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The differential risk of cervical cancer in HPV vaccinated and unvaccinated women: a mathematical modelling study

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Abstract

Background: With increased uptake of vaccination against HPV, protection against cervical cancer will also increase for unvaccinated women, due to herd immunity. Still, the differential risk between vaccinated and unvaccinated women might warrant a vaccination-status screening approach. To understand the potential value of stratified screening protocols, we estimated the risk differentials in HPV and cervical cancer between vaccinated and unvaccinated women.

Methods: We used STDSIM, an individual-based model of HPV transmission and control, to estimate the HPV prevalence reduction over time, after introduction of HPV vaccination. We simulated scenarios of bivalent or nonavalent vaccination in females-only or females and males, at 20% coverage increments. We estimated relative HPV type-specific prevalence reduction compared to a no-vaccination counterfactual and then estimated the age-specific cervical cancer risk by vaccination status.

Results: The relative cervical cancer risk for unvaccinated compared to vaccinated women ranged from 1.7 (bivalent vaccine for females and males; 80% coverage) to 10.8 (nonavalent vaccine for females-only; 20% coverage). Under 60% vaccination coverage, which is a representative coverage for several western countries, including the United States, the relative risk varies between 2.2 (bivalent vaccine for females and males) and 9.2 (nonavalent vaccine for females).

Conclusions: We found large cervical cancer risk differences between vaccinated and unvaccinated women. In general, our model shows that the relative risk is higher in lower vaccine coverages, using the nonavalent vaccine, and when vaccinating females only.

Impact: To avoid a disbalance in harms and benefits between vaccinated and unvaccinated women, vaccination-based screening needs serious consideration.

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Introduction

Personalized cancer screening is becoming an increasingly popular approach to improve harm-benefit and cost-benefit ratios.^{1,2} By selectively screening only those at higher risk, the per-screen detection rate improves, while potential harms such as false-positivity rates or over-screening are reduced. For cervical cancer, screening has been common practice in most high-income countries for decades, and it has been effective in reducing the burden of the disease substantially.³ Current cervical cancer screening guidelines in the United States and elsewhere, however, do not differentiate their recommendation based on the individual risk of developing the disease other than based on age, earlier screening test, and follow up results.⁴

Since the early 2000s, human papillomavirus (HPV) vaccination to prevent cervical cancer has been implemented in about 80 countries worldwide,⁵ either for pre-adolescent females only, or for both males and females.^{6–11} Coverage levels range between 1% and 80% worldwide,¹² with the United States reaching about 60% of those being eligible, although it differs substantially across the country.² The bivalent (2vHPV), quadrivalent (4vHPV) and nonavalent (9vHPV) vaccines are currently licensed in the United States, and they protect against HPV16/18, HPV16/18/6/11 and HPV16/18/6/11/31/33/45/52/58 types respectively.^{6,13,14}

Currently, the first vaccinated women are ageing into cervical cancer screening ages, resulting in a growing mixed population of vaccinated and unvaccinated women being eligible for screening. As full herd immunity will likely only occur at very high coverage levels for HPV vaccination,¹⁵ screening programs will be faced with a heterogeneous population with regard to the risk of HPV acquisition, and consequently, cervical cancer. This warrants the consideration of stratified screening approaches, and requires a quantification of the difference in cervical cancer risk between vaccinated and unvaccinated women in the coming decades. Although mathematical modeling studies^{15–19} have previously been used to identify the optimal cervical cancer screening strategy for populations offered vaccination, these analyses do not explicitly show the difference in risk between vaccinated and unvaccinated women under various vaccination scenarios, taking into account the herd immunity. Yet, identifying risk-differentials for different vaccination strategies and coverage levels is important to inform policy on the potential for personalized screening.

We estimated the difference in HPV and cervical cancer risk between vaccinated and unvaccinated women over time for different vaccination strategies and coverage assumptions, using the dynamic individual-based STDSIM model.^{20,21} We considered two different vaccine types (2vHPV and 9vHPV), two different targeting strategies (females-only versus females and males), and four different coverage levels (20%, 40%, 60%, and 80%).

