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Economic Evaluation of Human Papillomavirus Vaccination in Developed Countries

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Key Words
Human papillomavirus · Vaccine · Mathematical model · Cost-effectiveness · Economic evaluation

Abstract
Background: With promising efficacy results from randomized control trials of human papillomavirus (HPV) vaccines and the availability of new screening paradigms, policymakers are being asked to make recommendations and decisions regarding the optimal strategies to reduce HPV infection and disease. Such decisions are increasingly being made with significant input from mathematical and economic models. The demand for modeling has resulted in the publication of numerous mathematical models looking at the cost-effectiveness of HPV vaccination. ***Objective:*** To review published models that have been used to evaluate the cost-effectiveness of HPV vaccination in developed countries and highlight points of consensus and disagreement in methods and findings. ***Methods:*** This review consists of cost-effectiveness studies published in the peer-reviewed literature before August 2008. ***Results:*** Despite variations in methods, modeling studies are producing consistent conclusions: (1) vaccinating young girls against HPV is likely to be cost-effective; (2) vaccinating boys will most likely not be cost-effective in countries that can reach high coverage rates in girls, and (3) results are most sensitive to the duration of vaccine protection. However, results from analyses examining the effectiveness and cost-effectiveness of vaccinating boys when coverage rates are low (≤80%) and catch-up strategies have reached conflicting conclusions.

Background

With promising safety and efficacy results from randomized control trials of prophylactic human papillomavirus (HPV) vaccines [1–4] and the availability of new screening paradigms, policymakers are being asked to make recommendations and decisions regarding the optimal strategies to reduce HPV infection and disease. Policy questions mainly focus around important key issues such as:

- target ages of vaccination for girls;
- appropriate ages for a 'catch-up' program;
- inclusion of boys in the vaccination program;
- revisions in screening policies to optimize synergies with vaccination (e.g. HPV DNA testing).

Epidemiological and economic models are increasingly being used to inform decision making. The demand for modeling has resulted in the development and publica-

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tion of numerous mathematical models looking at the effectiveness and cost-effectiveness of HPV vaccination and screening [5–28]. Currently, over 20 HPV vaccine modeling papers have been published [5–28] and many more are in development. These studies differ substantially in the type of model used and the model structure chosen to represent HPV transmission and the natural history of infection and disease. The variability in HPV models is, in part, a consequence of the complexity of the natural history of HPV and considerable gaps in the scientific literature regarding age- and type-specific HPV transmission and progression rates, and is also due to the subjective appreciation of the level of complexity that is deemed important to include in the model (e.g. complexity in sexual behavior). The availability of several models is extremely helpful to provide evidence on robustness of conclusions when results are similar. However, when model results diverge, differences in model type and structure can be an important source of confusion (for both specialists and non-specialists) as to how results should be interpreted and used [29].

This paper has 3 main objectives: (1) to describe the general concepts of cost-effectiveness analyses; (2) to present important components of cost-effectiveness and their impact on the economic evaluation of HPV vaccination, and (3) to review current published cost-effectiveness analyses of HPV vaccination in developed countries and highlight research questions for which there is agreement and disagreement in conclusions.

General Concepts of Cost-Effectiveness Analyses

Why Is Cost-Effectiveness Needed?

Currently, the availability of health care interventions exceeds considerably society's capacity to pay for them [30]. Cost-effectiveness analysis is useful under such conditions as it provides an analytical framework in which to assess the desirability of an intervention compared with other uses of the same scarce resources [31]. More specifically, cost-effectiveness analyses try to answer the following questions [32]: (1) Is the health care intervention worth doing compared to alternative uses of the same resources? (2) If we are deciding to implement an intervention, who should receive the intervention, at what age, and what strategy should be used?

Why Are Mathematical Models Needed?

Cost-effectiveness analysis can be performed using either an empirical (clinical research) or a model-based approach. In most cases, a model-based approach is required since clinical efficacy trials are predominantly designed to measure efficacy (or individual effectiveness) rather than population-level effectiveness, and as a result are often limited in scope and duration (e.g. size, strict inclusion criteria for patients, limited in scenarios investigated) [33]. By combining clinical efficacy results with information from various sources (demographic, biological, epidemiological), models are able to address questions that cannot feasibly or ethically be answered in a trial setting. For prophylactic HPV vaccines, many of the benefits occur in the medium to long term, and therefore mathematical models are needed to project the impact of vaccination beyond the time horizon of clinical trials and, in the case of transmission dynamic models, to take into account the indirect effects of vaccination (herd immunity) [12, 33].

