Modeling of HPV seroconversion in adolescent girls in Switzerland

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FOREWORD

This report is the result of a request of the Swiss Commission for Vaccination (EKIF) to the *Groupe de Recherche sur la Santé des Adolescents* (GRSA) to perform a modeling of the HPV seroconversion among Swiss females after introducing the HPV vaccine. This research has been financed by GlaxoSmithKline AG, Switzerland

In the preliminary discussions, the EKIF had basically two questions that needed to be answered:

- at what age should Swiss females be vaccinated?
- up to what age should a catch-up vaccine be administered?

There is a clear consensus in the literature regarding the first question: females need to be vaccinated before beginning sexual activity. Although this fact is still under discussion in many countries, the current recommendations both from the American Advisory Committee on Immunization Practices and the American Cancer Society are to start vaccinating at ages 11-12. For this reason, it was decided that our model would be based on an hypothetical vaccination program that would be implemented at age 12 in Switzerland. The first question being solved, the principal interest of the EKIF was to have an answer to the catch-up question. This report focuses mainly on this point.

As the HPV vaccines currently marketed are mainly directed towards the prevention of cervical precancerous lesions and cancer, only the expected effect on the infection rates of HPV types 16 and 18 are analyzed in this report.

Furthermore, as there is evidence that the vaccination of both genders has little benefit over vaccinating females only, this report refers only to the potential impact of vaccinating females in Switzerland.

SUMMARY

Human papillomavirus (HPV) is a sexually transmitted infection (STI) of particular interest because of its high prevalence rates and casual association with cervical cancer. HPV infection is extremely common in sexually active adolescents and young adults, and the acquisition of HPV occurs soon after sexual debut as sexual intercourse (both vaginal and anal) is the primary route of genital HPV infection.

Sexual behavior is the most constant predictor of acquiring HPV infection. Although many risk factors have been described in the literature, number of sexual partners, together with having had a new sex partner in the 3 to 8 months prior to the visit are the most consistent. Additionally, 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.

HPV vaccines are characterized as therapeutic or prophylactic. Although the former ones are in very early stages of development and have shown limited success, the later have demonstrated high efficacy. However, the duration of the vaccine's protection is unclear and results to date indicate a sustained efficacy up to 5 years. As HPV acquisition occurs soon after sexual initiation, the vaccine would have greater effectiveness if administered to young adolescents before the onset of sexual activity. Evidence to date also indicates that vaccinating both genders had little benefit over vaccinating females only.

Two questions arise regarding HPV vaccination:

1. At what age should the vaccine be introduced in a routine schedule?
2. Up to which age should the vaccine be recommended in catch-up form?

To answer the first question, it is clear that the vaccine has to be implemented before the onset of sexual activity. Both the American Advisory Committee on Immunization Practices (ACIP) and the American Cancer Society (ACS) recommend to vaccinate females at age 11-12 years

To tackle the second question, the ACIP also recommends catch-up vaccination for females aged 13 to 26 years who have not received the vaccine or who have not completed the full vaccine series. On the other hand, the ACS recommends catch-up vaccination up to age 18 because there are insufficient data for or against vaccination among females aged 19-26 years. Vaccination beyond age 26 or for males is not recommended

Objective

The objective of this report is to create a mathematical model using Swiss data to explore the theoretical HPV infection and vaccine coverage rates in the female Swiss population using different scenarios that take into account both the upper catch-up age limit and three different efficacy time-frames (5 years, 10 years, and lifelong). In all cases, the routine vaccination program would start at age 12.

Model

The model is based on the classic SIR approach. Individuals are classified as either Susceptible of being infected (state S), Infective (I), or in Remission (R). Two additional states, Vaccinated (V) and Vaccinated-Infective (VI) are also considered to take into account the effect of a vaccination program. The principle of the model is to follow year after year a complete population made of individuals of ages 1 to 100 of both sexes. Each year, individuals are classified into one of the 5 mutually-exclusive states (S, I, R, V, VI). Possible transitions from one state to another are described as difference equations. Different types of

vaccination programs can be implemented to study their short- and long-term impact onto the population. Vaccination programs can include vaccination at a particular age, one or several boosters, and a catch-up procedure up to a given age, with or without booster. The impact of each vaccination scenario can be studied after a given number of years. It is also possible to obtain endemic results.

Results / Conclusions

Regarding the results of this report, the specific conclusions are:

1. Overall, and both from the reduction of the infection rate and the vaccination coverage rate points of view, any catch-up is better than no catch-up at all. However, our model indicates that a catch-up to age 18 or to age 20 would represent a very small difference. The same would be true between a catch-up to age 22 or to age 25, 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.
2. In the case of a 5-year efficacy vaccine (which is the current case as far as we know) without booster, the maximum expected vaccination coverage of 85% would only be maintained up to age 16/17, both in a 15 or 30-year horizon and independently of whether there is a catch-up or not. Under the same circumstances, half of the women aged 22 would still be protected. In a 15-year perspective, some coverage (23%) would still be expected among women aged 30 with a catch-up to age 18/20, while with a catch-up to age 22/25 the same coverage would be observed up to age 35. In a 30-year perspective, the same coverage rate would be observed up to age 40 (7%) independently of catch-up. In the case of a catch-up to age 22/25, the coverage would be extended to age 50, although it would be minimal (<5%).
3. In the case of a 5-year efficacy vaccine including 2 boosters (at ages 17 and 22), a 85% vaccination coverage would be assured, in any case, up to age 25. For a 15-year horizon, any catch-up would still maintain a 50% protection among women aged 30. A catch-up to age 22/25 would still maintain a protection slightly below 40% among women aged 35. In 30 years, this vaccination option would still maintain protection rates of 62%, 36% and 21% at, respectively, ages 30,35 and 40 years independently of catch-up. A catch-up to age 22/25 would still maintain some coverage (8%) at age 50.
4. In the case of a 10-year efficacy vaccine without booster (that could be overlapped to a 5-year efficacy vaccine with one booster at age 17), the maximum expected coverage would be maintained up to age 22 and would still be slightly above 60% at age 25 in any case. For a 15-year horizon, any catch-up would imply a coverage just under 40% at age 30 and also at age 35 but in this later case only for those with a catch-up to age 22/25. In 30 years, independently of catch-up, a vaccine coverage of 36, 21 and 12%, respectively, would be expected for ages 30, 35 and 40. A catch-up to ages 22/25 would only add a small coverage (8%) at age 50.
5. In the case of a 10-year efficacy vaccine that would include a booster 10 years later (age 22), the situation is different depending on the chosen horizon. In 15 years, maximum coverage up to age 25 would be assured in any case. Any catch-up would result in a 67% coverage at age 30, while a catch-up to ages 22/25 would imply a 65% coverage at age 35. In a 30 years perspective, the maximum projected coverage would be maintained up to age 30. Any option would result in a 62% coverage at age 35 and 36% at age 40. With a catch-up to ages 22/25, 23% of the women aged 50 would still be protected.

6. In the case of a lifelong efficacy vaccine, in 15-years time the projected maximum coverage would reach age 25. Any catch-up would still protect 74% of women aged 30 and a catch-up to ages 22/25 would result in a 72% coverage at age 35. In 30 years, any vaccination option would result in a maximum expected coverage up to age 40, while a catch-up to ages 22/25 would add a 72% coverage at age 50.

Recommendation

At the present time it is difficult to give clear recommendations about the best vaccination program option because we lack information on one of the main factors influencing this decision: the duration of the vaccine efficacy. To date, there is only evidence of a 5 year efficacy (1;2).

From this standpoint, the current recommendation would be to implement a vaccination program among girls aged 12 years with a catch-up to age 22 years, since a longer catch-up time (up to age 25) would mean an extremely small difference.

However, this recommendation should be reviewed in five years. At that point in time, we will be facing two possible situations:

1. There will be evidence of a longer duration of the vaccine's efficacy (up to 10 years) and no changes in the vaccination program would be needed.
2. There will be no evidence of an efficacy duration beyond 5 years and a decision regarding booster implementation will need to be taken.

BACKGROUND

Human papillomavirus (HPV) is a sexually transmitted infection (STI) of particular interest because of its high prevalence rates and casual association with cervical cancer (3). HPV infection is extremely common in sexually active adolescents and young adults (1;3), and the acquisition of HPV occurs soon after sexual debut (1;4) as sexual intercourse (both vaginal and anal) is the primary route of genital HPV infection (5). Even adolescents who abstain from sexual intercourse but not other forms of sexual behavior may still be infected because HPV is transmitted through skin-to-skin contact (6), although the risk of transmission through digital-genital and oral-genital contact seems to be minimal (5). Women under age 25 years have the highest acquisition of high risk HPV types per year (7).

In the United States, HPV has become the most common STI among adolescent and young women in the past 2 decades (4). It is estimated that 3 out of 4 new HPV infections occur among 15-24-year-olds (8). However, incidence appears to decrease after age 30 years (4;5;9;10).

Although most HPV infections result in no clinical changes, some experts consider that the detection of any HPV indicates undetectable changes in the epithelium (1).

Prevalence

Swiss data based on a clinical sample of adolescents aged 14 to 20 years show a prevalence of 14.2% for any HPV type (11). American data for women aged 18-35 years show a baseline prevalence of 43% and a cumulative prevalence at follow-up of 54% (12). Another US-based study among women aged 18-25 years showed an overall prevalence of 27%, that declined with age (13). 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 (14). Moreover, a prevalence of 14% was reported among those having had only one lifetime sexual partner (13). Another American study found an HPV prevalence of 64% in a clinical sample of 12-20 year-olds (15). Among 60 14-17year-olds, Brown et al. (3) found a baseline prevalence of 45% and a cumulative one of 82%, with higher rates for high risk HPV types (39%) compared to low risk ones (20%). Other studies have also reported higher prevalence rates for high risk HPV infections (22%) than low risk infections (15%) (16), while others (10) found that high risk types has a slightly lower prevalence (15.2%) than low risk types (17.8%).

Incidence

In general, oncongenic (high risk) HPV infections also show higher incidence rates than nononcogenic (low risk) HPV infections (5;12). The cumulative 24-month incidence of HPV for a sample of women with a mean age of 19 years was 39% both for those sexually active at enrollment and for those who started sexual activity during follow-up. Moreover, even virginal women showed a rate of 8% (17). Other studies have found a cumulative 36-month incidence of 43% (18).

In the United Kingdom, Woodman et al. (19) found a cumulative risk of HPV infection at 3 years of 44% and of 60% at 5 years. A study among females aged 13-21 years in California reported that 17% acquired the infection in the first year and 55% after 3 years (20). A Canadian study (21) found an overall incident HPV infection rate of 11% among women aged 15-49 years, with the highest rate (25%) among those aged 15-19 years (Table 1).

Table 1. Frequency of HPV infection

Author, year, country (ref)	Sample	N	Age	Response rate	Follow-up	Measure	Result [95% CI]
Ho et al., 1998, USA (18)	Convenience	608	20+/-3	Not mentioned	2.2 years (mean)	Prevalence Cumulative 36-months incidence	26% (at baseline) 43% [36/49] (among HPV(-) at enrollment)
Woodman et al., 2001, UK (19)	Clinical	1075	15-19 Median:16	53%	29 months (median)	Prevalence Cumulative risk at 3 years Cumulative risk at 5 years	37.9% 44% [40/48] 60%
Lüdicke et al., 2001, Switzerland (11)	Clinical	134	14-20	Not mentioned	None	Prevalence	14.2%
Giuliano et al., 2002, USA	Clinical	331	18-35 Mean: 24.2	42.1%	10 months (median)	Prevalence	42.9% (baseline) 53.5% (cumulative)
Winer et al., 2003, USA (17)	Random	603	18-20	20%	41.2 months (mean)	Cumulative 24-months incidence	Overall: 32.3% [28.0/37.1] Sexually active*: 38.8% [33.3/45.0] Virgins*: 38.9% [29.4/50.3] Virgin**: 7.9% [3.5/17.1]
Richardson et al., 2003, Canada (16)	Clinical	621	17-42 Mean: 23	Not mentioned	24 months	Prevalence	21.8% (high risk) 14.8% (low risk)
Sellors et al., 2003, Canada (21)	Random	253	15-49	50.6%	14 moths (mean)	Incidence	11.1%
Peto et al., 2004, UK (14)	Clinical	785	15-24	Not mentioned	Cohort	Prevalence	23% (overall) 19% (High risk HPV)
Tarkowski et al., 2004, USA (15)	Clinical	312	12-19 Mean: 16.1	>85%	None	Prevalence	64%
Brown et al., 2005, USA (3)	Clinical	60	14-17 Mean: 15.3	Not mentioned	2.2 years (median)	Prevalence	28.3% (at enrollment) 81.7% (cumulative)
Manhart et al., 2006, USA (13)	Population-based	3262	18-25 Mean: 21.7	Not mentioned	None	Prevalence	26.9% [23.7/30.1]
Winer et al,, 2006, USA (22)	Convenience	210	18-22 Mean: 19.3	86.4%	33.9 months(mean)	Cumulative 12-momth incidence	37.2% [27.2/49.4]
Dunne et al., 2007, USA (10)	Representative sample	1921	14-59	77%	None	Prevalence	23.3% [23.3/30.9] (14-59 year-olds) 24.5% [19.6/30.5] (14-19 year-olds)

*At enrollment / ** Throughout the study period

HPV types

More than 100 different HPV types have been identified and approximately 40 infect genital epithelia. About half of them are classified as high risk or oncogenic because of their association with cervical cancer. Currently HPV types 16,18,31,33,35,39,45,51,52,56,58,59,68,73 and 82 are included in this group (4).

Infections with multiple HPV types are common, ranging from 40% (10) to almost two thirds of HPV-positive women (13). In their study of 227 HPV-positive women, Molano et al. (23) reported that half of the infections were multiple. Among women under 25, 40% were single infections, 30% included 2 types and 30% three types or more. In most studies, HPV16 was the most commonly identified type (13;15-17;19;23;24) (Table 2).

Table 2. Frequency of HPV-16 and HPV18.

Author, year (ref)	**Measure**	**HPV-16 [95% CI]**	**HPV-18 [95% CI]**
Ho et al., 1998 (18)	Cumulative 24-month incidence	7% [4/9]	4% [3/6]
Woodman et al., 2001 (19)	Cumulative risk at 3 years	10.5 [8.3/12.7]	6.6 [4.8/8.4]
Giuliano et al., 2002 (13)	Period prevalence	14.5%	1.8%
Molano et al., 2003 (23)	Prevalence	16%	5%
Richardson et al., 2003 (16)	Prevalence	7.0%	3.1%
Winer et al., 2003 (17)	Cumulative 24-month incidence	10.4% [7.8/13.8]	4.1% [2.6/6.4]
Peto et el., 2004 (14)	Prevalence (ages 14-24)	9.0%	- -
Tarkowski et al., 2004	Prevalence	10.2%	5.1%
Brown et al., 2005 (3)	Prevalence	11.6%	4.8%
Manhart et al., 2006 (13)	Prevalence	5.8%	2.2%
Dunne et al., 2007 (10)	Prevalence	1.5% [0.9/2.6]	0.8% [0.4/1.5]

Clearance

Median time to clearance is defined as the time required for 50% of the women to have cleared the HPV infection (12). Most genital HPV infections are transient, asymptomatic and resolve without treatment (2). Although the incidence of HPV infection is high, most infections (up to 90%) are spontaneously cleared by the immune system (1;2;6). An American study describes that at 12 months after the infection only 30% of women were still infected, dropping to only 9% at 24 months (18). Another study carried in Colombia (23) reported that 23% of infections were still present at 1 year and 7% at 5-years follow-up. In an American study, the time frame for clearance was longer for oncogenic HPV infections (9.8 months) than for nononcogenic ones (4.3 months) (12). These results are similar to other studies (3;23). The median time to clearance for HPV-16 was reported to be of 8.5 months (12). Additionally, the risk of not clearing a high risk HPV increases with age (7).

Persistence

Persistence can be broadly defined as the detection of the same HPV type two or more times with a given time interval between the examinations (9). The longer an infection persists, the more likely it is to continue to persist (18). Persistent infection with high risk HPV types is the most important risk factor for cervical cancer precursor lesions (1). Risk factors for persistent HPV infection (over 6 months) were older age, infection with multiple HPV types and infection with a high-risk type HPV, while on the other hand, cigarette smoking seems to be protective against persistent infection (18).

Risk factors

Sexual behavior is the most constant predictor of acquiring HPV infection (2). Although many risk factors have been described in the literature, number of sexual partners (1;2;10;11;13;15;17;18;20-22;25;26), together with having had a new sex partner (1;10) in the 3 months (12) or 5-8 months prior to the visit (17) are the most consistent.

