



Review

Evolution of the health economics of cervical cancer vaccination

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ABSTRACT

This paper reviews the history of modelling for cervical cancer vaccination. We provide an interpretation and summary of conclusions pertaining to the usefulness of different models, the predicted epidemiological impact of vaccination and the cost-effectiveness of adolescent, catch-up and sex-specific vaccination strategies. To date, model results predict a critical role for vaccination in reducing the burden of cervical disease, with cost-effectiveness being consistently shown across studies using a common threshold of US \$50,000 per QALY, but further clinical and epidemiological data are required to confirm these findings. Through this paper, we aim to provide useful insights for decision-makers as they examine how to best evaluate the potential impact of vaccines against cervical cancer and determine how to best incorporate vaccination into practice.

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Introduction

Invasive cervical cancer (ICC) is the second most common cancer in women worldwide, with approximately 493,000 cases and 274,000 deaths annually [1]. Oncogenic human papillomavirus (HPV) can be detected in virtually all cervical cancer cases and it is established that the virus is a necessary cause for ICC [1]. Overall, it is estimated that HPV causes close to 8% of all cancer cases worldwide [2]. The economic and quality-of-life burden of cervical disease is significant and highlights the need for extensive treatment and prevention options [3]. Existing management strategies of cervical cancer screening with cytology have probably contributed to reducing approximately three quarters of the cervical cancer burden in developed countries with successful screening programmes. However, not all countries, particularly those in the developing world have widely implemented screening programmes. In addition, even in developed countries with such programmes, further reductions in cervical cancer incidence and mortality are still feasible [4,5].

Recent advances in prevention may help to reduce the cervical cancer burden that continues to persist across the globe. For the developing world, vaccination may help overcome cultural and economic barriers that have previously challenged implementation of cervical screening interventions. For the developed world, vaccination may be a successful complement to screening. Whilst screening is a secondary preventative measure based on detecting the presence of disease of the cervix, two prophylactic vaccines, which target HPV 16 and 18 (*Cervarix*TM) and HPV 16, 18, 6 and 11 (*Gardasil*TM), have shown high efficacy in protecting against HPV and associated lesions and these have a primary preventative role given that they target the disease cause [6–11]. Trials provide estimates of *efficacy* (i.e., benefit of a treatment under controlled conditions) up to 5 years [8,7] though they have yet to demonstrate the long-term *effectiveness* (i.e., benefit of treatment under real world conditions) of mass vaccination programmes. At this stage, the potential for using universal vaccination as a primary prevention measure would be difficult to investigate under controlled trial conditions for a large population, not least because of timescales involved. The long-term results of such a trial would not be available for decades. Mathematical modelling is an alternative methodological approach that can be used to translate short-term findings from clinical trials into predictions of long-term health outcomes.

Mathematical models have been used to evaluate strategies for managing chronic diseases and in health policy research for vaccines against childhood infections [12]. Moreover, mathematical models of preventive interventions for cervical cancer have evolved considerably [13–18]. These models have become essential for assisting in policy decisions on screening for cervical cancer. Additionally, adaptations of these models can now be used for evaluating whether vaccination against cervical cancer is an efficient or cost-effective use of resources. Vaccination against cervical cancer is a particularly special area of interest in health economics given that effective (but expensive) secondary prevention programmes are in place globally and benefits of programme implementation will take several years to be seen. Since value for money is of high concern in health policy, analyses of all the consequences of such vaccination are crucial for decisions concerning the allocation of resources. These types of evaluations are central to answering policy-specific questions about programme implementation, particularly in the area of primary prevention where often most health benefits are realized in the long-term with initial large budget investments [19,20].

One of the important health policy questions concerning vaccination, that can ideally be addressed with modelling, is: *What*

are the key components that will influence whether a vaccination programme against cervical cancer will be cost-effective? Crucial elements in answering this question involve a detailed understanding of the impact of including different age groups, catch-up strategies, adding male vaccination and programme durations. Another critical question that needs to be addressed, in the face of existing expenditures on prevention programmes, is: *How can vaccination be best integrated within the existing secondary prevention screening programme?* Answering these questions will certainly involve approaches tailored to reflect national circumstances and will depend on the information sources available for each country [21]. However, it must be noted that usefulness of such models is highly dependent on assumptions and data inputs chosen. While extensive calibration, validation and sensitivity analyses may help increase confidence and quantify uncertainty in a model, it is recognized that all models are imperfect. Rather than trying to focus on how accurate they are, knowing that perfect accuracy is an impossible proposition given lack of empirical data to feed model components, we should also consider “if this model is wrong; how misleading is it likely to be?”

Several models currently exist that can be used to evaluate vaccines against cervical cancer and there is great variability in model structures, assumptions, and the primary research questions investigated. As such, it is difficult to compare findings across the analyses and understand how to apply results in policy evaluations. This paper will provide a non-technical overview of cervical cancer vaccination modelling and is designed to assist in the interpretation and application of models that have been used to examine long-term vaccination impact. Technical terms and key concepts pertaining to modelling are described in [Appendix A](#) and will provide assistance in understanding these studies. This review considers models published up to April 2007 and describes results considered in light of important questions facing decision-makers globally. The following questions, pertaining to vaccination against cervical cancer will be addressed:

- Why are there different health economic models for vaccination against cervical cancer, and what are the advantages and disadvantages of each?
- What is the predicted long-term epidemiological impact of vaccination?
- How cost-effective is early adolescent female vaccination compared with screening?
- What is the cost-effectiveness of strategies that include different age and sex-specific vaccination options?
- What conclusions can be drawn and what questions still remain regarding the health economics of cervical cancer vaccination?

Through this discussion, we aim to provide useful insights for decision-makers as they examine how to best evaluate the potential impact of vaccines against cervical cancer and determine how to best incorporate vaccination into practice.

Why are there different health economic models for vaccination against cervical cancer and what are the advantages and disadvantages of each modelling approach?