What Are Cost-Effectiveness Analyses and the Cost-Effectiveness Ratio?

As mentioned earlier, the goal of cost-effectiveness analysis is to compare the health and economic impact of different interventions in order to identify which interventions maximize the health of the population, in a context of limited resources. The results of cost-effectiveness analyses are usually presented as a ratio. The Cost-Effectiveness Ratio (CER) is a measure of the incremental cost of obtaining a unit of health effect from an intervention when compared to an alternative [30–32]. For HPV vaccination, this would be the incremental cost of obtaining a health benefit from vaccination compared to no vaccination. The CER can be presented as follows:

$$\mathrm{CER} = \frac{\left(\text{Costs with intervention A} - \text{Costs with intervention B}\right)}{\left(\text{Effect of A} - \text{Effect of B}\right)} = \frac{\text{Net cost of intervention}}{\text{Net health benefit}}$$

For HPV vaccination the CER can be represented as follows:

$$\mathrm{CER} = \frac{\left(\text{Cost of vaccination} - \text{Cost offsets by preventing HPV disease}\right)}{\left(\text{Gains in health by preventing HPV disease}\right)}$$

For HPV vaccine cost-effectiveness, elements that are included as costs include the price of the vaccine, administration cost of vaccination, physician visits, hospitaliza-

tion, screening and treatment related to HPV disease. On the other hand, the health benefits can be measured as cases prevented, cancers prevented, deaths prevented, life-years gained and quality-adjusted life-years (QALYs) gained. The most common measure of health benefit in cost-effectiveness analysis is QALYs gained. The QALY was developed to capture, in a single measure, both gains from reduced morbidity and reduced mortality [32]. QALYs are thus capable of capturing not only the benefit of preventing death but also gains in other dimensions of health such as prevention of anxiety and pain. QALYs (utilities) range from 0 (death) to 1 (perfect health) [32]. For HPV vaccination, the QALYs gained is the difference, over time, between the overall QALYs in a world with and without vaccination.

Important Components of HPV Vaccination of Cost-Effectiveness Studies

There are many challenges in building epidemiologic and economic models of HPV prevention.

- Complex natural history of HPV: HPV infection is associated with pre-cancers and cancers of the anus, cervix, head and neck, penis, vagina and vulva [34], as well as anogenital warts and recurrent respiratory papillomatoses [35]. Furthermore, over 40 HPV genotypes are known to infect the anogenital tract. Each of these genotypes possesses its own natural history of infection (e.g. duration of infection) and disease (e.g. associated with different diseases and risks of progression). Finally, there is a long lag time between infection and the various HPV-related cancers.
- Different prevention strategies which have different impacts on the natural history of disease. A challenge in HPV modeling is to include, simultaneously, the impact of different prevention technologies (e.g. conventional screening, DNA screening, vaccination). Economic evaluation of the different prevention strategies requires models to include different levels of complexity. For example, modeling the impact of screening and HPV vaccination would require one to consider taking into account heterogeneity in screening rates, HPV transmission and type-specific history of infection and disease.

Given the above challenges, HPV models have had to make tradeoffs in the complexity of the models, the number of prevention strategies investigated and the amount of data used to parameterize the models [29]. Deciding the level of model complexity is a central part of modeling [36]. Ideally, tradeoffs in complexity should only be made if they do not produce unacceptable biases in the conclusions that can be made regarding the policy question investigated. Below we present different analytic choices that have been used, and which have been shown to affect modeling results.

Herd Immunity (Static vs. Dynamic Models)

Mass vaccination can produce complex indirect effects that require the modeling of infection and transmission (in addition to the natural history of disease), and thus the type of model used can be critical (see [37, 38] for more on the subject). Although there are many types of models that are used to predict the impact of vaccination, they can be broken down into 2 main categories: (1) transmission dynamic and (2) static (usually decision analysis or cohort models). The major difference between these types of models is that transmission dynamic models capture the indirect protection resulting from immunization (herd-immunity effects), whereas static models omit them. Herd immunity effects depend on the extent to which vaccination prevents transmission of infection in the population. If only a small proportion of the population is immunized (low coverage) or the vaccine has low efficacy against infection, then herd-immunity effects are negligible [37]. Under such conditions, static and dynamic models produce similar results [37]. Static models may also be used as a tool to estimate the worst-case scenario when herd immunity does not produce negative effects. In other circumstances, dynamic models should be used [37].

