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Modeling Cervical Cancer Prevention in Developed Countries

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Abstract

Cytology-based screening has reduced cervical cancer mortality in countries able to implement, sustain and financially support organized programs that achieve broad coverage. These ongoing secondary prevention efforts considerably complicate the question of whether vaccination against Human Papillomavirus (HPV) types -16 and 18 should be introduced. Policy questions focus primarily on the target ages of vaccination, appropriate ages for a temporary “catch-up” program, possible revisions in screening policies to optimize synergies with vaccination, including the increased used of HPV DNA testing, and the inclusion of boys in the vaccination program. Decision-analytic models are increasingly being developed to simulate disease burden and interventions in different settings in order to evaluate the benefits and cost-effectiveness of primary and secondary interventions for informed decision-making. This article is a focused review on existing mathematical models that have been used to evaluate HPV vaccination in the context of developed countries with existing screening programs. Despite variations in model assumptions and uncertainty in existing data, pre-adolescent vaccination of girls is consistently found to be attractive in the context of current screening practices, provided there is complete and lifelong vaccine protection and widespread vaccination coverage. Questions related to catch-up vaccination programs, potential benefits of other non-cervical cancer outcomes and inclusion of boys are subject to far more uncertainty, and results from these analyses have reached conflicting conclusions. Most analyses find that some catch-up vaccination is warranted but becomes increasingly unattractive as the catch-up age is extended, and vaccination of boys is unlikely to be cost-effective if reasonable levels of coverage are achieved in girls or coverage among girls can be improved. The objective of the review is to highlight points of consensus and qualitative themes, to discuss the areas of divergent findings, and to provide insight into critical decisions related to cervical cancer prevention.

Keywords

mathematical model; HPV vaccination; cervical cancer screening; cost-effectiveness; developed countries

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1.0. Introduction

In countries able to afford and support organized cervical cancer prevention programs, screening with cytology has reduced mortality from invasive cervical cancer [1]. Although a single cytology test has low sensitivity for detecting precancerous lesions [2], because of the slow nature of cervical carcinogenesis, screening women repeatedly at frequent intervals has proven to be an effective secondary prevention strategy.

Countries have established different guidelines with respect to screening intervals, ages and diagnostic algorithms in response to positive screening test results, and have achieved different levels of coverage (Table 1) [3-5]. The relevant challenges with respect to screening have varied as a result. For example, the United States of America (USA) has grappled with escalating costs associated with cervical cancer screening in which substantial resources are spent on mild abnormalities likely to regress, while Singapore and Italy have struggled to improve quality control and Japan faces declining coverage rates [6]. In the context of these challenges, there has been considerable interest in new screening technologies, such as Human Papillomavirus (HPV) DNA testing, shown to be more sensitive than cytology for detection of high-grade cervical disease. Accordingly, HPV DNA testing is increasingly being included in national screening recommendations. For example, in the USA, HPV DNA testing is recommended as a triage test for equivocal cytology results and as a primary screening test in conjunction with cytology in older women [7]. Provided screening is not more frequent than triennial, both have been found to be cost-effective [8-10].

The availability of prophylactic vaccines against HPV types -16 and 18 now presents an option for primary prevention of cervical cancer raising important policy issues. For example, specific questions being discussed in the USA, Canada, Australia, the United Kingdom (UK) and other European countries include the optimal target ages for vaccination, appropriate ages for a temporary “catch-up” program, potential revisions in screening practices to optimize synergies with vaccination, and whether to include boys in the vaccination program. Evaluating the comparative outcomes expected with different vaccination strategies is challenging given the many factors that will need to be considered. For example, countries with well-established screening programs will need to consider the potential avertable burden of disease relative to their *status quo*, the uncertainty in duration of vaccine protection, the relative performance of new screening strategies that utilize HPV DNA testing, the costs associated with different cervical cancer prevention options, and the likelihood of acceptability and uptake.

In order to explore such complex factors and uncertainties, decision-analytic models are increasingly being developed to synthesize multiple sources of epidemiological, clinical, and economic data, to simulate disease burden and interventions in different countries, to extrapolate data from short-term clinical studies to long-term population-based outcomes, and to evaluate the benefits and cost-effectiveness of primary and secondary preventive interventions for informed decision-making. These models can also be used to explore the implications of uncertain assumptions, as well as to identify priority areas of clinical research.

Recent reviews have identified elements of cost-effectiveness analysis and modeling that are most relevant to cervical cancer control evaluation and have discussed the methodological issues most pertinent to upcoming policy questions in the cervical cancer field [11-13]. Extending this work, this article provides a descriptive overview of the existing mathematical models used to evaluate HPV vaccination in the context of developed countries with established screening programs.

2.0. Mathematical Models for Decision-Making

In the context of cervical cancer prevention, several models have been developed, each associated with strengths and limitations, and each equipped with features suited to address different policy questions. In general, the choice of model type is a function of several considerations including: 1) the specific question(s) being addressed; 2) the features of natural history and disease that are important to capture for the specific problem being analyzed; 3) the data available to parameterize, calibrate and validate the model; 4) the familiarity of the analyst with different modeling techniques; 5) the time requirements for model development; and 6) the ease and speed of running the model and conducting the analysis [14].

There are modeling challenges that are of particular relevance to HPV-16/18 vaccination [11,13]. First, as with many vaccines, there are potentially complex epidemiological consequences at the population level due to herd immunity effects. Second, there is a long lag time between the intervention and the ultimate health benefits, as an HPV-16/18 vaccine delivered in adolescence is intended to prevent cancers in adulthood several decades later. Third, current vaccines prevent only two high-risk HPV types, introducing challenges related to the modeling of potential type interactions. Fourth, cervical cancer prevention strategies that are currently available in most developed countries have different mechanisms of action, considerably complicating the amount of detail required in a model that includes them all. For example, cytology is aimed at detecting abnormal cervical cells resulting from HPV infection with both low- and high-risk types; current HPV DNA tests used for screening detect the presence of any of 13 high-risk types; the bivalent vaccine targets high-risk types HPV-16 and 18; and the quadrivalent vaccine also targets two low-risk types, HPV-6 and 11. Because it is very difficult to capture all of these complexities to the fullest degree possible, as a general rule, all models involve tradeoffs.

