Chapter 21: Modelling the impact of HPV vaccines on cervical cancer and screening programmes

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Abstract

The impact of human papillomavirus (HPV)-16/18 vaccination on the incidence of infection and disease can be explored in a range of different models. Here we explore the epidemiological and economic impact of vaccination where screening is absent and where it is well established. The importance for epidemiology of assumptions about naturally-acquired immunity and heterogeneity in risk behaviours are highlighted, as are the importance for health economic outcomes of vaccine costs and the ability to modify screening strategies. To date, model results are consistent in predicting a useful role for vaccine, but further epidemiological data are required to help test the validity of models.

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1. Introduction

Trials of candidate HPV vaccines have demonstrated a high prophylactic efficacy against transient and chronic HPV infection with vaccine types (Chapter 13), therefore policies are urgently required for the rational introduction of HPV-16/18 vaccines into communities with and without existing screening programmes. As discussed in Chapter 18, modelling can be useful to estimate the potential impact of an HPV-16/18 vaccine and assess the cost-effectiveness of alternative cervical cancer control approaches by explicitly considering both primary and secondary prevention options.

While state-transition disease models, evaluated using cohort simulation, comprise the majority of published analyses focusing on only cervical cancer screening options (see Chapter 19), models of transmission dynamics are increasingly being used for analyses that include vaccination [1,2]. These models represent the probability of an individual acquiring an infection as being dependent on the sexual contact patterns of that individual and the distribution of the infection within the population. While alternative models each offer advantages and disadvantages (see also Chapter 18), a model that explicitly represents the infectious nature of HPV is the most appropriate way to project the epidemiological impact of an HPV-16/18 vaccine on patterns of viral infection over time. Therefore, we begin this paper with a discussion of the expected qualitative impact of a vaccine against a sexually transmitted infection like HPV. Because of uncertainty about the natural history of HPV types and cervical carcinogenesis, a number of assumptions are necessary, and this paper illustrates which of these are likely to be most influential. The results show that the expected high efficacy vaccines should provide benefits aligned with those assumed in cohort and individual simulation models. Therefore, an individual simulation model, calibrated to external data and well-suited to simulate complex screening strategies, is used to estimate the incremental cost-effectiveness of vaccination and screening strategies.
2. The impact of vaccines—key epidemiological assumptions

Before considering the complicated nature of HPV, a description of a simple model of a sexually transmitted infection can provide generic but fundamental insights. The impact of a vaccine at the population level will depend upon the existing pattern of infection and immunity. A key parameter in understanding this epidemiological context is the basic reproductive number, $R_0$, defined as the average number of infections caused by one infectious individual in an entirely susceptible population [3]. In the presence of infection, or immunity, some of the contacts of an infectious individual will be “wasted” on those already infected or immune, and the basic reproductive number is reduced to an effective reproductive number $R_e = R_0x$ where $x$ is the proportion of the population susceptible. If a vaccine is to eliminate infection, this effective reproductive number must be reduced below one, thus defining a critical vaccination threshold for elimination, $p_c$, where, if risk behaviour is similar across the at-risk population, $p_c = 1 - (1/R_0)$ [3]. When an infection has been locally eliminated, the only thing reducing the proportion susceptible will be vaccination. However, if vaccination fails to eliminate infection, the endemic prevalence of infection, $y^*$, is given by the relationship $y^* = 1 - (1/R_0) - p - z^*$, where $p$ is the proportion of the population protected by vaccine and $z^*$ the proportion immune through natural infection (the proportion immune is the average duration of immunity divided by the average duration of both infection and immunity) [4].

Whether or not infection generates immunity is important in understanding observed prevalence of infection and the role of vaccination. We can think of two extreme situations: one when there is complete lasting acquired immunity, where a susceptible-infected-removed (SIR) model is appropriate, and one where individuals return to the susceptible class on recovery, where a susceptible-infected-removed (SIR) model is appropriate [3,4]. In the former, vaccination replaces naturally-acquired immunity in regulating the incidence of infections, whereas in the latter, vaccination adds immunity where there previously was none. Thus, a given level of vaccination has a greater impact in a SIS system (Fig. 1a). To generate the same endemic prevalence prior to introducing the vaccine, a higher basic reproduction number is required when naturally derived immunity is present.