For evaluating chronic disease, such as cervical cancer, three types of models are used: cohort models, population models and more rarely, a combination of both. Cohort models are used to track the costs and outcomes associated with a group of individuals of identical age over time, where account is taken of the changing health status of all individuals. Cohort models concern either a cohort of specific size (e.g., 1000 females) or unspecific size where

the focus is on estimating the changing probabilities of being in different states. A population model, in contrast, is used to track changes in the health status of the population over time where individuals constantly enter and exit a model through birth and death [20,22]. Both types of models are based on assuming a set of health states with transitions reflecting the natural history of the disease. Both types of models can be used for the analysis of the consequence of events, such as screening, that may occur repeatedly over time. Population models can be classified as dynamic or non-dynamic models. In dynamic models, the age-specific probabilities of events actually change over time, whereas with non-dynamic models, all probabilities are fixed at the start of the simulation. In the context of modelling infectious disease, the notion of the 'force of infection' (FOI) is central. The FOI can be described as the rate at which susceptible individuals become infected in the population, and reflects what is known as 'transmission dynamics'. Some population dynamic models have been used to investigate how HPV infection is transmitted through the population and assumes that the FOI is dependent on the number of infectious individuals. Given this, a population dynamic model can assess herd protection (i.e., protection to the non-vaccinated individual due to a reduction in the transmission of infection) [23,22]. Cohort models are not designed to reflect the intricacies of infection dynamics although they are usually based on an assumption of age-dependent acquisition of infection.

There is a long history of modelling for screening in cervical cancer [13–18]. Prophylactic vaccination has been modelled more recently as another intervention for preventing cervical cancer. While efforts are now underway to evaluate the important impact in the developing world, published works to date have focused on adaptation of models to North America and United Kingdom. In total, nine cohort model [24–32] and five dynamic model [31,33–36] publications are available showing the impact of cervical cancer vaccination strategies. These published models have been used to track the progression of patients through health states reflecting HPV infection, pre-cancerous lesions, and cervical cancer. Epidemiological data have been used to estimate transition rates between the health states. Analysis also incorporates assumptions concerning the effects of cervical cancer screening (including assumptions about the effects of treatment of lesions and cancer) and vaccination. To assist the understanding of the impact of different interventions, such analyses have been used to quantify the number of life years saved (LYS), quality-adjusted life years (QALYs) gained and costs associated with each strategy (Appendix A).

Key differences do exist between these models, summarized to varying degrees in recent publications [37,18], that render unique interpretation for each model. Published models differ in their structure (e.g., number of HPV types modelled and inclusion of genital warts state), input values (e.g., vaccination efficacy), methodological approaches (e.g., calibration technique) and research questions addressed. Given this, it is important to consider each published model separately, understand their approaches and assumptions, and determine what common conclusions may be drawn given the available evidence.

Table 1 highlights the key distinctions between published models, unique features and research questions addressed. Differences between these models largely reflect technical advances over time due to several factors that are listed below.

Model structure

The structure of a model can refer to the choice of health states, and the method of interaction between such health states, which varies between HPV models. Cohort and population dynamic models are designed to answer different types of questions, the

most important difference being that herd protection is clearly and explicitly accounted for in a dynamic model. Cohort models based on the use of stochastic analysis methods represent the progression of a group of patients throughout their lifetime, they often require less data and assumptions than a dynamic transmission model, and as a consequence can be more complex in the level of detail considered related to the disease process. Because cohort models do not consider transmission dynamics and thus the impact of herd protection, they tend to have a simpler structure and are likely to provide conservative estimates [38,24]. Most published cervical cancer vaccination models (Table 1a) use a cohort model structure and their research questions are not critically dependent on the integration of transmission dynamics within the study. Population dynamic models are used to examine the spread of infectious disease in the population and have been developed recently in the area of vaccination to evaluate research questions of increasing complexity that depend on the level of herd protection generated with vaccination, such as the benefit of vaccinating boys (Table 1b). Dynamic models also involve different methodologies to simulate disease (i.e., compartmental or individual-based simulations) with special data requirements for each method. However, dynamic models introduce added complexity and uncertainty due to data inputs that are often unknown and difficult to estimate, particularly with respect to data concerning sexual behaviour.

Brisson and Edmunds demonstrated that choice of model structure can have an important influence on model results [38]. They noted that most economic evaluations of vaccine programmes ignore the impact of herd protection, often arguing that herd protection is beneficial, so by ignoring it the analysis is conservative. They showed that this was not always the case where a varicella vaccination programme became cost-ineffective when herd protection was considered. In the area of cervical cancer vaccination, these unexpected results so far have not been observed, rather conclusions from published studies to date demonstrate that including the impact of herd protection only seems to improve the cost-effectiveness of HPV vaccination.

Within each type of model, there is further variability concerning the choice of the model structure. Most published vaccination models use a similar core structural set-up (i.e., HPV infection, pre-cancer lesion, cervical cancer health states) with comparable implementation of interventions (vaccination and screening). However, small differences exist between the model structures used, that may yet have some implications on results. Perhaps the clearest example concerns the inclusion of a natural immunity health state and different assumptions about this have been made. There are SIS models (susceptible-infected-susceptible) where individuals are assumed to revert to being susceptible to re-infection once they have recovered from an infected state. An alternative is the SIR model (susceptible-infected-removed) where those who have recovered from an infection are deemed to have acquired natural immunity and are no longer susceptible to infection [41]. Inclusion of a health state of naturally acquired resistance can have a considerable effect on the predicted effectiveness of vaccination, however, there is much uncertainty concerning how to best take account of naturally acquired resistance with little data available to inform such a decision. The variation between model structures reflects uncertainty concerning epidemiological characteristics of the disease process of HPV and cervical cancer.

Model parameters

There is considerable variation in data used to inform models, in part reflecting variation in assumptions between different models. Model parameters can be broadly categorized into the following:

Table 1a
An overview of published HPV and cervical cancer cohort models related to vaccination

