Adherence to cervical screening in the era of human papillomavirus vaccination: how low is too low?

Chris T Bauch, Meng Li, Gretchen Chapman, Alison P Galvani

Human papillomavirus vaccine prevents infection by two major oncogenic types of the virus. Continued screening is needed in vaccinated women to prevent cancers caused by high-risk types not included in the vaccine. An exaggerated sense of protection from the vaccine could lead to a decline in the rate of screening among vaccinated women, which in principle could lead to an increase in the incidence of cervical cancer. We present a simple mathematical model of vaccination, screening, and disease incidence, including an analysis of the effect of data uncertainties. For a population with opportunistic screening and 30% vaccine coverage, screening rates in vaccinated women would have to decline by at least 80% (median value of probabilistic uncertainty analysis) before the incidence of cervical cancer would increase in the era since the introduction of the vaccine. By comparison, the decline needed is at least 49% in a population with organised screening and 70% vaccine coverage. In populations that have highly effective cervical screening programmes, incidence of cervical cancer starts to increase after smaller, but still substantial, decreases in screening. Introduction of vaccine is unlikely to lead to an increased incidence of cervical cancer as a result of diminished screening.

Introduction
Recently introduced human papillomavirus vaccines are highly effective in preventing infection by the predominant types of the virus, 16 and 18, that cause 70% of cervical cancer cases worldwide.1 The remaining 30% of cases are caused by high-risk (oncogenic) types of human papillomavirus not included in the vaccine, which can thereby only be prevented through continued screening.2 Cervical screening is invasive and costly, and screening frequencies might be too high in some groups.3 However, a new worry since the introduction of the vaccine is that women who have been vaccinated will reduce the frequency of their screening too much, because of an exaggerated sense of security from being vaccinated.3

Prevention and treatment of cervical cancer are changing substantially, not only because of the human papillomavirus vaccine but also because of new screening technologies. Highly sensitive molecular tests for the DNA of high-risk types of the virus are quickly becoming mainstream. Maintaining the number of yearly Papanicolaou tests needed to detect the 30% of cervical cancers originating from virus types other than 16 and 18 will likely prove inefficient in the era of an effective vaccine. However, integration of DNA testing for human papillomavirus into cervical screening can improve the effectiveness of the programme by increasing sensitivity for detection of cervical intraepithelial neoplasias, enabling screening for vaccine failures, and permitting longer screening intervals.14

So-called policy resistance has been defined by John Sterman as the “tendency for interventions to be defeated by the system’s response to the intervention itself”. An extreme example of policy resistance is where screening rates in women that have been vaccinated drop so much that the number of cervical cancer cases exceeds the number prevented through vaccination. The screening rate at which this happens is defined as the screening threshold. Being able to estimate the screening threshold would be valuable from both public health and clinical perspectives.

Mathematical models can be used to evaluate the potential risks and benefits of different cervical screening and human papillomavirus vaccination strategies. Numerous models have simulated the transmission dynamics and pathogenesis of the virus and the effects of vaccination.8–18 These models have varied widely in how disease pathogenesis and the structure of the virus type are represented.

A key challenge in applying mathematical models to infection with human papillomavirus and cervical screening has been the great uncertainty in the pathogenesis of disease among different virus types. Most available data relate to type 16, which progresses more quickly and is more pathogenic than other types.19 The parameters describing the risk of infection and progression of other types of the virus have usually been inferred indirectly, often through large curve-fitting experiments that rely on the structure of the model being used. Therefore, various different models that agree with the epidemiological data available can produce different projections because of the uncertainty in parameter values describing the pathogenesis of human papillomavirus.8,12–17,20

In the context of such large uncertainties, simple mathematical models can make the problem easier to understand, or define clear thresholds that have to be surpassed to meet public health goals.21 In cervical screening in particular, a simple model can be used to ask the fundamental question how much can adherence to cervical screening drop, in women that are vaccinated, before the incidence of cervical cancer will start to increase? A simple model might make this question easier understand, and unlike more complex models can better clarify fundamental relations among the key variables that affect the screening threshold.

