found that if vaccine-induced immunity declines over time, then the effect of vaccination is sensitive to the proportion of persistent infections attributable to new infections, and the greater this proportion, the more sensitive results are to declining immunity.

Vaccine and screening assumptions

Details of vaccine and screening base-case assumptions are shown in table 1. In their base-case models, all four studies assumed that vaccination occurred at age 12 years and examined various vaccination ages in their sensitivity analyses. In the only dynamic model,[17] ICERs were sensitive to vaccination coverage assumptions, particularly when vaccination of both boys and girls was considered. The ICERs in the three static models were insensitive to the level of coverage assumed, since herd-immunity effects were ignored and vaccination costs increased linearly with coverage.[21,22] Three studies seem to have modelled efficacy as a reduction in HPV incidence,[14,15,17] with one exception that modelled efficacy as a reduction in persistent HPV infection.[16] Only phase I trials had been completed when these modelling studies were undertaken, and the efficacy of HPV vaccines against either persistent or incident HPV infection was unknown.

Base-case estimates of conventional cervical cytological screening sensitivity and specificity assumptions varied slightly between the studies (sensitivity 51–66%,[14,16] and specificity 95·7–97·0%[14–16]). Only one study[16] included liquid-based cytology. Two studies[15,16] assumed 100% compliance with screening in their base-case analyses, but varied these assumptions in their sensitivity analyses. Goldie and colleagues[16] seem to have used estimated US screening compliance rates (table 1) when they modelled the addition of an HPV vaccine to current practice. They also assumed that, in current practice, 71% of women are screened every year.[16] Sanders and Taira[14] and Taira and colleagues[17] assumed 71% compliance every 2 years in their base-case analyses. This means that, if all other conditions are equal, the screening programme should cost about twice as much in Goldie and colleagues' analysis.[16] However, there were many other assumed differences in screening costs between the studies (table 2). Very high screening compliance rates[15,16] are likely to lead to an underestimation of the cost-effectiveness of vaccination programmes.

Health outcome measures

All four studies included quality-of-life (QOL) measures. However, Kulasingam and Myers[15] reported base-case results in cost per life-year saved. There was a wide variation in the grouping and definition of health states to which QOL weights were applied, which makes comparison difficult. However, health states that do correspond show differences. For instance, the range of stage I cervical cancer follow-up utility weights was 0·90–0·97.[14,16] This lack of consistency is surprising given that the studies use the same primary data source for much of their QOL weights and timings in those states.[23] Additionally, this source study elicited QOL weights from experts,[23] rather than from patients in each disease state, or the general public. Kulasingam and Myers[15] found that cost-effectiveness results were sensitive to changes in the utilities applied to health states. Further work on QOL weights are therefore urgently required.

Of note, in cases in which it has been included, the QOL impact of the programme has been limited to patients and has not been extended to third parties (ie, family and friends of patients). Although conventional Papanicolaou screening has a high specificity (>95%), because of the large number of women screened, a substantial number of false positives do occur. The QOL

	Sanders and Taira[14] (2003) and Taira et al[17] (2004)	Kulasingam and Myers[15] (2003)	Goldie et al[16] (2004)
Treatment			
CIN 1	672†	2145	1327
CIN 2 or 3	1300‡	3784	2975
Stage I	15 983	21 899	22 610
Stage II	23 272	33 594	24 056
Stage III	23 272	..	28 420
Stage IV	25 612	49 990	38 758
Hysterectomy	8411	..	..
Diagnostic			
Colposcopy and biopsy	..	465	458
Screening			
Conventional cytology	86	48§	16–54¶
Liquid-based cytology	..	..	29–67¶
Vaccine			
Vaccination series	320	213	315‖
Administration	..	..	81
Booster	107 (every 10 years)	213 (in sensitivity)	..

CIN=cervical intraepithelial neoplasia. ..=not applicable. *All costs standardised to the nearest 2004 US$ using consumer price indices. †An alternative classification system (Bethesda system) was used for these two studies, values were originally reported for low-grade squamous intraepithelial lesion. ‡Values were originally reported for high-grade squamous intraepithelial lesion, with additional costs given for false-positive squamous intraepithelial lesion of US$245. §In sensitivity analysis with time costs of US$65–80 included. ¶Weighted average of normal and abnormal cytological smears, with additional costs given for HPV DNA test of US$51, patient-time cost of US$22, and office visit of US$23. ‖Additional patient-time cost of US$17 also included.