Other described risk factors are more inconsistent. Younger age (1;2;10;13;18) and early age at first intercourse (2;13;25) have been described as risk factors, but other studies found no association with them (11;13;15;26), probably because younger age and early age at first intercourse are correlated with a higher number of sexual partners.

Some authors have reported a history of sexually transmitted infection as a risk factor (20;25), although others (13;17;21) have not confirmed it.

The effect of smoking on HPV acquisition is unclear (5): some describe it as a risk factor (17), others found no association (11;13;15;21;26). The same is true for alcohol and drug use related to sexual behaviors, with some describing them as risk factors (13;18;25) and others finding no association (15;17).

Most studies assessing the relationship between HPV infection and condom use have failed to demonstrate a protective effect (5). Correct and consistent condom use was not significantly associated with HPV infection in several studies (13;17). In their meta-analysis, Manhart and Koutsky (27) did not find consistent evidence that condom use prevented HPV infection, although it seemed to prevent HPV-related diseases. Nevertheless, consistent condom use by their partners seems to reduce (but not eliminate) the risk of HPV infection among women (22).

Association between HPV infection and hormonal contraceptive use is also inconsistent (5): although some indicate that current use of oral contraceptives is a risk factor (17), others found that the association was not significant (11;21;26) and still others that it was a protective factor (20).

A study found that a high frequency of vaginal sex was related to HPV infection (18), but others found that the association was not significant (11). Other risk factors described by single studies but not confirmed are: race (African-American) (25) or belonging to an ethnic minority (18); never having been married (10;13); douching (15); or anal sex (18).

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 (1;2;17;18;22;25). However, other factors such as partner's age, partner's race or male circumcision are not consistent (5;15;17;25;26) (Table 3).

Table 3. Risk factors for HPV infection.

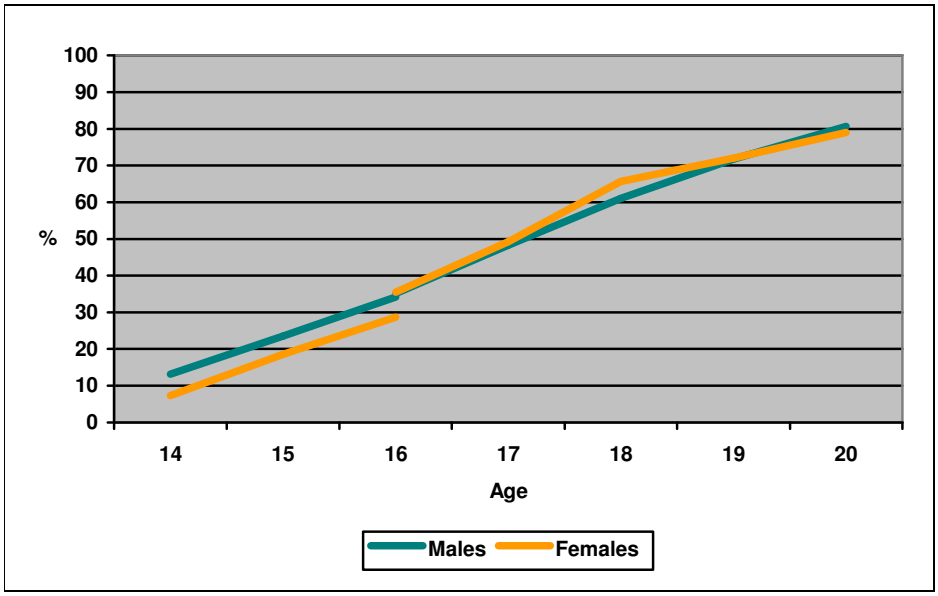
	Ho et al., 1998 (18)	Lüdicke et al., 2001 (11)	Kjaer et al., 2001 (26)	Kahn et al., 2002 (25)	Winer et al., 2003(17)	Sellors et al., 2003 (21)	Tarkowski et al., 2004 (15)	Manhart et al., 2006 (13)	Winer et al., 2006(22)	Dunne et al., 2007 (10)
Younger age	+	NS	NS	+			NS	NS		+
Number of sexual partners	+	+	+	+	+	+	+	+	+	+
Smoking		NS	NS		+	NS	NS	NS		
Alcohol and drug use	+			+	NS		NS	+		
Oral contraceptive use		NS	NS		+	NS				
Condom use					NS			NS	(-)*	
Tampon use					NS					
High frequency of vaginal sex	+	NS								
Anal sex	+									
Douching							+			
STI diagnosis/history				+	NS	NS		NS		
Not married						NS		+		+
Racial/minority group	+			+						NS
Age difference with partner			+				+			
Promiscuous partner	+			+	+				+	
Partner not in school	+									
Partner age				+						
Partner race				+	+					

* Protective factor; NS= Non Significant

Adolescent sexual behavior

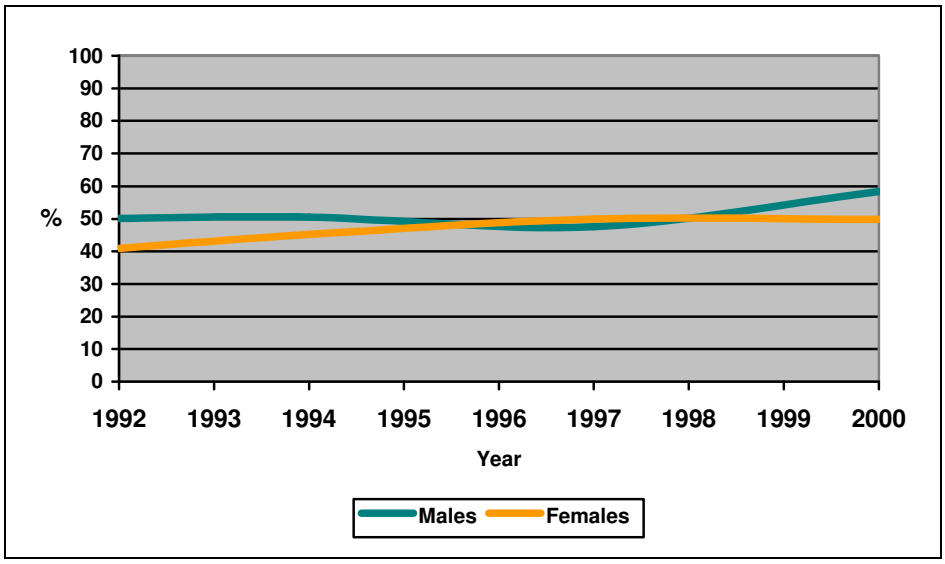
A study carried out among US youth aged 14-22 years reported that grossly two thirds of both males and females were sexually experienced (28). UK data report a median age of 17 years at first intercourse both for males and females (29). In Switzerland, median age at first intercourse is 18.5 years both 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 (30). 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 (31;32) (Figure 1).

Figure 1. Sexually active adolescents aged 14-20 in Switzerland (31;32).



Overall, the percentage of sexually active Swiss aged 17-20 years has slightly increased from 1992 to 2000 (Figure 2).

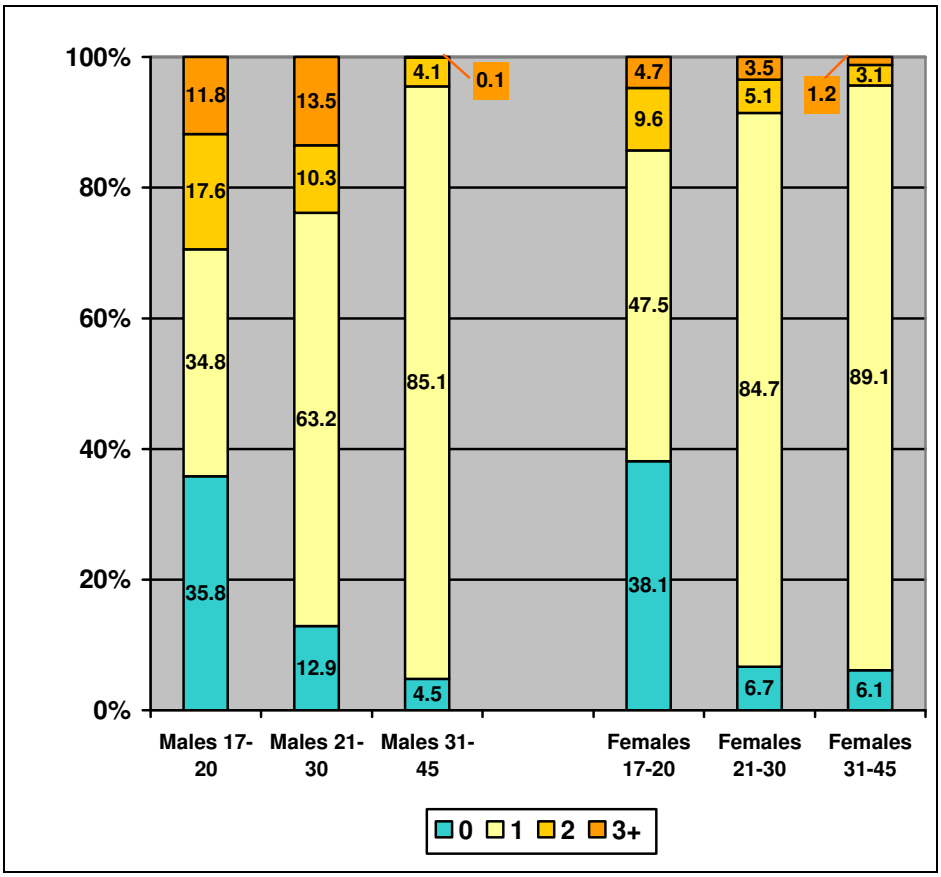
Figure 2. Percentage of sexually active 17-20 year-olds. Switzerland: 1992-2000 (33).



Among American females aged 14-22 years, 72% had had only one sexual partner in the previous 3 months, 8% had had 2 and 5% three or more. Among males, the rates were 50%, 12% and 14%, respectively, for the same age group. The lifetime number of sexual partners increased from 8% of females aged 14 reporting 6 or more partners to 31% of those aged 21. Among males, it varied between 14% and 45% for the same ages (28). Swiss data also indicate that one third of males aged 17-20 had had one partner in the previous year, 18% two, and 12% three or more. The

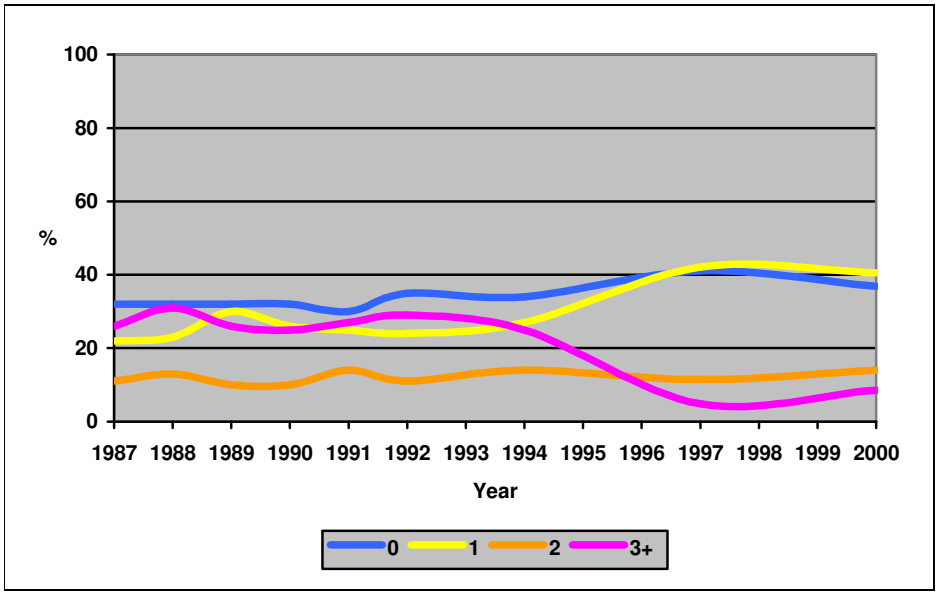
percentages for females in the same age group were, respectively, 48%, 10% and 5%. For males aged 21-30 years, 63% had had one partner, 10% two and 14% three or more. For females in this age group, the percentages were 85%, 5% and 4%. Finally, 85% of males aged 31-45 had had one partner, 5% two and 6% three, while for females the figures were 89%, 3% and 1% (33) (Figure 3). Among sexually active adolescents aged 16-20 years in Switzerland, 47% of females and 33% males had ever had one partner, 39% of both genders had had 2 to 4, and 13% of females and 28% of males had had five or more lifetime sexual partners (31).

Figure 3. Number of sexual partners in the previous year. Switzerland, 2000 (33).



However, the trends in the number of sexual partners among Swiss youth aged 17-20 years show some changes between 1987 and 2000. Overall, the rates remain quite stable until 1994. At this point in time, while those having had 2 sexual partners remain stable slightly over 10%, those reporting 3 or more partners decline dramatically while those reporting only one partner raise importantly as do those who did not have a partner, although the later do it less markedly (33;34) (Figure 4).

Figure 4. Trends in the number of sexual partners among 17-20 year-olds, Switzerland: 1987-2000 (33;34).



Among American youth, risk factors for having had two or more sexual partners in the previous 3 months are alcohol and illicit drugs use and first intercourse at age 13 years or below for males and black race, alcohol use and first sexual intercourse before age 16 for females. Being married is a protective factor for both genders. For both genders, risk factors for having had 6 or more sexual partners in their life are age, black race, alcohol and illicit drug use and first sexual intercourse before age 16 (28).

Vaccines

HPV vaccines are characterized as therapeutic or prophylactic. Although the former ones are in very early stages of development and have shown limited success, the later have demonstrated high efficacy (1). A model based on UK data (35) estimated that for a vaccinated cohort of 12-year-old girls there would be a reduction of 66% in the prevalence of high-grade precancerous lesions and a 76% reduction in cervical cancer deaths. A 95% reduction in the prevalence of HPV-16 and 18 associated lesions was also estimated.

The duration of the vaccine's protection is unclear (2) and results to date indicate a sustained efficacy up to 4.5 / 5 years (1;2). Consequently, the need for a booster is a research area of greatest importance (7). Moreover, if a booster is required, focusing vaccination programs on 12-year-olds is more cost-effective than focusing on infants (36).

As HPV acquisition occurs soon after sexual initiation, the vaccine would have greater effectiveness if administered to young adolescents before they have acquired vaccine HPV types (1), before the onset of sexual activity (37).

It has also been debated whether males should also be vaccinated. Although some authors (38) report that vaccinating both men and women would result in a higher decrease in HPV prevalence, evidence to date indicate that vaccinating both genders had little benefit over vaccinating females only (39). Taira et al. (36) reported that including males in a vaccination

program would only slightly reduce infections and cancer cases with an unattractive cost-effectiveness ratio.

Questions posed

Three questions arise regarding HPV vaccination:

3. At what age should the vaccine be introduced in a routine schedule?
4. Up to which age should the vaccine be recommended in catch-up form?
5. Would boosters be necessary?

To answer the first question, it is clear that the vaccine has to be implemented before the onset of sexual activity. The American Advisory Committee on Immunization Practices (ACIP) recommends to vaccinate females at age 11-12 years, and that the vaccination series can be started as young as 9 years of age (40). The American Cancer Society (ACS) (41) gives the same recommendations. This schedule is supported both by the American Academy of Pediatrics (42) and the Society for Adolescent Medicine (37).

To tackle the second question, the ACIP also recommends catch-up vaccination for females aged 13 to 26 years who have not received the vaccine or who have not completed the full vaccine series. Ideally, it should be administered before potential exposure to HPV through sexual contact. This schedule is also supported both by the American Academy of Pediatrics (42) and the Society for Adolescent Medicine (37). On the other hand, the ACS (41) recommends catch-up vaccination up to age 18 because there are insufficient data for or against vaccination among females aged 19-26 years. Vaccination beyond age 26 or for males is not recommended (41). In other countries such as the UK (43) and Canada (44) the recommendations are currently under review.

The third question is probably the most difficult to answer, as we currently do not know the efficacy time frame of these vaccines. As stated previously, most authors report a sustained efficacy up to 4.5 / 5 years (1;2).

Objective

The objective of this report is to create a mathematical model using Swiss data to explore the theoretical HPV infection and vaccine coverage rates in the female Swiss population using different scenarios that take into account both the upper catch-up age limit and three different efficacy time-frames (5 years, 10 years, and lifelong). In all cases, the routine vaccination program would start at age 12.