The presence of naturally derived immunity also has implications for the impact of waning vaccine-derived protection. If vaccine-derived protection is short lived, the vaccine will have little impact where there is lasting naturally-acquired immunity, but could significantly change prevalence where there is no natural immunity. For example, if we assume a vaccine provides 10 years of protection in a population where individuals are sexually active for 50 years, then, with complete coverage of each cohort, this would protect 20% of the population, halving prevalence in a SIS model, but only reducing it by 12% in the SIR model. Additionally, the effect of a short-lived vaccine would be further enhanced if it covered the ages with high levels of risk behaviour.

For any given prevalence, differences in risk across the population can allow a higher basic reproductive number. Increased variance in the distribution of numbers of sexual contacts reduces the numbers at risk but means those at risk have higher risks. This makes infection more likely to spread, but also limits the fraction of the population where immunity is required to reduce the effective reproductive number. This is illustrated in Fig. 1b for an extreme simplification where only a fraction of the population is at risk of infection. As this fraction decreases, the risk has to be concomitantly higher to maintain the overall prevalence of infection. This reduces the impact of a given vaccine coverage when coverage is across the whole population (i.e. the same in those at risk and those not at risk) unless it is targeted to those at risk. In the epidemiology of a sexually transmitted infection, like HPV, the relative role in the spread of infection of those with high numbers of sexual partners determines how difficult the infection will be to control through vaccination. Counterintuitively, this does not argue for targeting vaccination as the gains of vaccination will be most apparent in those with the lowest risk of acquiring infection [5]. Prior to vaccination, HPV prevalence can be maintained by those with high risks but spreads out through the populations as those with different risk behaviours mix. As vaccine coverage increases, there are diminishing returns because infection is increasingly concentrated in those with the highest-risk behaviours. The explanation of this non-linear decline in endemic prevalence with increasing vaccine coverage is illustrated in Fig. 1c for a population divided into those with high risk, those with low risk, and those with no risk, with an extreme assumption of fully assortative (i.e. like-with-like) mixing. The initial reductions in prevalence are most marked in the 18% of the population with moderate risk. Once eliminated from this group, there is still infection in the smaller high-risk fraction of the population and this reduces more gradually with increased coverage. The need for a universal vaccine is further emphasised if we consider the difficulties in predicting who amongst preadolescents will go on to have high-risk behaviours, and the difficulty experienced in targeting high-risk groups for vaccination against hepatitis B [6].

A key issue in the introduction of an HPV vaccine is whether it is protective for men as well as women, and whether vaccinating both sexes adds significantly to the impact of vaccinating only women. It would be erroneous to think of vaccination of a single sex as achieving half the coverage of vaccinating both sexes. Whilst such thinking could be applied for rubella where, despite the risk of disease being associated with pregnancy, both boys and girls have potentially infectious contacts within and between the sexes [7]. In a heterosexual population, men only have contacts with women, and vice versa, therefore for a sexually transmitted disease to spread heterosexually, the average reproductive number over two generations of transmission, from men to
Fig. 1. The influence of model assumptions on the impact of vaccination illustrated in simple models of infection: The relationship between equilibrium prevalence and effective vaccination coverage across the whole population is illustrated. (A) The prevalence in a model where 25% of the population is at risk. For the susceptible-infected-susceptible (SIS) model, the basic reproductive number of 1.25 generates a prevalence of 5% through a fifth of those at risk being infected. For the susceptible-infected-removed (SIR) model, a higher basic reproductive number generates the same prevalence, where it is assumed that infection takes up a quarter of the period post infection and naturally-acquired immunity three quarters. (B) The impact of vaccination in an SIS system where different fractions of the population are at risk but the prevalence of infection is similar in the absence of vaccination. A smaller fraction of the population at risk requires a higher basic reproductive number to maintain the observed prevalence, again in the equation provided in the text, with values of 6, 2.3, 2, and 1, respectively, for 6, 8, 10, and 20% of the population at risk. (C) The impact of vaccination in an SIS system where the population is subdivided into three groups that do not mix, 2% with a basic reproductive number of 2, 18% with a basic reproductive number of 18/14 and the remaining 80% with no risk. The prevalence contributed by the two at-risk groups and the overall prevalence is illustrated as a function of vaccine coverage across both at-risk groups. (D) The impact of vaccination in an SIS system where the at-risk 7.5% of the population is divided into two separate interacting sexes where the basic reproductive number is 3; the impact of vaccinating men and women or only women on the prevalence in men and in women is compared.

