Protecting the Next Generation: What Is the Role of the Duration of Human Papillomavirus Vaccine–Related Immunity?

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Background. There is strong evidence that human papillomavirus (HPV) is necessary for the development of cervical cancer. A prophylactic HPV vaccine with high reported efficacy was approved in North America in 2006.

Methods. A mathematical model of HPV transmission dynamics was used to simulate different scenarios of natural disease outcomes and intervention strategies. A sensitivity analysis was performed to compensate for uncertainties surrounding key epidemiological parameters.

Results. The expected impact that HPV vaccines have on cervical cancer incidence and HPV prevalence in the province of British Columbia in Canada revealed that, for lifelong vaccine-related protection, an immunization routine targeting younger females (grade 6), combined with a 3-year program for adolescent females (grade 9), is the most effective strategy. If vaccine-related protection continues for 10 years, then the targeting of adolescent females would be more beneficial than the targeting of younger females. The incremental benefit if boys, as well as girls, are vaccinated is small.

Conclusions. Optimization of the design of immunization strategies for treatment of HPV depends substantially on the duration of vaccine-induced immunity. Given the uncertainty in estimating this duration, it may be prudent to assume a value close to the lower limit reported and adjust the program when more-accurate information for the length of vaccine-induced immunity becomes available.

Human papillomavirus (HPV) is a sexually transmitted infection that has been linked to a variety of cancers in women and in men [1, 2]. HPV DNA is found in >99% of cervical cancer cases and is said to be the necessary, but insufficient, cause of cancer of the cervix [1–3]. Although the lifetime risk of contracting an HPV infection of the cervix has been reported to be 80%, most of these infections are transient and do not progress to cancer even when they are caused by an oncogenic HPV genotype [4–6]. Despite this, almost 500,000 women worldwide are diagnosed with cervical cancer each year and approximately half of them die as a result of the cancer, particularly in the developing world [7].

There are >100 HPV genotypes, at least 40 of which are mucosal types that occur in the genital tract, with ~15 of them being considered high-risk types that potentially can cause cervical cancer [5, 7]. It is estimated that genotypes 16, 18, 31, and 45 are responsible for almost 80% of cervical cancer cases worldwide, with genotype 16 alone accounting for almost 50% of the cases [8]. In British Columbia (BC), genotypes 16 and 18 are the most commonly encountered genotypes in cervical cancer samples [9]. Low-risk genotypes 6 and 11 cause the majority of genital warts, whereas most other low-risk types have no pathological effect [2, 5, 7]. The recently available HPV vaccine, which is manufactured by Merck under the brand name Gardasil, is highly effective against infection with genotypes 6, 11, 16, and 18 [10].

In recent years, mathematical models have provided valuable and novel insights into the impact that intervention strategies have for specific diseases, such as HIV/AIDS [11–14], syphilis [15], chlamydia [16], and HPV...
HPV 16/18 can be transmitted from an infectious individual to a susceptible individual via sexual interaction [2]. Once a woman acquires HPV, she has been exposed but is not infectious for several weeks [22]. An infected woman will either clear HPV or develop a persistent infection. There is evidence that persistent HPV infection is necessary for progression to the development of squamous intraepithelial lesions (SIL) and, eventually, to cancer [2].

It is estimated that >90% of HPV infections (all subtypes) in women clear in <2 years [5, 6]. The progression to precancerous lesions and carcinoma in situ occurs in a small fraction of infected females when clearance is incomplete [1, 2]. The time between HPV infection and development of precancerous conditions is estimated to be 7–10 years, although lesions may develop faster. The third and final step of HPV progression is invasive cancer, which takes approximately another 10 years to develop. One-third to two-thirds of women with precancerous conditions progress to this stage [2].

Not all women exposed to HPV develop natural immunity, and, in those who do so, it is unclear how long such immunity lasts. In the majority of existing HPV models, it is assumed that natural immunity is lifelong [20, 21]. HPV clearance to below the level of detection corresponds to natural immunity against the particular HPV genotype that caused the infection. Infection with other HPV genotypes can still occur; however, some cross-protection between specific HPV genotypes also seems to exist [23].

Estimates of the prevalence of HPV 16/18 in women, relative to that in the overall population, are ~2% for the United States, whereas the worldwide average is ~1.5% [5, 8]. The prevalence both in Canada and in BC is believed to be similar to that in the United States.

The natural history of HPV in men is not well understood. High-risk HPV is found in penile and other male-specific cancers, but the prevalence of male-specific cancers that are presumably caused by HPV is substantially lower than the prevalence of HPV-related female-specific cancers, of which cervical cancer is the most common [24]. It is known that, similar to what occurs in females, most males will eventually clear the HPV virus [24, 25], although little is known about clearance rates or natural immunity. Men are included in the model only as carriers and potential transmitters of HPV.

