

Vaccination against human papillomavirus in Switzerland: simulation of the impact on infection rates

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Abstract

Objectives Human papillomavirus (HPV) is a sexually transmitted infection of particular interest because of its high prevalence rate and strong causal association with cervical cancer. Two prophylactic vaccines have been developed and different countries have made or will soon make recommendations for the vaccination of girls. Even if there is a consensus to recommend a vaccination before the beginning of sexual activity, there are, however, large discrepancies between countries concerning the perceived usefulness of a catch-up procedure and of boosters. The main objective of this article is to simulate the impact on different vaccination policies upon the mid- and long-term HPV 16/18 age-specific infection rates.

Methods We developed an epidemiological model based on the susceptible–infective–recovered approach using Swiss data. The mid- and long-term impact of different vaccination scenarios was then compared.

Results The generalization of a catch-up procedure is always beneficial, whatever its extent. Moreover, pending on the length of the protection offered by the vaccine, boosters will also be very useful.

Conclusions To be really effective, a vaccination campaign against HPV infection should at least include a catch-up to early reach a drop in HPV 16/18 prevalence, and maybe boosters. Otherwise, the protection insured for women in their 20s could be lower than expected, resulting in higher risks to later develop cervical cancer.

Keywords Human papillomavirus · Vaccination · Catch-up · Booster · Epidemiological model · SIR model

Introduction

Human papillomavirus (HPV) is a sexually transmitted virus of particular interest, because of its high prevalence rate, and because of the causal association of the high risk (HR) HPV types, most often types 16 and 18, with cervical cancer (Bosch et al. 2002; Brown et al. 2005; IARC Monograph Working Group 2007). HPV infection is very common in sexually active adolescents and young adults (Dunne and Markowitz 2006; Wiley and Masongsong 2006), and the acquisition of HPV occurs soon after sexual debut (Brown et al. 2005; Centers for Disease Control and Prevention 2007) as sexual intercourse is the primary route of genital HPV infection (Burchell et al. 2006). More than 100 different HPV types have been identified, the most problematic ones being types 16 and 18. Women under age 25 years have the highest acquisition of HR HPV types per year (Bosch and Harper 2006). Swiss data based on a small clinical sample ($N = 134$) of adolescents aged 14–20 years show a prevalence of 14.2% for HR HPV type (Lüdicke

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et al. 2001). A US-based study among women aged 18–25 years showed an overall prevalence of 27% that declined with age (Manhart et al. 2006). In the United Kingdom, HPV prevalence rates decline from 19% for those under age 25 to less than 3% for those aged 40 and above (Peto et al. 2004).

Much attention has been recently ported to HPV, since two prophylactic vaccines (Cervarix and Gardasil) have proven to be well-tolerated, highly immunogenic, and effective in preventing type specific cervical HPV infection and associated intraepithelial neoplasia (Lowy and Schiller 2006). Both vaccines prevent HPV16 and 18 infections when three intramuscular doses are administered over 6 months to young adults. It must be noted that since all trials were performed among women aged 18 and over, protection in younger girls is only an extrapolation. Even if there is a consensus to recommend a vaccination before the beginning of sexual activity, there are, however, large discrepancies between countries with respect to the target ages for basic and catch-up vaccination. The need for boosters will also rely on the results of still ongoing phase III and IV trials. The purpose of this article is then to explore and compare different vaccination scenarios.

Sexual behavior is the most constant predictor of acquiring HPV infection (Centers for Disease Control and Prevention 2007). Although many risk factors have been described in the literature, number of sexual partners (Lüdicke et al. 2001; Moscicki et al. 2001; Tarkowski et al. 2004; Dunne and Markowitz 2006; Manhart et al. 2006; Dunne et al. 2007), together with having had a new sex partner (Giuliano et al. 2002; Winer et al. 2003; Dunne and Markowitz 2006; Dunne et al. 2007) are the most consistent. Other factors such as younger age (Ho et al. 1998; Dunne and Markowitz 2006; Manhart et al. 2006; Dunne et al. 2007), early age at first intercourse (Kahn et al. 2002; Manhart et al. 2006), or substance use have also been described as risk factors, but other studies found no association with them (Ho et al. 1998; Kjaer et al. 2001; Lüdicke et al. 2001; Kahn et al. 2002; Sellors et al. 2003; Winer et al. 2003; Tarkowski et al. 2004; Burchell et al. 2006; Manhart et al. 2006). The characteristics of the sexual partner's behavior are also important. It has been described that partner's promiscuity (defined as number of sexual partners) is the most important risk factor (Ho et al. 1998; Kahn et al. 2002; Winer et al. 2003; Dunne and Markowitz 2006; Winer et al. 2006).