3. Estimating parameters describing HPV epidemiology

To understand the potential impact of HPV vaccines and to assess their cost-effectiveness in different scenarios and settings, we need more detailed models of the natural history of HPV infections and progression to cervical cancer. As described in Chapter 5, the risks of progression and regression through stages of neoplasia to cancer are complex, and to measure all the relevant parameters of progression from directly observed cohorts would be impractical and unethical. Thus, there will always be substantial uncertainty about the detailed parameters describing the system. However, epidemiological data available from cross-sectional surveys of HPV prevalence by cytological category, from cohort studies looking at the incidence of cancer and disease, and from surveillance recording the incidence of lesions and cancer cases [8] can be compared with model predictions. Many inputs, such as patterns of sexual debut, sexual partner change, duration of transient HPV infections and contact with screening programmes can be estimated from further survey data [8]. Other parameters can be estimated based on how well predictions reflect disease patterns [Chapter 6; Ref. [9]]. When models predict a limited number of observed outcomes, many parameter combinations appear valid, but these are severely reduced as the number of predicted outcomes increases. However, when calibrating models, it is important
to consider the validity of the observed outcomes in addition to that of the model. In some instances there will be tradeoffs in parameter values, which will allow multiple combinations to fit to available data. We have seen how a higher basic reproductive number can compensate for the presence of acquired type-specific immunity (Fig. 1a). In this example, there would be a change in the pattern of infection with age associated with immunity, reducing incidence as people age, which can help distinguish SIS and SIR systems. The basic reproductive number itself can be thought of as the product of the contact rate, the transmission probability and the duration of infectiousness: an increase in one of these three requires that the others reduce to maintain prevalence [10]. For example, if we underestimate the number of sexual partners, we will overestimate transmission probabilities or durations of infectiousness. Often this will not matter as it is the reproductive number that determines the prevalence and the impact of the vaccine, rather than whether the transmission probability is high or the duration of infectiousness is long. Where parameters matter more is if they interfere with the specific interventions. For example, overestimating the number of women effectively screened could influence results on the usefulness of vaccines. Errors in estimating the age of first sexual intercourse could influence the predicted success of vaccination at a particular age. Further, caution is required in case errors and biases exist within certain types of data, for example overestimations of high-grade lesions due to misclassification or under-reporting of numbers of sexual partners due to poor recall or social desirability bias [11]. These biases could lead to erroneous best fit parameter estimates, which alter the predicted impact of vaccination.

4. Previously-published models assessing the impact of vaccination

A number of modelling and health-economic studies have been published that explore the potential impact of HPV vaccines. In some cases, acquisition of HPV infection has depended only on age and HPV type with vaccination providing protection for the individual [9,12,13]. In others, the exposure of individuals has been altered by a model of the transmission of infection [1,2].

Early work explored the impact of an HPV vaccine with moderate efficacy levels, based on analogous work in HIV and genital herpes vaccines, where candidate vaccines had limited protective efficacy [14,15]. Hughes and colleagues [16] predicted a moderate HPV vaccine impact based on such assumptions of limited protection, and identified concerns over increased progression of other high-risk types. The concern was that treatment of a type-16 or -18 lesion could concomitantly obliterate more slowly progressing lesions of other oncogenic viral types, and this effect would be lost if the prevalence of types 16 and 18 declined. A different concern would be if removal of vaccine types reduced cross-immunity to other types, thereby allowing their incidence to increase [17]. Concerns over competing risks, similar to those of Hughes et al., were expressed by Goldie and colleagues [9] using a cohort simulation model calibrated to data from Costa Rica. Here, type-16/18-specific vaccine was assumed to have a very high protective efficacy (98%) in individuals, and was predicted to reduce the lifetime risk of invasive cancer by 51%. In a separate study, Goldie and colleagues [12] projected the impact of vaccination in the context of US patterns of screening. Similar to findings reported by Kulasingam and Myers [13], they found that while vaccination against HPV types 16 and 18 provided a small incremental reduction in cervical cancer incidence, the cost-effectiveness of a combined primary and secondary prevention programme was critically dependent on the age of vaccination, age at which screening was initiated, screening frequency, and the intensity of conducting further tests for mild cytologic abnormalities.