	Unique model features ^a	Analysis question(s)	Unique insights provided
Institute medicine	<ul style="list-style-type: none"> • Genital warts, other cancer types states 	What is the cost-effectiveness (cost per QALY) of different vaccines against infectious disease in the USA?	<ul style="list-style-type: none"> • Comparison of HPV vaccine to other vaccines
Hughes et al. [31]	<ul style="list-style-type: none"> • HPV 16 state focus • Hysterectomy state 	What is the clinical impact of vaccination against cervical cancer on reduction of HPV infection and cervical cancer in the USA?	<ul style="list-style-type: none"> • Evaluation of competing risk of HPV types
Sanders and Taira [29]	<ul style="list-style-type: none"> • HPV HR, LR • Hysterectomy state 	What is the cost-effectiveness (cost per QALY) of vaccination against cervical cancer of girls compared with current screening in the USA?	<ul style="list-style-type: none"> • Number needed to vaccinate • Extensive one-way sensitivity analyses
Kulasingham and Myers [28]	<ul style="list-style-type: none"> • HPV HR, LR • Hysterectomy state 	What is the cost-effectiveness (cost per LY) of vaccination against cervical cancer of girls given changed screen strategies in the USA?	<ul style="list-style-type: none"> • Several hypothetical screening strategies • Focus on life years saved
Goldie et al. [25]	<ul style="list-style-type: none"> • Persistent HPV state • Transient HPV state • 16,18,HR, LR 	What is the clinical impact of vaccination against cervical cancer of girls on reduction of HPV, pre-cancerous lesions, and cervical cancer in Costa Rica?	<ul style="list-style-type: none"> • Calibration to extensive country data • Evaluation of competing risk impact
Goldie et al. [27]	<ul style="list-style-type: none"> • Persistent HPV state • Transient HPV state • 16,18,HR, LR 	What is the cost-effectiveness (cost per QALY) of vaccination against cervical cancer of girls compared with current and hypothetical screening in the USA?	<ul style="list-style-type: none"> • Numerous hypothetical screen strategies (80) • Numerous efficacy and waning scenarios
Kohli et al. [24]	<ul style="list-style-type: none"> • Seven HPV types • 16,18,31,45,52,HR, LR 	What is the impact of vaccination against cervical cancer of girls on reduction of cervical disease and screen outcomes in the UK?	<ul style="list-style-type: none"> • Inclusion of cross-protection benefits • Impact of vaccination on screening outcomes
Van de Velde et al. [30]	<ul style="list-style-type: none"> • Natural immunity state • Hysterectomy state • Genital warts state • 16,18,HR,LR 	What is the clinical impact of vaccination against cervical cancer of girls on reduction of cervical disease in Canada?	<ul style="list-style-type: none"> • Numerous calibration scenarios • Extensive vaccination scenarios
Brisson et al. [26]	<ul style="list-style-type: none"> • Natural immunity state • Hysterectomy state • Genital warts state • 16,18,HR,LR 	What is the cost-effectiveness (cost per QALY) of vaccination against cervical cancer of girls in Canada?	<ul style="list-style-type: none"> • Probabilistic sensitivity analysis • Extensive vaccination scenarios • Compare quadrivalent and bivalent vaccines

^a All model structures incorporate an HPV infected, CIN lesion(s) and cervical cancer health state and model at least oncogenic HPV. Unique model features are highlighted in the table; HR: high-risk (oncogenic) HPV; LR: low-risk (non-oncogenic HPV).

Table 1b
An overview of published HPV and cervical cancer transmission dynamic models

	Unique model features ^a	Analysis question(s)	Unique insights
Hughes et al. [31]	SIR; HPV 16 strata; hybrid model	How efficient is a female only versus female + male vaccine strategy? Is targeting of high-risk groups an efficient strategy?	<ul style="list-style-type: none"> Investigation of specific risk groups
Taira et al. [33]	SIS; HPV 16/18 strata; hybrid model	What is the cost-effectiveness (cost per QALY) of vaccination against cervical cancer of girls compared with girls and boys in the USA?	<ul style="list-style-type: none"> Impact of cost-effectiveness at various vaccine coverage levels
Barnabas et al. [34]	SIR; HPV 16 strata	What is the additional benefit of vaccinating boys? When will the maximum benefits of vaccination be realized?	<ul style="list-style-type: none"> Cost-effectiveness of catch-up strategies
Elbasha et al. [35]	SIR; HPV 16/18/6/11 strata; infection/disease model Genital warts state	What is the cost-effectiveness (cost per QALY) of different vaccination strategies of various age and sexes?	<ul style="list-style-type: none"> Multiple unique catch-up strategies evaluated
French et al. [36]	SIR; HPV 16 strata	What is the clinical benefit of including boys in a vaccination programme and incorporating catch-up strategies?	

^a All model structures incorporate an HPV infected, CIN lesion(s) and cervical cancer health state and model at least oncogenic HPV. Unique model features are highlighted in the table; SIR: susceptible–infected–removed; SIS: susceptible–infected–susceptible.

- Epidemiological (i.e., infectivity, disease progression, regression and death rates);
- Screening (i.e., population coverage rates, probabilities of specific practices, diagnostic test sensitivity and specificity);
- Vaccination (i.e., efficacy and waning estimates);
- Economic (i.e., utility values, treatment costs and discount rates).

Reasons for variation include use of country-specific inputs (e.g., screening programme parameters and treatment costs), differences in study methodology and populations used to capture data (e.g., epidemiological studies of disease progression), use of hypothetical versus real-world vaccine efficacy estimates and variation in model assumptions due to uncertainties in the data available (e.g., duration of vaccine protection, vaccination coverage, whether or not HPV type replacement (or competing risk) will exist with non-vaccine HPV types). Studies have consistently found that certain parameters do highly influence model results and include: vaccine efficacy and duration of protection, quality of life adjustments (i.e., utilities), cost of vaccine and discount rates. Since some model inputs used may be very specific to a particular region of interest, it would be important that inputs are explicitly identified in published work on the region of interest for the purpose of informing decision-makers.

Methodological approaches

HPV models can vary according to the methodology used in the evaluation. For example, within both cohort and population dynamic models, some models are calibrated extensively (i.e., transition rates are varied within established ranges so that model reproduces observed epidemiology data) [24–27,30] whereas others are not. The extent to which a model is matched to country-specific data can impact predicted vaccine effectiveness. For example, given that HPV 16 and 18 distribution in cancer varies across countries, the more accurately that the model reflects this observed data, the more accurate are the models' predictions on vaccine effectiveness. There has been debate over the best methods of calibration when only cross-sectional data are available [30,39]. Under certain dynamic conditions however, current observed data may not represent future cohorts (e.g., where screening or sexual behaviour is continuously changing in recent years and therefore future disease levels may be different), and therefore strict calibration techniques may not be suitably applied to models estimating vaccination impact in future populations.

The choice of discount rate and discounting approach, is yet another methodological consideration, and can result in variation in model forecasts. There has been some recent debate on the appropriate method for applying discounting methods of costs and outcomes to primary prevention strategies where intervention benefits are observed in the long-term [40]. Discount rates should be country-specific, as different standards have been set by authorities in determining which rates are preferable for a setting. However, this may limit applicability of results from one country to another and attempts to do so should consider using similar discounting rates if possible. If comparisons are done with publications, it will be important to understand how discounting influenced results, implying that ideally an extensive sensitivity analysis on discounting is presented.

Study question

Most published vaccination models address different questions (Table 1) and therefore incorporate different model structures, inputs and approaches in order to answer these questions. Although questions, results and conclusions may overlap across models, most

provide additional insights to help further the understanding of the health economic impact of vaccination against cervical cancer. The evolutionary development in the line of questioning within these models has expanded over the last decade as more data have become available.