DESCRIPTION OF THE HPV MODEL

Introduction

The tool developed by the GRSA for the modelling of HPV virus diffusion is based on the classic SIR model introduced first by Kermack & McKendrick (45) in 1927 and then broadly used in epidemiology (e.g. Anderson (46), Daley & Gani (47)). A similar, but less complete, HPV model has been proposed by Corley (48). Individuals in the model are classified as either Susceptible of being infected (state S), Infective (state I), or in Remission (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 immune after having received a vaccine or a booster. State VI groups individuals having received a vaccine or a booster when already infected. For the purpose of clarity, the rare individuals belonging to this last state will be aggregated with Infective when presenting the results. The model considers both females and males, but given the goal of the present study, only results for females will be reported.

The principle of the model is to follow a complete population made of individuals of ages 1 to 100 of both genders. The model works in discrete time with a time unit equal to one year. At the beginning of the simulation (year 0), an initial population is generated. Proportions of individuals of ages 1, 2, …, 100 follow the mortality tables computed by Swiss Statistics for Switzerland. Each subsequent year of the simulation, the individuals of one particular age move to the next age. For instance, 20 years old individuals at time t become 21 years old individuals at time $t+1$. Individuals leave the model after they reach 100 years old, and new individuals of one year old enter into the model to replace them. Each year of the simulation, individuals are classified into one of the 5 mutually-exclusive states (S, I, R, V, VI). Possible transitions from one state to another are described as difference equations. A set of parameters estimated from the literature ensures the best reproduction of transitions observed in the real world. By simulating the natural development of the population over a large number of years, the model is used to compute the yearly proportion of the total population belonging any time to each of the five states (S, I, R, V, VI).

Individuals of each age are divided into several mutually exclusive sexual profiles corresponding to different groups of sexual activity. Each group is defined by the average number of different partnerships formed each year. A process of sexual mixing between these groups and between individuals of different ages is implemented to take into account the fact that many sexual partnerships involve individuals with different characteristics. Because data on sexual habits of Swiss people are scarce, we chose to divide the population of the model into 9 classes of age 1-10, 11-14, 15-16, 17-20, 21-30, 31-45, 46-60, 61-80, 81-100. Sexual activity does not occur in the first and last classes. Parameters are fixed globally for all possible ages of a same class. For instance, individuals aged 21 to 30 years old share the same parameters.

Different types of vaccination programs can be implemented to study their short- and long-term impact onto the population. Vaccination programs can include vaccination at a particular age, one or several boosters, and a catch-up procedure up to a given age, with or without booster. The impact of each vaccination scenario can be studied after a given number of years. It is also possible to obtain endemic long-term results.

Transitions between states

Each year, individuals into the model move from one state to another following their sexual behaviour and the vaccination program if applicable. Figure 5 shows the possible transitions before vaccination occurs. Only states S, I, and R are then possible. Susceptible individuals can either stay Susceptible or become Infective. Infective individuals can either stay Infective or enter in Remission. Remission individuals can either stay in Remission or become Susceptible again. This last transition allows for the modelling of multiple successive HPV 16 or 18 infections by a same individual.

Figure 5: Possible transitions before vaccination.

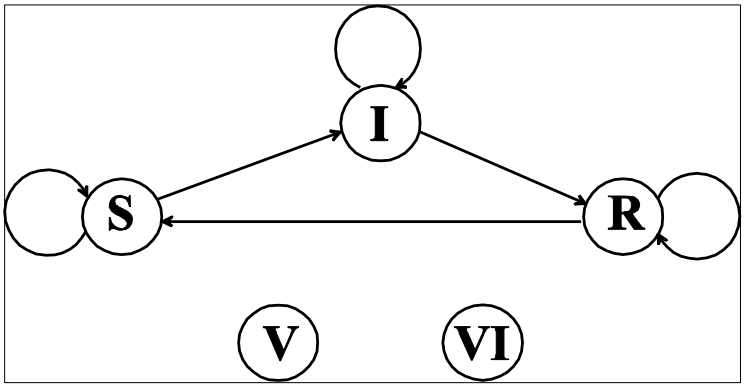
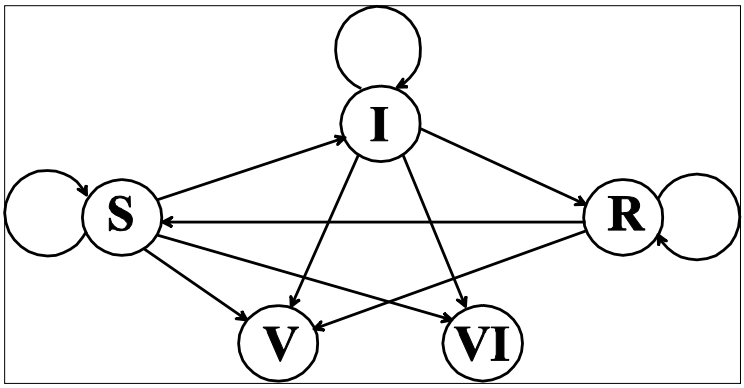


Figure 6 shows the possible transitions at the exact age of the vaccination. Compared to the situation of Figure 5, states V and VI are also active. In most cases, individuals become Vaccinated either from the Susceptible or Remission states, but they can also come from the Infective state if they clear infection the same year they are vaccinated. On the other hand, they 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.

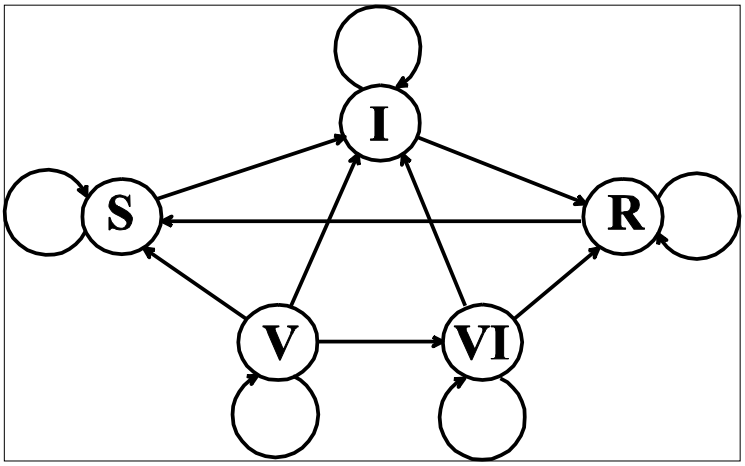
Figure 6: Possible transitions when vaccination occurs.



After vaccination (Figure 7), individuals can stay in the Vaccinated and Vaccinated-Infective states, but they can also leave these states to become Susceptible, Infective, or enter in Remission. 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

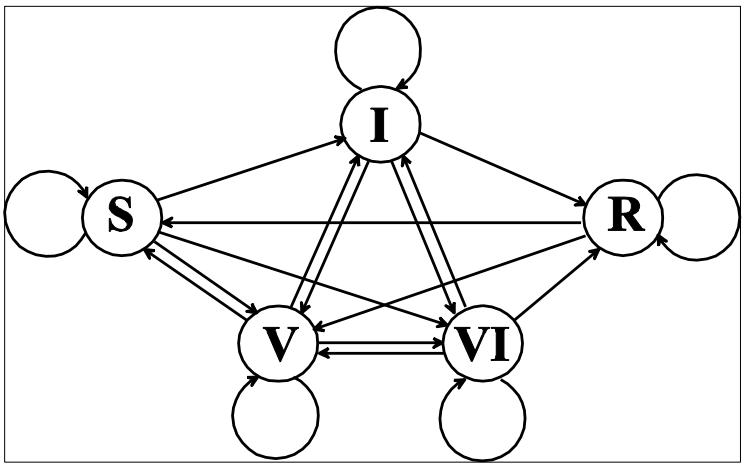
the vaccine doesn't provide a 100% percent protection. Vaccinated-Infective individuals become simply Infective if the immunity provided by the vaccine vanishes, and they enter in Remission if they clear the infection at the same time.

Figure 7: Possible transitions when vaccinated and non-vaccinated individuals coexist into the model.



An even more complex situation occurs at the exact time a booster is administered (Figure 8). 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.

Figure 8: Possible transitions at the time of a booster.



The years following a booster, transitions follow again the schema given on Figure 7.

Parameters of the model

Table 5 describes the parameters of the model and gives their values as estimated for Switzerland from the literature. As indicated in Table 5, the values of many parameters change in function of the vaccination scenario. Other parameters (duration, nbAge, Classes, p, Omega) have also been chosen in function of the objective of the study and of the availability of Swiss data. The

parameter popAge is used as an internal reference for the model. Its value is arbitrary chosen and does not influence the results of the model.

There are 20 profiles of sexual activity, each of them grouping exactly 5% of the total population of a particular age. Each profile corresponds to a different group of population. Such a large number of profiles is not mandatory, but given the Swiss data available for parameter estimation, it was the best choice. For each profile and each class of age, the average number of sexual partnerships formed by year is freely chosen (parameter C), but these values have to be identical for both genders, so a weighted average is computed from each gender data. If required, several profiles can be assigned the same characteristics.

The following matrix gives the value of C (average number of sexual partnerships per year) for each age class and each sexual activity profile. The first and last age classes are non-sexually active classes. These classes group people without any sexual activity involving partners, so they take only zeros values in the matrix.

Table 4: C matrix giving the average number of sexual partnerships formed each year, by age class and profile of sexual activity.

	Profiles of sexual activity																			
Age class	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
1-10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11-14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
15-16	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	2	2	5	7	9
17-20	0	0	0	0	0	0	1	1	1	1	1	1	1	2	2	2	2	3	5	7
21-30	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	3	3	3
31-45	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	3
46-60	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	2	3
61-80	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	2	3
81-100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

The parameter of sexual mixing (epsilon) takes a value of 0.8 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 Phivacc, PhiBoost, and PhiCatchup parameters have 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 low (41%) (49) since vaccination is not mandatory in all cantons, so we used data from other European countries (Italy: 92%, Germany: 84%, Austria: 92%) (50).

The number of yeard separating vaccination or catch-up from a booster (parameters AgeBoost and DelBoostCatchup) is equal to the assumed length of the total immunity provided by the vaccine. This strategy insures that no sudden diminution in the proportion of vaccinated females will occur before the end of the period covered by the chosen vaccination program.

Table 5: Parameters of the HPV model. We describe here all parameters of the simulation model, and we provide their values as estimated for Switzerland from the literature. When needed, the main source used to estimate the parameter is provided in the last column, but in many cases the estimation provided here is a combination of different sources. "Specific" indicates that the value has been chosen specifically in regard of the objective of the present study.

Parameter	**Estimation**	**Description**	**Main source for estimation**
		General	
duration	100	Length of the simulation in years.	Specific.
nbAge	9	Number of age classes.	Specific.
Classe	1-10, 11-14, 15-16, 17-20, 21-30, 31-45, 46-60, 61-80, 81-100	Initial and final age of each class.	Specific.
p	20	Number of sexual activity profiles.	Specific.
popAge	1000	Total number of one year old individuals (female and male) into the model.	Specific.
Surv	Available upon request.	Survival probability for individual of each age, by sex.	**Swiss Statistics**
Infect	Available upon request. Endemic values computed from the reference scenario without vaccination program.	Initial proportion of the population being infected by the HPV virus, by age, sex and sexual activity profile.	Specific.
		Vaccination	
ageVacc	12	Age of the vaccination.	***Taira et al. (36)***
PhiVacc	female : 85%, male : 0%	Percentage of individuals being vaccinated at age ageVacc, by sex.	Specific.
AgeBoost	dVacc years after vaccination or last booster	Age of the booster (if applicable). Multiple boosters are possible.	Specific.
PhiBoost	female : 85%, male : 0%	Percentage of individuals receiving a booster, by sex.	Specific.
dVacc	5 or 10 (depending on the scenario)	Length in years of the total immunity provided by the vaccine.	***Dunne & Markowitz (1); Clifford et al. (24)***
dBoost	5 or 10 (depending on the scenario)	Length in years of the total immunity provided by the booster.	***Dunne & Markowitz (1); Clifford et al. (24)***

catchup	0 or 1 (depending on the scenario)	Catch-up procedure (0 : no, 1 : yes).	Specific.
ageSupCatchup	18, 20, 22 or 25 (depending on the scenario)	Maximal age to receive the catch-up.	***ACIP (40); ACS (41)***
PhiCatchup	female : 85%, male : 0%	Percentage of individuals receiving the catch-up, by sex.	Specific.
DelBoostCatchup	dBoost years after catch-up or last booster (depending on the scenario)	Delay in years before receiving a booster post-catch-up. Multiple boosters are possible.	Specific.
maxAgeBoostCatchup	25	Maximal age to receive a booster post-catch-up.	***ACS (41)***
Sigma	0% during the first dVacc years following vaccination, then 10%	Proportion of vaccinated individuals losing their immunity by years during the period of total immunity, and then after this period.	***Koutsky & Harper (51)***
r	1	Relative risk of virus transmission between VI and I individuals.	***Hughes, Garnett & Koutsky (38)***
Sexuality			
C	See text.	Average number of sexual partnerships formed by year, for each sexual activity profile and each age class.	***IUMSP/UEPP* (33), *SMASH02 (31)***
Omega	5% per profile	Proportion of the total population belonging to each profile of sexual activity.	Specific.
epsilon	0.8	Proportion of the population forming sexual partnerships with individuals belonging to other profiles of sexual activity.	Specific.
Psi	female : 0%, male : 0%	Relative risk of infection between vaccinated and non-vaccinated individuals, by sex.	***Koutsky & Harper (51)***
Beta	female to male : 75% male to female : 75%	Transmission rate of the virus from one sex to another.	***Hughes, Garnett & Koutsky (38)***
States transitions			
gamma	70%	Proportion of infective individuals entering in remission each year.	***CDC (2)***
alpha	1	Relative rate of remission entering between states VI and V.	***Hughes, Garnett & Koutsky (38)***
delta	0.5	Proportion of remission individuals becoming susceptible again each year.	Specific.

Model

The model works in discrete time, each period being one year. The transitions from any state of the model (S, I, R, V, VI) to any other state are modelled through a set of difference equations. Each year of the simulation, the proportion of individuals of sexual activity profile *p* and age *a* going from state *s* to state *u* is computed.

The core of any model for sexually transmitted viruses is a complex process of sexual mixing between individuals. 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 (52). Each year of the simulation, a matrix called Rho indicating the proportion of sexual contacts occurring between each couple of sexual activity profiles is computed for each age. Then, a second matrix called Lambda giving the force of infection of each individual is computed from Rho and from the average number of partnerships C. On the contrary of the solution adopted in several previous models, the process implemented here takes explicitly into account the fact that partnerships between individuals of different ages are very frequent.

At the beginning of the simulation, an initial population is created. This population mimics the Swiss population by the use of the real Swiss mortality table and by an HPV infection rate by age corresponding to the endemic situation predicted by the model. Then, each subsequent year of the simulation consists in the following steps:

i. The sexual mixing between the different groups of population is computed from the final situation of the previous year.

ii. A new repartition of the population between the 5 states is computed using the set of difference equations and the final situation of the previous year.

iii. The results are adjusted according to the Swiss mortality table to respect the real repartition between the different ages.

Intermediary results are available after any number of simulation years. 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 model provides the endemic repartition of the population between the 5 states.

The model has been developed using Matlab 7. Stata 9 has been used for statistical computations.

RESULTS

Current scenario: no vaccination

Using current Swiss data in the model simulation, HPV infection rate would peak at ages 18 (15.5%) and 22 years (15.7%) to slowly decline afterwards to 8.2% at age 60.

The infection rate for HPV types 16 and 18 peaks at age 18 (9.4%), is reduced in half at the end of the third decade (4.7% at age 30) and remains around 2% from age 40 onwards (Figure 9 and Table 6).

Figure 9. Estimated HPV infection rate by age: global and for types 16 and 18, Switzerland.