A potential limitation of simple models is that the simplifying assumptions can restrict their usefulness when a best-guess projection is needed. However, this limitation can be avoided in most cases when a conservative (upper or lower bound) estimate is all that is needed. For
Panel: Derivation of model equations

The differential equation that describes the rate of change in the population size of \( n \) at-risk women over time \( t \) is

\[
\frac{dn}{dt} = H - (r + s_{\text{pre}}) n
\]

The equilibrium size \( n_{\text{pre}} \) of the at-risk population in the era before the introduction of the vaccine is obtained by solving \( dn/dt = 0 \) in equation (A1), yielding

\[
n_{\text{pre}} = \frac{H}{r + s_{\text{pre}}}
\]

According to this equation, the number of women at risk of developing cervical cancer that have not been vaccinated enter the at-risk population at rate \( Hf \) (1-\( e \)). We suppose that new guidelines and technologies after the introduction of a vaccine change the rate of removal through screening from \( s_{\text{pre}} \) to \( s_{\text{post}} \). Also, we suppose women that have been vaccinated change their frequency of cervical screening visits by a factor \( x \), such that the rate of removal from the at-risk population through screening and follow-up becomes \( x \cdot s_{\text{post}} \). Therefore, a fraction \( (1-f) \) of women that have not been vaccinated are removed through screening at rate \( s_{\text{post}} \) in the era where a vaccine is available, whereas a fraction \( f \) are removed at rate \( s_{\text{pre}} \). The panel shows the model equations.

If screening adherence for women that have been vaccinated declines too much after the introduction of the vaccine, then the size of the at-risk population could increase. In the panel we solve the model to show that the threshold value of \( x \) below which \( n_{\text{pre}} = n_{\text{post}} \), yielding equation 1. Note that we constrain \( x > 0 \).

### Mathematical model

We model a population of women who are infected with at least one high-risk type of human papillomavirus and thus at risk of cervical cancer. We suppose that \( H \) women per year enter the at-risk population because of infection by high-risk types. The per person rate at which women are removed from the at-risk population through screening and follow-up where needed is \( s_{\text{pre}} \) per year in the era before the vaccine; \( s_{\text{pre}} \) is the rate of effective screening, hence it is high in populations where both the rate of screening and the quality of cytology and follow-up of abnormal results are adequate. Processes other than screening—primarily natural clearance of infection, but also mortality and benign hysterectomies—remove women from the at-risk population at rate \( r \) per year.

We suppose that a fraction \( f \) of girls are vaccinated, and that vaccination reduces the rate at which they become infected by a factor \( e \), where \( e \) is the realised effectiveness of vaccination programmes for preventing infection. Therefore women that have not been vaccinated enter the at-risk population at rate \( H(1-f) \) and women that have been vaccinated enter the at-risk population at rate \( Hf(1-e) \).

The screening threshold \( x^* \) below which \( n_{\text{pre}} = n_{\text{post}} \) (policy resistance) can be obtained by solving \( n_{\text{pre}} = n_{\text{post}} \), yielding equation 1. Note that we constrain \( x^* > 0 \).

instance, if simpler models are valid at upper or lower credible values of certain crucial parameters, conservative (eg, upper or lower credible) estimates of crucial thresholds can be made. Here, we adopt such an approach by analysing a simple mathematical model that yields a conservative estimate of the cervical-screening threshold in vaccinated women below which policy-resistant outcomes emerge.

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We suppose that a fraction \( f \) of girls are vaccinated, and that vaccination reduces the rate at which they become infected by a factor \( e \), where \( e \) is the realised effectiveness of vaccination programmes for preventing infection. Therefore women that have not been vaccinated enter the at-risk population at rate \( H(1-f) \) and women that have been vaccinated enter the at-risk population at rate \( Hf(1-e) \). We suppose that new guidelines and technologies after the introduction of a vaccine change the rate of removal through screening from \( s_{\text{pre}} \) to \( s_{\text{post}} \). Also, we suppose women that have been vaccinated change their frequency of cervical screening visits by a factor \( x \), such that the rate of removal from the at-risk population through screening and follow-up becomes \( x \cdot s_{\text{post}} \). For instance, women that have been vaccinated seek screening half as often when \( x \) equals 0.5. Therefore, a fraction \( (1-f) \) of women that have not been vaccinated are removed through screening at rate \( s_{\text{post}} \) in the era where a vaccine is available, whereas a fraction \( f \) are removed at rate \( s_{\text{pre}} \). The panel shows the model equations.