Table 2: **Standardised costs* of treatment, diagnostic, screening, and vaccine, between studies**

impact of false-positive results could be substantial for patients and their families, and may be aggravated by the fact that HPV is a sexually transmitted infection. Any additional QOL impact attributed to the screening programme would clearly render vaccination more attractive, if frequency of screening could be reduced as a result of vaccination. However, because vaccination is likely to reduce the prevalence of HPV carriage, over time the positive predictive values of the tests are likely to decrease and the negative predictive values are likely to increase, all else being equal. This is a separate dynamic issue, which has not been addressed in these economic analyses.

Economic factors

Goldie and colleagues' base-case analysis[16] adopted the widest costing perspective (table 1). Direct cost estimates are shown to vary widely for some disease categories (table 2). All four studies used an annual discount rate of 3% in their base-case analyses for both costs and benefits. Only one study presented their results over a range of discount rates (0–5%).[14] As in any economic evaluation of a prevention strategy with long-term effects, the initial intervention costs and the choice of discount rate (usually 3% or 5%, depending on national guidelines) and discount model (stationary or non-stationary; ie, slow discounting[24,25]) have a great influence on the resulting cost-effectiveness ratios. In the context of HPV vaccination, higher discount rates increase the relative weight of the initial vaccination costs. At the same time, the potential postponement of the age at first screening or decreases in screening frequency after vaccination, or both, would lower the screening costs. A reduction in screening costs would be valued greater in relation to vaccination costs, the earlier the screening costs are avoided, particularly if discount rates are higher.

Clearly, the influence of discounting is very complex in this context. In general, higher discount rates should make the vaccination options seem less attractive, since the costs of the programme are immediate, but the benefits (through avoiding disease, postponing the age at first screen, and/or decreasing the screening frequency) are delayed. Indeed, Sanders and Taira[14] reported an ICER of US$9286 per undiscounted quality-adjusted life-year (QALY) gained, versus US$37752 per discounted (at 5%) QALY gained. Since different discount rates are recommended in different countries, results should be presented over a range of discount rates.[26,27]

Model validation

Ideally, we would have liked to see a comparison of the model results to type-specific and age-specific data on rates of HPV infection, cervical intraepithelial neoplasia, and cancer. However, none of the studies provided such a comparison. Two studies[15,16] reported that their models gave approximately a 3·5% lifetime risk of developing cancer in the absence of control, but no other comparison was presented. Even the original model provides no comparison of age-specific results to the data presented.[18] In an earlier paper, Goldie and colleagues[28] did provide a comprehensive comparison of a related model to age-specific epidemiological data. Overall, the lack of transparency around the validation process makes it difficult to judge whether the models provide a reasonable description of the epidemiological patterns expected before vaccination, and whether they can be used to predict the future incidence under changes to the current control strategies. The models do seem to differ in their pre-vaccination epidemiology. For instance, the discounted quality-adjusted life expectancy in the absence of vaccination is 27·7 years according to Sanders and Taira,[14] 28·7 years for Kulasingam and Myers,[15] and 26·0 years for Goldie and colleagues[16] (a difference of almost 2 years between the studies). This is despite the use of (presumably) the same background mortality schedules and discount rates, and similar QOL sources. These differences between the studies are large in comparison with the gains in quality-adjusted life expectancy that are estimated to result from vaccination. For instance, Goldie and colleagues[16] estimate that vaccination at 100% efficacy will increase quality-adjusted life expectancy of the cohort by 0·013 years (or 4·9 days).