Initial models focused on the correct method of modelling epidemiological changes anticipated with HPV vaccination, followed by investigations on whether it was cost-effective to vaccinate girls in the presence of current screening. Subsequent questions focused on whether it would be cost-effective to vaccinate 12 year old boys and girls, and the added benefit of vaccinating older age groups and including vaccination catch-up programmes. Dynamic models have been useful in addressing questions about the added benefit of vaccinating males, whilst cohort models are sufficient in answering most questions that would be of interest in incorporating a vaccination programme for women only.

Simpler models with less data requirements may be sufficient to answer several research questions with the limitation of simplified assumptions. More complex models may address sophisticated research questions however data may not always be available. In general, we must consider the results of cohort models and population dynamic models differently as they tend to focus on different research questions. When comparing and contrasting studies based on similar model structures, it is then important to compare results of models that use similar inputs and assumptions (e.g., vaccine coverage, efficacy, duration of protection and age at vaccination). Finally, cost-effectiveness results should be interpreted on a country-specific level, as several factors such as treatment costs, screening programme variation and discount rates can impact results. It is also essential to interpret results according to country-specific cost-effectiveness thresholds.

What is the predicted long-term epidemiological impact of vaccination against cervical cancer?

Cohort model results

Several cohort models have consistently predicted a substantial long-term reduction in cervical cancer incidence and mortality with vaccination of 12 year old girls, with a focus on North America and United Kingdom. Under similar assumptions of high vaccine coverage (i.e., 100%), high vaccine efficacy (i.e., 90–100%) and life-long vaccine protection, the predicted reductions in morbidity and mortality range from one-half to three-quarters of all types of cervical cancer prevented with vaccination [24–27,30]. Further, with these similar vaccine coverage rates, efficacy and duration assumptions, substantial reductions are predicted in other cervical outcomes. Kohli et al. [24] predicted reductions of 35%, 31% and 66% for HPV prevalence, CIN 1 lesions, and CIN 2/3 lesions, respectively. Predicted reductions were comparable, although lower in a similar model by Van de Velde et al. [30] of 21%, 24% and 49%, respectively. Kohli et al. [24] further demonstrated the predicted impact of cervical cancer vaccination on screening outcomes. Results show that approximately one-quarter of abnormal cytology tests and one-third of diagnostic tests and treatments can be averted with vaccination.

There is some variation in results between studies due to differences in data inputs, model structure and assumptions. Key contributing variables influencing results include differences in vaccine efficacy and immunity waning assumptions, inclusion of a natural immunity state, calibration and potential type replacement (or competing risk). As noted above, predicted reductions in cervical outcomes were comparable, although lower in the Van de Velde et al. model [30] compared with Kohli et al. [24] where these

differences are likely attributed to a combination of differences in calibration and inclusion of a natural immunity health state in the model by Van de Velde. Furthermore, variation in assumptions about HPV type replacement, and therefore infection risk, likely impacts results across studies. For example, Goldie et al. developed a natural history model of HPV and cervical cancer and calibrated the model to data from a Costa Rica epidemiologic study. They assumed that recipients of the vaccine are subject to competing risks (multiple types of HPV) associated with acquisition of other HPV types, once HPV 16 and 18 types are prevented [25]. Results showed that a vaccine that was 98% effective against HPV 16 and 18 would result in an approximate equivalent reduction in HPV 16 and 18 cancers, but only a 51% reduction in total cancers, due to the partial compensating effect of competing risk. In this analysis, it was assumed that approximately 60% of invasive cancers were attributed to HPV 16 or 18. Finally, with analyses that assumed waning of vaccine protection (e.g., only 10 years) or sub-optimal efficacy rates (i.e., <90%) [29], reductions in cervical cancer cases and other cervical outcomes were more limited with a less than ideal vaccination.

Dynamic model results

Population dynamic models have confirmed the results of cohort models with the additional advantage of being able to demonstrate time delays in reaching predicted reductions in outcomes, as well as the added benefit of herd protection. Most dynamic models assume real-population coverage levels of less than 100% and incorporate catch-up programmes involving older women during the first few years of vaccination. French et al. [36] recently demonstrated that with 70% coverage, vaccination of 12 year old girls can result in a predicted 68% reduction in HPV 16-related cervical cancer, where this complete benefit is realized 30–40 years post-vaccination. Barnabas et al. [34] showed comparable results with higher anticipated reductions due to higher vaccine coverage levels.

Dynamic models have also demonstrated the additional benefit of vaccinating boys, showing that approximately 2–20% of cervical cancer cases can be additionally prevented with inclusion of boys in the vaccination programme. Studies consistently show that at very low or very high coverage rates, the additional benefit is minimal. For example, French et al. [36] showed that at coverage levels of 50% for girls, vaccination of 12 year old boys (at the same coverage rate) would result in an additional 18.1% of cancer cases being prevented. If female coverage increased to 90%, only 5.8% of additional cases would be prevented. Similarly, Taira et al. [33] showed that male plus female vaccination has the most benefit at vaccine coverage rates between 30% and 70%, with minimal or no benefit at higher or lower rates. Elbasha et al. [35] showed comparable reductions to other studies in cancer cases with a coverage rate of 70% when including 12 year old boys in a vaccination programme [35]. Further, up to 97% of genital warts cases (caused by HPV 6, 11) can be prevented when both 12 year old girls and boys are vaccinated [35]. It must be noted that most of these models have assumed comparable coverage rates for both girls and boys, which may not be realistic in countries that will not include cervical cancer vaccination in the universal vaccination programme.

Another factor that will influence the extent of benefit of including boys in the vaccination programme is age at vaccination. French et al. [36] reported results of several age-specific analyses, concluding that vaccinating younger, rather than older boys, would be most beneficial. In the long-term, vaccination of both boys and girls (12–15 years) would prevent an additional 15% of cancer cases. If boys were vaccinated at age 21, vaccination would produce little effect and prevent only an additional 1% of cases. Elbasha et al. [35]

include 12–24 year old boys as part of a catch-up programme at lower coverage rates (i.e., 50%) for 5 years, and note some additional, but minimal reduction in cancer when including older ages. Other reasons for variation across studies may be due to fundamental differences in assumptions about HPV transmission dynamics, given limited data available that may impact the degree of herd protection estimated in the models.

How cost-effective is adolescent female vaccination against cervical cancer, in combination with current screening, compared with current screening practice alone?