Taira and colleagues [1] and Barnabas and colleagues [2] have modelled the transmission dynamics of HPV and progression to cancer in order to explore the impact of vaccinating males as well as females on cervical cancer rates. In a model that assumed no type-specific immunity and used reported distributions of sexual behaviour from the US, Taira and colleagues [1] predicted a high impact of vaccinating girls alone but little additional benefit from vaccinating boys. With a model that assumed long-lasting type-specific immunity, calibrated to HPV-16 seroprevalence and cervical cancer incidence in Finland, Barnabas and colleagues [2] also found little benefit in vaccinating boys. In both cases, because sexual behaviour was derived from self-reports in household-based surveys, one could question whether sufficient attention was given to the role of those with very high levels of risk behaviour that are not normally apparent in such surveys [11].

An important observation from comparing the results of these different modelling exercises is the similarity of the results. For example, Barnabas and colleagues [2] estimated that vaccinating 90% of young women before sexual debut has the potential to decrease HPV type- (e.g., type 16) specific cervical cancer incidence by 91%. Goldie and colleagues [12] found this same near linear decrease in type-16-associated cancer alone, using the cohort simulation model calibrated to Costa Rica. Furthermore, Goldie and colleagues [9] and Hughes and colleagues [16], using independent models, found an attenuated reduction in overall invasive cancer with an effective vaccine against types 16 and 18 due to the cancer attributable to the other high-risk types of HPV. This suggests that for many scenarios, state-transition models analysed using cohort or Monte Carlo simulation provide an adequate representation of vaccine impact on cervical cancer. Models that better reflect the transmission dynamics, however, should be used to explore either the conditions where model predictions differ or, as in the case of vaccinating men, where the transmission dynamics are central to the question.
5. Qualitative insights from models of HPV transmission dynamics

The results of a model of multiple high-risk HPV viral types used to estimate the impact of vaccination with and without screening are illustrated in Fig. 2. The incidence of HPV-16, -18 and an additional generic high-risk type is modelled in a heterosexual population stratified according to age and sexual activity. Assumptions for this example include:

- five years of type-specific immunity following natural infection;
- lifelong immunity following vaccination at age 12;
- vaccine is 100% efficacious in preventing HPV-16 and -18 infection;
- 70% of the eligible population is vaccinated.

As an effective vaccine prevents infection with types 16 and 18 in the absence of screening, the vaccine has a substantial impact on both prevalence of infection and disease. In the presence of screening, the magnitude of cancer incidence reduction is less. The time delay from vaccination to reductions in cancer deaths is shown to be decades, as would be expected.

The results of such a model can be used to explore the impact of different coverages, the impact of cross protection, age of vaccination and the impact of loss of vaccine-acquired protection. The optimum age at vaccination is of great practical significance since it determines the most appropriate healthcare provider for vaccine delivery, the opportunities to deliver the vaccine (the mode of delivery, e.g., school-based approach or national immunization days, etc.), and possibly the coverage achievable. It seems sensible to vaccinate girls before they first have sex and are exposed to potential HPV infection, and in model simulations such a strategy has the best long-term outcome (Fig. 3a). In this figure, the model described by Barnabas and colleagues [2] has been further stratified into single-year age categories and sexual debut is modelled as a continuous process with rates derived from a survey of sexual behaviour of adolescents within the US [18]. However, the epidemiological impact of vaccinating younger girls takes longer to appear as they age into the sexually active population, which might warrant initially vaccinating a wider age range. Vaccinating older women again may be necessary if vaccine-derived protection is short-lived. However, the impact of short-lived vaccine-derived protection depends greatly on whether the vaccine is replacing naturally-derived protection, the ages at which sexual risk behaviour is common, and on what happens to screening of vaccinated individuals.

In Fig. 3b, two assumptions are illustrated in a screened population, one where those who have been vaccinated no longer attend screening (reflecting a misplaced complacency) and one where they still attend. The number of cervical cancer deaths is compared for no vaccination, vaccination of 70% of girls at age 12 is modelled, with a 5-year introductory period where coverage increases to reach this level. The graphs illustrate the trends in HPV prevalence and incidence of deaths associated with cervical cancer. Where screening is included it is assumed to start 30 years before vaccination and coverage is assumed to increase linearly over that time to 85% of women screened every 2 years.

