Cervical screening adherence in era of HPV vaccination: how low is too low?

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The recently licensed human papillomavirus (HPV) vaccine can prevent most cervical cancers. However, continued screening is necessary in vaccinated women to prevent cancers caused by high-risk HPV types not included in the vaccine. In the HPV vaccine era, there is new concern that vaccinated women will reduce their rate of screening due to an exaggerated sense of protection from the vaccine. Some have suggested this could paradoxically lead to an increase in the incidence of cervical cancer cases. Here, we present a simple mathematical model suggesting that it would be difficult for such a perverse outcome to occur. We make a conservative estimate that screening rates in vaccinated women would have to decline by at least 39% for the incidence of cervical cancer in a population to increase relative to pre-vaccine levels. We also present results from a new nationwide survey of attitudes in the United States that are consistent with a decline of less than 39%. Finally, the model uncovers a surprising observation that in populations where screening rates are high in the pre-vaccine era, screening rates in vaccinated women can fall less before perverse outcomes start to occur.

Introduction

Human papillomavirus (HPV) vaccination prevents the 70% of cervical cancer cases caused by the two predominant HPV types 16 and 18 (1). The remaining 30% of cases are caused by high-risk HPV types not included in the vaccine and which can thereby only be prevented through continued screening (2). Cervical screening is invasive and costly and it has even been argued that screening frequencies are too high in some groups (3). However, a new concern of the vaccine era is that vaccinated women will reduce their rate of screening too much, due to an exaggerated sense of security from being vaccinated (4).

An outcome where screening rates in vaccinated women drop so much that the number of cervical cancer cases thereby created in the population exceeds the number averted through vaccination is an example of "population-level perversity" (5). We define the "screening threshold" as the critical screening rate at which this happens. Being able to estimate 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 HPV vaccination rates. Numerous models have simulated the transmission dynamics and pathogenesis of HPV as well as the impacts of HPV vaccination (6-12). These models have varied widely in how disease pathogenesis and HPV type structure is represented. For example, while some authors have included only type 16 or a combination of types 16 and 18 (10, 12, 13), other authors have argued that significant pathologies may arise when non-vaccine high-risk types of HPV are transmitted in the context of reduced HPV 16 and 18 prevalence (14). This "type replacement" may occur on two levels: (1) the prevalence of non-16/18 types may increase, due to new opportunities to infect hosts created by the removal of types 16/18 from the population, or (2) the incidence of cervical cancer due to non-16/18 types may increase as an artifact of medical management, because previously the removal of pre-cancerous pathologies induced by types 16/18 would also have removed slower-growing

lesions from other types among co-infected women, but now those slower-growing lesions may remain and progress (7).

A key challenge in applying mathematical models to HPV infection and cervical screening has been the great uncertainty in the natural history of disease among different HPV types. Most available data concerns type 16, which appears to differ notably from other HPV types in terms of its pathogenicity (2, 15). The parameters that describe the infection risk and rate of pathogenesis of other HPV types have usually been indirectly inferred, often through large curve-fitting experiments that are contingent upon the structure of the model being used. Thus, a variety of different models concordant with currently available epidemiological data produce different projections because of the uncertainty in parameter values describing HPV pathogenesis (6, 9-11, 13, 16).

In the context of such large uncertainties, simple mathematical models can provide intuitive context to problem, or define thresholds that have to be surpassed to meet public health goals (17). In the context of cervical screening in particular, a simple model can be used to ask the fundamental question: what is the minimum threshold screening rate needed to prevent perversity? A simple model may provide insight to this question, and--unlike more complex models--can better clarify fundamental relationships among the key variables that affect the screening threshold.

A potential limitation of simple models is that their simplifying assumptions can restrict their usefulness when a "best guess" estimate of an outcome is needed. However, this limitation can often be circumvented when a conservative (upper or lower bound) estimate is all that is needed. For instance, if simpler models are known to be valid at upper or lower credible values of certain crucial parameters it may be possible to thereby obtain conservative (e.g. upper or lower credible) estimates of crucial thresholds. Here, we adopt such an approach by analyzing a simple mathematical model that yields a conservative estimate of the screening threshold in vaccinated women below which population-level perversity emerges, when the outcome of interest is cervical cancer incidence.