Several earlier models have focused on addressing the question of the cost-effectiveness of vaccinating young women, typically at the age of 12 years, compared with current screening practice. In summary, three cohort models [27,29,26] and two dynamic models [35,33] have been used to address this question. The base-case results of all models suggest that the introduction of cervical cancer vaccination is likely to be cost-effective compared with current screening practice, in North America and under a wide range of assumptions, using a threshold of US \$50,000 per QALY and approximate vaccine price of US \$100 per dose (three doses total), with results ranging from a cost per QALY of US \$2964 to US \$31,000 (Table 2). Both dynamic models gave estimates of a lower cost-effectiveness ratio owing to the incorporation of herd protection, which follows since vaccination offers indirect protection to future partners of those vaccinated, and to the other partners that they in turn may subsequently have.

Most of these models are based on similar assumptions and structures and therefore show comparable results. However, there are some fundamental differences that should be noted when analyzing the model inputs and comparing results.

Epidemiological

Different modelling studies have been based on different assumptions concerning the natural history of the disease. There is variation in the transition probabilities assumed, due to variation between data sources used to estimate them. It is difficult to determine the extent to which assumptions about these parameters have influenced variation between results. Differences in whether or not models include a natural immunity may impact model results, as vaccine effectiveness can depend on assumptions about natural immunity. Modelled data regarding natural immunity to date are based on supposition rather than observation and therefore it is important to consider a wide range of values as considered in the Van de Velde et al. model [30] (e.g., 0–100% lifelong natural immunity).

Vaccination

Cost-effectiveness analyses published to date have included two different HPV vaccines (*Gardasil*TM and *Cervarix*TM) that are similar with respect to protection against HPV 16 and 18 types, but with other clinical differences. Recent analyses [26,35] have reported the cost-effectiveness of a quadrivalent HPV 16, 18, 6 and 11 vaccine that includes protection against genital warts in addition to cervical cancer (i.e., *Gardasil*TM). As genital warts have both a cost and quality of life impact, the results of these analyses will differ from those focusing on including benefits incurred by HPV types 16 and 18 only. Brisson et al. concluded that the cost per QALY was CA \$31,000 (HPV 16, 18 vaccine) versus CA \$21,000 (HPV 6, 11, 16 and 18 vaccine), with the additional benefit for the quadrivalent vaccine due to reduction of genital warts. Analyses will also need

to be conducted in a setting where cross-protection against non-vaccine HPV types can be better scrutinized in order to determine how protection against additional oncogenic HPV types translates into improved cost-effectiveness. Second, perhaps the largest difference between published models is the assumption pertaining to vaccine duration of protection. Taira et al. [33] assume waning of immunity and therefore inclusion of booster shots which has an impact on cost-effectiveness. Other models [27,35] are based on assumptions of lifelong protection without the need for a booster shot in base-case analyses. Further health economic evaluation of different vaccination waning scenarios will be critical, particularly as new data from vaccination trials becomes available.

Screening

Although most papers compare forecasts against current observed screening, there are some differences concerning the screening follow-up practices modelled, observed coverage rates, and associated costs. This can impact the forecast of the relative cost-effectiveness of HPV vaccination, however effects are perhaps most apparent when conducting analyses that alter the current screening strategy. One interesting observation is that modelling studies to date assume that diagnostic test results are statistically independent of each other (i.e., the results of a previous test do not influence results of a subsequent test), although the present authors are unaware of any study that has established this being the case. Evaluation of the impact of this key assumption should perhaps be tested in future analyses.

Economic

Analyses were similar on key economic parameters that would affect cost-effectiveness (e.g., discount rate, vaccination cost and price reductions over time). However, differences in utility values for CIN lesions, cervical cancer and genital warts may partially explain differences in results. For example, higher disutility values were used in Elbasha et al. [35] versus Taira et al. [33] model, partially explaining differences in cost-effectiveness results. Limited data are available on utilities associated with these states and thus it is important to vary all plausible ranges in sensitivity analyses. An additional important question that remains is the data and impact associated with indirect costs of cervical disease.

Transmission dynamics

Finally, the choice of a dynamic versus cohort model influences results, with dynamic models up to now showing lower cost-effectiveness ratios. Within dynamic models, differences in parameter values (i.e., sexual mixing, transmission rates and herd protection assumptions) may help to explain differences between results of dynamic models.

Most cost-effectiveness analyses to date have focused on vaccination in addition to current screening practices, assuming that this will not change. Several recent discussion papers note the potential for optimization of vaccination and screening strategies to maximize health benefits but at the same time be efficient [41–43]. Only few health economic analyses have addressed the question of the cost-effectiveness of vaccination in the presence of altered screening programmes, with studies only available from the USA. Goldie et al. [27] demonstrated that the most effective strategy with a cost-effectiveness ratio of less than US \$60,000 per QALY is one combining vaccination at age 12 with triennial cytology starting at older ages (e.g., 25 years). Lifetime risk of cancer would still be reduced by 94% with this strategy indicating that alterations to the current screening programme (i.e., presently annual interval

Table 2
Cost-effectiveness of 12 year old female vaccination compared with current practice