Fig. 2. The impact of a type 16 and 18 HPV vaccine on a population without (graphs A and B) and with screening (graphs C and D). Vaccination of 70% of girls at age 12 is modelled, with a 5-year introductory period where coverage increases to reach this level. The graphs illustrate the trends in HPV prevalence and incidence of deaths associated with cervical cancer. Where screening is included it is assumed to start 30 years before vaccination and coverage is assumed to increase linearly over that time to 85% of women screened every 2 years.
6. Qualitative insights from cost-effectiveness analyses of vaccination and screening

The results of a stochastic, first-order Monte Carlo simulation model calibrated to fit to multiple epidemiologic outcomes in the example middle-income country of Brazil are illustrated in Figs. 4 and 5. Health states in this model reflect HPV-16, -18, other high-risk HPV types, and low-risk HPV types. The model is used to estimate the cost-effectiveness of vaccination with and without screening. Different cervical cancer control approaches that incorporate screening alone, vaccination alone or a combined approach are evaluated. Screening strategies may differ by initial screening test, number of visits, targeted age and frequency. Vaccination strategies may differ in targeted age groups or populations, and assumptions about efficacy, coverage, waning and cross-protection.

Assumptions for this example include:

- lifelong immunity following vaccination at age 12;
- vaccine is 100% efficacious in preventing HPV-16 and -18 infection;
- 70% of the eligible population is vaccinated;
- type-specific immunity following a single natural infection is derived by calibrating to external data, and for HPV types 16 and 18, these parameters vary from 50 to 85%.

Fig. 4 shows efficiency curves depicting the incremental cost-effectiveness ratios associated with different approaches to cervical cancer control strategies in Brazil, assuming a cost per vaccinated woman (inclusive of three doses, wastage, delivery and programmatic costs) of $25, 50, 75, and 100. Strategies lying on the efficiency curve dominate those lying to the right of the curve (not shown) because they are more effective, and either cost less or have a more attractive cost-effectiveness ratio than the next best strategy (see Chapter 18). Vaccination alone, assuming 70% coverage, reduced overall cervical cancer incidence by 48%. Vaccination plus screening three times per lifetime (beginning between ages 30 and 35 and repeated at 5-year intervals) reduced overall cervical cancer incidence by 66%.

The incremental cost-effectiveness ratios associated with non-dominated strategies were most influenced by the cost of vaccination. At a cost of $25 per vaccinated woman, vaccination alone was cost saving relative to no intervention. Vaccination plus screening three times per lifetime was $148 per year of life saved (YLS). Provided the cost per vaccinated woman was less than $50, all strategies that employed only screening were dominated by vaccination. As the cost per vaccinated woman reached $100 the incremental cost-effectiveness ratio associated with vaccination alone increased to $530 per YLS, and screening options were no longer dominated. As the cost per vaccinated woman is increased from $100 to 225 (data not shown) the incremental cost-effectiveness ratio associated with vaccination plus screening three times per lifetime increased from $1,896 per YLS to $8,463 per YLS.

As discussed in Chapter 18, there is no universal criterion that defines a threshold cost-effectiveness ratio below which an intervention would be considered cost-effective. Provided
Fig. 4. Efficiency curves depicting the incremental cost-effectiveness ratios associated with different approaches to cervical cancer control strategies in developing countries. This graph depicts the per-woman average life expectancy, lifetime costs, and reduction in lifetime risk of cancer associated with screening (S) and vaccination (V) strategies in Brazil. The cost per vaccinated woman (includes three doses, wastage, delivery, and programmatic costs) was varied from $25 to 225. Results for $25–100 per immunized woman are shown on four efficiency curves. Vaccination alone, assuming 70% coverage, reduced overall cervical cancer incidence by 48%. Vaccination plus screening three times (3x) per lifetime (beginning between ages 30 and 35 and repeated at 5-year intervals) reduced overall cervical cancer incidence by 66%. The incremental cost-effectiveness ratios associated with non-dominated strategies, as shown on the efficiency curves, were most influenced by the cost of vaccination. At a cost of $25 per vaccinated woman, vaccination alone was cost saving relative to no intervention. A combined strategy of vaccination and screening three times per lifetime was $148 per YLS. Provided the cost per vaccinated woman was less than $50, strategies of screening alone two times, three times, or every 5 years (q5) were dominated by a strategy employing only vaccination alone. As the cost per vaccinated woman increased to $100 the incremental cost-effectiveness ratios associated with vaccination increased, and screening strategies were no longer dominated.

we acknowledge that cost-effectiveness is only one relevant input for policy decisions, we can use the per capita GDP in Brazil (US$7423) as an approximate and comparative indicator of monetary resource constraints. While the majority of vaccination strategies were only fractions of the GDP, and therefore unarguably cost-effective, vaccination plus screening three times per lifetime would also be considered very cost-effective using this GDP criterion.