Figure 1 depicts a general model of cervical carcinogenesis. The natural history of disease in an individual woman is represented as a sequence of transitions between mutually-exclusive health states. Health states in the model, descriptive of the underlying true health, are generally defined to include HPV infection status, grade of cervical intraepithelial neoplasia (CIN) and stage of cancer. Health states are stratified to reflect different levels of detail, depending on the nature of the question, type of model and data availability. For example, health states reflecting HPV infection may be stratified by specific individual HPV types (e.g., type -16, type -18), or by categories of HPV types (e.g., high-risk types, low-risk types), while those reflecting CIN may be stratified by specific grade (e.g., CIN 1, CIN 2,3). Health states may also be stratified according to dimensions important to the analysis (e.g., detected and undetected cancer) or according to classification systems for which there are data (e.g., stage 1-4 cancer, or local, regional and distant cancer).

As models evolve in complexity, the requirement for parameter values quickly multiplies and input values are rarely available for all parameters. Calibration techniques aimed at fitting uncertain model parameters to observed, epidemiologic data (e.g., age-related prevalence of type-specific HPV and CIN, age-related incidence of invasive cancer, and the distribution of HPV types within CIN and cancer) are increasingly being used [15-22]. Models utilize a wide range of approaches to estimate uncertain or unknown parameters and evaluate uncertainty and variability [23].

Models can be generally classified along several dimensions depending on whether they possess generic attributes, such as 1) whether populations within the model can interact or not (dynamic versus static models); 2) whether populations are allowed to enter the model or not (open versus closed models); 3) whether transition rates are fixed (deterministic) or subject to chance (stochastic); and 4) whether the population's behavior in a model is simulated using

values reflecting population averages (aggregate) or at a micro level where the behaviors of individuals in the population are tracked (individual-based) (Table 2). Models used to assess type-specific HPV vaccination can be further characterized by whether they reflect one or more HPV types, include other HPV-related non-cervical outcomes, and according to the degree to which they can represent screening, diagnostic and treatment protocols.

2.1 Static *versus* dynamic

In a static model of cervical cancer, the force of HPV infection may change as a function of age or other individual-based factors, but is constant over time, and explicit interactions between individuals are not modeled; for example, HPV incidence may be parameterized as an age-specific probability of infection that is calibrated to observed epidemiologic patterns. In contrast, in a dynamic model, the probability of an individual acquiring an HPV infection is parameterized as a function of three inputs: 1) the sexual contact patterns of that individual with others, 2) the transmissibility (i.e., infectiousness) of the HPV type; and 3) the type-specific prevalence of infection within the population. While static models may be acceptable to comparatively assess screening strategies, vaccination in such models protects a proportion of the population from infection, but those who are not vaccinated do not receive any protection or benefit. In dynamic transmission models, because of the explicit interactions between individuals in a population, vaccination is likely to change the risk of infection for unvaccinated individuals in the community; therefore, dynamic models are required to address questions which involve widescale vaccination of girls and boys.

To date, all dynamic models of HPV infection have involved only heterosexual transmission. Most have stratified the population into different levels of sexual activity by age, with corresponding numbers of sexual partnerships, and then modeled transmission as a probability per partnership. Sexual mixing can occur between people in different age groups, as well as in different sexual activity levels. Model inputs directly inform how sexual partnerships form between females and males, during which HPV can be transmitted between partners. Barnabas RV *et al.* [24], Kim JJ *et al.* [25] and Choi YH *et al.* [15] used behavioral survey data to inform initial model inputs (e.g., stratification of the *population* into low, medium, or high sexual activity levels and corresponding number of new partners per year, by age) and then calibrated the transmission probabilities per partnership to match population-based estimates of HPV prevalence.

2.2 Open *versus* closed

An open model allows individuals to enter and exit the model over time, while a closed model does not allow for new entrances over time. The most common closed model used for cervical cancer prevention is a single birth cohort simulation using a *Markov* model. The most common open models are dynamic transmission models that allow for the entry of “susceptible” (or uninfected) individuals into the model (e.g., births over time) replenishing the susceptible compartment. A microsimulation model that does not allow for interactions between individuals (i.e., is not dynamic) can also be open by simulating multiple birth cohorts over time. Open models are most appropriate for addressing questions that involve modeling temporal trends, and for interventions targeted to different age groups within a population and that may vary by calendar year (e.g., comparative ages to target catch-up vaccination).

2.3 Aggregate (or population-average) *versus* individual-based

In an aggregate model, individuals are assigned to health states, and movement between them depends on health status or other relevant variables. Individuals in each health state move according to parameter values at the aggregate level (i.e., averages of the individuals belonging to a compartment or the population as a whole), and the model records the number of individuals in each health state over time. Many characteristics could be modeled in aggregate but

increasing their number makes population average models more complex and unwieldy. Most dynamic transmission models that have been published for HPV-related cervical cancer are of this type.

In contrast, an individual-based model (or microsimulation model) keeps track (memory) of each individual's behavior, allowing for heterogeneity in behavior to be adequately explored. The ability to keep track of the individual life experiences of women (and indeed men), which may impact future risk of infection or future screening schedule, is a great advantage when behaviors are very diverse (as is the case for sexual mixing) or when the intervention is tailored to individuals (as is the case for screening). For example, if a woman has had treatment for CIN, she may be followed more frequently than the average woman in her birth cohort. An example related to vaccination is in modeling an individual woman's likelihood of screening patterns given her particular vaccination status.

2.4 Deterministic *versus* stochastic

While in a deterministic model, all events occur according to fixed parameter values, a stochastic model allows for events to occur by chance (randomly). Most dynamic models of HPV transmission have been deterministic; since microsimulation randomly samples individuals with their own sets of assigned attributes, microsimulation models are naturally stochastic. Even with fixed parameter values in a microsimulation model, the individual realization of each transition may differ from person to person due to chance. It is important to note that the variance associated with individual sampling (first-order uncertainty) in microsimulation is different from the uncertainty related to the parameter values (second-order uncertainty). In contrast, variability refers to the often “known” heterogeneity across subgroups or in a population (e.g., age or sex).

Different types of models can be coupled to leverage different model attributes for a given analysis. For example, dynamic models of HPV (which represent transmission and herd immunity benefits of vaccination of vaccine-targeted types) have been coupled with static models (which incorporate other HPV types and detailed screening strategies) [25-27]. One advantage of using multiple models is that projected results can be compared using independently structured models, which can greatly enhance evaluating the impact of model structure on cost-effectiveness results. However, this approach usually involves making a number of approximations and requires the influence of one model's results on the other to be handled carefully.