Methodological issues and limitations

Uncertainty, particularly around vaccine efficacy and duration of protection, has been accounted for through the wide range of values used in sensitivity analyses. However, although all four studies did sensitivity analyses, only two of the studies did two-way[15] or multi-way analyses.[14] All studies found that their results were fairly robust around changes in vaccine efficacy, although Taira and colleagues[17] found that when they modelled female plus male vaccination, cost-effectiveness was highly dependent on vaccine efficacy (only at intermediate levels of efficacy was vaccination of men and boys estimated to be cost effective). All the studies found that results were sensitive to duration of vaccine efficacy, although the extent of this sensitivity varied between studies. Part of this variation can be explained by the difference in costs attributed to the booster shots. Sanders and Taira[14] found that a vaccine remained relatively cost effective (US$45 599 per QALY gained), with booster shots costing US$107 every 3 years, when compared with current practice. However, Kulasingam and Myers[15] found that a booster shot costing US$213 given at age 17 years would increase the costs of vaccination to more than US$300 000 per life-year saved.

Those studies that assessed the effect of hysterectomies found that this had little effect on results.[14] Only one study modelled the protective effect of other treatments for cervical intraepithelial neoplasia and early-stage cancer (such as loop excision).[15] They found that their results were sensitive to this factor, and future models may wish to include this effect in sensitivity analysis.

Two studies[15,16] examined the introduction of a vaccine in combination with a variety of screening options, and modelled different initiation ages and screening intervals. With this approach, the most effective combination of screening and vaccination can be identified and compared with the next best strategy, which is not necessarily current practice (table 1). This strategic information is vital for policy making, particularly in countries that may not have the same screening programme as in the USA.

One of the most likely vaccine candidates targets both oncogenic HPV types (HPV16 and HPV18) and the HPV types responsible for genital warts (HPV6 and HPV11).[13] None of the studies assessed the impact of the reduction in genital warts, although this condition does seem to place a substantial burden on health-care systems.[29,30] The correct way to assess these issues in economic evaluation is to do incremental analyses of the costs and effects of using a quadrivalent vaccine versus a bivalent vaccine. Furthermore, none of the studies take into account the effect of vaccination on other HPV-associated non-cervical cancers, such as head, neck, vulva, penis, and anal cancers.[7] Together, the incidence of these cancers is substantial and may require an exploration of their effect in sensitivity, if not in the base-case analysis.

Some researchers have suggested that vaccination against certain HPV types may cause a shift in prevalence towards currently less common types, often referred to as strain replacement.[8] Goldie and colleagues[16] modelled the possibility of strain replacement, in that, as the number of individuals effectively vaccinated increased (and consequently the number of those infected with HPV16 and HPV18 decreased), the number of individuals who were now susceptible to other HPV infections increased. This happened on the basis that in their model, natural infection with HPV16 or HPV18 protects against infection with other HPV types (ie, co-infection is not possible), but vaccine-induced immunity to HPV16 and HPV18 does not protect against other HPV infections (vaccination offers no cross-protection). Various methodological choices mean that none of the other studies will have produced this form of strain replacement.

Strain replacement may also be the result of strain interactions, whereby previous or current infection with one HPV type may affect an individual's risk of infection with another HPV type. Recently, a model has been developed to assess the effect of strain interactions after mass vaccination.[31] None of the four models examined such interactions between HPV types. Another issue pertaining to co-infection is the influence of multiple infections on risk of disease (not risk of infection, as discussed above). Several studies have found that the co-infection with HPV6 and HPV11 reduces the likelihood of developing cervical cancer in those also infected with HPV16.[32,33] On the basis of this effect, the elimination of HPV6 and HPV11 may increase the oncogenic potential of certain infections.[34]

Modelling design

Three of the economic analyses used static Markov models.[14–16] This type of modelling design is unable to take into account the dynamics of viral transmission within a host population, and therefore is unable to properly assess herd immunity (ie, the protective effect conferred on a population by immune individuals within the population).[22,35,36] If the contribution of herd immunity is ignored, then the effectiveness and cost-effectiveness of a vaccination programme is likely to be underestimated,[37] except when complications increase with age of infection (ie, varicella),[22] which is not the case in HPV infection. However, if a conservative model is used, then the results are only useful if they indicate that such a programme would be cost effective.[38] At current vaccine prices, the ICERs versus the next best alternative (table 1) were of borderline cost-effectiveness, and therefore may require a reconsideration of the analytical framework.