As also noted in Chapter 18, there may indeed be a lower “threshold ratio” for vaccination that would be required to compete for scarce vaccination resources if existing vaccines being used (e.g., childhood immunisation) have ratios

Fig. 5. The impact of coverage of vaccination and screening three times per lifetime on reductions in cervical cancer cases and discounted lifetime costs per women. When vaccination coverage is below 50%, the incremental cancer reduction (Ca Redux) achieved by adding screening is appreciable (shown by the lines). In contrast, when vaccination coverage exceeds 75%, incremental benefits by also increasing screening coverage are considerably less.
that are much lower than the GDP rule of thumb. Even with this more stringent criterion, if the cost per vaccinated woman is less than $25, HPV vaccination will be very competitive.

Decision makers in individual countries will need to consider the coverage rates achievable in their specific context for vaccination and screening separately. Because these interventions are applicable to such different age groups, they require the mobilisation of different types of resources and rely on different degrees of existing infrastructure. The feasibility of implementing programmes that are able to cover a large segment of the eligible population may vary greatly between individual settings. A graph like the one shown in Fig. 5 allows one to visualize the change in programme impact as vaccination and screening coverage are varied from 0 to 100%. When vaccination coverage is below 50%, the incremental cancer reduction achieved by adding screening is appreciable (shown by the lines). In contrast, when vaccination coverage exceeds 75%, incremental benefits from increasing screening coverage are considerably less. This type of sensitivity analysis, when combined with country-specific data on costs required to achieve high coverage rates, will allow strategies to be tailored to individual settings and inform the balance between screening and vaccination.

Many developed countries currently conduct regular screening. Here, the rationale of introducing vaccination may depend upon the ability of screening programmes to modify their approach. An incremental cost-effectiveness analysis assumes that dominated programmes (i.e. those that are more expensive with less gain) are not considered, but there is a danger that inertia could allow inappropriate screening programmes to continue. The efficiency curve for a vaccine with 90% efficacy combined with a number of alternative screening approaches is illustrated in Fig. 6. This example of vaccine efficacy is part of a more comprehensive analysis described by Goldie and colleagues [12]. Here, it can be seen that screening combined with vaccination provides incremental health benefits. For screening programmes at less frequent intervals (e.g., 5 years) and starting at older ages (e.g., 25), these are relatively inexpensive, but as frequency increases and age at starting declines, the costs per QALY gained increase dramatically. The introduction of vaccination mandates that the entire screening strategy should be re-examined both where screening is yet to be successfully introduced and where it is aggressively pursued.

7. Conclusions

The imminent introduction of HPV vaccines offers an opportunity to develop cervical cancer protection in new and more effective directions. The many questions about the use of vaccines have led to models exploring the transmission dynamics of HPV, patterns of progression to cancer and the cost-effectiveness of vaccination and screening strategies. These analyses are preliminary but share many common insights and uncertainties. The models show that vaccination with current candidate vaccines can have a substantial impact in settings without effective screening programmes. Moreover, provided the per-woman cost of vaccination is under $25, vaccination will be extremely cost-effective and, in some cases, cost saving. In countries with established ongoing screening programmes, vaccination can be cost-effective provided screening strategies are modified. The key uncertainties about the role of naturally-acquired immunity and “core” sexual activity groups on HPV epidemiology have implications for the vaccine coverage required to dramatically reduce HPV
incidence and the importance of waning vaccine-derived protection. Current models suggest that there are limited benefits from vaccinating boys in addition to girls and that even a vaccine with moderate (i.e., 10 years) duration of protection can have a major impact. The consistency of model results is reassuring, but further exploration of model assumptions is required. Further collection of empirical data to parameterize and validate the models is imperative before we can be fully confident of the best combinations of vaccination and screening in cervical cancer prevention.

**Disclosed potential conflicts of interest**

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