For HPV vaccination, static models should only be used to examine the question whether vaccinating girls is cost-effective (as results will be conservative [25]). Other questions such as the incremental cost-effectiveness of vaccinating boys, optimal catch-up strategies or optimal screening and vaccination strategies should only be examined using a dynamic model as the non-linear effects of vaccination can have a significant impact on results/conclusions [13, 27]. For example, it is unclear whether using a static model will produce conservative estimates for catch-up strategies. This is because the potential for incremental gains in the catch-up cohorts may be smaller under a dynamic framework where some vaccinees would have been indirectly protected through herd immunity.

Dynamic models are usually open populations whereas static models follow cohorts through time (closed population) [29]. A few HPV modeling studies have taken into account herd immunity effects by using hybrid models [6, 17, 24] (table 1). The hybrid modeling approach

Table 1. HPV vaccine cost-effectiveness studies in developed countries, using cost per QALY gained as the main outcome

	Sanders [19] 2003	Goldie [18] 2004	Taira [17] 2004	Elbasha [14] 2007	Brisson [11] 2007		Kulasingam [6] 2007	
Study characteristics								
Country	USA	USA	USA	USA	Canada		Australia	
Model type	Static	Static	Hybrid	Dynamic	Static		Static and hybrid	
HPV types	HR, LR	16, 18, HR, LR	16, 18	6/11, 16/18	6/11, 16/18, HR		16, 18, HR, LR	
Coverage	NA	NA	70%	70%	NA		80%	
Vaccine efficacy	75% against all HR	100%	90%	90%	95%		100%	
Cost of vaccination	USD 300 boost: USD 100	USD 393	USD 300 boost: USD 100	USD 360	CAD 400 boost: CAD 133		AUD 381 boost: AUD 146	
Discount rate	3%	3%	3%	3%	3%		5%	
Sensitivity analysis								
Natural history	1-way	1-way	No	No	Multivariate		No	
Vaccine parameters	1-way	1-way	1-way	1-way	1-way		1-way	
Economic parameters	1-way	1-way	1-way	1-way	Multivariate		1-way	
Cost per QALY gained								
Vaccine type (model)	Bivalent	Bivalent	Bivalent	Quadrivalent	Bivalent	Quadrivalent	Bivalent (static)	Bivalent (hybrid)
Vaccinating girls								
10 years	–	–	–	Dominated[a]	>200,000	>200,000	53,000	49,000
20–30 years	–	–	–	–	115,000 (38,000–20,800)	66,000 (26,000–96,000)	–	–
Lifelong	13,000	21,000	–	3,000	31,000 (15,000–55,000)	21,000 (11,000–33,000)	19,000	13,000
Booster	23,000[b]	–	15,000[c]	–	56,000[c] (27,000–96,000)	37,000 (21,000–59,000)	25,000[c]	–
Vaccinating boys	–	–	442,000	Dominated	–	–	–	34,000[d]
Catch-up in women								
to 18 years	–	–	–	–	–	–	17,000	–
to 24–26 years	–	–	–	42,000	–	–	35,000	–

'Cost per QALY gained' is reported in the same currency as 'Cost of vaccination'. Figures in parentheses are 10th and 90th percentiles for Brisson [11], and 5th and 95th percentiles for Jit [23]. NA = Not applicable; HR = high risk; LR = low risk; B = benefits; C = costs.

[a] Dominated indicates that the intervention is less effective and more costly. [b] Booster doses given every 10 years. [c] Booster dose 10 years after initial vaccination provides lifelong protection. [d] Cost-effectiveness of vaccinating girls and boys compared to current screening.

uses dynamic models to represent transmission and herd immunity effects and static models to represent progression of disease and screening [29]. Hybrid models were built to address the same policy questions as dynamic models (vaccination of boys and catch-up). However, there are limitations to this approach. Deciding how the open dynamic model predictions should feed into the closed cohort (static) model is not straightforward and the exact methods used are not often described. Furthermore, hybrid modeling techniques can produce issues regarding synchronization of events that occur in both the dynamic and cohort models. For example, the dynamic and cohort models must take into account natural history of disease and mortality to accurately model transmission and disease progression. However, it is unclear whether, within these models, the natural history of HPV disease is synchronized over age and time (e.g. whether, over time, age-specific prevalence and incidence of cervical intra-epithelial neoplasia, cervical cancer and mortality are the same in the dynamic and cohort models). Given these uncertainties, more work is needed to understand how results from traditional dynamic models compare to those from hybrid models.