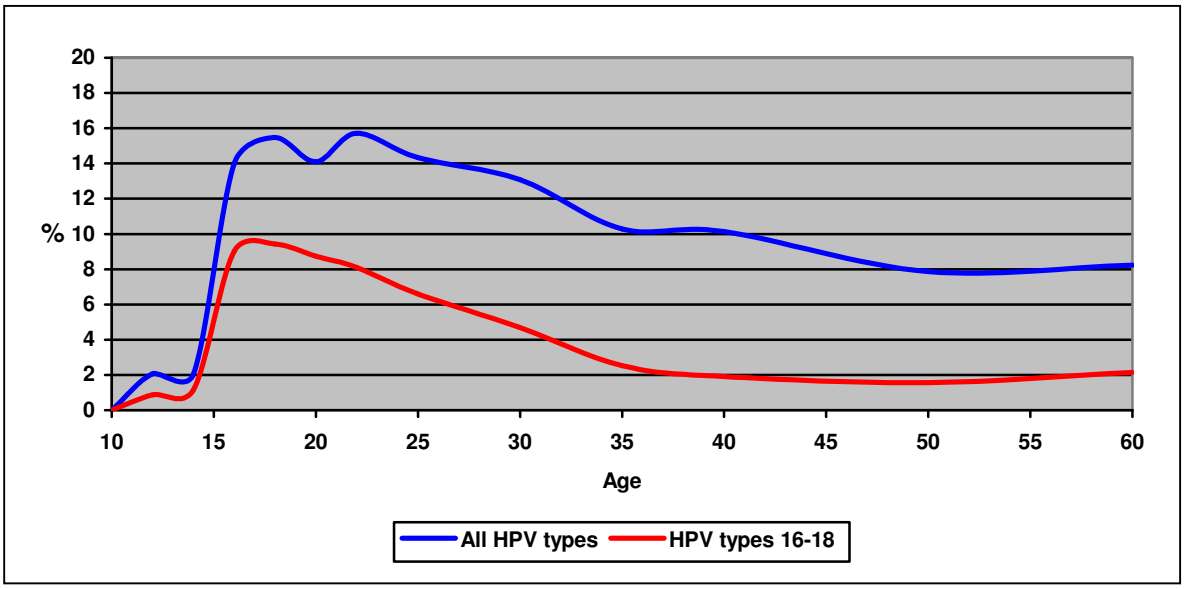


Table 6. Estimated HPV infection rate by age: global and for types 16 and 18, Switzerland (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
All HPV types	2.1	2.0	14.0	15.5	14.1	15.7	14.3	13.1	10.3	10.1	7.9	8.2
HPV types 16-18	0.9	1.1	9.0	9.4	8.7	8.1	6.6	4.7	2.5	1.9	1.6	2.1

Estimated situation in 15 years: infection rate

Scenarios 1 to 5 define what would be the theoretical situation fifteen years after the initiation of the vaccination program depending on whether or not there is a catch-up and, if there were one, up to what age.

The 15-year horizon has been chosen because at that moment the first vaccinated cohort at age 12 will reach age 27, beyond the maximum age described currently in the literature as the maximum catch-up age.

For each scenario, 5 possibilities regarding the vaccine have been tested:

1. Vaccine with 5-year efficacy, no booster.
2. Vaccine with 5-year efficacy with two boosters at ages 17 and 22.
3. Vaccine with 10-year efficacy, no booster.
4. Vaccine with 10-year efficacy with a booster 10 years later (age 22).
5. Vaccine with lifelong efficacy.

We have avoided to introduce a sixth possibility (vaccines with 5-year efficacy plus one booster 5 years later) because it is barely the same situation than for a 10-year efficacy vaccine.

For all scenarios some assumptions have been made:

- Only girls would be vaccinated.
- Universal vaccination program.
- An expected vaccination coverage rate of 85%.

In all the scenarios including a catch-up, it has been assumed that it would be done in the first year of the implementation of the vaccination program. Although longer catch-up periods (three years, for example) could have been assumed, they would have little influence on the results.

Finally, the infection rates described below include only females and are only referred to HPV types 16 and 18.

Scenario 1: No catch-up, estimated situation in 15 years.

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 2 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. The addition of a booster would imply that the rate would remain below 1% up to age 25 and under 4% up to age 30. A lifelong efficacy vaccine would follow a very similar curve. In all cases, from age 35 onwards, the rates are as if no vaccination was administered (Figure 10 and Table 7).

Figure 10. Estimated HPV infection rate by age, Switzerland. Scenario at 15 years without catch-up.

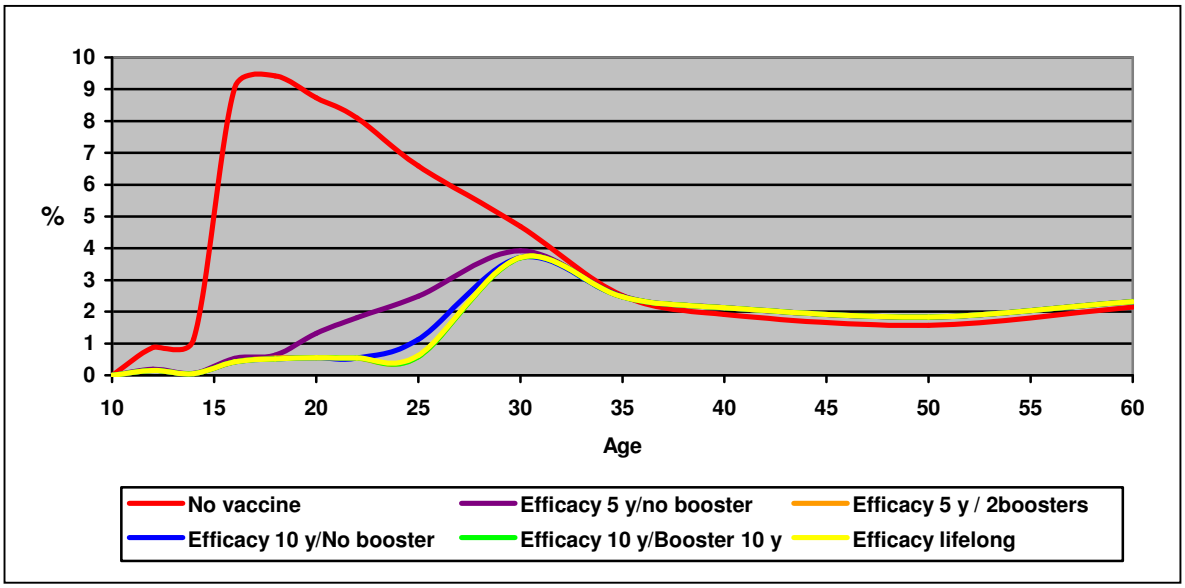


Table 7. Infection rate by age and type of vaccination. Scenario at 15 years without catch-up (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.19	0.06	0.53	0.63	1.32	1.81	2.49	3.92	2.5	2.12	1.83	2.32
Efficacy 5 y/2 boosters	0.15	0.05	0.42	0.54	0.55	0.53	0.58	3.7	2.47	2.12	1.83	2.32
Efficacy 10 y/No booster	0.15	0.05	0.42	0.51	0.55	0.54	1.13	3.71	2.47	2.12	1.83	2.32
Efficacy 10 y/Booster 10 y	0.15	0.05	0.42	0.51	0.55	0.54	0.58	3.7	2.47	2.12	1.83	2.32
Efficacy lifelong	0.15	0.05	0.42	0.51	0.55	0.54	0.62	3.71	2.47	2.12	1.83	2.32

Scenario 2: Catch-up to age 18, estimated situation in 15 years.

With a catch-up to age 18, 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 2 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 adding a booster 10 years later or using a lifelong efficacy vaccine, the scenario would be very close to the 5-years+boosters case. In all cases, the infection rate would be similar to non-vaccination from age 40 onwards (Figure 11 and Table 8).

Figure 11. Estimated HPV infection rate by age, Switzerland. Scenario at 15 years with catch-up to age 18.

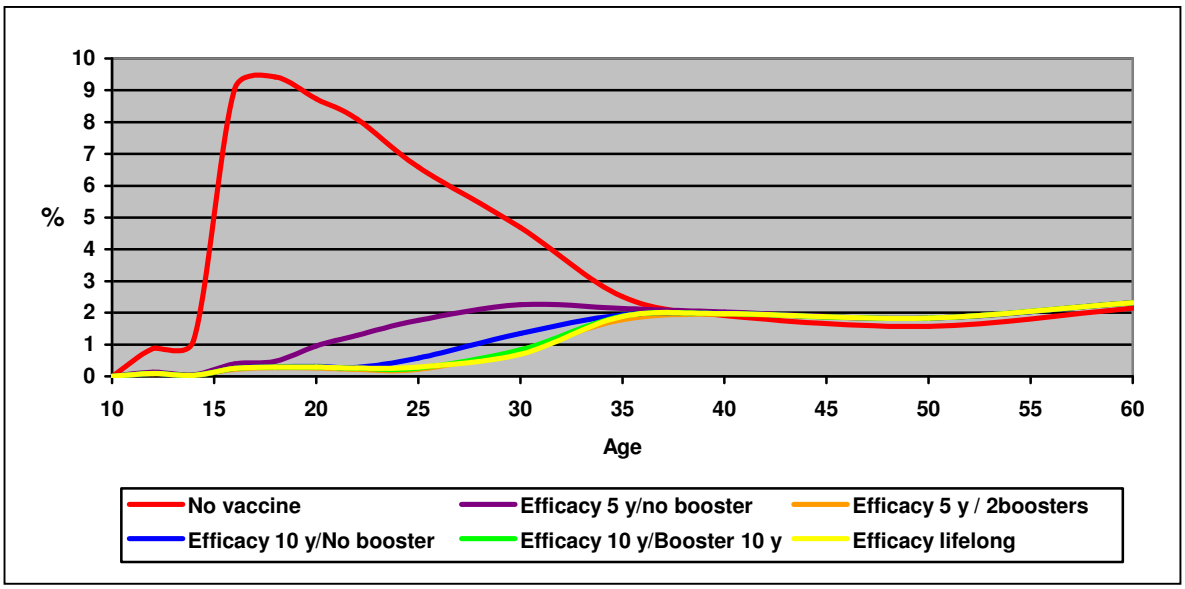


Table 8. Infection rate by age and type of vaccination. Scenario at 15 years with catch-up to age 18 (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.13	0.05	0.39	0.47	0.96	1.29	1.76	2.25	2.13	2.02	1.83	2.32
Efficacy 5 y/2 boosters	0.08	0.03	0.22	0.27	0.26	0.22	0.22	0.82	1.78	1.95	1.83	2.32
Efficacy 10 y/No booster	0.09	0.03	0.25	0.3	0.31	0.28	0.57	1.35	1.93	1.98	1.83	2.32
Efficacy 10 y/Booster 10 y	0.09	0.03	0.25	0.29	0.29	0.25	0.26	0.84	1.89	1.97	1.83	2.32
Efficacy lifelong	0.09	0.03	0.25	0.29	0.29	0.26	0.29	0.69	1.88	1.97	1.83	2.32

Scenario 3: Catch-up to age 20, estimated situation in 15 years.

A catch-up to age 20 would maintain the infection rate below 1% up to age 20 and to a maximum of 2% up to age 35 with a 5-yer efficacy vaccine without booster. By adding 2 boosters or using a 10-year efficacy vaccine with booster or a lifelong efficacy vaccine, the rate would remain under 1% up to age 30 and below 2% up to age 35. I f no booster was administered after the 10-year efficacy vaccine, the rate would be kept under 1% up to age 25 and under 2% up to age 35 (Figure 12 and Table 9).

Figure 12. Estimated HPV infection rate by age, Switzerland. Scenario at 15 years with catch-up to age 20.

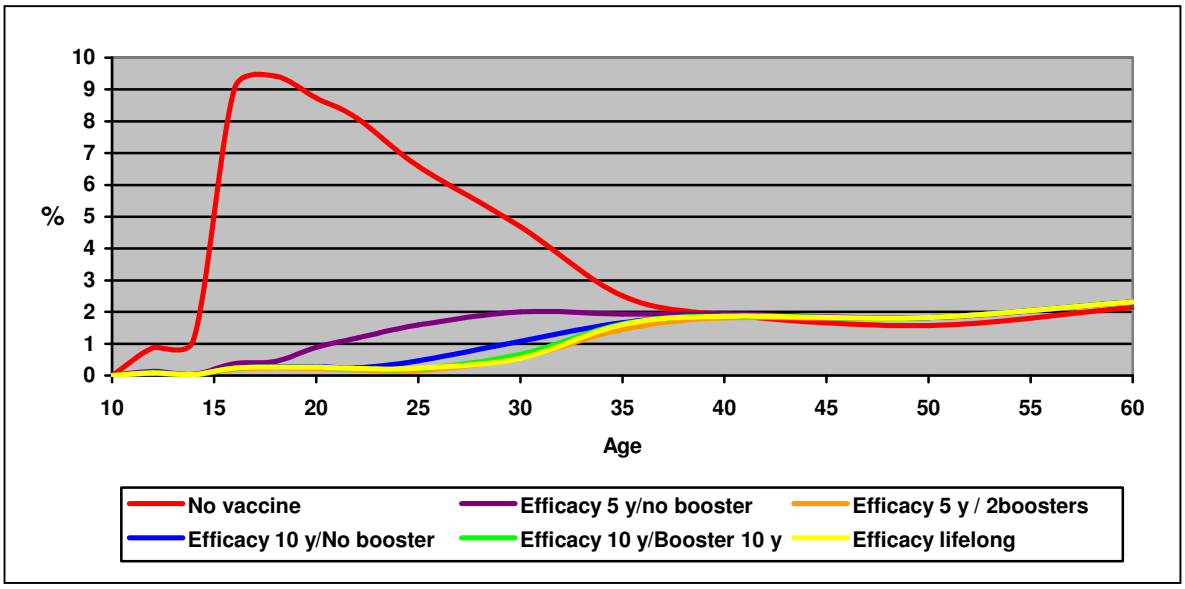


Table 9. Infection rate by age and type of vaccination. Scenario at 15 years with catch-up to age 20 (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.13	0.04	0.37	0.44	0.89	1.18	1.59	2	1.93	1.94	1.82	2.32
Efficacy 5 y/2 boosters	0.07	0.03	0.2	0.24	0.22	0.18	0.15	0.56	1.45	1.81	1.82	2.32
Efficacy 10 y/No booster	0.08	0.03	0.23	0.27	0.28	0.24	0.46	1.08	1.66	1.87	1.82	2.32
Efficacy 10 y/Booster 10 y	0.08	0.03	0.23	0.26	0.26	0.22	0.21	0.66	1.62	1.87	1.82	2.32
Efficacy lifelong	0.08	0.03	0.23	0.26	0.26	0.22	0.23	0.54	1.6	1.86	1.82	2.32

Scenario 4: Catch-up to age 22, estimated situation in 15 years.

A catch-up to age 22 would result in an infection rate below 1% up to age 20 and below 2% up to age 35 with a 5-year efficacy vaccine. In all other cases, the rate would be maintained below 1% up to age 35 (Figure 13 and Table 10).

Figure 13. Estimated HPV infection rate by age, Switzerland. Scenario at 15 years with catch-up to age 22.

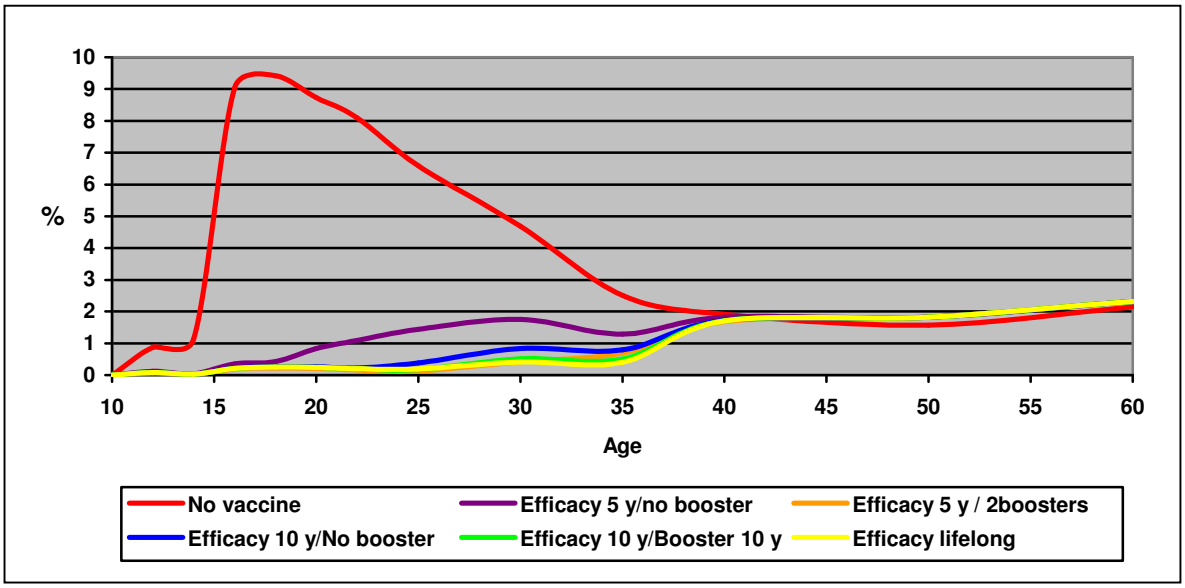


Table 10. Infection rate by age and type of vaccination. Scenario at 15 years with catch-up to age 22 (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.12	0.04	0.35	0.42	0.84	1.09	1.44	1.75	1.29	1.82	1.82	2.32
Efficacy 5 y/2 boosters	0.07	0.03	0.19	0.22	0.21	0.16	0.13	0.42	0.69	1.68	1.82	2.32
Efficacy 10 y/No booster	0.08	0.03	0.22	0.26	0.26	0.22	0.38	0.84	0.79	1.72	1.82	2.32
Efficacy 10 y/Booster 10 y	0.08	0.03	0.21	0.25	0.24	0.2	0.17	0.51	0.5	1.71	1.82	2.32
Efficacy lifelong	0.08	0.03	0.21	0.25	0.24	0.2	0.19	0.41	0.4	1.7	1.82	2.32

Scenario 5: Catch-up to age 25, estimated situation in 15 years.