**METHODS**

At the center of the present study is a deterministic compartmental model of HPV transmission between females and males that allows simulation of scenarios involving varied natural history and intervention strategies, along with comprehensive sensitivity analyses to account for uncertainty in parameter estimates. The model contains several epidemiological compartments, each of which represents a particular stage of HPV infection in an individual. At any point in time, each compartment contains a fraction of the overall population.

In accordance with the natural history of HPV, the following compartment labels were used for females in the model: susceptible, S; infected without lesions, I; infectious with low-grade SIL (L-SIL), L; infectious with high-grade SIL (H-SIL), H; immune, M; and cancer, C. With the exception of I, H, and C, similar compartments were used for males. Transfer diagrams of HPV transmission dynamics in women and men, together with a detailed description of the model, are provided in the appendix (which is available only in the electronic edition of the journal).

In addition to being stratified by epidemiological compartments, the population used in the model was further stratified by age group and sexual behavior, both of which were used to characterize sexual mixing. There were 4 classes of sexual activity in the HPV model: nonactive, active, very active, and core. Furthermore, 3 types of sexual mixing were included in the model: within-group mixing, proportionate mixing, and the preference for males to choose female partners of a younger age.

Although there is substantial uncertainty with regard to the values of the parameters related to the natural history of HPV, we performed a literature review and extracted plausible ranges for parameters that were used in our model. After testing several million parameter combinations for the preintervention era, we chose a sample of 32 representative preintervention baseline scenarios for BC, as described in the appendix (which is available only in the electronic edition of the journal).

To model screening and treatment interventions, the existing natural-history model was extended to include a treatment compartment, T. Treatment was modeled as a transfer from the H to the T compartment, representing treatment of H-SIL; treatment of H-SIL is standard in BC, whereas the vast majority of L-SIL cases are identified and monitored during screening but are not definitively treated [26]. Applying 3 different treatment strategies—low, medium, and high—to each of the preintervention baseline scenarios allowed us to define a set of 96 extended baseline scenarios with treatment. The treatment strategies were chosen so that the range of resulting annual HPV 16/18–related cervical cancer incidence included the value that was observed in BC. There were 151 new cervical cancer cases in BC during 2003, ~100 of which could be attributed to HPV 16/18 [8, 26].

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We then chose the 5 extended-baseline scenarios that were closest to this value and that also approximated the ~3000 women with HPV 16/18–related H-SIL in BC during 2004 [26]. All figures in the Results section are based on 1 of these 5 scenarios, but we confirmed that the results are qualitatively the same for all 5 of them (see the appendix, which is available only in the electronic edition of the journal).

Finally, we extended the model to include prophylactic vaccination, by adding a vaccination compartment, $V$. Because the vaccination routines of interest were based on the age of vaccine recipients, a fraction of susceptible individuals were diverted to compartment $V$ when they entered the age group specified in the routine. This fraction was determined on the basis of the vaccine efficacy and vaccine coverage for that age group. Vaccinated individuals were shielded from becoming infected until vaccine-induced immunity waned. The loss of vaccine-related protection was modeled by a transfer rate from $V$ to $S$; similarly, the loss of natural immunity was modeled by a transfer rate from $M$ to $S$. For the vaccination simulations compartmental chains were used within the model to more accurately represent arrival time distributions.

The main focus of the present study was to study vaccination strategies for a population for which screening and treatment programs already were in place, because that is the situation both in BC and in most developed countries. We assumed that each immunization strategy began in 2007 and used a time horizon of 50 years. We performed simulations under various assumptions for the duration of vaccine-induced immunity. The following vaccination strategies were explored: F11, universal vaccination of 11-year-old females; F14, universal vaccination of 14-year-old females; F17, universal vaccination of 17-year-old females; F11+F14(3), universal vaccination of 11-year-old females, in addition to a temporary vaccination of 14-year-old females during the first 3 years.

We used effective vaccine coverage fractions of 85% for 11-year-old girls, 80% for 14-year-old girls, and 75% for 17-year-old girls; this approach reflects the assumption that school-based vaccination programs reach fewer older girls, because older individuals are more likely to drop out of school or decide not to participate in the program. These percentages are in agreement with those for current BC school-based immunization programs, in which vaccination occurs at grade 6 (for hepatitis B), grade 9 (for tetanus/diphtheria), and grade 12 (for meningococcus C) [27].

Although vaccination of school-age girls was our primary focus, we also investigated a strategy that included vaccination of boys also. For this purpose, we extended strategy F14 to universal vaccination of 14-year-old females and males.