HPV transmission is directly linked to the sexual behavior of adolescents and young adults. In Switzerland, median age at first intercourse is 18.5 years both for males and females, and the proportion of those having had sexual intercourse before age 15 is 6.8% for males and 3.4% for females (Wellings et al. 2006). The rate of sexual activity (intercourse) among Swiss youth ranges from 13% of

males and 7% of females at age 14 to 80% for both genders at age 20 (Kuendig et al. 2003; Narring et al. 2004). Swiss data also indicate that 36.6% of males aged 17–20 had one partner in the previous year, 18% two, and 12% three or more. The percentages for females in the same age group were, respectively, 48, 10, and 5%. For males aged 21–30 years, 63% had one partner in the previous year, 10% two and 14% three or more. For females in this age group, the percentages were 85, 5, and 4%. Finally, 85% of males aged 31–45 had one partner in the previous year, 5% two and 6% three, while for females the figures were 89, 3, and 1% (Balthasar et al. 2003).

As for any new vaccine, the duration of the vaccine's protection is yet undefined (Centers for Disease Control and Prevention 2007), but results available to date only demonstrate a sustained efficacy up to 4.5/6 years (Dunne and Markowitz 2006; Ault 2007; Centers for Disease Control and Prevention 2007). Consequently, the potential need for a booster is a research area of greatest importance (Bosch and Harper 2006). Moreover, if a booster is required, focusing vaccination programs on 12-year-olds may be more cost-effective than focusing on infants (Taira et al. 2004).

It has also been debated whether males should be vaccinated. Although some authors (Hugues et al. 2002) report that vaccinating both men and women would result in a higher decrease in HPV prevalence, modeling evidence to date indicates that vaccinating both genders would have little benefit over vaccinating females only (Barnabas et al. 2006).

This article follows from a request made by the Swiss Commission for Vaccination to perform a modeling of the impact of a vaccine upon the infection rate by HR HPV types among Swiss females. Here, we compare the mid- and long-term efficacy of the different combinations of catch-up and/or boosters on the basis of an epidemiological model of the HPV infection prevalence estimated from Swiss data. In all cases, the routine vaccination program would start at age 12.

Methods

Our model of HPV virus diffusion is derived from the classic susceptible–infective–recovered (SIR) model introduced first by Kermack and McKendrick (1927) and then broadly used in epidemiology (Anderson 1982; Daley and Gani 2001). A similar, but less complete, HPV model was proposed by Corley (2006); other approaches are due to French et al. (2007) and Insinga et al. (2007). SIR models describe year after year a cohort of individuals mimicking a real population. Individuals in the model are classified as either susceptible of being infected (state S),

infective (state I), or recovered (state R). Two additional states, V for vaccinated and VI for vaccinated–infective are also considered to take into account the effect of a vaccination program. State V groups individuals that are immune after having received the vaccine. State VI groups individuals having received the vaccine when already infected. For the purpose of clarity, the rare individuals belonging to this last state are aggregated with infective when presenting the results. The model considers individuals of both genders, but only results for females are reported.

The level of sexual activity depends on the individuals and must be taken into account into the modeling. For that purpose, the population was divided into several mutually exclusive sexual profiles corresponding to different groups of sexual activity. The repartition among groups was specific for each class of age. Each group is defined by the average number of different partnerships formed each year. The core of any model for sexually transmitted viruses is a process of sexual mixing between individuals (Aral et al. 1999). This process manages all sexual contacts made between individuals, hence all possibilities of virus transmission. The process of sexual mixing used in this model is derived from the one proposed by Garnett (2002). On the contrary of the solution adopted in previous models, the process implemented here takes explicitly into account the fact that partnerships between individuals of different ages are very frequent.