If screening adherence for women that have been vaccinated declines too much after the introduction of the vaccine, then the size of the at-risk population could increase. In the panel we solve the model to show that the threshold value of \( x \) below which this happens is

\[
(1) \quad x^* = 1 - \frac{1}{f} \left(1 - \frac{s_{\text{pre}}}{s_{\text{post}}} \right) e \frac{(r+s_{\text{post}})}{s_{\text{post}}}
\]

The values of \( e \), \( r \), \( s_{\text{pre}} \), and \( f \) can be estimated from published work. A recent study in the USA found a prevalence of about 1.5% for type 16, about 0.8% for type 18, and about 15% for any high-risk type. Clinical-trial data suggest that the vaccine is at least 95% effective in preventing infection by types 16 and 18. Our baseline assumption is lifelong vaccine-derived immunity and no type replacement. Hence, a baseline value for vaccine effectiveness \( e \) can be approximated as the type-specific vaccine efficacy weighted by type prevalence, yielding

\[
(2) \quad e = \frac{0.95 \times 0.14 + 0.8 \times 0.15 \times 2}{15.2} = 0.14
\]

We note that most other surveys have found higher prevalence of types 16 and 18, hence use of the lower prevalence reported by Dunne and colleagues is conservative. The rate \( r \) is dominated by natural clearance, which has been previously estimated as 0.83 per year for types 16 and 18, hence we adopt this value as our baseline estimate. The estimated screening rate is 44% per year under opportunistic screening programmes in the USA where quality of cytology and follow-up are high. Hence, we take \( s_{\text{pre}} \) as 0.44 per year under the baseline prevaccine opportunistic screening scenario.

The value of \( s_{\text{pre}} \) cannot be known, but \( s_{\text{post}} \) is likely to be greater than \( s_{\text{pre}} \). Under the conservative assumption that \( s_{\text{post}} \) is equal to \( s_{\text{pre}} \), which is equal to \( s \), equation 1 reduces to

\[
(2) \quad x^* = 1 - \frac{r+s_{\text{post}}}{s}
\]

The figure shows that \( x^* \) depends on \( e \), \( r \), and \( s \) in equation 2. In the region of the baseline parameter...
values, variation in $e$ or $r$ has a larger affect on $x^*$ than variation in $s$. This implies that the screening threshold is substantially affected by the prevalence of types 16 and 18. At the baseline parameter values, we calculate $x^*$ to be 0.61 from equation 2. This means the rate at which women that have been vaccinated seek screening would have to drop by at least 39% before the size of the at-risk population (women infected with high-risk human papillomavirus but not yet screened) would increase after the introduction of the vaccine.

The estimated $x^*$ of 0.61 relies upon very specific parameter values, hence it is neither robust nor applicable to all populations. To apply the model to a broader range of populations, we added a scenario of organised screening, in which $s_{pre}$ is higher than under the baseline scenario of opportunistic screening,27 and a scenario of limited screening, in which $s_{pre}$ is lower than the baseline, as might happen in countries where access to cytology screening is limited, or where the quality of cytology and management of abnormal cases are inadequate. The latter scenario is relevant to low-income countries, for which cervical cancer vaccination programmes might be on the horizon.27