Mathematical model

We model a population of women who are infected with at least one high-risk HPV type and are thus defined to be at risk of developing cervical cancer. We suppose that H women per year enter the at-risk population due to infection by high-risk types. They are screened (and also receive appropriate medical intervention where necessary) and thus removed from the at-risk population at rate s per woman. Processes other than screening--natural regression of infection, mortality, and benign hysterectomies--remove women from the at risk population at rate r per woman. 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 realized effectiveness of the vaccine in preventing infection. Therefore unvaccinated women enter the at-risk population at rate $H(1-f)$ and vaccinated women enter the at-risk population at rate $Hf(1-e)$. Also, we suppose vaccinated women reduce their frequency of medical screening visits by factor x, such that $x=1$ means they continue obtaining screening at the same baseline rate s, while $x=0$ means that vaccinated women do not obtain any screening. Therefore, a fraction $(1-f)$ of women continue being screened at rate s in the vaccine era, while a fraction f are screened at rate sx. The model equations appear in the Appendix. The model does not include type structure, type replacement effects, herd immunity effects, or varying pathogenicity/progression rates among HPV types; we analyze the implications of these simplifying assumptions and also develop a type-structured version of the present model later.

If the screening rate for vaccinated women declines too much in the vaccine era, then the number of high-risk infections that persist due to reduced screening rates could exceed the number of high-risk infections prevented through vaccination. We show in the Appendix that the threshold value of x^* below which this occurs, according to the model, is

$$x^* = 1 - e\frac{r+s}{s}. \quad (1)$$

We note that the model does not capture disease transmission mechanisms and therefore x^* is not a function of vaccine coverage or the recruitment rate H. We also emphasize that Equation (1) describes the screening threshold when the outcome of interest is the

size of the at-risk population; we analyze the implications of Equation (1) for the case where cervical cancer incidence is the outcome of interest later.

With Equation (1), we can compute x^* from published estimates of e, r, and s. A recent study in the United States suggests that HPV 16 has a prevalence of ~1.5% in the population, type 18 has a prevalence of ~0.8%, and all high-risk types have a cumulative prevalence of ~15.2% overall (18). Clinical trial data indicate that the vaccine is approximately 95% efficacious in preventing infection by types 16 and 18 (19). Our baseline assumption is lifelong vaccine-derived immunity and no type replacement. Hence, vaccine effectiveness e can be approximated as the type-specific clinical vaccine efficacy weighted by type prevalence, yielding $e = 0.95 \times (1.5 + 0.8) / 15.2 = 0.14$. The rate r is dominated by natural regression, which has been previously estimated to occur at rate 0.83 per year for types 16 and 18, hence we estimate r=0.83 per year. The screening rate has been estimated as s = 0.44/yr in the United States (20, 21). Together, these parameter estimates yield x^*=0.61. Hence, screening rates in vaccinated women must drop by at least 39% relative to screening rates in the pre-vaccine era before the size of the at-risk population of women will increase.

The way that x^* depends on e, r, and s is seen graphically in Figure 1. In the neighbourhood of the baseline parameter values, variation in e yields significant changes in x^*, whereas variations in r or s yield relatively small changes in x^*. This suggests that the threshold x^* could differ in populations with differing relative prevalence of types 16/18 versus other high-risk types. Figure 1 suggests that a higher vaccine effectiveness e means screening rates for vaccinated women can fall more, relative to screening rates in the pre-vaccine era, before the size of the at-risk population will increase in the vaccine era.

Figure 1 also suggests that if the pre-vaccine screening rate s is higher, then screening rates for vaccinated women can fall *less* relative to pre-vaccine rates, before the size of the at-risk population becomes larger in the vaccine era. This surprising result simply reflects that fact that women undergoing a high screening rate in the pre-vaccine era would receive only a small incremental reduction in cancer risk from also having the vaccine, and therefore screening rates in the vaccine era would have to remain high to keep the size of the at risk population small. On the other hand, a population with very

low screening rates (such as in the developing world) would experience very large benefits from the introduction of vaccination programmes, and therefore screening rates can drop more in the vaccine era before the size of the at-risk population increases.