The model works in discrete time, each period being 1 year. The transitions from any state of the model (S, I, R, V, and VI) to any other state are modeled through a set of difference equations. Figure 1 shows the possible

transitions. Before vaccination occurs, only states S, I, and R are possible. When vaccination occurs, states V and VI become active. In most cases, individuals become vaccinated either from the susceptible or recovered states, but they can also come from the infective state if they clear infection the same year they are vaccinated. Individuals can become vaccinated–infective (VI) if they are vaccinated when staying infected, or if they are susceptible and get an infection the same year they are vaccinated. After vaccination, individuals can stay in the vaccinated and vaccinated–infective states, but they can also leave these states to become susceptible, infective, or recovered. Vaccinated individuals become susceptible again when the immunity provided by the vaccine vanishes, and they become infective when they lose their immunity at the same time they get infected. Finally, they can also become vaccinated–infective if they get infected when keeping the immunity provided by the vaccine, but this very particular situation can occur only if the vaccine does not provide 100% protection. Vaccinated–infective individuals become simply infective if the immunity provided by the vaccine vanishes, and they enter in the recovered state if they clear the infection at the same time. An even more complex situation occurs at the exact time a booster is administered. This complexity comes from different reasons: not all individuals will receive the booster; simultaneously to receiving the booster, an individual can also become infected, or clear an infection; a significant proportion of the population can be still protected by the vaccine. Finally, the years following a booster, transitions follow again the schema given in Fig. 1c.

Table 1 describes the main parameters of the model and gives their values as estimated for Switzerland from the literature. A more detailed description of all parameters is provided in Suris et al. (2007). There are 20 profiles of sexual activity, each of them grouping 5% of the total population of a particular age. Each profile corresponds to a different group of population and is defined as the average number of sexual partners per year. Such a large number of profiles is not mandatory, but it was the best choice given available Swiss data. For each profile and each class of age, the average number of sexual partnerships formed by year was computed from Swiss data. For instance, the first profile indicates total abstinence, whatever the age class; the ninth profile corresponds to an average of 1 sexual partner per year between ages 17 and 60, and no partner before or after that; the last profile corresponds to an average of 2 sexual partners per year between ages 11 and 14, 9 partners between 15 and 16, 7 partners between 17 and 20, and 3 partners between 21 and 80. The parameter of sexual mixing is the probability that a sexual partnership is formed with someone belonging to a

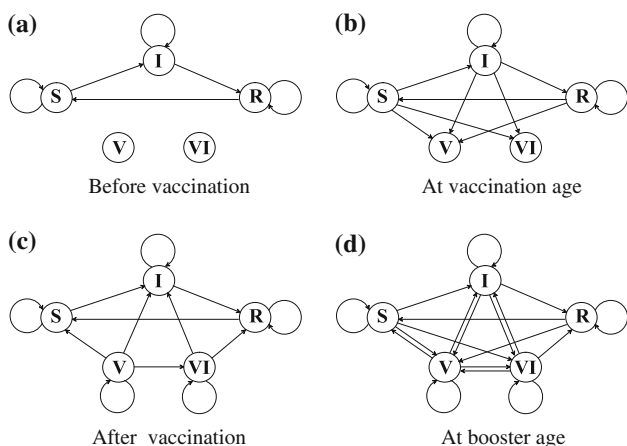


Fig. 1 Possible transitions at different times between the five states considered in the model: susceptible of being infected (S), already infective (I), having recovered from the infection (R), vaccinated (V), and vaccinated when being infective (VI). The arrows indicate the possible transitions between the five states

Table 1 Main parameters of the HPV model

Parameter	Estimation	Main source for estimation
Number of age classes	9	Specific
Age classes	1–10, 11–14, 15–16, 17–20, 21–30, 31–45, 46–60, 61–80, 81–100	Chosen in regard of available data
Number of sexual activity profiles	20	Specific
Survival probability for individual of each age, by sex	Available upon request	Swiss Statistics
Initial proportion of the population being infected by the HPV virus, by age, sex and sexual activity profile	Available upon request	Endemic values computed from the reference scenario without vaccination program
Age at vaccination	12	Taira et al. (2004)
Percentage of individuals being vaccinated, by sex	Female: 85%, male: 0%	For females: Average from the Hepatitis B vaccination rate in various European countries
Age(s) of the booster(s)	5 years after vaccination, or 5 and 10 years after vaccination in the case of two boosters	Our analysis is based on the assumption that the period of full efficacy of the vaccine is 5 years, so the booster must be administered at the end of this period
Percentage of individuals receiving a booster, by sex	Female: 85%, male: 0%	See vaccination rate
Length in years of the total immunity provided by the vaccine and/or the booster(s)	Variable	Clifford et al. (2005), Dunne and Markowitz (2006)
Catch-up procedure (yes or no)	Variable	–
Maximal age to receive the catch-up	Variable	ACIP (2007), Saslow et al. (2007)
Percentage of individuals receiving the catch-up, by sex	Female: 85%, male: 0%	See vaccination rate
Proportion of vaccinated individuals losing their immunity by years during the period of total immunity, and then after this period	0%, then 10%	Koutsky and Harper (2006)
Average number of sexual partnerships formed by year, for each sexual activity profile and each age class	Available upon request	Narring et al. (2004); Balthasar et al. (2003)
Proportion of the population forming sexual partnerships with individuals belonging to other profiles of sexual activity	0.8	Specific
Transmission rate of the virus from one sex to another	Female to male: 75%, male to female: 75%	Hugues et al. (2002)
Proportion of infective individuals entering in remission each year	70%	Centers for Disease Control and Prevention (2007)
Proportion of remission individuals becoming susceptible again each year	0.5	Specific