Discounting

Individuals usually prefer to receive benefits sooner rather than later and prefer to incur costs later rather than sooner [39]. Discounting is a technique used in cost-

Bergeron [13] 2008	Chesson [22] 2008				Dasbach [26] 2008	Kulasingam [20] 2008	Kim [24] 2008		Jit [23] 2008
France	USA				UK	UK	USA		UK
Static	Static and hybrid				Dynamic	Static	Hybrid		Dynamic
HPV	HPV				6/11, 16/18	HPV	16, 18, HR, LR		6, 11, 16, 18, HR
NA	NA				80%	NA	75%		80%
100%	100%				90%–98.9%	98%	100%		100%
EUR 467	USD 360				GBP 236	GBP 235 boost: GBP 78	USD 501 boost: USD 167		GBP 191–252
3.5% B 1.5% C	3%				3.5%	3.5%	3%		3.5%
No	1-way				No	No	No		Multivariate
1-way	1-way				1-way	Multivariate	1-way		1-way
1-way	1-way				1-way	1-way	No		Multivariate
Bivalent	Bivalent (static)	Bivalent (hybrid)	Quadrivalent (static)	Quadrivalent (hybrid)	Quadrivalent	Quadrivalent	Bivalent	Quadrivalent	Quadrivalent
–	–	–	–	–	Dominated[a]	68,000	144,000	–	34,000 (19,000–50,000)
–	–	–	–	–	–	31,000	–	–	22,000 (14,000–33,000)
14,000	13,000	10,000	9,000	5,000	6,000	21,000	44,000	35,000	15,000 (10,000–22,000)
–	–	–	–	–	–	27,000[c]	83,000[c]	–	–
–	–	–	–	–	–	–	–	–	520,000 (305,000–987,000)
–	–	–	–	–	–	–	97,000	81,000	12,000 (2,000–24,000)
–	–	–	–	–	11,000	–	153,000	134,000	106,000 (62,000–337,000)

effectiveness analysis to take these time preferences into account. It consists of scaling down future costs and benefits such that they are less important the further in the future they occur and/or the higher the discount rate [39]. There is debate as to what discount rate should be used and there is variability between countries in the rates that are used (discount rates vary between 3 and 5%) [39]. For treatment, benefits occur shortly after the intervention is given, and the cost-effectiveness of these interventions is therefore largely independent of these methodological disagreements on discounting. However, the cost-effectiveness of prevention programs is highly sensitive to discounting due to the long time spans over which benefits accrue [11]. Discounting is of particular importance when assessing the cost-effectiveness of HPV vaccination as costs of the program are incurred at the moment of vaccination while benefits can occur in the short (genital warts) to long term (cervical cancer) [11]. A slight decrease in discount rate (from 5 to 3%) could change the cost-effectiveness of HPV vaccination strategies from unacceptable to attractive (fig. 1) [22]. Until a consensus is made regarding the appropriate discount rates that should be used for prevention strategies, analysts should use country-specific recommendations as their base case and present sensitivity analyses. See Beutels et al. [39] for more information regarding discounting in the context of vaccination.

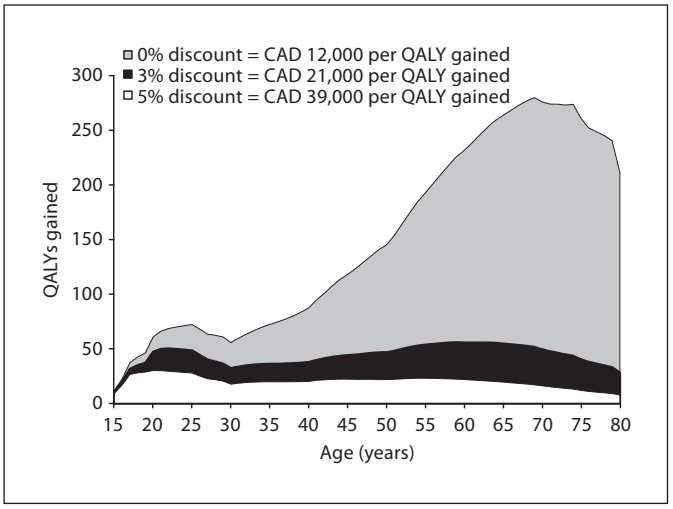
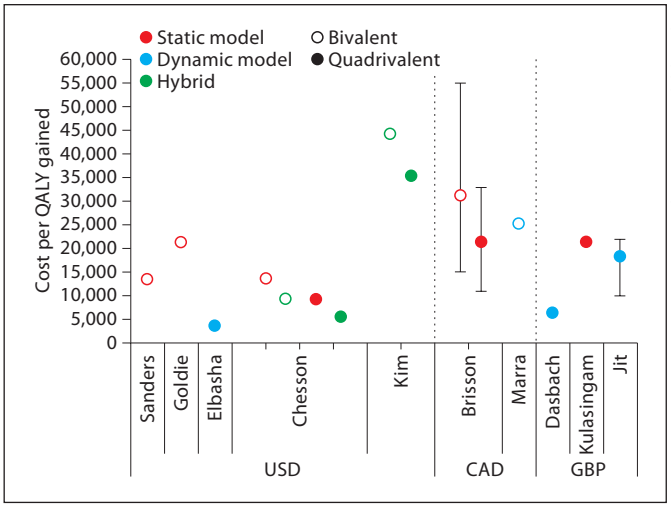