2.5. Natural history data required to develop a mathematical model of HPV and cervical carcinogenesis

Because of the epidemiological variation in age-related HPV, cervical cancer incidence and proportion of cancer attributable to HPV-16 and -18, primary prevention strategies may have differential impact in different settings. These differences will be most pronounced in countries without effective screening [28,29]. Therefore, irrespective of the type of model chosen, it is important to tailor the models to each particular setting using country-specific data, where possible. To simulate a particular country's burden of cervical cancer and prevention policies, a substantial amount of data is required to inform parameter inputs, either directly or, in the absence of empirical data, through model fitting or calibration. For example, estimates of age- and type-specific HPV incidence from longitudinal studies can be used directly as input into static models, whereas in a dynamic model, direct inputs for HPV incidence would require data on sexual behavior, such as number of new sexual partners, and transmission probability of HPV infection.

HPV prevalence, on the other hand, is a function of a number of transitions occurring simultaneously in the model, such as HPV incidence, clearance and progression, and therefore, cannot be input directly. In this situation, empirical data on HPV prevalence in the population can be used as a calibration target, which is used to infer other uncertain parameters in the model such that good model fit to the empirical data can be achieved. A wide array of model calibration techniques have been employed [15-17,20-22,24] and range from fitting a limited number of model parameters and comparing model results to data visually or by using more statistically rigorous techniques, to fitting multiple model parameters to data and retaining those combinations of input parameter values whose results are within certain target ranges for key outputs [16,20,22]. Calibration target data in these analyses have included HPV-16 seroprevalence, age-specific prevalence of HPV and CIN, incidence of cervical cancer (by type and overall), and HPV type-distribution among CIN and cervical cancer cases. The process of calibration enables the analyst to identify multiple good-fitting parameter values, or sets of parameter values; when the analyses are repeated using multiple good-fitting values, they can serve as uncertainty analyses over the natural history parameters.

Another important piece of information in evaluating the long-term prospects of the HPV vaccine in a particular setting is the burden of the vaccine-targeted HPV types in cervical lesions and invasive cancer (including adenocarcinomas), and in the case of the quadrivalent vaccine, in genital warts. Estimates of type-specific HPV prevalence in different countries show regional variation and have been reported and discussed extensively in previous publications [4].

Although vaccine efficacy against vulvar and vaginal lesions have been reported in clinical trial data [30] the impact of vaccines on other HPV-16/18 related diseases and conditions (e.g., penile cancer, anal cancers, oral cancers) has not yet been observed and is less certain. While HPV-16/18 are estimated to contribute to roughly 32% vulvar/vaginal cancer, 25% penile cancer, 83% anal cancers, and 3-11% oral cancers [31,32], there are also less natural history data on these diseases than in the case of cervical cancer. Similarly, while infections with HPV-6/11 are associated with recurrent respiratory papillomatosis, the ultimate impact of the quadrivalent vaccine on this condition is not yet known. Although the burden of these conditions varies by setting, to the extent that the vaccines will avert additional morbidity and mortality due to these diseases (and their associated costs), the cost-effectiveness of vaccination strategies could improve. Better data on the natural history and burden of these other HPV-related conditions and interventions (and ideally, direct reporting of these outcomes in clinical trials) will be useful for revising current models to incorporate the potential benefits of the vaccine on non-cervical cancer outcomes.

While model parameterization and calibration are necessary steps required for model development, good modeling practice also requires that models undergo validation exercises to assess that model predictions are consistent with observed data that were not used to inform input parameters [33]. Most models report face validity against recent estimates of cancer incidence and mortality in the presence of screening, such as from the Surveillance Epidemiology and End Results- (SEER) cancer registry [16,17,34,35].

2.6 Model outcomes

2.6.1 Health benefits—The most common outcomes generated by models to express the health benefits associated with vaccination are life expectancy, quality-adjusted life expectancy, reductions in lifetime risk of cervical cancer and reductions in prevalence of HPV infection and CIN over time. In developing countries often disability-adjusted life years (DALYs) averted are reported instead of quality-adjusted life years (QALYs) [28,29]. Analyses evaluating the quadrivalent vaccine also reported estimates of reductions in genital warts [25,36-40], and one analysis also reported potential vaccine benefits related to other

HPV-16/18 associated cancers and HPV-6/11 associated juvenile onset recurrent respiratory papillomatosis (JORRP) [25]. Two analyses reported the number needed to vaccinate to avert one cervical cancer case [35,41].

For outcomes expressed in QALYs, utility weights are assigned to different health states to reflect decrements in quality of life associated with residing in a particular state. In analyses that reported QALYs, utility weights associated with different stages of cancer (applied multiplicatively to baseline, age-specific utility weights) were most common. Some analyses also included temporary disutility associated with a positive screening test result, diagnosis of or treatment for precancerous lesions [26,35-37,39,42], and development of genital warts [25,36-40].

2.6.2 Costs and cost-effectiveness—All analyses that reported costs included direct medical costs of the interventions. Direct non-medical costs, such as cost of transportation, and patient time costs were included only in Goldie SJ *et al.* [17], Kim JJ *et al.* [25], and Goldhaber-Fiebert JD *et al.* [43]. Vaccine costs (assuming three doses) ranged from $200 to $500, which included different cost components in the different analyses; all else equal, analyses assuming lower vaccination costs would make vaccination strategies more attractive. Roughly half of the studies explicitly included costs associated with administration of the vaccine program [25,35,36,42,44,45]. In principle, analyses should include the same component costs for both vaccination and screening interventions.

Using the models, total lifetime costs and health benefits are estimated for each strategy. Comparisons across strategies are expressed using the incremental cost-effectiveness ratio (ICER), calculated as the incremental costs divided by the incremental benefits of a strategy compared to the next less costly strategy. Strategies that are more costly and less effective than another strategy are considered “strongly dominated”, and strategies that are less cost-effective (i.e., have higher cost-effectiveness ratios) than a more costly alternative are considered “weakly dominated”; both types of dominated strategies are excluded from the final calculations of the cost-effectiveness analysis. Consistent with published guidelines on cost-effectiveness analysis in health and medicine [46-49], life expectancy (unadjusted and adjusted for quality) and lifetime costs were discounted at rates ranging from 1.5% to 5% per year; Bergeron C *et al.* [36] discounted costs and benefits differentially at 3.5% and 1.5% per year, respectively. At higher discounting rates, cervical cancer screening strategies tend to be favored compared to vaccination since vaccination costs accrue immediately, yet benefits accrue over a longer time horizon.