**RESULTS**

Simulations based on the HPV 16/18 model produced a variety of results. In this section, we focus on the impact that different vaccination strategies have on (1) annual cervical cancer incidence, for cancers caused by HPV 16/18; (2) cumulative cancer cases from 2007 onward; and (3) overall HPV 16/18 prevalence in females, which we define as the number of infectious cases in the female $I$, $L$, and $H$ compartments in all demographic subgroups, divided by the size of the overall model population, including males and females $\geq$ 9 years of age, in BC.

Figure 1 shows, for the 4 vaccination strategies, the time-related evolution of the annual incidence of cervical cancer caused by HPV 16/18, for lifelong (figure 1A) and 10-year vaccine-related protection (figure 1B). The initial value mimics the incidence of observed HPV 16/18 cervical cancer cases in BC [26].

For the assumption of lifelong vaccine-related protection, all strategies caused the annual cancer incidence to drop significantly over 50 years, after an initial delay due to the long time lag between HPV infection and development of full-blown cervical cancer. Furthermore, it can be seen that the reduction in cancer incidence after 50 years is largest when the vaccine is administered at a young age and is smallest when it is administered at an older age.

The results for the assumption of 10-year vaccine-related protection were qualitatively different. Even though, for all strategies, the annual cancer incidence dropped after an initial delay, the reduction was significantly smaller than that for the assumption of lifelong vaccine-related protection, and, for all strategies, a rebound was observed around the year 2030. The equilibrium cancer incidences attained after the rebound were lower than the initial values in the absence of vaccination, and strategy F14 displayed the lowest cancer incidence after 50 years, followed by strategy F17, whereas strategies F11 and F11+F14(3) showed the least reduction.

Regardless of the duration of vaccine-related protection, strategies F11 and F11+F14(3) converge toward the same equilibrium value, because, from 2010 onward, both strategies effectively represent strategy F11. The additional vaccination, in the F11+F14(3) strategy, of 14-year-old girls during the first 3 years causes the cervical cancer incidence to drop faster than it does for strategy F11. Thus, one would expect to see a lower number of cumulative cancer cases for strategy F11+F14(3) than for strategy F11. This expectation is confirmed by figure 2, which shows these numbers for 3 different durations of vaccine-related protection. This figure also shows that, compared with the other strategies, strategy F17 became less efficient as the duration of vaccine-related protection became longer.

Overall, in figure 2 it can be seen that the number of cumulative cervical cancer cases caused by HPV 16/18 during the vaccination era bends away from the “no-vaccination” straight line that corresponds to a linear increase of 104 new cases per year in BC. The set of strategies for lifelong vaccine-related protection...
displayed the least growth in cumulative cancer cases, which matched the observation that cancer incidence was lowest for that case.

For a 10-year duration of vaccine-related protection, the total number of cumulative cancer cases during 50 years was 4653–4775, depending on the strategy, with strategy F14 having the lowest number of cumulative cancer cases and strategy F11 having the highest. For a 25-year duration of vaccine-related protection, the range of cumulative cancer cases was 3657–4107, with the F11+F14(3) strategy having the lowest value and strategy F17 having the highest. Moreover, for a lifelong duration of vaccine-related protection, the range of cumulative cancer cases...
was 2805–3691, with the F11+F14(3) strategy having the lowest value and strategy F17 having the highest. These values should be compared against the 5200 (104 × 50) cases, which is the linear projection, under the no-vaccination strategy, of the current value of new cancer cases to the next 50 years.

The HPV 16/18 prevalence in females, for each of the 4 vaccination strategies, is displayed in figure 3. The curves in that figure are qualitatively similar to the annual-cancer-incidence curves in figure 1; however, a state of equilibrium is reached more quickly, because, in exposed women, the I, L, and H states present much sooner than does the occurrence of cervical cancer (in women who develop cervical cancer). Again, for a shorter duration of vaccine-related protection, a rebound was observed, and equilibrium prevalence values were much less reduced than were those for lifelong vaccine-related protection.

Several existing studies have looked into the impact when boys, in addition to girls, are vaccinated [19–21, 28]. We performed extended simulations for strategy F14, in which 14-year-old boys and girls were vaccinated. Little is known about the vaccine efficacy for boys. Because of the marked sex-related difference in responsiveness to the herpes simplex virus–2 vaccine, there is concern that the HPV vaccine efficacy for boys may be reduced, compared with its efficacy for girls. We chose 3 different vaccine efficacies for boys—100%, 50%, and 20% of the vaccine efficacy for females.