With the development of HPV vaccines targeted at both oncogenic HPV types and those responsible for genital warts,[13] there is an increasing need to consider the possibility of universal vaccination, because such a vaccine offers direct benefits to men as well as women. The cost-effectiveness of vaccinating boys (which constitutes a major policy issue) and the effects of herd immunity can only be estimated by an approach in which the underlying infectious disease transmission process is modelled (ie, a so-called transmission dynamic model). After widespread vaccination, changes over time in the age-specific incidence of infection will determine if and by how much the start of screening could be postponed or screening frequency decreased without compromising effectiveness. Clearly, if herd immunity is ignored, then the answer to these questions will be different. In view of the success of cervical screening programmes around the world, any changes to the programme should be based on the best possible evidence, and to do this, herd immunity effects need to be incorporated in the most realistic way.

Taira and colleagues[17] used a dynamic model, and were able to examine the effects of herd immunity and the possibility of universal vaccination (of both boys and girls). They used a stratified susceptible–infected–susceptible (SIS) model, in which individuals who clear an infection return to the susceptible state, with no acquisition of immunity to any HPV type. This model design differs from other models of HPV infection, such as a susceptible–infected–recovered (SIR) model in which individuals gain type-specific immunity after recovery from infection.[34,39] These contrasting model designs may indicate the lack of epidemiological data about immune protection after natural HPV infection, and the conflicting findings that epidemiological studies have produced.[40–44] The implications can be profound. With an SIR structure, individuals can only be infected once (by a particular HPV type, or group of types), and vaccination acts to bring forward the age at which they

become immune. To eliminate the infection from the population, one has to immunise more people than would cumulatively be immunised over their lifetime through natural infection (this is usually high, and therefore difficult to achieve). In an SIS structure, as adopted by Taira and colleagues,[17] individuals can be continually re-infected, and a large fraction of the population is susceptible. To eliminate such an infection, it is only necessary to immunise more people than are currently infected. Because the proportion of infected people at any one time is usually low, this is relatively easy to achieve, and, other things being equal, the impact of vaccination will be far greater than in an SIR model. Clearly, it is crucial to establish which of these models (or where on the spectrum between them) is most appropriate for HPV. This has not been done, and the reasons for choosing one model structure over the other was not discussed, nor elaborated in sensitivity analyses. Without such information, the results of such models should be regarded as speculative.

Taira and colleagues[17] structured their transmission model to use both age (with nine age-groups) and sexual activity (with four sexual activity classes). The model used assortative mixing, with a preference to select partners of a similar sexual activity class, and age mixing primarily between older men and younger women. The use of both age and sexual activity groupings adds a level of complexity beyond that of a previous dynamic model of HPV transmission, which was structured only around sexual activity class.[34] In their base-case analysis, Taira and colleagues[17] found that universal vaccination offered only a minimum of additional reduction in disease, with a highly unattractive ICER of US$442 039 per QALY gained. This is because vaccination of only girls was estimated to reduce the incidence of vaccine types by 95% (an unsurprising result given the SIS structure assumed). This means that vaccination of boys as well can only reduce the incidence by a further 5%. Since the cost is the same, the additional vaccination of boys can be at best 20 times less cost effective than vaccination of girls. Only if vaccine efficacy or coverage in girls is significantly lower, or vaccine-induced protection is short lived, are there sufficient cases left for it to be worth vaccinating both sexes. A non-economic dynamic model of HPV vaccination also found that vaccinating boys offered little additional benefit in terms of preventing cervical disease, for similar reasons.[39]

Future directions

Ideally, future HPV vaccine cost-effectiveness studies should be based on dynamic modelling. However, the validity of future dynamic models will be dependent on the accuracy of the data used to determine the transmission dynamics. Given the uncertainty around many of the variables, studies should do comprehensive sensitivity analyses, involving both univariate sensitivity analysis and multivariate probabilistic sensitivity analysis. The results should be presented as incremental (ie, compared with the next best alternative) costs per infection prevented, per death averted, and per life-year and QALY gained. Uncertainty should be represented in cost-effectiveness acceptability curves for various scenarios (such as different vaccination strategies, prices, and discount rates). Sensitivity analyses around the model structure should also be done in cases in which this may alter conclusions. Future models should attempt to have greater transparency, particularly around the numerous assumptions and variables used. Greater consistency in terms of the methodology and the reporting of results (between models) would ensure increased comparability. Further epidemiological research is needed to obtain more reliable information on disease progression for the various HPV types, the proportion of infections caused by reactivation, the effect of co-infections, and the epidemiology of strain replacement. As vaccine efficacy trials have used only female participants,[12,13] further research into vaccine efficacy in men and boys must be done. Further directions for improving HPV model validation have been described by Dasbach and colleagues.[45]