2.6.3 Interpretation of results—The cost-effectiveness of a strategy measures its value for money, or how much benefit a strategy provides for each additional dollar, compared to other strategies. There is no consensus on the appropriate threshold for cost-effectiveness, and indeed, different countries have adopted different thresholds. Some countries use specific thresholds as guides for resource allocation decisions; for example, the UK cites a threshold of (x020A4)30,000 per QALY gained [50]. Other countries, such as the USA rely on an implicit threshold, such as $50,000 or $100,000 per QALY gained [51], using it as a benchmark to denote efficiency, but rarely as sole justification for decision-making around health coverage. The Commission on Macroeconomics in Health and Medicine has suggested that interventions with cost-effectiveness ratios less than the country's per-capita Gross Domestic Product (GDP) should be considered *very cost-effective* [52].

It is important to note that an analysis of cost-effectiveness is different from an analysis evaluating affordability. While a cost-effectiveness analysis measures efficient use of resources (value for money), an assessment of affordability seeks to make the impact on a specific budget transparent and to estimate the real-time financial costs to implement and sustain a program.

While information on affordability, in conjunction with cost-effectiveness, is often requested by decision makers in developing countries, where budget limitations are often profound, this information is increasingly being requested by a range of health care payors in higher-income countries.

3.0 Key Messages on Benefits and Cost-Effectiveness

The main results of cost-effectiveness analyses conducted in high-income countries with existing screening programs are summarized in this section, categorized by policy question. Most studies assumed high vaccine efficacy (90-100% against HPV-16/18 infections) over the lifetime and high achievable vaccine coverage (70-100% within the first five years of the program).

3.1 Vaccination of pre-adolescent girls in the context of current screening

In all analyses, a program of HPV-16/18 vaccination of pre-adolescent girls in addition to current screening was projected to result in greater health benefits than screening alone; however the magnitude of this benefit depends largely on assumptions of baseline screening. In the USA, where screening with cytology is frequent and begins at an early age, additional reductions in lifetime cancer risk due to vaccination ranged from 17.9% with annual screening (76.3% (screening alone) to 94.2% (with vaccination)) to 38.2% with five-year screening (50.4% screening alone, 88.6% with vaccination) [43]. In the context of Australia's screening program (every 2 years), Kulasingam S *et al.* [42] found that reductions in lifetime risk of cancer increased by 17% after introducing a program of vaccinating 12-year-old girls.

Under assumptions of lifelong vaccine immunity, the vast majority of published cost-effectiveness analyses have suggested that targeting pre-adolescent girls (ages 12 or younger) with an HPV-16/18 vaccine is very attractive in the context of current screening (Table 3). Although assumptions about screening frequency, coverage and ages varied by setting, cost-effectiveness ratios for pre-adolescent vaccination of girls generally fell below $50,000 per QALY gained. When additional benefits of averting HPV-6/11 genital warts with the quadrivalent vaccine were included, Elbasha EH *et al.* [39] estimated a cost-effectiveness ratio of $3,000 per QALY for vaccinating 12-year-old girls; when outcomes of other cancers, genital warts, and JORRP were included, Kim JJ *et al.* [25] found that the cost-effectiveness ratio for pre-adolescent vaccination decreased by 10%-20%, depending on assumptions of vaccine efficacy.

Brisson M *et al.* [41] estimated that the number needed to vaccinate to prevent one cervical cancer case was 324; when vaccine efficacy was assumed to wane at 3% per year, the number needed to vaccinate increased to 9,080. Sanders GD and Taira AV [35] projected that 250 12-year-old girls would need to be vaccinated in order to prevent one cervical cancer case if the vaccine was protective over the lifetime, and 600 girls if the vaccine waned after 10 years (1,484 girls to prevent a cervical cancer death).

Several analyses evaluated the effect of waning vaccine immunity, with assumptions ranging from a 30-year average duration of protection with constant waning over time [37] to full protection for 10 years or more followed by complete loss of protection [26,34,35,42]. Without a booster, cost-effectiveness ratios for vaccinating 12-year-old girls exceeded $50,000 per QALY [37,42,45]. When Bergeron C *et al.* [36] assumed waning immunity at 20 or 10 years, cost-effectiveness ratios for vaccinating 14-year-old girls increased from €8,400 to €14,900 and €37,200 per QALY, respectively. With a duration of vaccine protection of 10 years, Taira AV *et al.* [26] and Elbasha EH *et al.* [39] found that vaccinating 12-year-old girls was less cost-effective than programs targeting older girls, such as 18-year-old girls or women up to age 24 in a catch-up program, respectively.

Assuming that a single booster was required to sustain vaccine-induced protection over the lifetime, the cost for pre-adolescent vaccination ranged from $14,600 to CAN$37,000 per QALY, when the booster cost only one-third of the initial vaccine course [26,37,42] and €13,400 per QALY, when only 50% of the original vaccinated cohort received a booster [36]. Boot HJ *et al.* [44] evaluated the vaccination program under multiple scenarios of booster requirements, including four boosters every 10 years up to age 50; this strategy increased cost per QALY from €24,000 (lifelong immunity) to €39,500 per year of life saved (YLS).

3.1.1 Summary points

- Despite variations in cost-effectiveness results (influenced by different modeling assumptions), the vast majority of analyses concluded that vaccination of pre-adolescent girls with screening was more effective than screening alone, and was cost-effective in the context of current screening practice, provided vaccine-induced protection was complete and lifelong.
- When protection was assumed to last 10-30 years, pre-adolescent vaccination of girls became less attractive, and according to at least two analyses, was no longer cost-effective; with a duration of only 10 years, vaccination at age 12 was less attractive than targeting older females.
- When only a single booster vaccination was required to extend lifelong protection, vaccination of pre-adolescent girls was considered cost-effective. When boosters were required at multiple ages, vaccination of pre-adolescent girls became less attractive compared to screening alone.

3.2 Revisions to current screening post-vaccination

Even in the absence of vaccination, many modeling analyses have demonstrated that increasing the frequency of screening beyond every three years yields diminishing marginal returns at the population level, leading to increasingly unattractive cost-effectiveness ratios [8,10,34]. For example, in the USA, annual cytology screening has been estimated to exceed the threshold of cost-effectiveness when compared incrementally to biennial screening, with ratios typically near or exceeding $1 million per YLS or QALY gained [8,10].