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 under 1.5% up to age 40 (Figure 14 and Table 11).

Figure 14. Estimated HPV infection rate by age, Switzerland. Scenario at 15 years with catch-up to age 25.

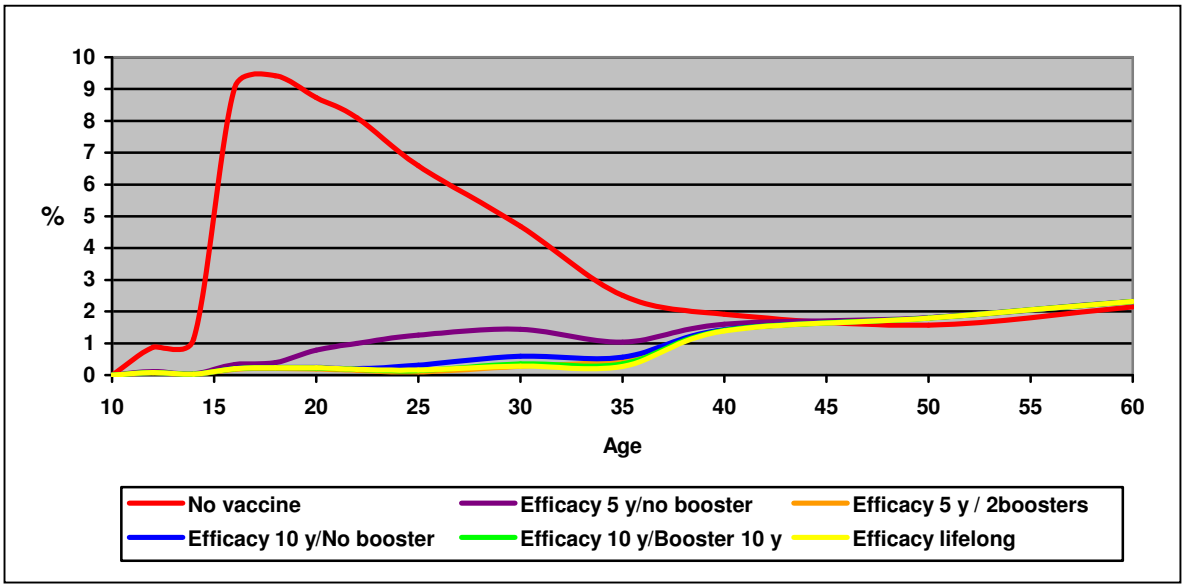


Table 11. Infection rate by age and type of vaccination. Scenario at 15 years with catch-up to age 25 (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.11	0.04	0.33	0.39	0.78	1	1.26	1.44	1.04	1.6	1.8	2.32
Efficacy 5 y/2 boosters	0.07	0.02	0.18	0.21	0.19	0.15	0.1	0.28	0.49	1.42	1.8	2.32
Efficacy 10 y/No booster	0.08	0.03	0.21	0.24	0.24	0.2	0.31	0.59	0.56	1.43	1.8	2.32
Efficacy 10 y/Booster 10 y	0.08	0.03	0.2	0.23	0.22	0.18	0.14	0.35	0.35	1.41	1.79	2.32
Efficacy lifelong	0.08	0.03	0.2	0.23	0.23	0.18	0.16	0.28	0.27	1.39	1.79	2.32

Estimated situation in 30 years: infection rate

Scenarios 6 to 10 define what would be the theoretical situation thirty years after the initiation of the vaccination program depending on whether or not there is a catch-up and, if there were one, up to what age.

The 30-year horizon has been chosen because from that moment onwards the model remains stable.

As for the 15 years situation, for each scenario 5 possibilities regarding the vaccine have been tested:

1. Vaccine with 5-year efficacy, no booster.
2. Vaccine with 5-year efficacy with two boosters at ages 17 and 22.
3. Vaccine with 10-year efficacy, no booster.
4. Vaccine with 10-year efficacy with a booster 10 years later (age 22).
5. Vaccine with lifelong efficacy.

We have avoided to introduce a sixth possibility (vaccines with 5-year efficacy plus one booster 5 years later) because it is barely the same situation than for a 10-year efficacy vaccine.

Similarly, the same assumptions as above have been made for all scenarios:

- Only girls would be vaccinated.
- Universal vaccination program.
- An expected vaccination coverage rate of 85%.

In all the scenarios including a catch-up, it has been assumed that it would be done in the first year of the implementation of the vaccination program. Although longer catch-up periods (three years, for example) could have been assumed, they would have little influence on the results.

As previously mentioned, the infection rates described below include only females and are only referred to HPV types 16 and 18.

Scenario 6: No catch-up, estimated situation in 30 years.

A 5-year vaccine with no booster would maintain the infection rate below 1% up to age 25 and below 1.3% up to age 40. All other options would result in a rate below 1% up to age 40. In all cases, the rates would be as if not vaccinated afterwards, For a lifelong efficacy vaccine, the rates would remain under 0.2% up to age 40 (Figure 15 and Table 12).

Figure 15. Estimated HPV infection rate by age, Switzerland. Scenario at 30 years without catch-up.

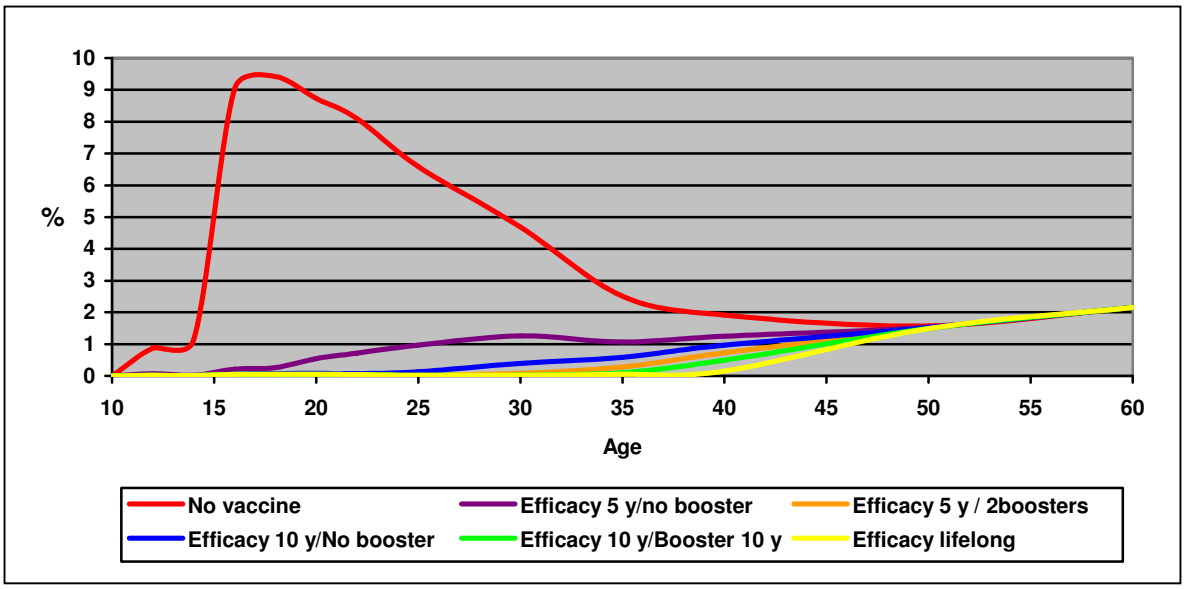


Table 12. Infection rate by age and type of vaccination. Scenario at 30 years without catch-up (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.07	0.02	0.21	0.26	0.54	0.71	0.97	1.26	1.07	1.25	1.54	2.15
Efficacy 5 y/2 boosters	0.02	0.01	0.05	0.06	0.05	0.04	0.03	0.08	0.28	0.72	1.5	2.15
Efficacy 10 y/No booster	0.02	0.01	0.06	0.07	0.08	0.07	0.13	0.39	0.58	0.97	1.52	2.15
Efficacy 10 y/Booster 10 y	0.02	0.01	0.05	0.05	0.05	0.04	0.02	0.02	0.1	0.49	1.49	2.15
Efficacy lifelong	0.02	0.01	0.05	0.05	0.05	0.04	0.02	0.02	0.05	0.15	1.49	2.15

Scenario 7: Catch-up to age 18, estimated situation in 30 years.

With a catch-up to age 18, and with the exception of a 5-year vaccine with no booster at age 40 (1.08%), the rate would always be maintained below 1% up to age 40 for any other type of vaccination (Figure 16 and Table 13).

Figure 16. Estimated HPV infection rate by age, Switzerland. Scenario at 30 years with catch-up to age 18.

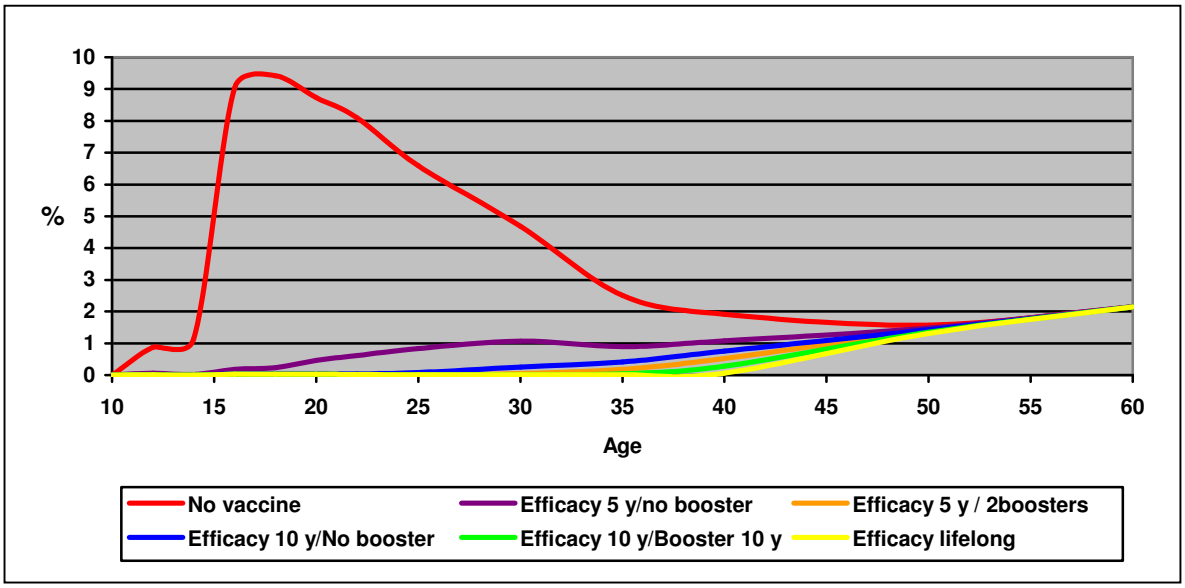


Table 13. Infection rate by age and type of vaccination. Scenario at 30 years with catch-up to age 18 (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.06	0.02	0.18	0.23	0.46	0.61	0.83	1.07	0.9	1.08	1.48	2.15
Efficacy 5 y/2 boosters	0.01	0	0.03	0.03	0.03	0.02	0.02	0.05	0.18	0.52	1.4	2.14
Efficacy 10 y/No booster	0.01	0	0.04	0.05	0.05	0.04	0.08	0.25	0.41	0.75	1.43	2.14
Efficacy 10 y/Booster 10 y	0.01	0	0.03	0.03	0.03	0.02	0.01	0.01	0.04	0.28	1.35	2.14
Efficacy lifelong	0.01	0	0.03	0.03	0.03	0.02	0.01	0.01	0.01	0.06	1.31	2.14

Scenario 8: Catch-up to age 20, estimated situation in 30 years.

With the exceptions of age 30 (1.02%) and 40 (1.03%), a 5-year efficacy vaccine would result in a rate under 1%, like in all the other options up to age 40 (Figure 17 and Table 14).

Figure 17. Estimated HPV infection rate by age, Switzerland. Scenario at 30 years with catch-up to age 20.

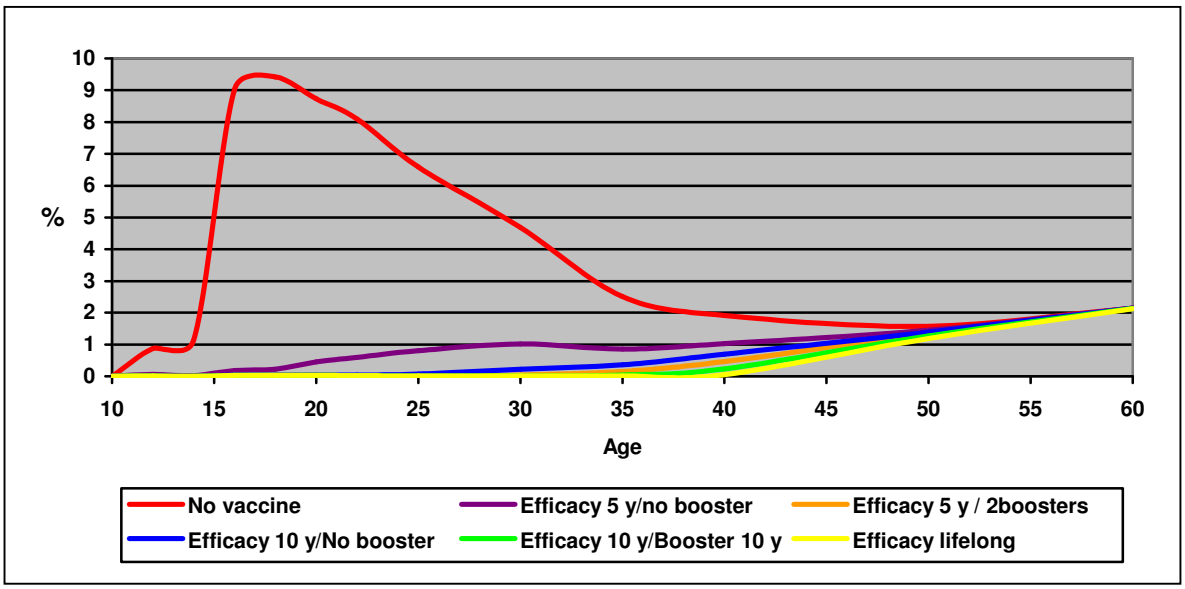


Table 14. Infection rate by age and type of vaccination. Scenario at 30 years with catch-up to age 20 (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.06	0.02	0.18	0.22	0.45	0.59	0.8	1.02	0.86	1.03	1.45	2.14
Efficacy 5 y/2 boosters	0.01	0	0.02	0.03	0.03	0.02	0.01	0.04	0.15	0.46	1.34	2.13
Efficacy 10 y/No booster	0.01	0	0.04	0.04	0.04	0.04	0.07	0.22	0.36	0.69	1.39	2.14
Efficacy 10 y/Booster 10 y	0.01	0	0.03	0.03	0.03	0.02	0.01	0.01	0.04	0.23	1.27	2.13
Efficacy lifelong	0.01	0	0.03	0.03	0.03	0.02	0.01	0.01	0.01	0.05	1.19	2.12

Scenario 9: Catch-up to age 22, estimated situation in 30 years.

In all cases, an infection rate below 1% up to age 40 would be expected. This low rate would even be maintained up to age 50 in the case of a 10-year efficacy vaccine with a booster 10 years later or a lifelong efficacy vaccine. In the other cases, the rate would be below 1.4% at age 50 (Figure 18 and Table 15).

Figure 18. Estimated HPV infection rate by age, Switzerland. Scenario at 30 years with catch-up to age 22.