Base-case results	Sensitivity results	Key assumptions
Sanders and Taira [29] US \$22,755 per QALY gained	Cost per QALY remained below US \$50,000 if efficacy is lower (40%) or if vaccine cost increased to US \$600 per course (i.e., total of 3 doses) Assuming lifetime immunity reduced ICER to US \$12,682 Assuming booster shot every 3 years increases ICER to US \$45,599 Increasing discount rate to 5% causes ICER to increase to US \$37,752 Varying incidence of HPV from 0.5 to 2 times base-case results in an ICER ranging from US \$43,088 to US \$12,664 per QALY	Vaccine protection for 10 years; booster every 10 years 100% of 12 year olds received vaccine Reduction in acquisition of HPV high risk is 75% Current USA screening practices Vaccine cost at US \$300 per course (i.e., total of three doses) Competing risk assumptions not detailed Discount rate of 3% (costs, QALYs)
Goldie et al. [27] US \$24,300 per QALY gained	Reducing efficacy to 70% increases cost per QALY to US \$33,700 Cost per QALY remained below US \$100,000 when assuming that proportion of persistent infection attributable to new (vs. latent) infection was equal to or less than 75%	Lifelong vaccine duration; no booster 100% of 12 year olds received vaccine Reduction in acquisition of HPV types 16 and 18 is 90% Current USA screening practices Vaccine cost at US \$377 per course Competing risk assumptions incorporated Discount rate of 3% (costs, QALYs)
Taira et al. [33] US \$14,583 per QALY gained	Female-only vaccination programme remained economically attractive under a wide range of assumptions. Details of results not shown	Vaccine protection for 10 years; booster every 10 years 70% of 12 year olds received vaccine Reduction in acquisition of HPV 16 and 18 is 90% Current USA screening practices Vaccine cost at US \$300 per course Competing risk assumptions not detailed Discount rate of 3% (costs, QALYs)
Elbasha et al. [35] US \$2,964 per QALY gained	Removing benefits of prevention of HPV 6/11 and effects of herd immunity, the ICER increased to US \$21,404 per QALY Other sensitivity analyses were performed involving strategies with older age groups and boys	Lifelong vaccine duration; no booster 70% of 12 year olds received vaccine Reduction in acquisition of HPV 16, 18, 6 and 11 is 90% Current USA screening practices Vaccine efficacy against CIN lesions (16/18) is 100% Vaccine cost at US \$360 per course Competing risk assumptions not detailed Discount rate of 3% (costs, QALYs)
Brisson et al. [26] CA \$21,000 to CA \$31,000 per QALY gained	Cost per QALY increases up to CA \$56,000 per QALY with waning at 30 years plus booster shot Vaccination of older women (25 years) increases cost per QALY up to CA \$65,000 per QALY	Lifelong vaccine duration; no booster 100% of 12 year olds received vaccine Reduction in acquisition of HPV 16, 18, 6 and 11 is 95% Current Canadian screening practices Vaccine cost at CA \$400 per course Competing risk assumptions not detailed Discount rate of 3% (costs, QALYs)

Table 3
Comparison of key model inputs from Taira et al. [33] and Elbasha et al. [35] dynamic HPV models

	Taira et al. [33]	Elbasha et al. [35]
Time horizon	0–100 years	0–100 years
Target population	12 years girls + boys	12 years girls + boys 12–24 years girls + boys (5 years) ^a
Vaccine efficacy (16, 18)	90%	90%
Vaccine efficacy (CIN lesion)	Not explicitly modelled	100%
Booster shot	After 10 years	None
Vaccine waning	10 years after booster shot	None
Vaccine coverage	70% for lifetime	Reaches 70% after 5 years 50% in catch-up cohorts
Vaccine cost	US \$300 per series	US \$360 per series
Utility values CIN lesions	0.97	0.87–0.91
Utility values genital warts	Not included	0.91
Utility values cancer state	0.62–0.79	0.48–0.76
Discount rate (Costs, QALYs)	3%, 3%	3%, 3%
Transmission rates	Lower (0.35)	Higher (0.7–0.8)
HPV 6 and 11 efficacy	0%	90%

^a Elbasha et al. did not explicitly evaluate 12 year old girls and boys, rather focused on 12 year old girls and boys plus catch up cohorts of 12–24 year olds.

in USA) in the presence of vaccination, would not only be rational, but also cost-effective. Similarly, Kulasingam and Myers [28] concluded that vaccination plus biennial screening delayed until 24 years had the most attractive cost-effectiveness ratio (US \$44,889 per LYS). These studies collectively indicate that in the presence of vaccination it is important to evaluate different approaches to screening from both a clinical effectiveness and cost-effectiveness standpoint. Implementation of a cost-effective policy including vaccination with changes to screening programmes will only be likely to be acceptable to policy makers if it resulted in comparable or greater effectiveness than screening alone. The cost of vaccination might then be partially offset by savings achieved to alterations of the screening programme. This strategic information is vital to policy makers, particularly in countries that may not have the same screening practices as the USA. Further, there is also the issue of potential changes to cytology test performance in the presence of vaccination where it is anticipated that with reductions in HPV prevalence, cytology sensitivity and specificity may be significantly influenced due to multiple factors related to those reductions [42]. Studies have not yet addressed this issue and thus more work needs to be completed in this area. Overall, further global health economic research is required to assess how vaccination strategies and screening strategies can co-exist and function optimally and efficiently.

What is the cost-effectiveness of strategies that include different age and sex specific vaccination options?

Although few studies have assessed the cost-effectiveness of vaccinating at older ages, some preliminary conclusions can be

drawn from the limited data available. Three studies have provided preliminary results for the cost-effectiveness of vaccinating at ages older than 12 years [26,29,35]. These studies demonstrate that vaccinating up to the age of 25 years may still be cost-effective, however not as cost-effective as vaccinating 12 year old girls. Dynamic models have demonstrated that although a substantial number of cervical cancer cases and deaths can still be prevented with vaccination of older ages and catch-up groups, there are diminishing returns with increasing age at vaccination [36]. Women at older ages are more likely to have been exposed to HPV and thus have persistent infection or pre-cancerous lesions at the time at vaccination, thus rendering the vaccine less efficacious. It will be important to further determine the impact of vaccinating at older ages under a variety of assumptions and across a range of countries to help inform fundamental policy decisions regarding different age groups for vaccination.

Most studies published to date have focused on assessing the cost-effectiveness of a universal vaccination programme aimed at adolescent girls. Two recent studies, both using dynamic models, have evaluated the cost-effectiveness of vaccinating both girls and boys, including older age groups. Tables 3 and 4 show the inputs and cost-effectiveness results from these two studies, highlighting the inconsistency in the conclusions regarding the cost-effectiveness of including boys in a vaccination programme. In summary, Taira et al. [33] demonstrate that vaccinating 12 year old boys, in addition to girls, is not cost-effective at expected vaccine coverage levels compared with vaccinating girls only (i.e., US \$442,039 per QALY). In contrast, Elbasha et al. [35] conclude that vaccinating 12–24 year old boys is cost-effective (i.e., US \$45,056 per QALY).

Table 4
Cost-effectiveness of multiple age and sex specific vaccination strategies compared with the next best strategy (costs and QALYs each discounted at 3%)

	Total cost (US \$)	Total QALYs	Δ cost (US \$)	Δ QALYs	Cost per QALY (US \$)
Taira et al. [33]					
No vaccination	40,423	27.7422			
12 years girls	40,667	27.7590	244	0.01671	14,583
12 years girls + boys	40,929	27.7596	261	0.00057	442,039
Elbasha et al. [35]					
No vaccination	726	26.98711			
12 years girls	740	26.99178	14	0.00467	2,964
12 years girls + boys	787	26.99327	47	0.00149	Dominated
12 years girls, 12–24 years girls	748	26.99343	–39	0.00016	4,666
12 years girls + boys, 12–24 years girls	797	26.99461	49	0.00118	41,803
12 years girls + boys, 12–24 years girls + boys	818	26.99506	21	0.00045	45,056

Comparison of Taira et al. [33] and Elbasha et al. [35] results.