Most studies that have considered revisions to screening policy after introduction of HPV vaccination have taken place in the setting of the USA, where screening is recommended annually or biennially. Goldie SJ *et al.* [17] projected that vaccination in the context of annual screening costs over $700,000 per QALY with conventional cytology, and over $3 million per QALY with liquid-based cytology, resulting in >98% reduction in lifetime risk of cervical cancer, compared to no intervention; in the context of biennial cytology screening, strategies remained over $280,000 per QALY and were associated with >96% reduction in cancer risk. They found strategies involving less frequent screening (i.e., every 3 or 5 years) starting at later ages (i.e., 21 or 25) were more attractive after introducing a pre-adolescent HPV vaccination program, resulting in 90-95% reductions in lifetime cancer risk (Table 4). Assuming waning vaccine efficacy after 10 years and a total vaccine cost of only $200, Kulasingam SL and Myers ER [34], also projected that delayed screening was attractive, but in contrast found that pre-adolescent vaccination combined with 2-year cytology screening (delayed to age 24) cost $44,900 per YLS and annual cytology (delayed to age 22) cost $154,200 with reductions in lifetime cancer incidence (mortality) of 83% (90%) and 92% (96%), respectively. More recently, Goldhaber-Fiebert JD and colleagues [43] conducted an extensive analysis exploring different primary screening tests, start ages of screening, and screening frequency, with and without vaccination. Allowing screening to start from ages 18, 21, or 25 and at intervals of every one to every five years, the investigators found that for a cohort of vaccinated 12-year-old girls, five-year cytology screening with HPV DNA testing as triage delayed to age 25, with

a switch to HPV DNA testing with cytology as triage at age 35, cost $41,000 per QALY, compared with the next best strategy (91.7% reduction in lifetime cancer risk compared to no intervention), and was more cost-effective than current screening; triennial screening with the same strategies cost $188,000 per QALY.

3.2.1 Summary point

- Widespread vaccination of pre-adolescent girls may allow for revisions to screening policies in the USA, involving less frequent screening starting at later ages using HPV DNA testing.

3.3 Disparities in vaccination and screening coverage

Most analyses have assumed that vaccination coverage in adolescence is equitable among those who do and do not get screened as adults; however, disparities in vaccination and screening coverage will likely impact the overall benefits and cost-effectiveness of vaccination strategies. For example, Kim JJ *et al.* [25] demonstrated that if vaccination uptake of pre-adolescent girls was highest among those who are more likely to get screened frequently as adults, the benefits of vaccination over screening alone would be marginal, and the cost-effectiveness ratio of pre-adolescent vaccination would more than double, resulting in over $100,000 per QALY, compared to screening alone. In a hypothetical example exploring racial and ethnic disparities in cervical cancer screening and vaccination in the USA, Goldhaber-Fiebert JD *et al.* [43] illustrated that if screening with newer technologies (e.g., HPV DNA testing) and HPV vaccination are less accessible to racial minorities who are currently less likely to be screened, disparities in cervical cancer incidence among racial groups would widen; however, if equitable coverage were achieved among these racially diverse groups, disparities in cervical cancer risk would lessen.

3.3.1 Summary point

- Achieving widespread coverage of HPV vaccination among pre-adolescent girls will help minimize disparities in lifetime risk of cervical cancer and associated mortality.

3.4 Catch-up vaccination

Temporary catch-up vaccination programs have been recommended to cover females who have missed their opportunity to be vaccinated because they are beyond the principal target ages of 11 or 12 years. Because sexual activity - and probability of HPV exposure - increases with age, the HPV vaccine is likely to be less effective among females in older age groups; indeed, when Taira AV *et al.* [26] assumed 70% vaccine coverage and 90% efficacy against HPV-16/18, they projected that a one-year catch-up program for a birth cohort of 30-year-old women would result in 17% reduction in overall lifetime risk of cervical cancer, in contrast to 46% reduction among the first vaccinated birth cohort of 12-year-old girls. The upper age limit for a catch-up program varies by setting, and in the USA has been recommended as either age 18 [53] or age 26 [54].

French KM *et al.* [55] evaluated catch-up programs that involved 3 to 12 additional age groups (from ages 15 to 24) in a one-year catch-up program, and found that with high coverage, catch-up to older age groups could decrease the time to observed cancer reductions and increase the total number of prevented cases, although there were diminishing marginal returns after age 18. Regan DG *et al.* [56] estimated that a 1-year catch-up program including ages 13-26 years would reduce time to achieve 50% of total benefits in terms of HPV-16 prevalence reduction by a factor of 4-6, compared to no catchup program. Although they did not project longer-term outcomes (i.e., reductions in cervical cancer), the authors note that these immediate reductions in HPV-16 prevalence can have implications for cervical cancer screening results and costs.

Elbasha EH *et al.* [39] also found that catch-up can reduce the time to observed reduction and magnitude of reduction.

Three analyses formally evaluated the cost-effectiveness of a temporary catch-up vaccination program, two in the context of the USA [25,39], and one in the UK [40]. Examining the effects of the quadrivalent vaccine on cervical cancer and genital warts, Elbasha EH *et al.* [39] found that vaccination of pre-adolescent girls with a five-year catchup program of females up to age 24 cost $4,700 per QALY, when compared to vaccination of pre-adolescent girls only. When vaccine efficacy was assumed to wane after 10 years, the ratio increased to $21,100 per QALY, compared to screening alone (the strategy of pre-adolescent vaccination was weakly dominated). Kim JJ *et al.*[25] evaluated catch-up programs up to ages 18, 21 and 26 and found that targeting catch-up efforts to age 18 was attractive across a wide range of scenarios, and catch-up to age 21 was reasonable when including the potential benefits of other non-cervical HPV-related outcomes, such as other cancers, and JORRP; however, extending catch-up to women age 26 had a cost-effectiveness ratio that consistently exceeded generally accepted cost-effectiveness thresholds in the US Jit M *et al.* [40] evaluated a range of catch-up campaigns and compared the incremental cost-effectiveness to each other and schoolgirl vaccination alone. They found that the mean incremental cost-effectiveness of a campaign up to 16 years of age was actually more cost-effective than routine vaccination of 12-year-old girls, as the risk of infection in the campaign age groups remained very low, but the 16-year-old girls were being vaccinated at closer to their risk age at infection (which is particularly important if the vaccine offers only temporary protection). Indeed, vaccination of girls up to the age of 18 would be deemed cost-effective compared to norms often used in the UK, even though vaccination of girls over the age of 16 was assumed to incur additional administration costs as the vaccine is unlikely to be offered through school-based programs. Extending the campaign to women up to the age of 25 was highly unlikely to be cost-effective, as the risk of infection increases rapidly during the late teens and early twenties in the UK.