We describe here the main parameters of the simulation model, and we provide their values as estimated for Switzerland from the literature. “Specific” indicates that the value has been chosen specifically in regard of the availability of Swiss data. “Variable” indicates that the parameter varies in function of the vaccination scenario

different sexual profile. This parameter takes a high value of 0.8 (maximum 1) reflecting the fact that with no less than 20 different profiles of sexual activity, it is likely that the majority of the sexual partnerships are formed with individuals belonging to another profile.

The vaccination coverage has been fixed to 85% (female) and 0% (male). The latter case is a consequence of the choice of not exploring male vaccination. Since no data exist at the time for HPV, the vaccination rate for females

has been derived from the one for Hepatitis B. In Switzerland this rate is still low (63% in 2006) since vaccination is not mandatory in all cantons, so we used data from other European countries (Italy: 92%, Germany: 84%, and Austria: 92%) as provided by the World Health Organization (2007).

At the beginning of the simulation, an initial population is created. Each subsequent year of the simulation consists then in the following steps:

1. The sexual mixing between the different groups of population is computed. This mixing takes into account the proportion of sexual contacts occurring between each couple of sexual activity profiles, and the average number of partnerships per age class and sexual profile.
2. A new repartition of the population between the five states is computed using a set of difference equations and the final situation of the previous year. For instance, considering the situation of Fig. 1a, we have three equations giving the number of individuals belonging to states S, I, and R at time $t + 1$ in function of the number of individuals in these same states at time t :

$$S_{t+1} = S_t - \alpha s_t I_t + \delta R_t \quad (1)$$

$$R_{t+1} = R_t + \beta I_t - \delta R_t = (1 - \delta) R_t + \beta I_t \quad (2)$$

$$I_{t+1} = I_t + \alpha s_t I_t - \beta I_t = (1 + \alpha s_t - \beta) I_t \quad (3)$$

The parameter α is the average number of infections that could be caused by an infective individual during one period. Since only susceptible individuals can become infective, the number of new infective at time $t + 1$ is given by $\alpha s_t I_t$, where s_t is the proportion of susceptible individuals in the population at time t . After a certain time, infective individuals recover, and we note β the proportion of individuals doing so each period. Finally, δ is the proportion of recovering individuals becoming susceptible again each time period. Equation 1 tells that the number of susceptible individuals at time $t + 1$ is equal to the number of susceptible individuals at time t minus the number of susceptible individuals infected between t and $t + 1$, plus the number of recovering individuals becoming susceptible again between t and $t + 1$. Equation 2 tells that the number of recovering individuals at time $t + 1$ is equal to the number of individuals already recovering at time t plus the number of infective individuals recovering between t and $t + 1$, minus the number of recovering individuals becoming susceptible again between t and $t + 1$. Finally, Eq. 3 tells that the number of infective individuals at time $t + 1$ is equal to the number of infective individuals at time t plus the number of individuals infected between t and $t + 1$, less the number of individuals having recovered between t and $t + 1$.

3. Results are adjusted according to the Swiss mortality table to respect the real age repartition of the population.

If a vaccination program is implemented at the beginning of the simulation, the impact of this program can be analyzed after any given number of years. The equilibrium of the epidemiological model provides the endemic repartition of the population between the five states.