Materials and Methods

Model quantification

STDSIM has previously been used to predict the transmission and control of HPV16 and HPV18 in the Netherlands.^{20,22,23} The model is event-driven, and simulates a dynamic population in which each individual has his or her own characteristics that are static (such as sex) or subject to change (age, infection status and relationship status). HPV transmission occurs by explicitly simulating sex acts within three types of heterosexual relationships: steady (long-term), casual (short-term), and one-off contacts. We did not simulate screening, treatment, and surveillance for pre-invasive cervical cancer, assuming these are similar for vaccinated and unvaccinated women. A detailed description of the model can be found elsewhere.^{20–23} For the Netherlands, we previously quantified and validated the sexual network.²² We then calibrated per-act transmission probabilities, clearance rates, and natural immunity development to reproduce observed pre-vaccination HPV16 and HPV18 prevalence by age.²⁰ Yet, later studies showed that the data we used were likely an underestimation of actual HPV prevalence in The Netherlands.^{24,25} Therefore, for the current study, we recalibrated our model to reproduce the United States HPV prevalence levels as follows. First, we compared sexual behavior outputs of the model to data,^{26,27} and concluded that this model can be used to describe HPV transmission in United States sexual networks, although the model does not reproduce data perfectly (Figure S1, supplements). The slight overestimation of the number of reported recent partners may be due to social desirability bias, resulting in underreporting, especially among women. There are also clear discrepancies between numbers of lifetime partners between the two datasets for women, and we believed that, as an average of the total female population, NHANES data seems to be unrealistic with an average of more than 20 lifetime partners. We increased the age of sexual debut by one year, to an average of 18 years (13 to 23; uniform distribution) to reproduce observed sexual debuts by age in the United States.²⁷ Second, we recalibrated natural history parameters to reproduce observed HPV prevalence levels in the United States by repeatedly randomly sampling transmission probabilities, clearance rates, and natural immunity waning for HPV16, HPV18, and HPV31/33/45/52/58 (simulated as a single type, hereafter referred to as HPV h5) until 100 acceptable parameter combinations that closely reproduced observed HPV prevalence levels in the United States were identified.²⁸ By reproducing multiple sets of acceptable parameter combinations rather than a single ‘best fit’, our model incorporates parameter uncertainty in its predictions. A detailed description of the parameter values (Table S1) and the fit to data (Figure S2) are given in the supplements.

Vaccination scenarios

In the model, HPV vaccination was applied to adolescent females and males at the age of 12, *i.e.*, before sexual debut. Vaccine efficacy for both 2vHPV and 9vHPV was set to lifelong protection of 100% against all HPV types covered by the vaccine, for both females and males.^{29–31} We simulated a total of 16 unique combinations of 2vHPV or 9vHPV, females-only or females and males vaccination strategies, and coverage levels of 20%, 40%, 60%, and 80%. In addition, we also simulated a ‘no vaccination’ baseline. We did not incorporate

any 2vHPV-cross-protective effect against other common oncogenic HPV types, because the potential duration and effectiveness of the vaccine on these types is unknown.^{32,33}

Analysis

We used the model to project population-level HPV prevalence by type and age for each scenario over a period of 90 years since the introduction of vaccination, and calculated the age-specific and type-specific relative prevalence reductions compared to the baseline of no vaccination for each year. We then estimated cervical cancer incidence reduction due to vaccination by multiplying HPV prevalence reductions with observed HPV type distribution in cervical cancer cases as derived from the New Mexico Pap Registry: 53% of all cervical cancers are due to a persistent HPV16 infection, 19% to HPV18, 20% to HPV18 and the remaining 8% to other non-9vHPV high-risk types.³⁴ This is a direct reduction in cervical cancer incidence at the same time and age as the HPV prevalence reduction, e.g. a 50% reduction in HPV16 prevalence in 30 year-olds in 2020 equates to a 50% reduction in HPV16 cancers in 30 year-olds in 2020. We assume that simultaneous or successive infections do not affect each other in their likelihood of causing cervical cancer.²³ The relative risk (RR) for cervical cancer among unvaccinated women was calculated as $(1-B)/(1-A)$, where A and B are cervical cancer risk reduction in vaccinated and unvaccinated women, respectively. We performed these analyses separately for all 100 unique parameter combinations that reproduce observed HPV prevalence data. The median predictions on each outcome were used to reflect median estimates, while the 2.5th and 97.5th percentile were used to reflect the lower and upper bounds of an uncertainty interval respectively. We have included estimates of absolute disease risk for vaccinated and unvaccinated population in an unscreened setting, as well as under the current screening practices, to provide additional context for the differing impact of screening on vaccinated and unvaccinated women in the Appendix.