3.4.1 Summary points

- While analyses agree that the main target group for vaccination is young adolescents prior to sexual activity (e.g., ages 9-12), most found that a temporary catch-up program for girls a few years older than the target age (e.g., ages 13 to 18) was reasonably cost-effective provided there was high vaccine efficacy and coverage.
- There are conflicting findings with respect to the upper age limit for a temporary catch-up vaccination program; most analyses find diminishing marginal health benefits of vaccination as catch-up age is extended to females in their 20s, resulting in cost-effectiveness ratios that exceed commonly cited thresholds.

3.5 Inclusion of boys

Although no clinical trial data have been reported on vaccine efficacy in males, a few studies have evaluated strategies of including boys in vaccination programs. Most of these analyses have assumed that the vaccine is equally efficacious for males as it is for females and have reported benefits with respect to cervical cancer reduction for their female partners (indirect benefits in the form of cervical cancer reduction can be observed since vaccinated males can reduce transmission to their female partners). Only a few studies include direct benefits for males in the form of reduced genital warts.

Generally, the benefits of including boys were greater when vaccine coverage of girls was lower. Regan DG *et al.* [56] found that, although there was little difference between vaccinating girls only and adding boys to a catch-up program in terms of decreasing time to observed benefit (i.e., < 2 years), the biggest benefit of vaccinating boys was in the reduction of HPV-16 prevalence among unvaccinated girls. This herd immunity effect has been shown to be marginal

when vaccination of girls was either very low or very high [24,55]. French KM *et al.* [55] demonstrated that including boys in a catch-up program was maximized when vaccination coverage was 50%, resulting in an additional 18% reduction in HPV-16-associated cancers, although this incremental benefit diminished to <1% by age 21. Taira AV *et al.* [26] projected a similar trend but found that the added benefit of vaccinating boys was maximized at 30% coverage, resulting in 20% added reduction in lifetime cancer compared to screening alone.

Although including boys in a vaccination program consistently resulted in higher health benefits than vaccinating girls alone in all analyses [25,55,56], the results from cost-effectiveness analyses evaluating the vaccination of boys have led to conflicting conclusions. Elbasha EH *et al.* [39] found that pre-adolescent vaccination of girls and boys, plus a temporary catch-up program of both girls and boys was $45,100 per QALY; when the vaccine was assumed to wane at 10 years, this strategy increased to $54,900 per QALY. Taira AV *et al.* [26], on the other hand, found that including pre-adolescent boys in a vaccination program (with no catch-up for either gender) was not cost-effective, with a ratio of $442,000 per QALY, compared to vaccinating girls alone. When they assumed that coverage of girls decreased from 70% (in the base case) to 30%, the cost-effectiveness of including boys improved dramatically to $40,900 per QALY, yet achieving higher vaccine penetration in girls was more cost-effective than covering boys. Jit M *et al.* [40] found that vaccination of boys in the UK context was highly unlikely to be cost-effective, with incremental costs per QALY of roughly US$100,000 - US$1,000,000 depending on assumptions about vaccine-induced immunity (the longer the protection afforded, the less cost-effective it is to vaccinate boys). An analysis by Kim JJ *et al.* [25] in the context of the USA also suggested that including boys, either with or without a catch-up program, was either less cost-effective compared to strategies of vaccinating girls only, or had excessively high cost-effectiveness ratios. Like Taira AV *et al.* [26], they also found that dollar-for-dollar, increasing coverage for girls was always more effective and cost-effective than including boys, regardless of coverage level.

3.5.1 Summary points

- There are conflicting findings with respect to inclusion of boys in an HPV vaccination program, although the majority of studies suggest that vaccination of boys is unlikely to be cost-effective if reasonable levels of coverage are achieved in girls.
- Under assumptions of equal vaccine efficacy in girls and boys, increasing vaccine coverage of girls is always more cost-effective than extending coverage to boys.

4.0. Key Differences in Models that May Contribute to Different Results

Among analyses with comparable duration and degree of vaccine-induced protection, variations in results were due primarily to assumptions about the baseline screening strategy, duration and degree of natural immunity and outcomes included in the analysis. Key differences among models can be grouped into two categories: 1) assumptions related to uncertainties in the natural history of HPV infection and disease, as well as vaccine properties; and 2) analytic assumptions that are discretionary to the analyst (see Table 5).

5.0. Conclusion and Key Points

As better and longer-term data become available to fill the data gaps with respect to the natural history of HPV post-vaccination, duration of vaccine-induced protection, the vaccines' effects on other health conditions, and vaccine efficacy in males, models will need to be revised - and analyses updated - to iteratively inform decision-making and policies in countries with screening and vaccination programs. Using the best available data, and across a wide array of

assumptions, the following themes have emerged from model-based analyses of cervical cancer prevention in developed countries with existing screening programs:

- The cost-effectiveness of HPV-16/18 vaccination in countries with organized screening programs will likely be optimized by achieving high and equitable vaccination coverage in adolescent girls.
- Although vaccination has been shown to contribute additional benefits compared to status quo organized screening programs, it will be important to continue screening for cervical outcomes related to other high-risk types. In settings with more aggressive screening programs (such as the USA), cervical cancer prevention programs will be more efficient if these girls are screened at later ages, with wider intervals and better tests. Analyses have generally favored a screening interval of every 3 or 5 years and starting at later ages for vaccinated women [17,34,43]; utilizing HPV DNA testing in primary screening may also facilitate surveillance of HPV types post-vaccination [57].
- Disparities in vaccination uptake and screening coverage have the potential to greatly compromise the cost-effectiveness of vaccination strategies; achieving universal vaccination coverage in young girls prior to sexual activity, and ensuring equitable screening coverage among adult women should be of highest priority.
- Catch-up vaccination programs for females are likely to be cost effective up to 16-21 years of age; however, as the risk of prior exposure to vaccine-targeted types increases as women age, vaccinating women over 21 is likely to be unattractive, resulting in diminishing marginal health benefits, but requiring similar, if not greater, costs.
- Evidence gaps in the natural history of HPV, transmission, and vaccine efficacy prohibit conclusions regarding the magnitude of population-level benefits from vaccinating boys. Most exploratory analyses suggest that inclusion of boys in a vaccination program is unlikely to be cost-effective assuming moderate coverage of girls is achievable. Even when coverage is low for girls, however, analyses have demonstrated that increasing coverage in girls is always more cost-effective than extending vaccination to boys.