Based on the recommendations of several countries, we considered the vaccination of 12 years old girls. Four scenarios were then compared regarding the efficacy of the vaccine:

1. Full efficacy of the vaccine during 5 years, no booster.
2. Full efficacy of the vaccine during 5 years, two boosters after 5 and 10 years.
3. Full efficacy of the vaccine during 10 years, no booster.
4. Lifelong full efficacy of the vaccine.

Two additional scenarios (full efficacy during 5 years, one booster after 5 years; full efficacy during 10 years, one booster after 10 years) were also considered, but we did not report results here. The first of these scenarios is always very close to the 10 years/no booster scenario. The second scenario behave like an intermediary situation between the 10 years/no booster and the 5 years/2 boosters scenarios after 15 years of vaccination, and it becomes very close to the lifelong efficacy scenario when considering the endemic situation.

Three catch-up possibilities were also studied:

- A. No catch-up.
- B. Catch-up up to 18 years.
- C. Catch-up up to 25 years.

Our results are reported in terms of proportion of infected girls by HPV 16/18 types by age. For each type of catch-up, we compared the vaccination scenarios 15 years after the beginning of the vaccination campaign. We also report the long-term endemic situation.

The model has been developed using Matlab 7 (2004). Stata 9 (2007) has been used for additional statistical computations.

Results

Figure 2 reports the infection rate by age for females in Switzerland, both for all HPV types and for HPV 16/18 only. These are the endemic rates estimated from the model in the absence of vaccination.

The first simulation does not consider any form of catch-up. Figure 3 reports the expected infection rate by age for HPV types 16/18, 15 years after the beginning of the vaccination campaign. Using a 5-year efficacy vaccine the infection rate would remain below 1% up to age 18, below 2% up to age 22, and below 4% up to age 30. By adding two boosters, the rate would remain below 1% up to age 25 and under 4% up to age 30. A 10-year efficacy vaccine would maintain the infection rate under 1% up to age 22, slightly over 1% at age 25, and below 4% at age 30. A lifelong efficacy vaccine would follow a very similar curve.

Fig. 2 HPV infection rate among Swiss females such as estimated by the epidemiological model in the absence of vaccination

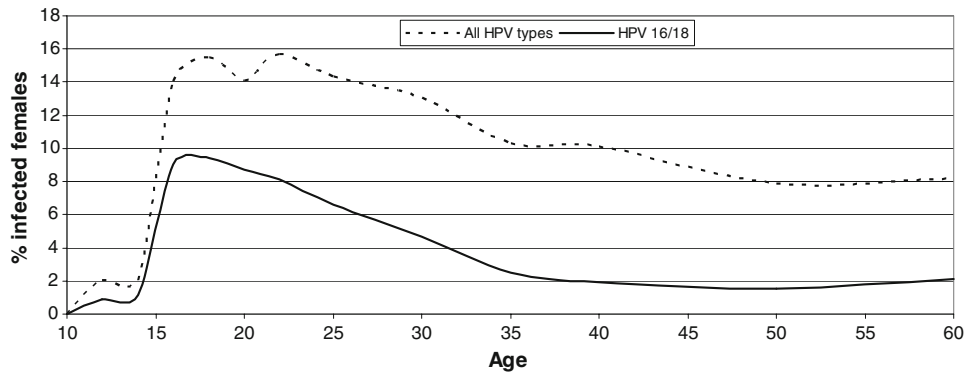
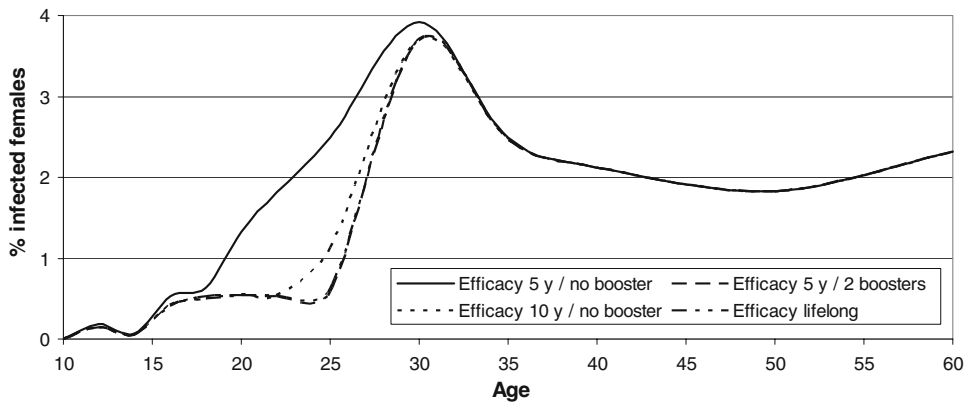


Fig. 3 Estimated HPV 16/18 infection rate for females by age. The vaccination targets 12 years old girls with 85% coverage. No catch-up. Situation 15 years after the beginning of the vaccination campaign



In all cases, from age 35 onwards, the rates are as low (2% infected) as if no vaccination was administered.