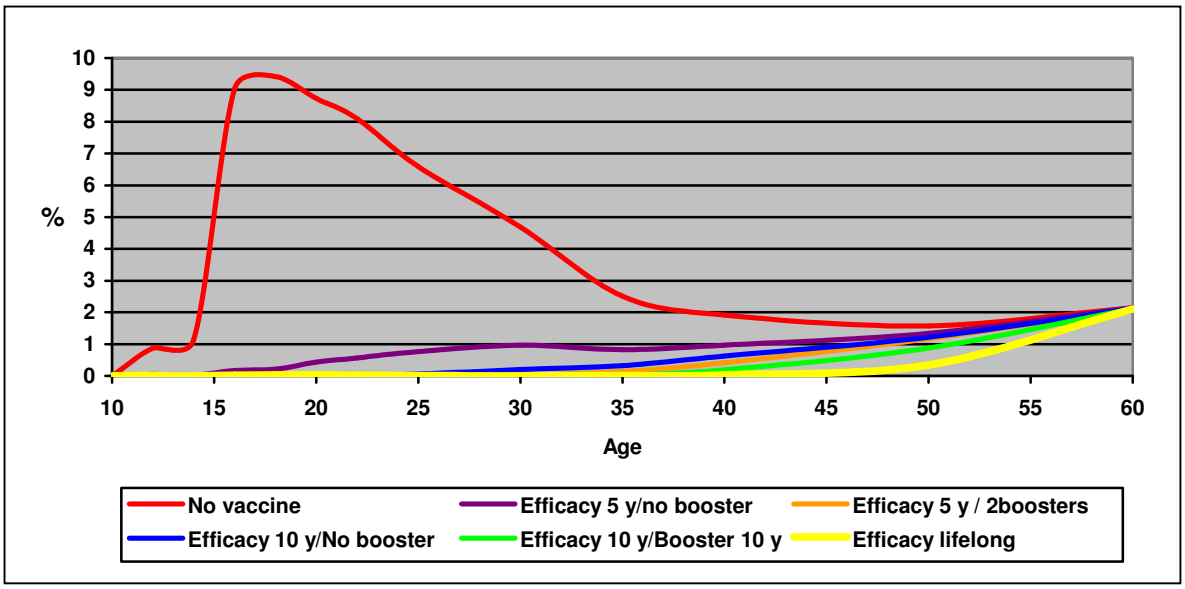


Table 15. Infection rate by age and type of vaccination. Scenario at 30 years with catch-up to age 22 (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.05	0.02	0.17	0.21	0.43	0.56	0.76	0.97	0.82	0.97	1.34	2.14
Efficacy 5 y/2 boosters	0.01	0	0.02	0.03	0.02	0.02	0.01	0.03	0.14	0.41	1.17	2.12
Efficacy 10 y/No booster	0.01	0	0.03	0.04	0.04	0.03	0.06	0.2	0.32	0.62	1.22	2.13
Efficacy 10 y/Booster 10 y	0.01	0	0.02	0.03	0.03	0.02	0.01	0.01	0.03	0.19	0.88	2.11
Efficacy lifelong	0.01	0	0.02	0.03	0.03	0.02	0.01	0	0.01	0.03	0.34	2.1

Scenario 10: Catch-up to age 25, estimated situation in 30 years.

A lifelong efficacy vaccine or a 10-year vaccine with a booster would maintain the infection rate below 1% up to age 50. In all the other options, the rate would be under 1% up to age 40 and slightly over 1% at age 50 (Figure 19 and Table 16).

Figure 19. Estimated HPV infection rate by age, Switzerland. Scenario at 30 years with catch-up to age 25.

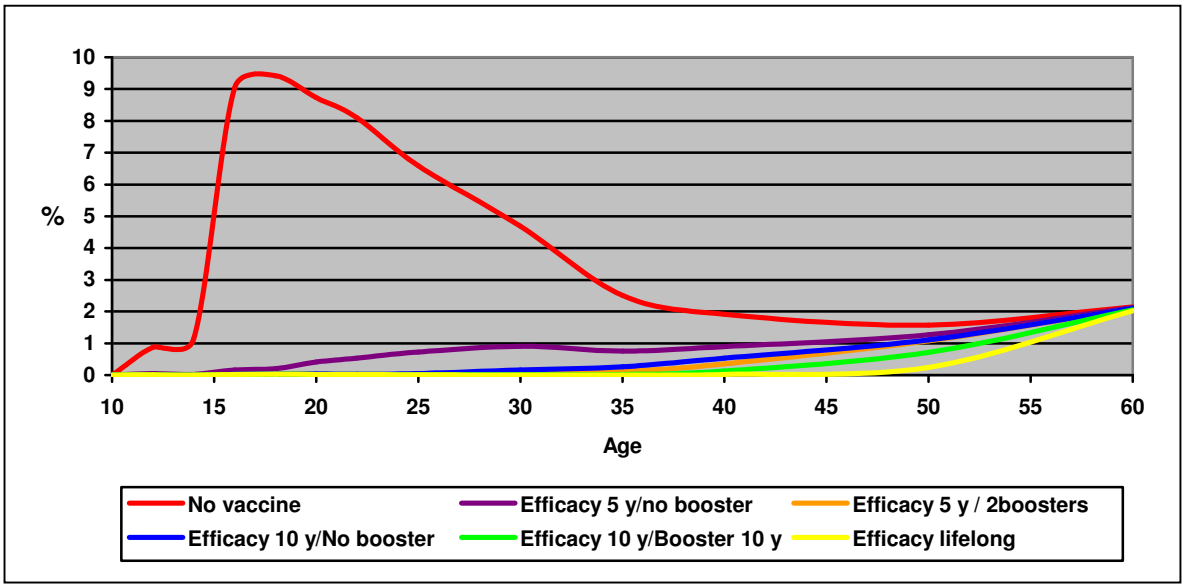


Table 16. Infection rate by age and type of vaccination. Scenario at 30 years with catch-up to age 25 (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No vaccine	0.88	1.14	9.03	9.42	8.73	8.1	6.59	4.69	2.52	1.91	1.57	2.14
Efficacy 5 y/No booster	0.05	0.02	0.16	0.2	0.41	0.53	0.72	0.91	0.75	0.9	1.27	2.12
Efficacy 5 y/2 boosters	0.01	0	0.02	0.02	0.02	0.02	0.01	0.03	0.11	0.35	1.08	2.09
Efficacy 10 y/No booster	0.01	0	0.03	0.04	0.04	0.03	0.05	0.16	0.26	0.53	1.11	2.10
Efficacy 10 y/Booster 10 y	0.01	0	0.02	0.03	0.02	0.02	0.01	0.01	0.02	0.13	0.71	2.05
Efficacy lifelong	0.01	0	0.02	0.03	0.02	0.02	0.01	0	0	0.02	0.24	2.02

Estimated situation in 15 years: vaccination coverage

Scenarios 11 to 15 define what would be the theoretical situation fifteen years after the initiation of the vaccination program from the point of view of the vaccination coverage.

Each scenario represents a different vaccination option and is described for the different catch-up possibilities (none and up to 18, 20, 22 and 25 years).

In all the possibilities including a catch-up, it has been assumed that it would be done in the first year of the implementation of the vaccination program. Although longer catch-up periods (three years, for example) could have been assumed, they would have little influence on the results.

The same assumptions that have been used all through the report have also been made for all scenarios:

- Only girls would be vaccinated.
- Universal vaccination program.
- An expected vaccination coverage rate of 85%.

Scenario 11: 5-year efficacy vaccine without booster. Estimated situation in 15 years.

In the case of a 5-year efficacy vaccine without booster, whatever there is a catch-up or not, the maximum vaccination coverage (85%) would be maintained up to age 17. Afterwards it would slowly diminish to reach 50% of the females aged 22. Without a catch-up, there would be no coverage at all for those aged 30 years or older. With a catch-up to ages 18 or 20, no coverage would be observed from age 35 onwards, and with a catch-up to ages 22 or 25, the vaccination coverage would be inexistent for those aged 40 or more (Figure 20 and Table 17).

Figure 20. Estimated vaccination coverage by age, Switzerland. Scenario at 15 years for a 5-year efficacy vaccine without booster.

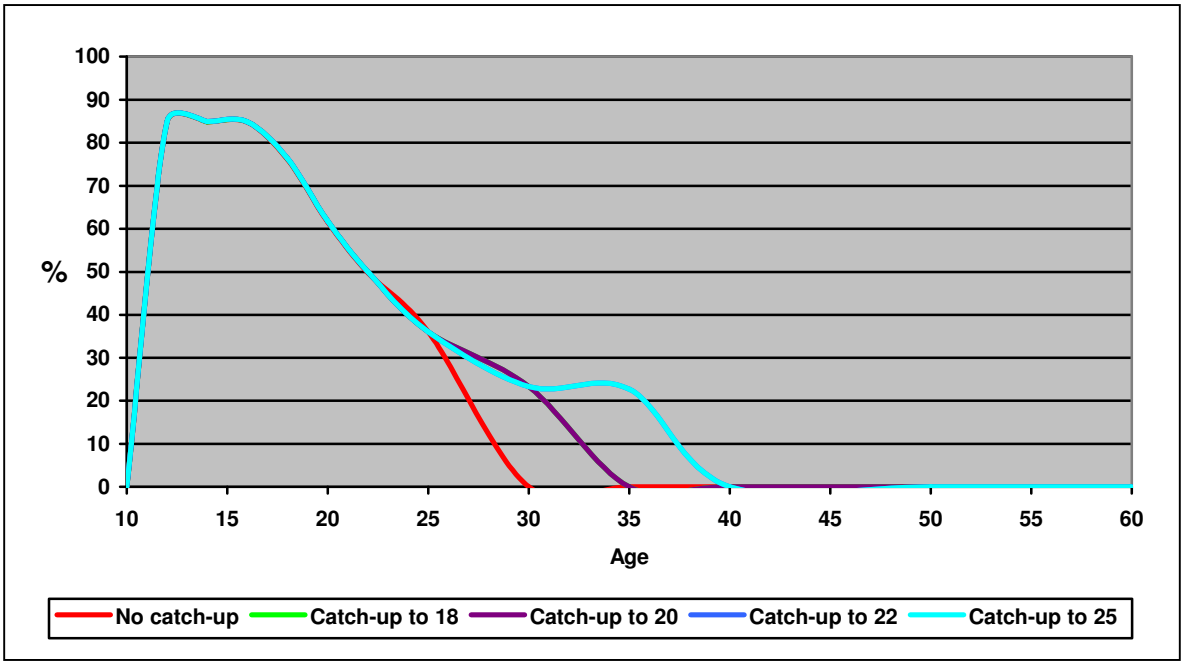


Table 17. Vaccination coverage using a 5-year efficacy vaccine without booster by age. Scenario at 15 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	84.8	84.8	84.7	76.2	61.6	49.8	36.1	0.0	0.0	0.0	0.0	0.0
Catch-up to age 18	84.9	84.9	84.8	76.3	61.8	49.9	36.1	23.3	0.0	0.0	0.0	0.0
Catch-up to age 20	84.9	84.9	84.8	76.3	61.8	49.9	36.1	23.3	0.0	0.0	0.0	0.0
Catch-up to age 22	84.9	84.9	84.9	76.3	61.8	50.0	36.1	23.3	22.7	0.0	0.0	0.0
Catch-up to age 25	84.9	84.9	84.9	76.3	61.8	50.0	36.1	23.3	22.7	0.0	0.0	0.0

Scenario 12: 5-year efficacy vaccine with 2 boosters. Estimated situation in 15 years.

A 5-year vaccine with 2 boosters (at ages 17 and 22) would maintain the maximum expected vaccination coverage up to age 25 in all cases. Without catch-up, no coverage would be observed at age 30 and up. Any catch-up would still give a 50% coverage of those aged 30. Only a catch-up at ages 22 or 25 would allow some coverage (38.4%) at age 35 (Figure 21 and Table 18).

Figure 21. Estimated vaccination coverage by age, Switzerland. Scenario at 15 years for a 5-year efficacy vaccine with 2 boosters.

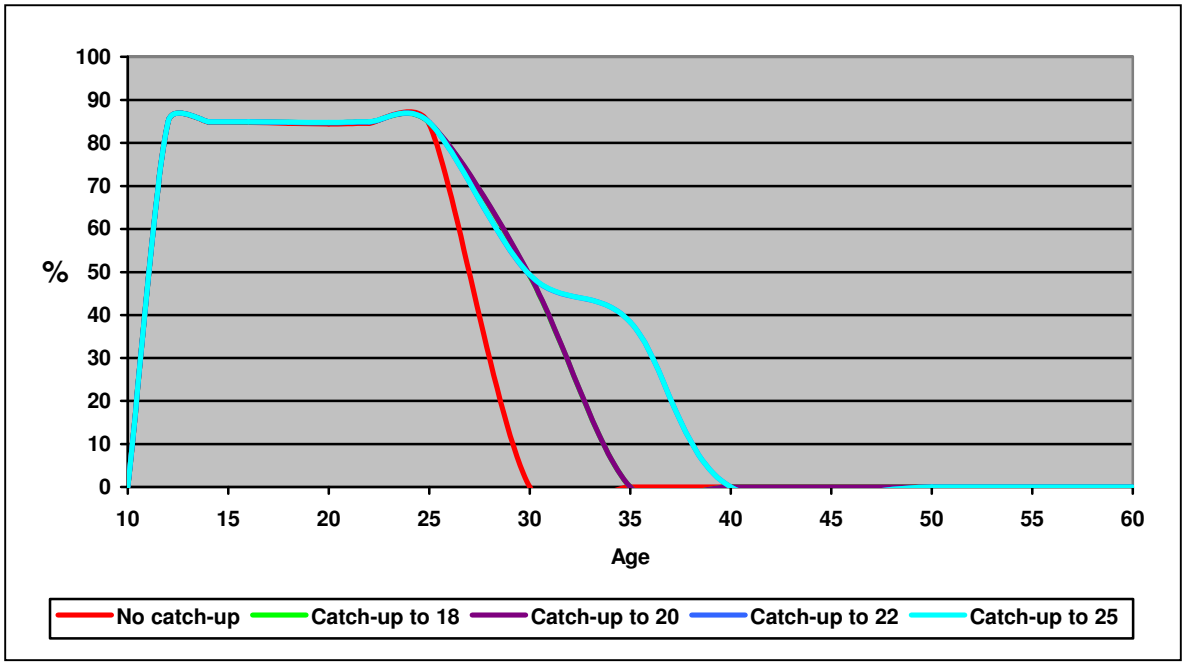


Table 18. Vaccination coverage using a 5-year efficacy vaccine with 2 boosters by age. Scenario at 15 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	84.9	84.8	84.7	84.5	84.4	84.6	84.3	0.0	0.0	0.0	0.0	0.0
Catch-up to age 18	84.9	84.9	84.9	84.8	84.7	84.8	84.7	49.1	0.0	0.0	0.0	0.0
Catch-up to age 20	84.9	84.9	84.9	84.8	84.7	84.8	84.7	49.2	0.0	0.0	0.0	0.0
Catch-up to age 22	84.9	84.9	84.9	84.8	84.7	84.9	84.8	49.3	38.4	0.0	0.0	0.0
Catch-up to age 25	84.9	84.9	84.9	84.8	84.7	84.9	84.8	49.4	38.4	0.0	0.0	0.0

Scenario 13: 10-year efficacy vaccine without booster. Estimated situation in 15 years.

A vaccine with an efficacy of 10 years not including a booster would maintain the maximum coverage up to age 22 years no matter whether a catch-up or not was incorporated. With a catch-up at age 18 or 20, a 39% coverage would still be observed at age 30, and with a catch-up up to age 22 or 25, 38% of women aged 35 would still be protected (Figure 22 and Table 19).

Figure 22. Estimated vaccination coverage by age, Switzerland. Scenario at 15 years for a 10-year efficacy vaccine without booster.