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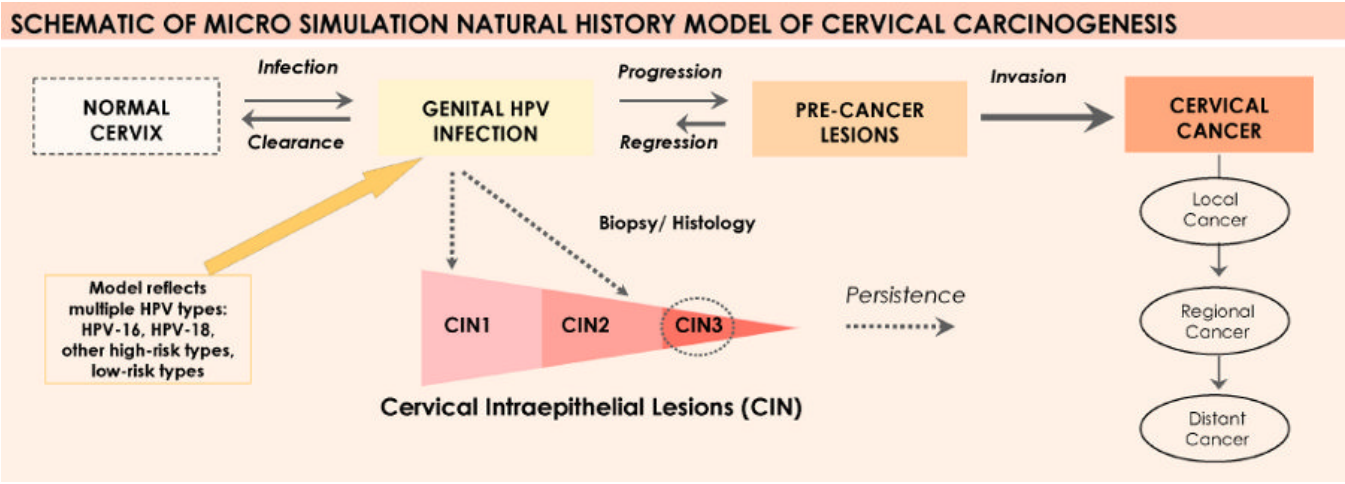

Figure 1. Model schematic of cervical cancer natural history

The natural history of disease in an individual woman is represented as a sequence of transitions between mutually-exclusive health states. Health states in the model, descriptive of the underlying true health, are generally defined to include HPV infection status, grade of cervical intraepithelial neoplasia (CIN), and stage of cancer. Health states are stratified to reflect different levels of detail, depending on the nature of the question, type of model, and data availability. For example, health states reflecting HPV infection may be stratified by specific individual HPV types (e.g., type -16, type -18), or by categories of HPV types (e.g., high-risk types, low-risk types), while those reflecting CIN may be stratified by specific grade (e.g., CIN 1, CIN 2,3). Health states may also be stratified according to dimensions important to the analysis, (e.g., detected and undetected cancer) or according to classification systems for which there are data (e.g., stage 1-4 cancer, or local, regional and distant cancer).

Table 1

Screening policies in developed country settings

Setting	Screening interval	Ages	Coverage	Source
United States of America	1-year (conventional); 2-year (liquid-based); 3-year after three consecutive negative tests	3 years after sexual debut, no later than 21 no defined stop age	53% annual or more 17% biennial 11% triennial 18% less than triennial	CDC's NHIS, 2005 [5]
Canada	1-year; 2-year after three consecutive negative tests; 1-year, if high-risk	18 and above	89% ever screened; 53% in the last 12 months (ages 18-69); 73% in the last 3 years (ages 18-69) (2000-2001)	WHO/ICO HPV Info Centre [4]
United Kingdom	3-year (liquid-based) for ages 25-49; 5-year for ages 50-64; (12 smears in a lifetime)	25-64	84% in the last 5 years (ages 20-64); 81% in the last 5 years, 71% in last 3 years (2003)	WHO/ICO HPV Info Centre [4]
Netherlands	5-year; (6 smears in a lifetime)	30-60	80% in the last 2 years (1996-1997)	WHO/ICO HPV Info Centre [4]
France	3-year	25-65	54% in the last 3 years (1998-2000); 60% in the last 3 years (ages 25-64)	WHO/ICO HPV Info Centre [4]
Finland	5-year; (6 smears in a lifetime)	30-60	70% in organized screening; 93% in all smears	WHO/ICO HPV Info Centre [4]
Australia	2-year	18-69 (sexually-active women)	61.8% (2000-2001); 32% re-screened within <2-years interval (2000-2001)	WHO/ICO HPV Info Centre [4]
Israel	3-year	35-54	34.7% (2001-2002)	WHO Health Survey [3]

CDC's NHIS: Centers for Disease Control and Prevention National Health Interview Survey; WHO: World Health Organization; WHO/ICO HPV Info Centre: World Health Organization / Institut Català d'Oncologia Information Centre on HPV and Cervical Cancer.