Table 5
Summary of health economic findings to date from cervical cancer vaccine models and remaining questions

Topic	Available findings	Outstanding questions
Epidemiological impact	<p>Vaccination is predicted to substantially reduce cervical cancer cases, deaths, pre-cancer lesions, genital warts, and screening tests, with vaccination of 12 year old girls having the greatest benefit</p> <p>Full benefit of vaccination will not be realized for many years post-vaccination</p> <p>Reduction depends on assumptions of vaccine waning and natural immunity</p> <p>Vaccination of boys has some additional benefit in reducing cancer through herd protection, but effect is limited at very low or high vaccine coverage rates</p>	<p>How does type replacement (competitive risk) affect predicted impact of vaccination?</p> <p>What is the long-term epidemiological impact of HPV vaccination given actual clinically established vaccine waning estimates?</p> <p>What is the impact of HPV vaccination on other HPV associated cancers such as vulval, penile and anal cancers?</p> <p>Does predicted epidemiological impact vary across the world?</p>
Cost-effectiveness of mass vaccination	<p>It is cost-effective to vaccinate 12 year old girls in North America</p> <p>Herd protection benefits improves cost-effectiveness</p> <p>Results most sensitive to assumptions about vaccine waning</p>	<p>How will cost-effectiveness of mass vs. opportunistic vaccination differ?</p> <p>Does cost-effectiveness of mass vaccination vary in other regions and settings?</p> <p>What is the cost-effectiveness of vaccination with real-world vaccine waning data?</p> <p>What is the budgetary impact of mass vaccination in different regions and settings?</p>
Cost-effectiveness of age and sex specific vaccination	<p>There is inconsistency in conclusions regarding the cost-effectiveness of vaccinating boys in addition to girls</p> <p>Cost-effectiveness of vaccinating boys improves with lower coverage</p> <p>Cost-effectiveness is reduced when vaccinating girls at older ages but is still demonstrated up to age 25 years</p>	<p>How will cost-effectiveness conclusions regarding both sex vaccination change with more sophisticated dynamic modelling techniques and real-world data?</p> <p>How does cost-effectiveness of older age groups change in different regions?</p> <p>How do the cost-effectiveness of different vaccines compare?</p> <p>What is the most cost-effective vaccine catch-up strategy?</p>
Screening and vaccination	<p>Vaccination is cost-effective in combination with current screening</p> <p>Vaccination can still remain effective and cost-effective under altered screening programme strategies (i.e., starting age and frequency)</p>	<p>What is the effectiveness and cost-effectiveness of vaccination in combination with new primary screening techniques such as HPV testing?</p> <p>How will predicted changes to the cytology test performance with vaccination change the health economics of vaccination against cervical cancer?</p> <p>What are the most cost-effective cytology screening strategies in regions with different screening programmes (i.e., ages, frequencies and strategies)?</p>

When comparing analyses such as those from these two recent studies, it is difficult to arrive at a final conclusion. Each study must be considered separately, in light of unique model structures, inputs and assumptions. Taira et al. explicitly evaluated the impact of vaccinating 12 year old girls and boys, whereas Elbasha focused on 12 year olds, in addition to catch-up of older ages. In the study of Elbasha et al. HPV 6 and 11 benefits were included, as opposed to the Taira analysis. However, when Elbasha excluded these benefits of serotypes 6 and 11, the cost per QALY only increased to US \$74,151, demonstrating that several other factors influence the large discrepancy between the two study results. There are also differences between the models in the method in which herd effect is incorporated. For example, different assumptions are made regarding HPV transmission rates and whether or not a natural immunity health state is included, which can impact herd protection calculations. Also, differences in utility values may be presumed to have impacted the results since increasing the utility values in a sensitivity analysis by Elbasha almost doubled the cost-effectiveness ratio for vaccinating boys (i.e., US \$83,714 per QALY). Coverage levels were assumed to be different for catch-up cohorts in the Elbasha analysis (i.e., 50%). This factor may impact cost-effectiveness given that in the presence of herd protection, lower vaccine coverage levels may exert a positive impact on the cost-effectiveness ratio as it is well accepted that the value of vaccinating boys is dependent on female coverage levels [33].

In summary, these studies are very different in their assumptions and conclusions, and from a decision-making perspective, it will be important to interpret the results from the perspective that most closely matches those of the region and reflects the best available evidence to date. Further data are required from clinical trials to provide more solid evidence of the efficacy of vaccination in male populations as current efficacy estimates are solely based on immunogenicity data rather than clinical outcomes or evidence on actual transmission blocking. Given this, it may be important to focus efforts on aiming for high female vaccination coverage rates first, with the potential inclusion of male vaccination once efficacy data are available.

What conclusions can be drawn and what questions still remain regarding the health economics of vaccination against cervical cancer?

Table 5 summarizes the conclusions that can be made, given the published studies of cervical cancer vaccination modelling available. Although each study must be interpreted in light of its particular assumptions and parameters, there are several conclusions that can be generalized that could help facilitate decision-making processes on a global level:

- Health economic models of cervical cancer vaccination are useful tools that can provide detailed predictions of the long-term health and economic impact of vaccination to inform decision-making in a variety of settings.
- Vaccines against cervical cancer have the potential to substantially reduce the incidence of HPV infection, genital warts, pre-cancerous lesions, cervical cancer cases and cervical cancer related deaths and the associated economic burden, when given to women prior to initiation of sexual activity (i.e., 12 year old girls).
- Studies have consistently shown that vaccination against cervical cancer is cost-effective, when combined with current screening, demonstrating higher costs but with improved effectiveness (i.e., measured by LYS or QALYs). Cost-effectiveness is reduced at older ages, but remains below the threshold of US \$50,000 per QALY

Table 6
Requirements for future research to inform health economics of HPV vaccination

Parameter	Required data
Epidemiological data	HPV type replacement (competing risk) in presence of vaccination Proportion of infections due to re-activation of latent infection HPV type specific progression probabilities
Clinical data	Long-term vaccine waning profiles by HPV type Vaccine efficacy in boys Natural immunity levels and duration Head to head comparisons of cervical cancer vaccines (immunogenicity) Alternative vaccine dosages and formulations
Screening management	Effectiveness data for HPV primary and triage testing Changes to cytology screening quality with vaccination
Sexual behaviour data	HPV transmission rates
Modelling	Multivariate and probabilistic sensitivity analyses Individual-based transmission dynamic modelling
Economic data	Costs and outcomes associated with other HPV-related cancers Quality of life associated with genital warts (and duration) Quality of life associated with pre-cancerous lesions

up to the age of 25 years. Using a more stringent threshold of US \$20,000 per QALY, vaccination of 12 year old either remains cost-effective, or approaches cost-effectiveness, depending on if herd protection and indirect costs are considered.