The second simulation adds a catch-up up to age 18. Figure 4 reports the expected infection rate by age for HPV types 16/18, 15 years after the beginning of the vaccination campaign. In this situation, a 5-year efficacy vaccine would maintain the infection rate under 1% up to age 20 and below 2.5% up to age 35. By adding two boosters, the rate would stay below 1% up to age 30 and below 2% up to age 35. A 10 year efficacy vaccine would keep the rate below 1% up to age 25 and below 2% up to age 35. By using a lifelong efficacy vaccine, the scenario would be very close to the 5-years/2 boosters case. In all cases, the infection

rate would be similar to non-vaccination from age 40 onwards.

The third simulation extends catch-up up to age 25. Figure 5 reports the expected infection rate by age for HPV types 16/18, 15 years after the beginning of the vaccination campaign. A 5-year efficacy vaccine without booster would result in an infection rate below 1% up to age 20 and below 2% up to age 40. For all other cases, the rate would be maintained below 1% up to age 37.

The last simulation reports the endemic situation in the absence of any form of catch-up, that is the equilibrium situation which would be reached at 50 and subsequent years after the beginning of the vaccination campaign.

Fig. 4 Estimated HPV 16/18 infection rate for females by age. The vaccination targets 12 years old girls with 85% coverage. Catch-up up to 18 years. Situation 15 years after the beginning of the vaccination campaign

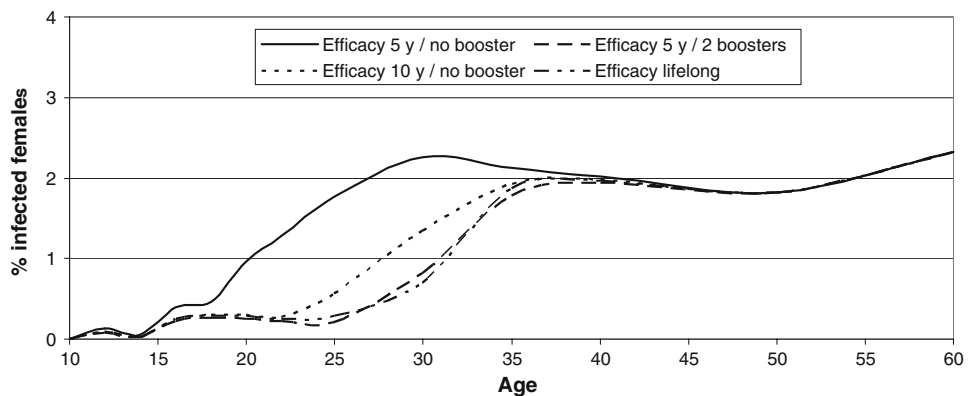


Fig. 5 Estimated HPV 16/18 infection rate for females by age. The vaccination targets 12 years old girls with 85% coverage. Catch-up up to 25 years. Situation 15 years after the beginning of the vaccination campaign

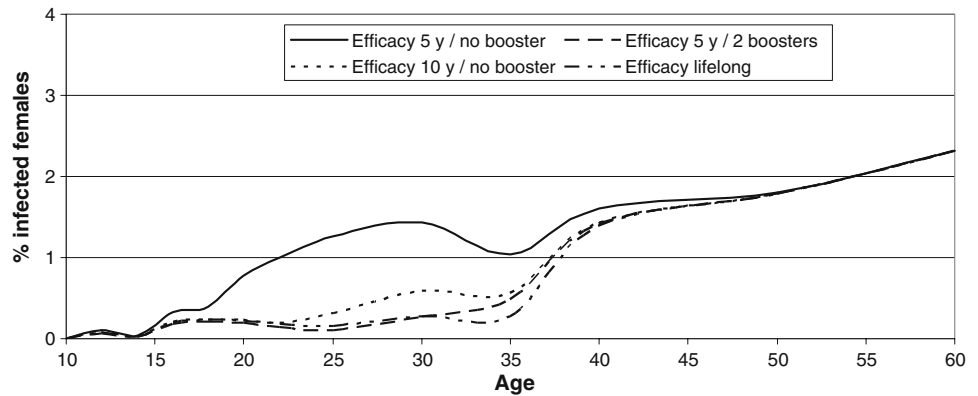


Fig. 6 Estimated HPV 16/18 infection rate for females by age. The vaccination targets 12 years old girls with 85% coverage. No catch-up. Endemic situation