In a sensitivity analysis, we investigated the effect of a lower vaccine efficacy (90%) and the possibility of waning over time by reducing the duration of protection from lifelong to 20 years after vaccination. We also estimated the relative cervical cancer risk assuming that 10% or 30% of the (unmarried) population have a high risk sexual behavior (*i.e.*, frequent once-off contacts) compared to 20% in the baseline, and determined the impact of higher and lower overall partner change rates on cervical cancer risk differentials. Detailed information is presented at Table S2 in the Appendix.

Results

Figure 1 shows the predicted HPV prevalence reduction in unvaccinated women by time since vaccination was introduced, for HPV16, HPV18 and HPV18 separately. Steady state HPV prevalence reductions ranged between 5% and 38% for females-only scenarios, and between 19% and 75% when vaccinating females and males, depending on vaccination coverage. Steady state prevalence reductions are achieved after about 60 years. There is a peak in prevalence reduction around 20 to 30 years after initiation of vaccination, after which it decreases, implying that there is a cohort effect. Herd immunity effects are highest in the most sexually active groups, and declines thereafter.

Our model predicted that herd immunity resulted in an HPV prevalence reduction of 52%, 54%, and 57% for HPV 16, HPV 18, and HPV18/16/11/31/45 respectively among unvaccinated women, under 60% vaccination coverage for females and males (Table 1a). We found the highest cervical cancer risk reduction in unvaccinated women in the scenario with 80% vaccination coverage of females and males, 52% and 67% for 2vHPV and 9vHPV, respectively, and the lowest reduction occurring in the scenario of females-only vaccination at 20% coverage, 4% and 5% for each vaccine type (Table 1b). In women who have been vaccinated with 2vHPV, cervical cancer incidence reduction is 72%, regardless of the coverage and whether or not males have been vaccinated, reflecting the residual risk due to types against which the vaccine offers no protection. In women vaccinated with 9vHPV, this reduction is estimated at 91%. The highest difference in risk between vaccinated and unvaccinated women in scenarios that we evaluated was predicted when applying 9vHPV among females only (Table 1c). These varied from 8 (UI: 5.9-8.6) under 80% vaccination coverage to 10.8 (UI: 10.7-10.8) when vaccination coverage was 20%.

As shown in Figure 2, the relative cervical cancer risk differences were more pronounced at higher coverage rates, and when both females and males were vaccinated. When only 60% of the females were vaccinated with the 2vHPV, the relative risk varied from 3.3 (UI: 3.2-3.3) at 10 years after vaccination to 3.1 (UI: 2.9-3.1) at 90 years after vaccination. For the 9vHPV vaccine (females only) the relative risk over time varied from 10.3 (UI: 10.1-10.4) to 9.4 (UI: 8.6-9.5). If males were vaccinated as well, the relative risk changed from 9.6 (UI: 9.2-9.9) to 5.9 (UI: 3.9-6.3).

Sensitivity analysis (Table 2) showed that our results were more sensitive to the duration of protection and the increased proportion of population in the high risk group. Changing vaccine protection from lifelong to 20 years increased the relative risk from 5.9 (UI: 4.0-6.1) to 7.6 (UI: 7.3-7.8) for the 9vHPV with 60% coverage in females and males. Increasing proportion of the population in the high risk group (30% of the population instead of 20%) increased the relative risk from 5.9 (UI: 4.0-6.1) to 6.8 (UI: 5.1-7.2) under the same scenario. Meanwhile, the estimated risks were less sensitive to vaccine efficacy, the decrease of the proportion of population at high risk and overall partner change rates, compared to the base-case assumption.

Discussion

Our study showed that, compared to HPV vaccinated women, the risk of cervical cancer is substantially higher in unvaccinated women, even at high vaccination coverage levels. In a steady state situation, unvaccinated women are two to eleven times more likely to develop cervical cancer compared to vaccinated women, depending on the vaccination strategy. The risk is eight to eleven times higher when only females are vaccinated with the 9vHPV. Under 60% vaccination coverage, which is a representative coverage for the United States and many other western countries, the relative risk varies between two (bivalent vaccine for females and males) and nine (nonavalent vaccine for females-only). These results have clear consequences for policy decision making on screening programs in countries with HPV vaccination.