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Table 2

Attributes of mathematical models used to evaluate HPV vaccination[a]

Author	Setting	Static or dynamic	Open or closed	Aggregate or individual-based	HPV types included	Health conditions includedb
Goldie SJ *et al.*, 2004 [17]	USA	Static	Closed	Aggregate	HPV-16, HPV-18, HPV-HR other, HPV-LR	Cervical
Kulasingam SL and Myers ER, 2003 [34]	USA	Static	Closed	Aggregate	HPV-HR, HPV-LR	Cervical
Sanders GD and Taira AV, 2003 [35]	USA	Static	Closed	Aggregate	HPV-HR, HPV-LR	Cervical
Goldhaber-Fiebert JD *et al.*, 2008 [43]	USA	Static	Closed	Individual-Based	HPV-16, HPV-18, HPV-HR other, HPV-LR	Cervical
Taira AV *et al.*, 2004 [26]	USA	Dynamic Static	Open Closed	Aggregate Aggregate	HPV-16, HPV-18	Cervical
Elbasha EH *et al.*, 2007 [39]	USA	Dynamic	Open	Aggregate	HPV-16+18 HPV-6+11	Cervical, anogenital warts
Kim SY *et al.*, 2007 [14]	USA	Dynamic Static	Open Open	Aggregate Individual-Based	HPV-16, HPV-18, HPV-HR other, HPV-LR	Cervical, anogenital warts, JORRP, other cancers
van de Velde N *et al.*, 2007 [22]; Brisson M *et al.*, 2007 [37,41]	Canada	Static	Closed	Aggregate	HPV-16, HPV-18, HPV-HR other, HPV-LR	Cervical, anogenital warts
Kohli M *et al.*, 2007 [21]	UK	Static	Closed	Aggregate	HPV-16, HPV-18, HPV-31, HPV-45, HPV-52, HPV-HR other, HPV-LR	Cervical
Choi YH *et al.*, 2007 [15,38] Jit M et al., 2007 [19,40]	UK	Dynamic	Open	Aggregate	HPV-16, HPV-18, HPV-6, HPV-11, HPV-HR other	Cervical (adeno and squamous cell carcinoma), anogenital warts
Boot HJ *et al.*, 2007 [44]	Netherlands	Static	Closed	Aggregate	HPV	Cervical
Bergeron C *et al.*, 2008 [36]	France	Static	Closed	Aggregate	HPV	Cervical, anogenital warts
Barnabas RV *et al.*, 2006 [24] French KM *et al.*, 2007 [55]	Finland	Dynamic	Open	Aggregate	HPV-16	Cervical
Regan DG *et al.*, 2007 [56] Kulasingam S *et al.*, 2007 [42]	Australia	Dynamic Static	Open Closed	Aggregate Aggregate	HPV-16 HPV-16+18, HPV-HR other, HPV-LR	Cervical
Ginsberg GM *et al.*, 2007 [45]	Israel	Static	Open	Aggregate	Any	Cervical

[a] HPV: Human Papillomavirus; HR: High-risk; JORRP: Juvenile onset recurrent respiratory papillomatosis; LR: Low-risk; UK: United Kingdom; USA: United States of America.

[b] Health condition noted “cervical” refers to cervical dysplasia and cervical cancer.

Table 3

Cost-effectiveness of a pre-adolescent vaccination program in context of current screening[a]

Author	Setting	Cost per vaccinated person	Duration of vaccine- induced protection (years)	ICER HPV-16,18 ($ per QALY)	ICER HPV-6,11,16,18 ($ per QALY)	Currency (year)
Sanders GD and Taira AV, 2003 [35]	USA	300 100 (booster)	Lifelong wane (10 years), booster	12,700 22,800	-- --	US (2001)
Taira AV *et al.*, 2004 [26]	USA	300 100 (booster)	Wane (10 years), booster	14,600	--	US (2001)
Goldie SJ *et al.*, 2004 [17]	USA	400	Lifelong	20,600	--	US (2002)
Elbasha EH *et al.*, 2007 [39]	USA	360	Lifelong wane (10 years), no booster	-- --	3,000 dominated	US (2005)
Kim SY *et al.*, 2007 [14]	USA	500	Lifelong	<50,000	<50,000	US (2006)
Brisson M *et al.*, 2007 [37]	Canada	400 167 (booster)	Lifelong wane (30 years), no booster wane (30 years), booster	31,100 114,800 56,000	21,500 64,600 37,000	Canada (2005)
Boot HJ *et al.*, 2007 [44]	Netherlands	320	Lifelong boosters (every 10 to 50 years)	24,000 (YLS) 39,500 (YLS)	-- --	Euros
Bergeron C *et al.*, 2008 [36]	France	470	Lifelong wane (20 years), no booster wane (10 years), no booster booster (50% coverage)	-- -- -- --	8,400 14,900 37,200 13,400	Euros (2005)
Kulasingam S *et al.*, 2007 [42]	Australia	380 150 (booster)	Lifelong wane (10 years), no booster wane (10 years), booster	18,700 52,600 25,000	-- -- --	Australia (2005)
Ginsberg GM *et al.*, 2007 [45]	Israel	430	Lifelong wane (every 10 years), no booster	81,400 272,000	-- --	International (2007)

[a]ICER: Incremental cost-effectiveness ratios; QALY: Quality-adjusted life years; YLS: Year of life saved.

Table 4

Cost-effectiveness of revising current screening policy post-vaccination[a]

Author	Strategies included Primary screening test(s) Frequency Start ages	Screening strategies <$100,000 per YLS or QALY[b] (start age)	Reduction in lifetime risk of cancer (%)	ICER ($ per QALY)	Currency (year)
Goldie SJ *et al.*, 2004 [17]	Conventional, liquid-based cytology 1- to 5-year 18, 21, 25, 30, 35 years	5-year cytology (30) 5-year cytology (25) 5-year cytology (21) 3-year cytology (25) 3-year cytology (21)	88.9 89.8 89.7 94.0 95.4	17,200 31,200 57,400 58,500 83,000	US (2002)
Kulasingam SL and Myers ER, 2003 [34]	Conventional cytology 1-, 2-, 3-, 5-year 18, 22, 24, 26, 30 years	2-year cytology (24) 2-year cytology (18)	82.6 84.1	44,900[c] 92,700[c]	US (2001)
Goldhaber-Fiebert JD *et al.*, 2008 [43]	Cytology, HPV DNA test 1-, 2-, 3-, 5-year 18, 21, 25 years	5-year cytology (25) 5-year cytology (25), with switch to HPV DNA test (35)	88.8 91.7	33,000 41,000	US (2004)

[a] ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life years; YLS: Years of life saved.

[b] Only strategies that include pre-adolescent vaccination.

[c] Results are reported as $ per year of life saved (YLS).

Table 5

Key Differences in Models

Natural History or Vaccine Assumptions (uncertainties in the data)
- Natural immunity following first infection and clearance
- Duration and degree of vaccine-induced protection
- Cross-protection of vaccine against other high-risk HPV types
- Type replacement of other high-risk HPV types post-vaccination
- Vaccine uptake in the population

Analytic Assumptions (choices made by the analyst)
- Model structure
- Health outcomes included
- Costs included
- Baseline screening strategy
- Time horizon of analysis
- Discount rate