Fig. 1. Impact of the discount rate on the estimated QALYs gained and cost-effectiveness in a cohort of 100,000 girls vaccinated at 12 years of age (vaccine efficacy = 95%, average duration of vaccine protection = life). Results are derived from Brisson et al. [11].



Color version available online

Fig. 2. Comparison of HPV vaccine cost-effectiveness predictions (12-year-old girls, no waning) for modeling studies conducted in the US [14, 18, 19, 22, 24], Canada [11, 41] and the UK [23, 25, 26]. Error bars for Brisson et al. [11] and Jit et al. [23] represent the 10th and 90th percentile and the 5th and 95th percentile of model predictions, respectively.

Uncertainty

The development of models are based on assumptions, which necessarily introduce uncertainty regarding the conclusions that can be drawn from their results [38]. It is therefore important to examine the uncertainty of model predictions to provide policymakers with the necessary information to make appropriate decisions. In the case of HPV, it is particularly important to quantify uncertainty due to the complex natural history of HPV infection (encompasses numerous stages of disease which depend on HPV type, screening and treatment) and the limited data on age and type-specific HPV natural history [10, 12]. Moreover, for some model parameters, such as progression rates to cancer, empirical studies cannot be carried out for ethical reasons. Despite considerable uncertainty surrounding type-specific natural history parameters, most HPV modeling studies have derived predictions regarding the impact of HPV vaccination by using only one parameter set (table 1). In these studies, only 1-way sensitivity analyses were performed, which are limited in scope because they do not take into account the joint uncertainty of all natural history parameters. A second more recent approach, in the context of HPV modeling, has been to identify and utilize multiple good-fitting parameter sets (which can loosely be viewed as multiple models) to provide decision makers with a range of results that encompass the uncertainties in the natural history of HPV infection and disease [5, 10–12, 23]. Recent papers by Brisson et al. [11] and Jit et al. [23] present predictions from multiple parameter sets that capture the structural and parameter uncertainty regarding the natural history of HPV diseases (table 1, fig. 2). When examining different cost-effectiveness studies of HPV vaccination (and screening) one should ensure that adequate care has been taken to illustrate uncertainty of results and that conclusions are clearly framed as conditional upon the input estimates used [40].

Cost-Effectiveness of HPV Vaccination: Key Findings

In this review we only include studies published before August 2008 that have examined the cost-effectiveness of prophylactic HPV vaccination in developed countries using the cost per QALY gained as the main outcome measure. Below we highlight, for key policy questions, areas of agreement and disagreement in conclusions regarding the cost-effectiveness of HPV vaccination.

Vaccinating Girls

Results from published studies consistently suggest that, under current screening programs, vaccinating ad-

olescent girls against HPV is likely to be cost-effective: (1) if duration of vaccine protection is greater than 30 years, or (2) when booster doses are given if duration of vaccine efficacy is limited (table 1, fig. 2). It should also be pointed out that most studies suggest that the main benefit of HPV vaccination will be in preventing cervical cancer mortality rather than reducing the medical costs related to screening and treatment of HPV-related diseases (assuming screening is not changed).

The type of model used has little impact on the conclusions regarding the cost-effectiveness of vaccinating girls (table 1, fig. 2). Three studies [6, 14, 22] directly compared cost-effectiveness results with and without herd immunity effects. As expected, including herd immunity effects produces more attractive cost-effectiveness results (table 1, fig. 2). The inclusion of herd immunity decreased cost-effectiveness ratios by 23–44% [6, 14, 22]. Only 3 studies [22–24] examined the impact of including HPV-related diseases other than cervical cancer and genital warts. Including other HPV-related diseases reduced cost-effectiveness ratios by 20–35% [22–24].