To our knowledge, this is the first study that explicitly shows the relative cervical cancer risk between unvaccinated and vaccinated women, by comparing two types of HPV vaccines, under various vaccination strategies including both females and males, where the herd immunity is taken into account. A previous study, using 16 different transmission-dynamic models¹⁵ was conducted to predict relative prevalence reductions in HPV after vaccination. They showed that some models resulted in more herd immunity than others due to differences in sexual activity, natural immunity or cervical cancer natural history. The higher the herd immunity, the lower the relative risk for cervical cancer between vaccinated and unvaccinated women. By considering differences in risk for developing cervical cancer by vaccination status, we take these analyses a step further to properly incentivize thinking on the best approach towards the optimal cervical cancer screening in partly vaccinated populations.

It was difficult to validate our model results against data from the United States, as such data on cervical cancer incidence in vaccinated versus unvaccinated women is lacking. However, our model predictions are comparable to the results of a Swedish study by Lei et al,³⁵ according to which the cumulative incidence of cervical cancer was 47 cases per 100,000 persons among women who had been vaccinated and 94 cases per 100,000 persons among those who had not been vaccinated. Meanwhile, our model predicts a cumulative cervical cancer incidence of 43 cases per 100,000 persons among vaccinated women and 113 cases per 100,000 persons among unvaccinated.

For HPV vaccination and cervical cancer, the relative risk is between two and eleven, and thus much higher compared to various diseases, with the relative risk, i.e. for colorectal cancer being less than two between females and males, yet, personalized (*i.e.*, risk-based) screening is being considered. In addition, several studies have assessed individual risk for colorectal cancer based on gender, family history, genetic, and environmental risk factors to investigate whether screening policies should be adapted for subpopulations.^{36–38} Meanwhile, although HPV vaccinated women will soon reach (or have already reached) the screening age in many countries, the recommended cervical cancer screening protocols do not differ with regard to vaccination status. Reasons for not adapting screening protocols may be the fact that HPV vaccination status is not recorded, thus vaccinated women cannot be identified. In addition, although studies suggest that a less intensive screening program for vaccinated women is advised, it is unknown how women will perceive screening programs that differ according to HPV vaccination status and ethical questions may raise as well.³⁹

In this study, we use the relative risk reduction to convey the message that personalized screening needs serious consideration. But, while a relative risk reduction of two or three shown in our study seems to be a notable difference, the absolute disease risk will ultimately determine optimal screening strategies. As shown in the Appendix, the absolute risk of cervical cancer would be approximately 2 per 100 000 women in vaccinated and 20 per 100 000 in unvaccinated women for female-only 9vHPV at 60% coverage. In this situation, optimizing screening based on the risk in unvaccinated women, so that this higher risk group is screened sufficiently, would lead to over-screening, resulting in unnecessary financial costs and harms, for vaccinated women. By showing that the absolute disease risk is high

enough, we argue that relative risk is a reasonable measure to draw conclusions on screening. Therefore, a relative risk of ten would imply that the benefits of applying the same screening program will be more or less 10 times lower in vaccinated women. Meanwhile, the harms and costs, which are both much more determined by the number of lifetime screens, would be far from 10 times lower. In these circumstances, vaccination-status-specific screening may be an optimal solution compared to current screening recommendations, which are optimized for unvaccinated women. However, making such a change entails additional costs, feasibility and ethical issues related to the routine data collection and linking of vaccination and screening records.