We also did a probabilistic uncertainty analysis on equation 1 to test how robust the model was and understand the effect of data uncertainty. This involved defining plausible lower and upper bounds for $e$, $r$, $s_{pre}$, and $s_{post}$ and sampling repeatedly from the resulting intervals. We assumed $e$ was between 0.09 and 0.25, and $r$ was between 0.5 and 1.5 per year for all three screening scenarios (see webappendix). The intervals for $s_{pre}$ differed for the three screening scenarios and are given in the table. It is reasonable to suppose $s_{pre}$ is greater than $s_{post}$. We obtained a value of $s_{pre}$ from each sample of $s_{pre}$ by multiplying the sampled value of $s_{pre}$ by a factor $h$ is greater than 1, which was a random number where $h$ was between 1.0 and 1.2. We then sampled repeatedly from these four intervals to generate 5000 realised parameter sets, calculated $x^*$ from equation 1 for each parameter set, and established the median and standard deviation of all realised values of $x^*$.

This was done for both $f$ equals 0.3 and $f$ equals 0.7.

The table shows the results of the probabilistic uncertainty analysis under the three screening scenarios. In the limited-screening scenario the median threshold is zero for both values of $f$, meaning that women that had been vaccinated could stop screening altogether and there would not be an increase in the incidence of cervical cancer in the population. The median thresholds are also relatively low in the opportunistic-screening and organised-screening scenarios for both values of $f$, needing steep declines of 49% or more in screening adherence before policy resistance emerges. The large variability in $x^*$ across the realisations, which is largely driven by uncertainty in parameters $e$ and $r$, should be interpreted in view of equation 1 being a conservative (upper bound) estimate of the true threshold.

The median threshold increases as the prevaccine screening removal rate $s_{pre}$ increases across these three screening scenarios (figure). Hence, in populations with excellent screening programmes before the introduction of the vaccine, policy resistance emerges for smaller declines in screening adherence after the introduction of the vaccine. This seemingly counterintuitive result shows that, on the one hand, in populations with high screening rate with high-quality cytology and adequate management of atypical cases would receive the incremental reduction in cancer risk from having the vaccine would be smallest. Therefore screening rates before the introduction of the
Table: Results of probabilistic uncertainty analysis for three screening scenarios

<table>
<thead>
<tr>
<th>Parameter ranges for uncertainty analysis</th>
<th>Limited screening</th>
<th>Opportunistic screening</th>
<th>Organised screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevaccine screening removal rate ( \lambda_p )</td>
<td>0.15–0.25</td>
<td>0.4–0.5</td>
<td>0.70–0.80</td>
</tr>
<tr>
<td>Simulated screening threshold ( x^* ) for low vaccine coverage, ( f=0.3 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0.20</td>
<td>0.33</td>
</tr>
<tr>
<td>Range*</td>
<td>0–0.22</td>
<td>0–0.57</td>
<td>0–0.69</td>
</tr>
<tr>
<td>Simulated screening threshold ( x^* ) for high vaccine coverage, ( f=0.7 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0.38</td>
<td>0.51</td>
</tr>
<tr>
<td>Range*</td>
<td>0–0.30</td>
<td>0–0.4–0.72</td>
<td>0.26–0.77</td>
</tr>
</tbody>
</table>

*Median plus or minus two SDs.

Vaccine would have to remain high to prevent the at-risk population from growing. On the other hand, populations with poor screening programmes—as in many low-income countries—would experience large benefits from the introduction of vaccination programmes, and therefore screening rates could decline more before policy resistance emerges.

**Discussion and model extensions**

This model includes a number of simplifying assumptions. For instance, it ignores type structure, type replacement, varying pathogenicity and progression rates among types, herd immunity, and heterogeneity in screening rates within populations. Here, we argue that most of these assumptions have the convenient dual purpose of both simplifying the model and ensuring that the resulting estimate of the screening threshold is conservative. We also relax some of these assumptions in extended versions of the model to explore how the screening threshold changes.

Equation 1 provides a screening threshold when the outcome of interest is infection by any high-risk type. Several lines of evidence suggest that the screening threshold will be substantially lower when the outcome of interest is the incidence of cervical cancer. First, equation 1 does not distinguish between pathogenicity of types. However, types 16 and 18 are more pathogenic, accounting for about 70% of all cases of cervical cancer despite constituting only 15% of high-risk infections. Therefore, because the vaccine is highly effective against types 16 and 18, the screening threshold when the incidence of cervical cancer is the outcome of interest should be well below the screening threshold when high-risk infection is the outcome of interest.