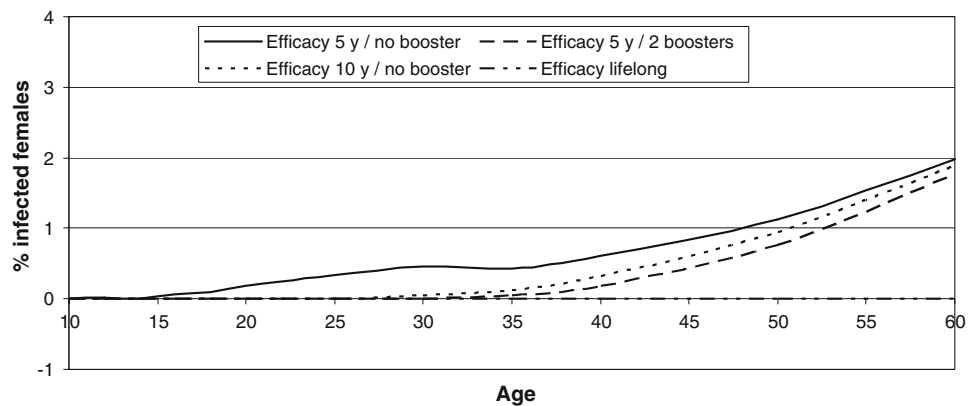


Figure 6 reports the infection rate for HPV types 16 and 18 by age. Using a 5-year efficacy vaccine without booster, the infection rate would remain below 0.2% up to age 20 and below 0.5% up to age 35. All other scenarios would prove even more efficient. After 35 years of age, the infection rate would slowly go up for all scenarios, except for the lifelong efficacy scenario for which the infection rate would stay null. Endemic situations with a catch-up up to 18 or 25 years are virtually identical to the endemic situation without catch-up, so we did not report the results.

Discussion

Results can be analyzed from two points of view: considering first the long-term endemic situation many years after the introduction of the vaccination, it appears clearly that whatever the duration of the protection offered by the vaccine, the administration of boosters or the introduction of a catch-up procedure, the HPV 16/18 infection rate will be dramatically decreased compared to the default situation without any vaccination. Even in the lowest vaccination scenario (5 years efficacy without booster or catch-up), the infection rate will stay below 0.5% up to 35 years of age, when the same rate would be higher than 9% by age 18 without vaccination. However, this optimistic view has to

be moderated by the fact that such an endemic situation can be reached in the most favorable case only 50 years after the beginning of the vaccination campaign. In the meantime, as indicated by results after 15 years of vaccination, the infection rate will stay non-negligible, emphasizing the need for an optimal vaccination scenario.

Looking now at the mid-term impact of the vaccination, three elements are to be considered: the duration of the full efficacy of the vaccine, the use of boosters, and the catch-up procedure. At the present time, we expect that vaccine efficacy may last for decades as HPV vaccine elicit immune memory and this memory is readily reactivated by a booster dose. However, we are still unsure whether such booster doses will be needed and if so at which intervals, so we can here only speculate. Not surprisingly, the longer the full efficacy of the vaccine, the smaller the infection rate by age. The use of one or two boosters, if required to sustain the full efficacy of the vaccine, clearly improves the vaccination plan. Finally, any catch-up is better than no catch-up at all. However, our model indicates that the improvement provided by a catch-up up to age 18 compared to no catch-up at all is much more important than the improvement provided by a catch-up up to 25 compared to a catch-up up to 18. Additional unreported results also show that a catch-up up to age 20 is similar to a catch-up up to 18. Catch-ups up

to age 22 or 25 provide also similar results, although the later would result in better coverage and infection rates than the former. This statement is independent of the efficacy of the vaccine and of whether or not a booster is implemented.