- From HPV transmission dynamic studies, there is inconsistency in the conclusions regarding the value of vaccinating boys in addition to girls. Further work in disease transmission dynamics is warranted and more data are required to accurately inform the parameters of these models. In addition, more evidence is required from clinical trials to demonstrate vaccine efficacy in male populations.

Outstanding questions are summarized in Table 6, along with proposed methods and data sources that are required to answer these questions. Several health economic questions still need to be answered, and appropriate data gathered, in order for policy-makers to be fully informed when making decisions about the most efficient and cost-effective implementation of cervical cancer vaccination programmes globally. Most of these questions can be addressed through health economic modelling and with the availability of longer-term clinical and epidemiological data from ongoing studies.

Finally, budget impact assessments are particularly important for vaccination interventions and will be useful to policy-makers in specific settings. This will be an important next step for evaluations as two cervical cancer vaccines become more widely available on the market and not only cost-effectiveness but affordability must be determined.

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Box 1: Definition of the incremental cost-effectiveness ratio (ICER)

$$\frac{\text{Cost}(B) - \text{Cost}(A)}{\text{Effect}(B) - \text{Effect}(A)} \quad \text{or} \quad \frac{\text{difference in cost}}{\text{difference in effect}}$$

- where *B* is more effective and generally more expensive than *A*.
- if *B* is more effective and less expensive than *A*, it dominates *A*.

(GlaxoSmithKline). MD: Consultant (GlaxoSmithKline Biologicals through an i3 Innovus contracted research project; Merck and Co., Inc.).

Appendix A. Overview of terms and definitions used in health economic evaluation

A cost-effectiveness analysis is the type of health economic evaluation where both the costs and consequences of therapies are examined. The central question is how much health improvement can be gained, per unit of cost, compared with an alternative use of resources. Results of cost-effectiveness analyses are summarized using a cost-effectiveness ratio where all health outcomes for two interventions are included in the denominator and all costs are included in the numerator. Central to calculation of this ratio, is decision on the treatments to be compared, costs that are incorporated, and outcomes that are evaluated [44,20] (Box 1).

In a cost-effectiveness analysis, the treatment comparator will be defined by country-specific guidelines and often represents the most cost-effective alternative intervention available or the most widely used alternative treatment (“current practice”). In some cases, current practice may involve a ‘do-nothing’ approach where costs and consequences are still measured and valued. For vaccination against cervical cancer, the most widely used means of prevention is cervical cancer screening. In an evaluation, new interventions are often combined with current treatment (e.g., vaccination + annual screening) and compared with current standard of care alone (e.g., annual screening). However, the choice of the interventions to be compared may vary by region. Reasonable comparators in low-resource settings may include vaccination and screening three times per lifetime. Further, multiple interventions or strategies may be compared in a cost-effectiveness analysis if several comparators exist, or to evaluate a number of hypothetical strategies that are plausible. For example, when compared with screening alone, plausible vaccine strategies can include different vaccine ages, vaccination of one or both sexes, and vaccination combined with altered screening programmes.

All forms of economic evaluation involve assessment of both the inputs (i.e., use of resources) and the level of outputs (health benefits) of the interventions to be compared and so facilitate the process of choosing the most appropriate use of scarce resources. If a treatment strategy is both better and less costly, it dominates the alternatives. More often, a treatment strategy that is better will also be more expensive and a judgment will have to be made as to whether the additional benefit is worth the additional cost. The numerator of the cost-effectiveness ratio incorporates the difference in *total* costs associated with a new intervention compared with the next best strategy. The costs of a treatment are defined as both the costs of administering and of treatment (e.g., vaccination cost + administration fees) minus the costs avoided because of the treatment (e.g., cervical cancer costs reduced); these can

Box 2

Decision analysis: An approach for examining choices under uncertainty and has long been applied to health care decision-making. Complex problems can be broken down into component parts, each of which can be analyzed in detail before combined in a logical, quantitative manner to indicate the best course of action.

Cost-effectiveness analysis: A method for comparing clinical strategies that evaluates their economic costs against their health effects.

Incremental cost-effectiveness ratio: The difference in costs divided by the difference in effectiveness in a comparison of two strategies. The ICER is a measure of the additional cost needed to gain an additional unit of effectiveness. The usual metric for cost-effectiveness analysis is money spent per quality-adjusted life year gained.

Quality-adjusted life year (QALY): The most commonly used measure in economic evaluation; calculated as the number of years of life saved adjusted for the quality of life during those years and measured through the use of utility.

Life years saved: A common measure used in economic evaluation calculated as the number of years of life saved as a result of implementing a specific intervention.

Direct costs: Costs related to the use of resources due to either the disease or its treatment (e.g., diagnostic tests, drug costs, physician visits and hospital care). They include costs to the health care system but also costs to social services and to patients.

Indirect costs: Costs related to the loss of production (e.g., work hours missed), due to either the disease or treatment, which occur to society.

Discounting: Future monetary cost and benefits are reduced or ‘discounted’ to reflect the fact that money spent or saved in the future should not weigh as heavily in programme decisions as money spent or saved today. Discounting is also applied to health gains. This is primary due to existence of time preference where we prefer to have money or health now as opposed to later.

Dominance: The situation in which one clinical strategy is both less expensive and more effective than another strategy.

Extended dominance: A situation observed in multi-strategy comparisons, when the incremental cost-effectiveness ratio for a given treatment is higher than that of the next more effective alternative.

Utility: A measure of the relative preference for, or desirability of, a specific level of health status or a specific health outcome.

include both *direct* and *indirect* costs. Health outcomes, expressed in the denominator of a cost-effectiveness ratio, can be expressed as *disease measures* such as events avoided or delayed (e.g., cervical lesions or cervical cancer cases avoided), *survival* measured as life years saved, or *quality-adjusted survival* expressed as quality-adjusted life years (QALYs). QALYs are a common outcome used for measuring health gain associated with an intervention, calculated as the number of years of life saved adjusted for the quality of life during those years, and is often used to compare results of economic evaluations. Fundamental concepts in economic evaluations are described in Box 2.

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