Compensatory effects might partly close this gap. For example, the incidence of cervical cancer due to types other than 16 or 18 might increase as an artefact of medical management: before vaccination, the removal of precancerous lesions associated with types 16 and 18 would also have removed any lesions associated with other slower-progressing types. However, after the introduction of the vaccine, these removals will happen less often and so lesions from other high-risk types could continue progressing. Type replacement is also a possibility, whereby types other than 16 and 18 fill the empty ecological niche create by removal of types 16 and 18. However, there is a lack of empirical evidence for this effect, and this outcome is unlikely because of the genetic diversity of types of human papillomavirus.

For these compensatory factors to close the gap completely, the prevalence of other high-risk types or their pathogenicity would have to increase enormously after the introduction of the vaccine to make up for large difference in pathogenicity between types 16 or 18 and other high-risk types. The likelihood of greatly increased pathogenicity is low, because reduced screening frequencies should suffice to detect lesions caused by high-risk types that progress more slowly than types 16 or 18, and since our analysis conservatively assumes that all high-risk types progress as quickly as type 16. We developed a type-structured version of the model to aid understanding the potential effect of these compensatory factors (webappendix). In a scenario where type replacement causes a 10% increase in the prevalence of other high-risk types under 30% vaccine coverage, the percentage of infections by other high-risk types that lead to cervical cancer must increase by 240% for the screening threshold \( x^* \) to exceed 0.61.

Vaccination confers herd immunity, whereby unvaccinated members of the population experience a reduced risk of infection. Herd immunity is neglected in equation 1, which further suggests that it provides an upper bound on the screening threshold. However, some models suggest that the effects of herd immunity will be limited in the case of vaccination against human papillomavirus.

Equation 1 assumes that all women are screened and followed up in the same way. However, cervical screening programmes are often characterised by substantial inequities. By comparison, school-based vaccination programmes tend to be more equitable. In the webappendix, we develop an equity-structured model for a population where all women have the same vaccine coverage but some women have a low screening rate and the remainder have a high screening rate. The equity-structured model predicts that, for a broad range of parameter values and the same average population screening rate, the threshold \( x^* \) is lower in populations with more inequity.

In summary, equation 1 seems to provide a conservative estimate of how much screening adherence in women that have been vaccinated can drop before total incidence of cervical cancer in the population increases once vaccine is introduced. We note that the model makes the important assumption that vaccine-derived immunity does not wane. The long-term duration of immunity from the vaccine is unknown, although it does show well-sustained protection for at least 7.5 years. Likewise, the model does not explicitly include transmission of the virus, age structure, disease natural history, or the time delay between infection and onset of
invasive cervical cancer. The strength of the model is its use of simplifying assumptions that tend to make its predictions conservative while also giving a simple, transparent, and easily understood model.

Conclusions
Recent surveys of attitudes are consistent with the possibility of changing screening adherence in the era when the vaccine is available (see webappendix for survey results).13 Whether or not these changes will materialise remains to be seen. The analysis we have presented suggests that any decline in screening adherence in women that have been vaccinated would have to be quite severe before the incidence of cervical cancer would increase. However, the required decline is somewhat less steep in populations that already have a highly effective cervical screening programme.

These results do not suggest immediate changes to screening programmes: vigilance should be maintained to ensure adequate screening adherence in women that are vaccinated and unvaccinated. However, the results do suggest that screening intervals in women that have been vaccinated could lengthen somewhat without resulting in a net increase in the incidence of cervical cancer in this group.

Contributors
CTB designed the model, interpreted its output, and wrote the paper. ML and GC analysed survey data. AG conceived the study. All authors contributed to discussions and revisions of the paper.

Conflicts of interest
CTB holds a research contract from, and has previously consulted for, GlaxoSmithKline. AG has previously consulted for Merck Research Laboratories. Neither company played a part in this research. ML and GC declare that they have no conflicts of interest.

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References