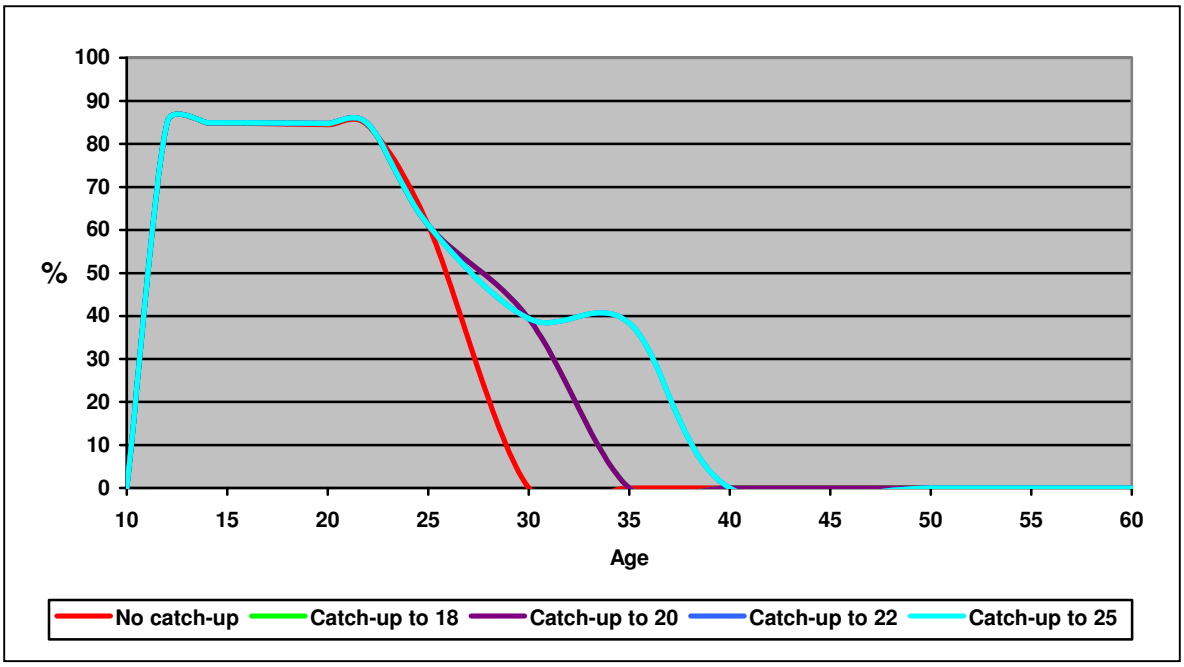


Table 19. Vaccination coverage using a 10-year efficacy vaccine without booster by age. Scenario at 15 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	84.9	84.8	84.7	84.6	84.5	84.3	61.1	0.0	0.0	0.0	0.0	0.0
Catch-up to age 18	84.9	84.9	84.9	84.8	84.7	84.6	61.1	39.4	0.0	0.0	0.0	0.0
Catch-up to age 20	84.9	84.9	84.9	84.8	84.7	84.6	61.1	39.4	0.0	0.0	0.0	0.0
Catch-up to age 22	84.9	84.9	84.9	84.8	84.7	84.6	61.1	39.4	38.4	0.0	0.0	0.0
Catch-up to age 25	84.9	84.9	84.9	84.8	84.7	84.6	61.1	39.4	38.4	0.0	0.0	0.0

Scenario 14: 10-year efficacy vaccine with booster. Estimated situation in 15 years.

By adding a booster 10 years later to a 10-year efficacy vaccine, a vaccination coverage of 85% would be maintained up to age 25. With any catch-up, two thirds of women aged 30 would still be covered, and with a catch-up to ages 22 or 25, 65% of those aged 35 would still be under the influence of the vaccine (Figure 23 and Table 20).

Figure 23. Estimated vaccination coverage by age, Switzerland. Scenario at 15 years for a 10-year efficacy vaccine with booster.

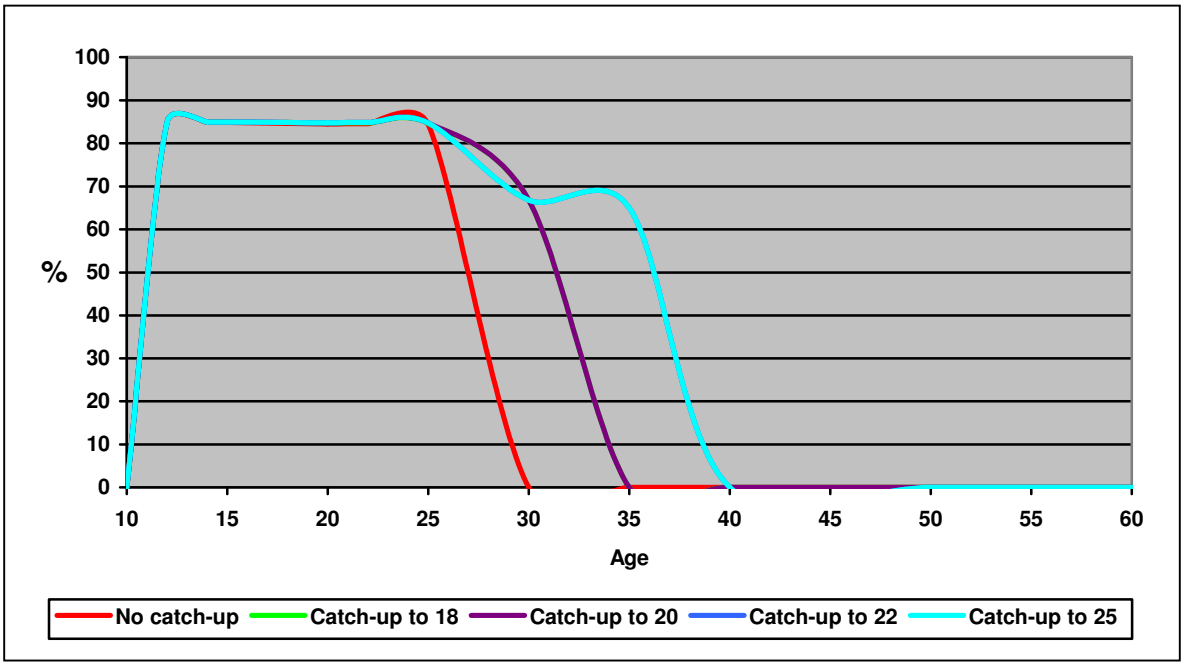


Table 20. Vaccination coverage using a 10-year efficacy vaccine with booster by age. Scenario at 15 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	84.9	84.8	84.7	84.6	84.5	84.5	84.3	0.0	0.0	0.0	0.0	0.0
Catch-up to age 18	84.9	84.9	84.9	84.8	84.7	84.8	84.6	66.7	0.0	0.0	0.0	0.0
Catch-up to age 20	84.9	84.9	84.9	84.8	84.7	84.8	84.6	66.7	0.0	0.0	0.0	0.0
Catch-up to age 22	84.9	84.9	84.9	84.8	84.7	84.8	84.7	66.7	65.0	0.0	0.0	0.0
Catch-up to age 25	84.9	84.9	84.9	84.8	84.7	84.8	84.7	66.7	65.0	0.0	0.0	0.0

Scenario 15: lifelong efficacy vaccine. Estimated situation in 15 years.

In the case of a vaccine with lifelong efficacy, 15 years after the implementation of the program the maximum coverage would be accomplished up to age 25. With any catch-up, at age 30 still three out of every four women would be covered. A catch-up to age 22 or 25 would still maintain a 72% coverage at age 35 (Figure 24 and Table 21).

Figure 24. Estimated vaccination coverage by age, Switzerland. Scenario at 15 years for a lifelong efficacy vaccine.

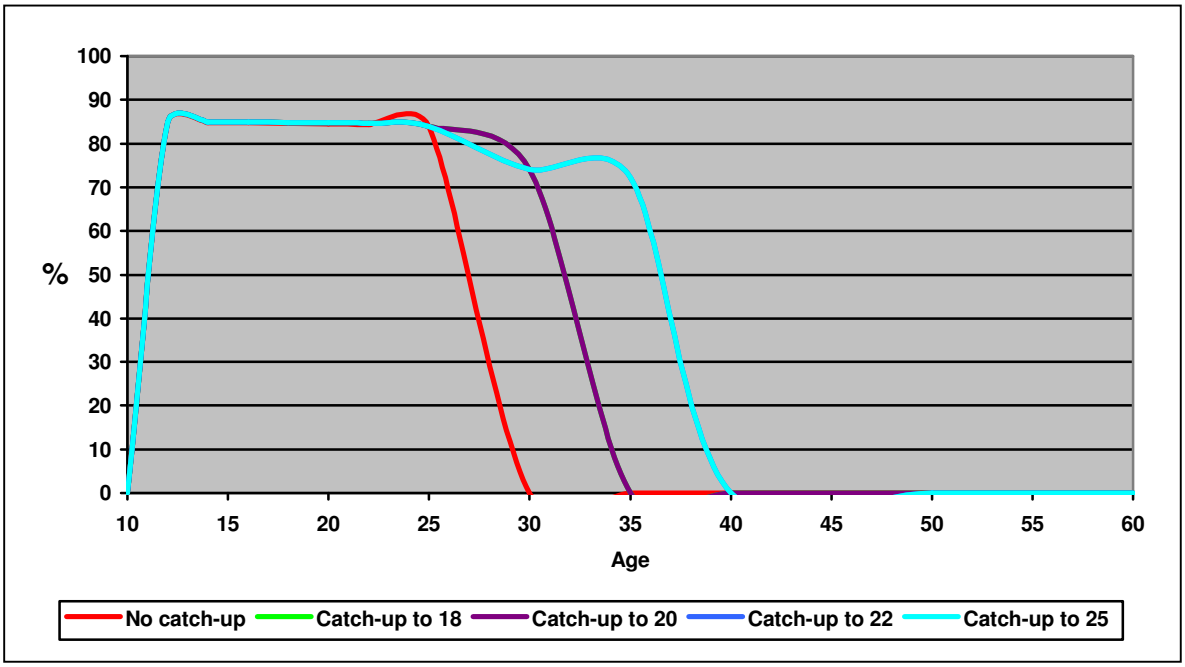


Table 21. Vaccination coverage using a lifelong efficacy vaccine by age. Scenario at 15 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	84.9	84.8	84.7	84.6	84.5	84.3	83.8	0.0	0.0	0.0	0.0	0.0
Catch-up to age 18	84.9	84.9	84.9	84.8	84.7	84.6	83.8	74.2	0.0	0.0	0.0	0.0
Catch-up to age 20	84.9	84.9	84.9	84.8	84.7	84.6	83.8	74.2	0.0	0.0	0.0	0.0
Catch-up to age 22	84.9	84.9	84.9	84.8	84.7	84.6	83.8	74.2	72.2	0.0	0.0	0.0
Catch-up to age 25	84.9	84.9	84.9	84.8	84.7	84.6	83.8	74.2	72.2	0.0	0.0	0.0

Estimated situation in 30 years: vaccination coverage

Scenarios 16 to 20 define what would be the theoretical situation thirty years after the initiation of the vaccination program from the point of view of the vaccination coverage.

Each scenario represents a different vaccination option and is described for the different catch-up possibilities (none and up to 18, 20, 22 and 25 years).

In all the possibilities including a catch-up, it has been assumed that it would be done in the first year of the implementation of the vaccination program. Although longer catch-up periods (three years, for example) could have been assumed, they would have little influence on the results.

The same assumptions that have been used all through the report have also been made for all scenarios:

- Only girls would be vaccinated.
- Universal vaccination program.
- An expected vaccination coverage rate of 85%.

Scenario 16: 5-year efficacy vaccine without booster. Estimated situation in 30 years.

In a 30 year perspective, a vaccine with an efficacy of 5 years without booster would maintain the maximum expected coverage of 85% up to age 17. By age 22, a 50% coverage would still be sustained. Only 7% of those aged 40 would still be covered whatever the case. With a catch-up to age 22 or 25, a 5% coverage could be observed at age 50 (Figure 25 and Table 22).

Figure 25. Estimated vaccination coverage by age, Switzerland. Scenario at 30 years for a 5-year efficacy vaccine without booster.

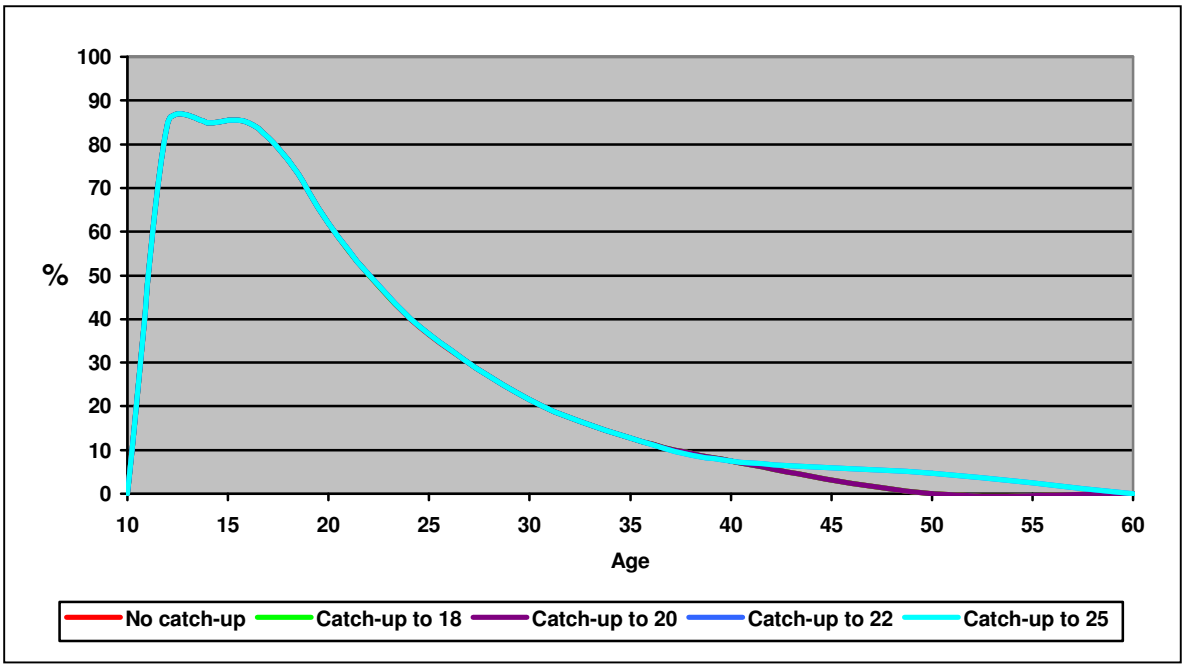


Table 22. Vaccination coverage using a 5-year efficacy vaccine without booster by age. Scenario at 30 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	84.9	84.9	84.9	76.4	61.9	50.1	36.5	21.5	12.7	7.4	0.0	0.0
Catch-up to age 18	85.0	84.9	84.9	76.4	61.9	50.1	36.5	21.6	12.7	7.4	0.0	0.0
Catch-up to age 20	85.0	84.9	84.9	76.4	61.9	50.1	36.6	21.6	12.7	7.4	0.0	0.0
Catch-up to age 22	85.0	85.0	84.9	76.4	61.9	50.1	36.6	21.6	12.7	7.4	4.7	0.0
Catch-up to age 25	85.0	85.0	84.9	76.5	61.9	50.2	36.6	21.6	12.7	7.4	4.7	0.0

Scenario 17: 5-year efficacy vaccine with 2 boosters. Estimated situation in 30 years.

A 5-year efficacy vaccine including 2 boosters would maintain the maximum expected coverage up to age 25. At age 30, 62% of the women would still be protected and rate would drop to 21.4% at aged 40. With a catch-up to age 22 or 25, 8% of women aged 50 would still be protected (Figure 26 and Table 23).

Figure 26. Estimated vaccination coverage by age, Switzerland. Scenario at 30 years for a 5-year efficacy vaccine with 2 boosters.

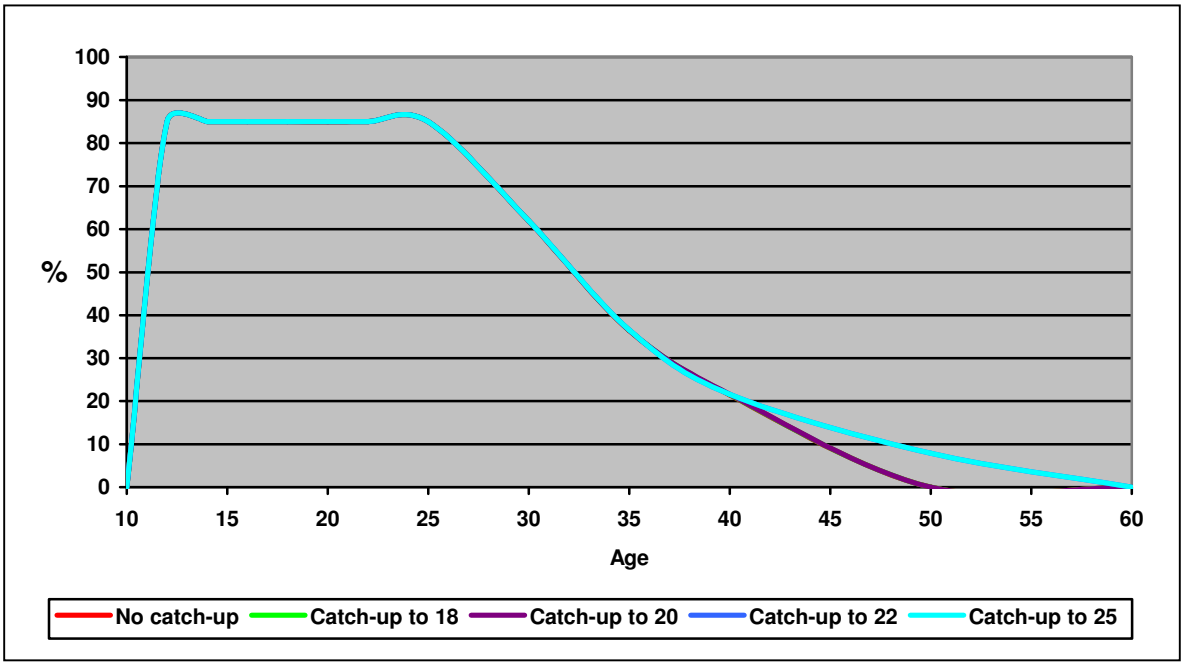


Table 23. Vaccination coverage using a 5-year efficacy vaccine with 2 boosters by age. Scenario at 30 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	85.0	85.0	85.0	84.9	84.9	85.0	84.9	61.9	36.5	21.4	0.0	0.0
Catch-up to age 18	85.0	85.0	85.0	85.0	85.0	85.0	85.0	61.9	36.5	21.5	0.0	0.0
Catch-up to age 20	85.0	85.0	85.0	85.0	85.0	85.0	85.0	61.9	36.5	21.5	0.0	0.0
Catch-up to age 22	85.0	85.0	85.0	85.0	85.0	85.0	85.0	61.9	36.5	21.5	7.9	0.0
Catch-up to age 25	85.0	85.0	85.0	85.0	85.0	85.0	85.0	61.9	36.5	21.6	7.9	0.0

Scenario 18: 10-year efficacy vaccine without booster. Estimated situation in 30 years.