The results are shown in figure 4, which also includes, for better comparison, the results for strategy F14. For the assumption of 10-year vaccine-related protection (figure 4A), it can be seen that the cancer incidence drops faster and has a lower minimum when vaccination of boys is included; these effects are more prominent for a higher vaccine efficacy for boys, independent of the duration of vaccine-induced immunity. Surprisingly, there is a crossover point around the year 2038, after which the annual cervical cancer incidence is higher when vaccination of boys is included. The closer the vaccine efficacy for boys is to the vaccine efficacy for girls, the higher the observed annual cervical cancer incidence after 2038. When the duration of vaccine-induced immunity increases to 25 years and lifelong, the aforementioned crossover does not occur (figure 4B).

**DISCUSSION**

The results of the present study show that, compared with a “no vaccination” strategy, any of the studied vaccination programs reduced the incidence of cervical cancer and the prevalence of HPV 16/18 in females in a population screened for cervical cancer. Strategy F14 showed an earlier decrease in HPV prevalence and cancer incidence, compared with strategies F11 and F11+F14. This observation reflects the fact that 14–16-year-old females are involved in more sexual partnerships than are 11–13-year-old females.
It is important to point out that the results were strongly dependent on the duration of vaccine-related protection. With lifelong protection, vaccine-induced immunity will not wane; therefore, vaccination of girls at as early an age as possible displays the best performance, especially when this is combined with a 3-year catch-up program for 14-year-old girls. Under the assumption of 10-year vaccine-related protection, some effects of early vaccination become more prominent. A girl who has been vaccinated when she is 11 years old but who does not become sexually active until she is 13 years old would not have needed to be vaccinated for the intervening 2 years, and her immunity will wane when she is ~21 years old, an age when...
sexual activity is high. A girl who is vaccinated when she is 14 years old may have already had her sexual debut, but, if she has not been infected with HPV 16/18, she will be protected until she is 24 years old, providing her with immunity that extends 3 years later than if she had been vaccinated when she was 11 years old; this is of great importance because, at age 24 years, sexual activity is often high.

One of the interesting features shown in figures 1, 3 and 4 is the rebound phenomenon observed for short assumed durations of vaccine-related protection, in which the annual incidence of cervical cancer caused by human-papillomavirus genotypes 16/18, for vaccination strategies that, in addition to vaccination of 14-year-old girls, also include vaccination of 14-year-old boys but use different vaccine efficacies for the boys. The colors in panel B indicate different durations of vaccine-related protection: 10 years (red), 25 years (blue), and lifelong (green).

**Figure 4.** Annual incidence of cervical cancer caused by human-papillomavirus genotypes 16/18, for vaccination strategies that, in addition to vaccination of 14-year-old girls, also include vaccination of 14-year-old boys but use different vaccine efficacies for the boys. The colors in panel B indicate different durations of vaccine-related protection: 10 years (red), 25 years (blue), and lifelong (green).
idence (figures 1 and 4) and prevalence (figure 3) of cervical cancer first reach a minimum level, after the introduction of the vaccination program, and then settle into a new equilibrium level between the prevaccine level and the minimum level. Whether a rebound occurs depends strongly on the relation between the duration of vaccine-related protection and the duration of natural immunity. There is no definitive evaluation of the duration of vaccine-induced immunity. Recent studies indicate that the existing HPV vaccines have been highly effective during the 5 years that the vaccine trials have been underway, and evidence of an anamnestic response has been seen [29]. There is, however, no consensus as to how long the vaccine will maintain immunity in women, especially if boosting due to natural exposure to vaccine strains of HPV fails to occur [30]. In the present study, we used 10-year vaccine-related protection as a pessimistic assumption and lifelong vaccine-related protection as an optimistic assumption. We also assumed that the duration of natural immunity is lifelong, an assumption that is consistent with data reported by several other published studies. Under these assumptions, simulation results suggest that, as the duration of vaccine-induced immunity increases and becomes comparable to the duration of natural immunity, the impact of rebound diminishes until it disappears altogether.

In addition to reducing cervical cancer incidence, vaccination programs will also reduce HPV prevalence, as is shown in figure 3. This effect allows the monitoring of program performance, with the possibility of applying additional measures (e.g., increased frequency of screenings) when a rebound in HPV prevalence is observed and cancer incidence therefore is expected to rise in subsequent years. This option is not available for treatment-only programs, because the impact that treatment has on HPV prevalence is relatively small.

The results of the present study indicate that the vaccination of 14-year-old boys, in addition to the vaccination of 14-year-old girls, would further reduce the number of cumulative cervical cancer cases after 50 years; however, the impact would be of great benefit if more-accurate estimates of its uncertainty regarding the duration of vaccine-induced immunity are necessary in the design of an optimal strategy. Given the great uncertainty regarding the duration of vaccine-induced immunity, it would be of great benefit if more-accurate estimates of its value could be provided by future studies.

**References**