Two HPV prophylactic vaccines, which target HPV-16/18 (Cervarix®) and HPV-6/11/16/18 (Gardasil®) are now available in many countries. Policymakers may have to decide, given the respective characteristics and costs of the bivalent (Cervarix) and quadrivalent (Gardasil) vaccines, whether 1 or both of these vaccines should be included into the routine vaccine schedule. Two modeling studies provide a comparison of the cost-effectiveness of a bivalent versus a quadrivalent vaccine [11, 23]. Results from these studies predict that the cost per dose of the bivalent vaccine would have to be around CAD 18–55 [11] and GBP 13–21 [23] less expensive to be as cost-effective as an equally effective quadrivalent vaccine in a vaccination program directed at 12-year-old girls. For both studies, the price differential was greatest when the vaccines provided lifelong protection.

Vaccinating Boys, Catch-Up Vaccination and Vaccinating Women

Current evidence suggests that if vaccine coverage is high in girls, including boys in a vaccination program will not be cost-effective (even when including the health benefits to boys/men; table 1). The incremental effectiveness and cost-effectiveness of vaccinating boys varies greatly between studies when coverage rates are low (≤80%) [9, 14, 16]. It should be noted that a high level of uncertainty exists when predicting the effectiveness of vaccinating boys given the lack of data on the natural history of HPV in men and vaccine efficacy in boys/men.

Evidence on the cost-effectiveness of catch-up strategies and vaccinating older women are still limited. Studies published by Elbasha et al. [14] and Dasbach et al. [26] suggest that a catch-up campaign in girls/women up to 24 years of age would be cost-effective in the USA (USD 42,000 per QALY gained) and the UK (GBP 11,000 per QALY gained), respectively. This is in sharp contrast with the results from Kim and Goldie [24] and Jit et al. [23] which suggest that the incremental cost-effectiveness ratio of catch-up to 25 or 26 years of age in the USA and the UK would be greater than USD 100,000 and GBP 100,000 per QALY gained, respectively. On the other hand, evidence suggests that a catch-up program in girls up to the age of 18 years may be cost-effective [23, 24]. More work is required in this area before consensus can be made.

Vaccination and Screening

Very few studies have tried to identify optimal vaccination and screening strategies in terms of cost-effectiveness. Studies that have looked at this research question have suggested that increasing screening intervals combined with HPV vaccination of girls is likely to be cost-effective [6, 17, 18, 20]. Furthermore, for vaccinated women, HPV DNA testing as a triage test for equivocal results in younger women and as a primary screening test in older women is likely to be more cost-effective than current screening [5]. Substantially more work is needed as currently published studies have either not been performed using dynamic models or have examined only a limited number of alternative screening paradigms in conjunction with vaccination.

Most Important Parameters

All studies conclude that the duration of vaccine efficacy is the most influential parameter on the cost-effectiveness of HPV vaccination (table 1). Other important parameters are those that represent the natural history of HPV in older women (e.g. rate of HPV infection and progression and regression of disease) [12, 18] and the degree and duration of type-specific natural immunity following clearance of infection [12]. Efforts should thus be made to better characterize natural immunity following HPV infection and the epidemiology of HPV in older age groups. Similarly, more studies should be focused on quantifying the rate of waning protection following vaccination by measuring antibody decay in clinical trials and/or duration of vaccine protection from surveillance data.

Summary

In summary, there has been an exponential rise in cost-effectiveness analyses in the field of HPV due to the recent availability of prophylactic vaccines and new screening tools. The publication of multiple studies with different methodologies and results can lead to skepticism and confusion. Modeling studies have however produced consistent conclusions regarding the cost-effectiveness of vaccinating girls and boys against HPV: vaccinating girls is likely to be cost-effective, whereas vaccinating boys will most likely not be cost-effective in countries that can reach high vaccine coverage rates in girls. Cost-effectiveness analysis can be a powerful tool in helping decision makers choose the most effective intervention in the context of scarce health care resources. Future work should be focused on increasing the robustness of HPV models (i.e. perfecting the fit of models to data, including herd-immunity effects, capturing the heterogeneity in screening practices and studying structural uncertainties). This will enable modelers to examine the crucial HPV policy question: what are the optimal HPV vaccination and screening strategies to reduce the morbidity and mortality of HPV diseases, in the context of limited resources?

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