In the case of a vaccine with an efficacy of 10 years without booster, the maximum coverage would be sustained until age 22 and would still be of 62% at age 25. No catch-up or a catch-up to ages 18 or 20 would reach a 13% coverage at age 40. A catch-up to age 22 or 25 would still maintain an 8% at age 50 (Figure 27 and Table 24).

Figure 27. Estimated vaccination coverage by age, Switzerland. Scenario at 30 years for a 10-year efficacy vaccine without booster.

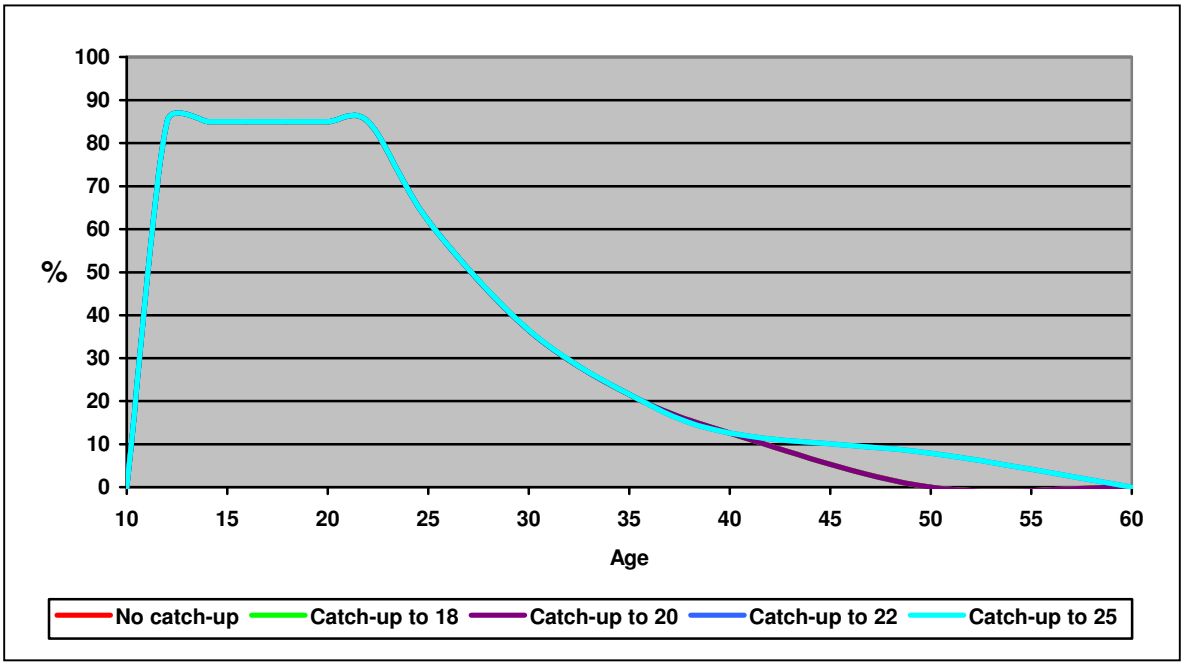


Table 24. Vaccination coverage using a 10-year efficacy vaccine without booster by age. Scenario at 30 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	84.98	84.98	84.97	84.96	84.95	84.94	61.90	36.50	21.48	12.58	0.00	0.00
Catch-up to age 18	84.99	84.99	84.98	84.98	84.97	84.96	61.92	36.54	21.53	12.58	0.00	0.00
Catch-up to age 20	84.99	84.99	84.98	84.98	84.97	84.96	61.93	36.54	21.54	12.58	0.00	0.00
Catch-up to age 22	84.99	84.99	84.98	84.98	84.97	84.97	61.93	36.54	21.54	12.58	7.90	0.00
Catch-up to age 25	84.99	84.99	84.99	84.98	84.98	84.97	61.93	36.55	21.54	12.58	7.90	0.00

Scenario 19: 10-year efficacy vaccine with booster. Estimated situation in 30 years.

In all cases, a 10-year efficacy vaccine with booster would maintain the maximum coverage of 85% up to age 30 years and a 36% coverage at age 40. A catch-up to age 22 or 25 would still keep a 23% coverage at age 50 (Figure 28 and Table 25).

Figure 28. Estimated vaccination coverage by age, Switzerland. Scenario at 30 years for a 10-year efficacy vaccine with booster.

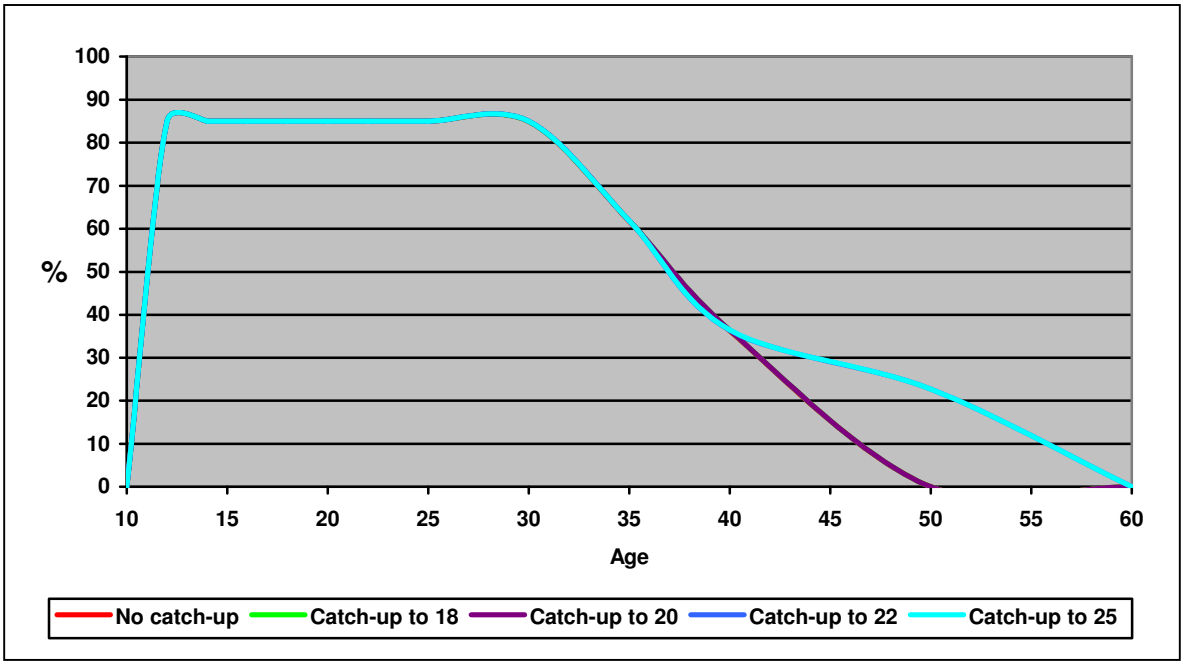


Table 25. Vaccination coverage using a 10-year efficacy vaccine with booster by age. Scenario at 30 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	84.99	84.98	84.97	84.97	84.96	84.97	84.95	84.89	61.74	36.28	0.00	0.00
Catch-up to age 18	84.99	84.99	84.99	84.98	84.97	84.98	84.97	84.94	61.86	36.42	0.00	0.00
Catch-up to age 20	84.99	84.99	84.99	84.98	84.98	84.98	84.98	84.95	61.87	36.44	0.00	0.00
Catch-up to age 22	84.99	84.99	84.99	84.98	84.98	84.98	84.98	84.95	61.88	36.46	22.65	0.00
Catch-up to age 25	84.99	84.99	84.99	84.98	84.98	84.99	84.98	84.95	61.89	36.47	22.65	0.00

Scenario 20: lifelong efficacy vaccine. Estimated situation in 30 years.

After 30 years, a vaccine with lifelong efficacy would result in a 85% coverage up to age 40. A catch-up to age 22 or 25 would maintain a 72% coverage up to age 50 (Figure 29 and Table 26).

Figure 29. Estimated vaccination coverage by age, Switzerland. Scenario at 30 years for a lifelong efficacy vaccine.

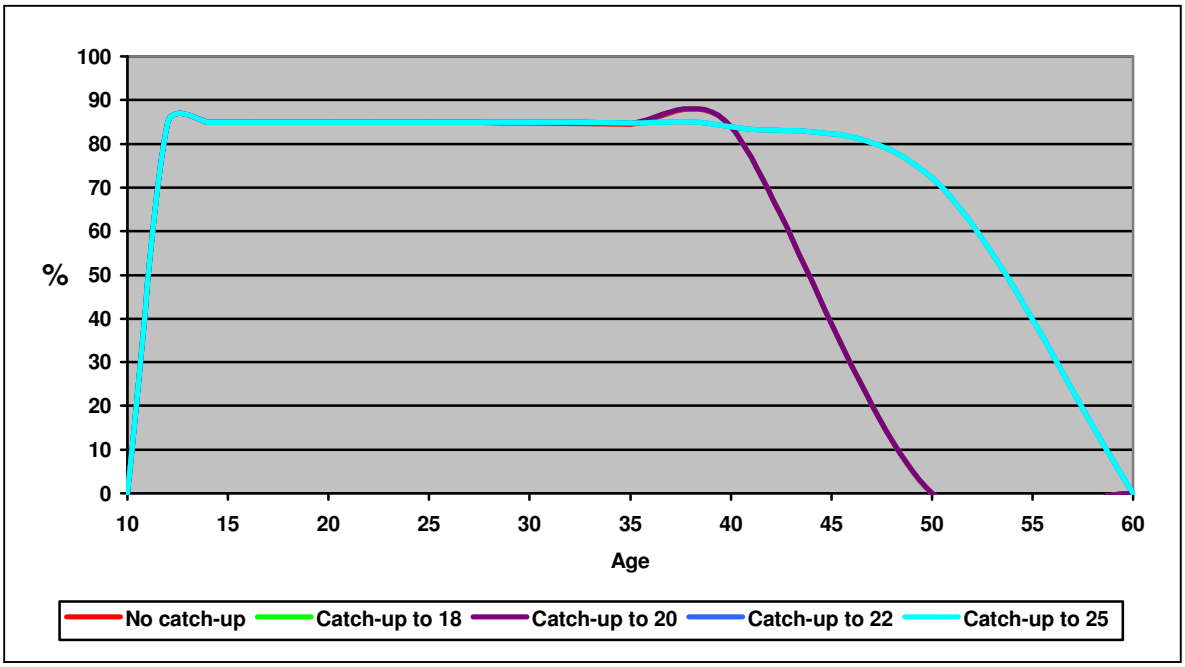


Table 26. Vaccination coverage using a lifelong efficacy vaccine by age. Scenario at 30 years (in percentage).

Age (years)	12	14	16	18	20	22	25	30	35	40	50	60
No catch-up	85.0	85.0	85.0	85.0	85.0	84.9	84.9	84.8	84.5	83.8	0.0	0.0
Catch-up to age 18	85.0	85.0	85.0	85.0	85.0	85.0	84.9	84.9	84.7	83.8	0.0	0.0
Catch-up to age 20	85.0	85.0	85.0	85.0	85.0	85.0	84.9	84.9	84.7	83.8	0.0	0.0
Catch-up to age 22	85.0	85.0	85.0	85.0	85.0	85.0	85.0	84.9	84.7	83.8	72.2	0.0
Catch-up to age 25	85.0	85.0	85.0	85.0	85.0	85.0	85.0	84.9	84.7	83.8	72.2	0.0

LIMITATIONS OF THE STUDY

One limitation of this study is the scarcity of data concerning HPV infection in Switzerland. In fact, the only prevalence we have found is among a small (N=143) clinical sample of adolescents in Geneva (11). As a result, to construct our model we have been forced to rely on data from other countries, mainly the United States. Nevertheless, this fact should not influence much our results.

A more important limitation is the fact that there are not a lot of data regarding the sexual behavior of Swiss. As an example, the only data that we have found for the number of sexual partners (33) include quite wide age ranges (17-20, 21-30, 31-45). We had then to divide the whole modelled period into only 8 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.

CONCLUSIONS

Regarding the results of this report, the specific conclusions are:

7. Overall, and both from the reduction of the infection rate and the vaccination coverage rate points of view, any catch-up is better than no catch-up at all. However, our model indicates that a catch-up to age 18 or to age 20 would represent a very small difference. The same would be true between a catch-up to age 22 or to age 25, 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.
8. In the case of a 5-year efficacy vaccine (which is the current case as far as we know) without booster, the maximum expected vaccination coverage of 85% would only be maintained up to age 16/17, both in a 15 or 30-year horizon and independently of whether there is a catch-up or not. Under the same circumstances, half of the women aged 22 would still be protected. In a 15-year perspective, some coverage (23%) would still be expected among women aged 30 with a catch-up to age 18/20, while with a catch-up to age 22/25 the same coverage would be observed up to age 35. In a 30-year perspective, the same coverage rate would be observed up to age 40 (7%) independently of catch-up. In the case of a catch-up to age 22/25, the coverage would be extended to age 50, although it would be minimal (<5%).
9. In the case of a 5-year efficacy vaccine including 2 boosters (at ages 17 and 22), a 85% vaccination coverage would be assured, in any case, up to age 25. For a 15-year horizon, any catch-up would still maintain a 50% protection among women aged 30. A catch-up to age 22/25 would still maintain a protection slightly below 40% among women aged 35. In 30 years, this vaccination option would still maintain protection rates of 62%, 36% and 21% at, respectively, ages 30,35 and 40 years independently of catch-up. A catch-up to age 22/25 would still maintain some coverage (8%) at age 50.
10. In the case of a 10-year efficacy vaccine without booster (that could be overlapped to a 5-year efficacy vaccine with one booster at age 17), the maximum expected coverage would be maintained up to age 22 and would still be slightly above 60% at age 25 in any case. For a 15-year horizon, any catch-up would imply a coverage just under 40% at age 30 and also at age 35 but in this later case only for those with a catch-up to age 22/25. In 30 years, independently of catch-up, a vaccine coverage of 36, 21 and 12%, respectively, would be expected for ages 30, 35 and 40. A catch-up to ages 22/25 would only add a small coverage (8%) at age 50.
11. In the case of a 10-year efficacy vaccine that would include a booster 10 years later (age 22), the situation is different depending on the chosen horizon. In 15 years, maximum coverage up to age 25 would be assured in any case. Any catch-up would result in a 67% coverage at age 30, while a catch-up to ages 22/25 would imply a 65% coverage at age 35. In a 30 years perspective, the maximum projected coverage would be maintained up to age 30. Any option would result in a 62% coverage at age 35 and 36% at age 40. With a catch-up to ages 22/25, 23% of the women aged 50 would still be protected.
12. In the case of a lifelong efficacy vaccine, in 15-years time the projected maximum coverage would reach age 25. Any catch-up would still protect 74% of women aged 30 and a catch-up to ages 22/25 would result in a 72% coverage at age 35. In 30 years, any vaccination option would result in a maximum expected coverage up to age 40, while a catch-up to ages 22/25 would add a 72% coverage at age 50.

RECOMMENDATIONS

At the present time it is difficult to give clear recommendations about the best vaccination program option because we lack information on one of the main factors influencing this decision: the duration of the vaccine efficacy. To date, there is only evidence of a 5 year efficacy (1;2).

From this standpoint, the current recommendation would be to implement a vaccination program among girls aged 12 years with a catch-up to age 22 years, since a longer catch-up time (up to age 25) would mean an extremely small difference.

However, this recommendation should be reviewed in five years. At that point in time, we will be facing two possible situations:

3. There will be evidence of a longer duration of the vaccine's efficacy (up to 10 years) and no changes in the vaccination program would be needed.
4. There will be no evidence of an efficacy duration beyond 5 years and a decision regarding booster implementation will need to be taken.

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