Our study has some limitations. First, we only evaluated vaccination before sexual debut with 100% vaccine efficacy. In reality, vaccine efficacy will be lower. Trial estimates showed efficacy rates of slightly below 100% in pre-adolescent girls, and because in some countries, especially the United States, some women are vaccinated later in life,² also resulting in lower efficacy.² This implies that vaccination effect is overestimated, as vaccine efficacy will be lower if people are vaccinated at older ages. However, our sensitivity analysis showed that the relative cancer risk between unvaccinated and vaccinated women was only slightly lower in case of substantially reduced efficacy (from 100% to 90% for all), suggesting that these simplifications had little impact on our predictions. It would be essential to take into account the actual vaccination uptake at different ages when examining the cost-effectiveness of vaccination or screening in a given situation or country. Meanwhile, our goal is not to examine any particular country, but rather to use the situation in the United States as an example to draw a broader conclusion. The advantage of this simplified approach is that our findings apply to many other developed countries. Second, we did not consider cross protection of vaccines against other types that were not included in HPV-2 and HPV-9. Although cross-protection is likely limited,³² it would protect women against types not included in the vaccine, and thus result in even lower cancer incidence in vaccinated women compared to our estimates. Hence, by ignoring cross-protection, our cancer risk reduction estimates in unvaccinated women could be underestimated, implying that cancer relative risk in vaccinated and unvaccinated women would be higher. Third, in our study, we assumed that women were completely immune with variable duration, after clearing an HPV infection. Applying a different natural immunity mechanism, such as a cumulatively decreasing susceptibility to reinfection, could have changed our estimates. However, a previous study from our group in which two immunity mechanisms were considered, showed that the small differences in estimated reductions in HPV incidence would hardly affect policy decisions.²³ Fourth, we assume that vaccination coverage is evenly distributed across the population due to differences in access and acceptability of HPV vaccines. For instance, it is possible that some of the highest-risk populations are the least likely to be exposed and accept the vaccine, especially prior to sexual debut. However, by modeling multiple coverage levels from very low to very high, we capture this heterogeneity, not only as a representation of other high-income countries, but also as representation of heterogeneity within the United States. By estimating the relative cancer risk in vaccinated and unvaccinated women across a broad range of vaccination coverage levels, we could roughly demonstrate the effect of heterogeneity in uptake, and demonstrate that lower coverage results in higher risk differentials. These effects are likely attenuated if

selection bias based on e.g. risk behavior occurs. Finally, it takes some time for prevalent infections to progress to cancer (i.e. the dwell time). However, there is still uncertainty around this delay between HPV prevalence reduction and the corresponding reduction in cancer incidence. A comparative modelling study by Burger et al,⁴⁰ showed that the dwell time ranged from 17.5 to 26.0 years depending on the model assumptions. In our case, it was not necessary to consider such a delay for the purpose of our study, as most of our results and the key message concern the steady state, regardless of when it is reached. We used this simplified approach to avoid undue complexity of incorporating complex natural history assumptions on disease progression, considering this has been much debated.⁴⁰ However, for future studies, it will be important to consider such a delay in the context of estimating disease risk for the next few years (i.e. for the next 50 years).

In conclusion, we demonstrated a substantial difference in the risk of cervical cancer in unvaccinated compared to vaccinated women, incentivizing a deliberation on developing individualized screening approaches. Uniform screening strategies in partly vaccinated populations will likely lead to a considerable imbalance in the distribution of harms and benefits of screening between vaccinated and unvaccinated women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. HPV 16, HPV 18 and HPV h5 (i.e. HPV types 31/33/45/52/58) prevalence reduction in unvaccinated women due to herd immunity (including UI), by year since introduction of vaccination, vaccination coverage level (20% - 80%) and vaccination strategy (females only (F) or females and males (F + M)). Females-only are shown in solid lines, dashed lines reflect vaccination of females and males.

Fig. 2.

Relative risk of cervical cancer in unvaccinated compared to vaccinated women, by year since the introduction of vaccination with 2vHPV and 9vHPV, under four vaccination coverage scenarios (20%, 40%, 60% and 80%) among females alone (F) or both females and males (F+M), in the absence of screening.

*DT (dwell time) refers to the time from HPV acquisition to cancer detection.

Table 1.

Impact of different vaccination scenarios in the steady state situation (after the implementation of HPV vaccination) on **a)** HPV 16, HPV 18, HPV h5 (i.e. HPV types 31/33/45/52/58) and other (non-vaccine) oncogenic HPV types (i.e. HPV types 35/39/51/56/59/66/68) prevalence reduction in unvaccinated women, **b)** Cervical cancer risk compared to the no vaccination scenario, for vaccinated and unvaccinated women and vaccine type (2vHPV or 9vHPV), and **c)** Relative risk (RR) for the incidence of cervical cancer in unvaccinated vs vaccinated women per vaccine type (2vHPV or 9vHPV). The 2.5th and 97.5th percentile were used to reflect the lower and upper bounds of the uncertainty intervals.