Equation (1) provides a screening threshold when the outcome of interest is infection by any high-risk type. Several lines of evidence indicate that Equation (1) also serves as a conservative (upper bound) screening threshold when the outcome of interest is cervical cancer incidence in particular. Firstly, Equation (1) only describes infection by any high-risk type as an outcome and does not distinguish between pathogenicity of types. However, as noted above, types 16/18 account for approximately 70% of all cervical cancer cases, despite constituting only 15% of high-risk infections (2, 22). Therefore, because the vaccine is highly efficacious against types 16/18, the screening threshold when the outcome of interest is cervical cancer incidence must be well below the screening threshold $x^*=0.61$ for when the outcome of interest is high-risk infection of any type. Because Equation (1) only includes parameters that are relevant to the treatment of individual women, it represents a conservative bound for the emergence of individual-level perversity.

This gap between the two threshold values is partially closed by type replacement effects. However, for type replacement to close the gap completely, the prevalence of other high-risk types and/or their pathogenicity would have to increase enormously in the vaccine era to make up for large difference in pathogenicity between types 16/18 and other high-risk types. The likelihood of dramatically increased pathogenicity is low, since reduced screening frequencies may suffice to detect lesions caused by slower-progressing high-risk types not included in the vaccine, and since our analysis conservatively assumes that all high-risk types progress as quickly as types 16/18. In the Online Appendix we develop and analyze a more complex type-structured version of the model where the impact of type replacement effects on cervical cancer incidence is described. The findings from the type-structured model are consistent with $x^*=0.61$ being a conservative threshold: very strong type replacement effects are required before this threshold estimate is exceeded. For instance, in the scenario where the prevalence of other high-risk types increases by 20% under 50% vaccine coverage, the percentage of

infections by other high-risk types that lead to cervical cancer must increase by 120% before the screening threshold rises above $x^*=0.61$.

Vaccination also confers herd immunity, whereby unvaccinated members of the population experience reduced infection risk (23). Herd immunity is neglected in Equation (1), meaning that cervical cancer cases will be lower than suggested by this model due to reduced infections in unvaccinated women. This further suggests that $x^*=0.61$ is a reasonable upper bound.

Therefore, $x^*=0.61$ is a conservative (upper bound) estimate of how much screening rates in vaccinated women can be reduced before population-level perversity emerges, when cervical cancer incidence is the outcome of interest. The model used to generate this threshold uses three simplifying assumptions that also ensure the estimate is conservative: (a) it does not account for the higher pathogenicity of types 16/18 compared to other high-risk types; (b) it assumes that other high-risk types progress as quickly as types 16/18; (c) it neglects herd immunity benefits. However, we note that the model also assumes that vaccine-derived immunity does not wane; the long-term duration of immunity from the HPV vaccine is unknown, although it does show strongly sustained efficacy over at least 4.5 years (24).

Survey results

In a recent population-wide survey conducted in the United States, 150 participants were recruited from a commercial internet survey company (Survey Sampling International). They were parents of girls who were11-12 years old at the first phase of the study, with only one parent recruited per household. Two questions concerning Pap smear were embedded in a larger Internet survey about the HPV vaccine: “If your child was vaccinated against HPV, how frequently would you recommend her to have a Pap smear?” and “If you child was NOT vaccinated against HPV, how frequently would you recommend her to have a Pap smear?” Participants responded by choosing among 8 different frequencies: “every ‘6 months’, ‘1 year’, ‘2 years’, ‘3 years’, ‘4 years’ ‘5 years’, ‘10 years’, ‘20 years’” or “Never”. Responses were converted into number of screenings per 10 years to calculate the mean response, which were then converted to number of

months between screenings reported in the paper. One year later, these participants were contacted for a follow-up Internet survey on the HPV vaccine, and 66 out of the initial 150 participants responded. Two Pap smear questions were also embedded in the follow-up survey, but they asked participants to estimated screening frequency among the average U.S. women: "Before the HPV vaccine became available, how frequently do you think the average US woman received a pap smear test?" and "People who get the HPV vaccine might feel that their decreased risk of cervical cancer means it is less important to get Pap smears. Imagine an average US woman who had been getting a pap smear test at the average frequency. Now this same woman gets the HPV vaccine. Now how frequently do you think she will receive a Pap smear test?" Participants responded by choosing among 8 different frequencies: 'more than once per year', 'each year', 'every 18 months', 'every 2 years', 'every 3 years', 'every 5 years', 'every 10 years' or "Never". Responses were converted into number of screenings per 10 years to calculate the mean response ('more than once per year' was assumed to represent twice a year), which were then converted to number of months between screenings reported in the paper.