This study presents several limitations. First of all, the model was intended for the case of Switzerland, but data for estimating the model were very scarce. In fact, the only prevalence of HPV infection we have found for Switzerland is among a small ($N = 134$) clinical sample of adolescents in Geneva (Lüdicke et al. 2001). As a result, we have been forced to rely on data from other countries, mainly the United States. Nevertheless, this fact should not influence much our results, since there are no reasons to believe that the situation regarding HPV in Switzerland differs significantly from the situation in other western developed countries. Moreover, the use of data from different countries contributes to make the model more universal.

We chose to build an epidemiological model allowing transitions from any state to any other state. It could be argued that some of these transitions should not have been included, for instance the transition from recovered to vaccinated, since the vaccine seems to be effective only for woman naive to the virus. However, this is still an area of controversy (Hildesheim and Herrero 2007). Moreover, our model tackles simultaneously HPV types 16 and 18, so we had to take into account the fact that a woman previously infected with one of these types could nevertheless obtain protection against the other one through vaccination. Finally, such transitions account for only a small number of all the transitions of the model.

The time step of the model is 1 year. This is maybe too long, since median time to clearance from HPV infections has been reported to be less than 1 year (Ho et al. 1998; Giuliano et al. 2002; Dunne and Markowitz 2006), resulting in a distortion of the results. However, the same authors also reported that clearance time was longer for the HR HPV types concerned by our study. Moreover, if our model could potentially find as still infective women which have already cleared the infection in less than 1 year, this would be counterbalanced by women found no more infective after several years by the model.

A more important limitation is the fact that there are not much data regarding the sexual behavior of Swiss. As an example, the only data that we have found for the number of sexual partners (Balthasar et al. 2003) include quite wide age ranges (17–20, 21–30, and 31–45). We had then to divide the whole modeled period into only 9 age classes. This is clearly insufficient, especially after 30 years, the consequences being a lower reliability of the exact HPV infection prevalence by age, and too abrupt changes in prevalence at the limit between age classes.

This paucity of data has not allowed us to fully calibrate our model. Given these limitations, the model should not be used to predict the exact prevalence of HPV infection age by age. However, the model correctly reproduces the relative change in prevalence due to the implementation of different vaccination scenarios, so the results are correct in regard of the objective of the present study.

The model described here focuses only on the effect of vaccination upon HPV 16 and 18 infection rates. We did not consider infection by other HPV types, what could limit the generalization of our results. We also did not consider the influence of vaccination upon screening policies, nor the impact of vaccination upon the later development of cervical cancers. The cost/benefit analysis of the vaccination is also beyond the scope of the present article. All of these questions should be addressed through additional researches.

Based on the preceding analyses, the proposals made to the Swiss Commission for Vaccination were to implement a vaccination procedure for all female adolescents between the age of 12 or 13 and to propose a catch-up procedure up to at least 18, but preferably 25 years of age. Another proposal was to envision one (or two) boosters if needed to insure that females would be protected during the main part of the period of maximal risk, that is at least up to age 30, but ideally up to age 35. As the maximal duration of protection of the vaccine is yet to be determined, whether no, one or two boosters would be needed remains to be defined by the long-term follow-up of vaccinated cohorts.

Other factors beyond those appraised by the epidemiological model are also to be considered when choosing an optimal vaccination plan. First of all, even if no serious side effects following vaccination have been reported yet (>15 million doses administered), we always lack information about possible mid- and long-term side effects when a new vaccine is introduced. From that point of view, there is a need to carefully monitor the effects of HPV vaccination. Given the fact that the odds for developing any neurological or autoimmune diseases increase with age (Siegrist et al. 2007), it has to be understood that to vaccinate older individuals (after 19 or 20 years of age) entails an increasing risk for lay people to falsely attribute the occurrence of illness to the vaccine. Also, the decision regarding the ideal age range for catch-up procedure must take into account cost-effectiveness calculation, which obviously differs from one epidemiological situation to another. Finally, it must be clear that vaccination cannot fully replace other prevention tools such as screening and information campaigns directed toward adolescents and young adults.

Keeping these considerations in mind, the final recommendation of the Swiss Commission for Vaccination was to vaccinate all female adolescents aged 11–14 years and

to propose a catch-up procedure to all females aged 15–19 years during a 5-year period (Swiss Commission for Vaccination 2007). The Swiss Commission for Vaccination recognized the fact that, for sexually active adolescents and young adults, the advantage of being immunized diminished as the number of previous sexual partners increased. The usefulness of HPV vaccination, particularly from age 20, will thus have to be determined on an individual basis.

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