Conclusions

Overall, and with the assumption that the main model input variables (eg, HPV incidence, disease progression, QALY weights) are accurate, the three static models are likely to have underestimated the cost-effectiveness of HPV vaccination.[14–16] Their base-case results therefore suggest that the introduction of HPV vaccination could be considered cost effective compared with current practice in the USA. The only published economic analysis based on a dynamic model found vaccination (of girls only) to be of acceptable cost-effectiveness, when compared with current practice, even if the screening frequency remained unchanged (US$14 538 per QALY gained), although their model structure might have overestimated the impact of vaccination.[17]

The additional vaccination of boys (which cannot be analysed by use of a static model) was found to be unattractive under most plausible scenarios, because there are few cases left to prevent after having vaccinated girls. Thus, Taira and colleagues' results[17] indicate that a rational decision maker should vaccinate girls against HPV (because it compares well with other established health-care programmes, even if the screening programme remains unchanged), and that they should screen vaccinated women not more often than once every 4 years (because a higher frequency compares unfavourably with other health-care programmes). If both of these changes take place, the base-case analysis shows that net savings would occur in health-care resources, compared with current practice in the USA. However, if any of these published analyses were subjected to multivariate sensitivity analyses (most appropriately by repetitively sampling all variables simultaneously from

Search strategy and selection criteria

Publications were primarily identified through Medline and EconLit searches and from citations from identified publications. Search terms included "papillomavirus, human", "cost-benefit analysis", "models, theoretical", and "vaccination". This process identified five English language cost-effectiveness analyses of HPV vaccination, four of which were included in the study. An early, crude, explorative assessment, which was made for the US Institute of Medicine,[23] was not reviewed here in view of its preliminary nature. An additional economic assessment has now been published,[44] which was not included because it was not available at the time of the review, in December, 2005. Non-economic modelling studies were examined if appropriate.

their likely distributions), the uncertainty ranges may cover ICER values above what is considered cost effective (eg, US$50 000 per QALY gained). This is a consequence of substantial uncertainty around key variables, and is a major issue to be addressed in future analyses, along with assessment of the impact of the choice of model structure.

Although HPV vaccines offer great scope for disease prevention, there are still many unresolved issues, such as who should be vaccinated, at what age, and what implications vaccination will have on current screening programmes. Modelling can help assess these issues. However, the models will, by necessity, be complex. This complexity raises its own concerns in terms of the availability of relevant epidemiological data for both parameterisation and model validation. HPV vaccination also raises other issues, such as its public acceptability as a tool to prevent sexually transmitted infection when given to a pre-adolescent target group. Care will also need to be taken to ensure that those vaccinated do not become complacent with regards to screening, as this may seriously undermine the effectiveness or cost-effectiveness of the programme. Whereas this review has focused on HPV vaccination in high-income countries, most cervical cancers occur in low-income countries, where effective screening programmes do not exist. The need for vaccination in this setting is thus much greater. However, as with screening programmes, implementation and financial inhibitions are likely to deter the widespread use of HPV vaccines in low-income countries longer than necessary. Appropriate and timely model-based economic evaluations, such as those that are beginning to appear,[46] may help reduce such deterrents.

Conflicts of interest

ATN attended a funded trip (paid for by CSL Ltd, Parkville, VIC, Australia) to the 22nd Papillomavirus Conference in 2005. The National Centre for Immunisation Research and Surveillance did a national serosurvey of HPV, which was entirely investigator driven, but the testing was funded by CSL Ltd, and done by Merck USA. None of the other authors have conflicts of interest to declare.

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