In this group, parents indicated that they would recommend their child to screen every 11.53 months, but that this would change to every 13.03 months if their child were vaccinated. This reduction is statistically significant ($Z=2.91$, $p<.004$, Wilcoxon Signed Ranks Test) and corresponds to $x=0.89$. Sixty-six of these parents also responded to a follow-up survey one year later, and reported that that they think the average U.S. woman is screened every 15.56 months on average, but that this would change to every 17.24 months on average in women who have been vaccinated. This reduction is statistically significant ($Z=4.04$, $p<.0001$, Wilcoxon Signed Ranks Test) and corresponds to $x=0.90$. If these results were to reflect emerging realities, the U.S. population would remain well above the $x^*=0.61$ threshold.

Conclusions

Whether or not vaccinated women will actually change their screening rate remains to be seen, though these survey results indicate that it is a strong possibility. Until large-scale longitudinal cohort data are available, a cautious approach of recommending the same

screening frequency as in the pre-vaccine era seems advisable from public health and clinical perspectives. However, the simple analysis presented here provides some reassurance that any drop in screening rates in vaccinated women would have to be quite steep before population-level perversity would emerge.

Appendix: Derivation of model equations

We model a population of n women who are infected with at least one high-risk oncogenic HPV type, and are thus at risk of cervical cancer. The rate at which women enter the at risk population is H women per year. They are screened and removed from the at risk population through the appropriate subsequent medical intervention at rate s per capita. Processes other than screening and treatment--natural regression of infection, mortality, and benign hysterectomies--remove women from the at risk population at rate r per capita. Hence, the equation that describes the rate of change in the population size n over time t is:

(A1) $$\frac{dn}{dt} = H - (r + s)n .$$

At equilibrium, the rate of change in n is zero (dn/dt=0) and thus the equilibrium size n_{pre} of the at risk population in the pre-vaccine era is obtained by solving Equation (A1):

(A2) $$n_{pre} = \frac{H}{r + s} .$$

According to this equation, the number of women at risk of cancer due to infection by high-risk HPV types increases linearly with the infection rate H, and decreases if either the screening/treatment rate s or the removal rate through other processes r increase.

To introduce vaccination into this model, Equation (A1) has to be modified. Suppose a fraction f of girls are vaccinated, and that vaccination is effective in reducing the rate at which they become infected by a vaccine effectiveness factor e. Therefore, in the vaccine era, unvaccinated women enter the at risk population at rate $H(1-f)$ and vaccinated women enter the at risk population at rate $Hf(1-e)$. (We discuss the implications of neglecting type structure later.) Also, suppose vaccinated women reduce their frequency of medical screening visits by factor x, such that x=1 means they continue obtaining screening at the same baseline rate s, while x=0 means that vaccinated women

do not obtain any screening. Therefore, a fraction (1-*f*) of women will continue to be screened at rate *s* in the vaccine era, while a fraction *f* will be screened at rate *sx*. Accordingly Equation (A1) becomes:

(A3) $$\frac{dn}{dt} = H(1 - f + f(1 - e) - (r + s(1 - f + fx))n$$

And the equilibrium solution of this equation is

(A4) $$n_{post} = \frac{H(1 - fe)}{r + s(1 - f + fx)}$$

If the screening rate for vaccinated women declines too much in the vaccine era, then the number of high-risk infections prevented through vaccination could be outweighed by the number of high-risk infections that are allowed to persist due to reduced screening rates. Hence, under these circumstances it is conceivable that the net number of women at risk could actually increase due to increased high-risk infections in vaccinated women. Mathematically, this means that $n_{post} > n_{pre}$. From Equations (A2) and (A4), the screening threshold value *x** below which n_{post} exceeds n_{pre} can be calculated, yielding $x^* = 1 - e\frac{r + s}{s}$, which is Equation (1).

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Figure 1: Screening rate threshold x^* as a function of (**a**) vaccine effectiveness e, (**b**) screening rate s, (**c**) regression rate r. Parameter values are e=0.14, s=0.44/year, r=0.83/year except where parameters are being varied along horizontal axis. Arrows denotes baseline parameter values.