Vaccination Coverage	I) Vaccination among females				II) Vaccination among females and males			
	20%	40%	60%	80%	20%	40%	60%	80%
a) HPV prevalence reduction among unvaccinated women (%)								
HPV 16	5 (5-7)	12 (10-15)	19 (16-25)	30 (23-42)	19 (18-22)	36 (32-41)	52 (47-60)	73 (63-92)
HPV 18	6 (6-7)	13 (16-19)	22 (24-37)	33 (32-72)	20 (22-23)	38 (40-48)	54 (54-95)	72 (67-100)
HPV high-5	7 (4-9)	15 (15-17)	25 (24-32)	37 (34-64)	21 (22-21)	41 (41-46)	57 (56-78)	75 (71-100)
Other oncogenic types	0	0	0	0	0	0	0	0
b) Cervical cancer risk reduction compared to no vaccination (%)								
2vHPV								
A) Vaccinated women	72 (72-72)	72 (72-72)	72 (72-72)	72 (72-72)	72 (72-72)	72 (72-72)	72 (72-72)	72 (72-72)
B) Unvaccinated women	4 (4-5)	9 (8-12)	14 (13-20)	22 (18-36)	14 (13-16)	26 (25-31)	37 (35-50)	52 (46-67)
9vHPV								
C) Vaccinated women	91 (91-91)	91 (91-91)	91 (91-91)	91 (91-91)	91 (91-91)	91 (91-91)	91 (91-91)	91 (91-91)
D) Unvaccinated women	5 (5-6)	12 (12-15)	19 (18-26)	30 (25-48)	18 (18-20)	34 (33-40)	48 (46-65)	67 (60-87)
c) RR for cervical cancer, unvaccinated versus vaccinated women								
2vHPV	3.4 (3.4-3.5)	3.2 (3.1-3.2)	3 (2.8-3.1)	2.8 (2.3-2.9)	3.1 (3.0-3.1)	2.6 (2.5-2.7)	2.2 (1.8-2.3)	1.7 (1.2-1.9)
9vHPV	10.8 (10.7-10.8)	10.1 (9.7-10.1)	9.2 (8.4-9.4)	8 (5.9-8.6)	9.4 (9.1-9.4)	7.5 (7.0-7.7)	5.9 (4.0-6.2)	3.8 (1.5-4.6)

Table 2.

Results of sensitivity analysis: Relative cervical cancer risk (2.5th and 97.5th percentile reflect uncertainty intervals) for unvaccinated versus vaccinated women, due to 2vHPV and 9vHPV, in the steady state situation (when herd immunity is fully developed) after the implementation of HPV vaccination.

Coverage	I) Vaccination among females				II) Vaccination among females and males			
	20%	40%	60%	80%	20%	40%	60%	80%
Base case								
2vHPV	3.4 (3.4-3.5)	3.2 (3.1-3.2)	3 (2.8-3.1)	2.8 (2.3-2.9)	3.1 (3.0-3.1)	2.6 (2.5-2.7)	2.2 (1.8-2.3)	1.7 (1.2-1.9)
9vHPV	10.8 (10.7-10.8)	10.1 (9.7-10.1)	9.2 (8.4-9.4)	8 (5.9-8.6)	9.4 (9.1-9.4)	7.5 (7.0-7.7)	5.9 (4.0-6.2)	3.8 (1.5-4.6)
Sensitivity analysis								
A) Vaccine efficacy of 90% (instead of 100%)								
2vHPV	3.4 (2.7-2.7)	3.3 (2.5-2.6)	3.1 (2.3-2.5)	2.9 (2.0-2.4)	3.1 (2.4-2.5)	2.7 (2.0-2.2)	2.3 (1.6-1.9)	1.9 (1.2-1.7)
9vHPV	10.9 (5.2-5.4)	10.4 (4.9-5.2)	9.9 (4.6-4.9)	9.2 (3.8-4.7)	9.5 (4.5-4.7)	7.8 (3.5-3.9)	6.3 (2.5-3.2)	4.6 (1.2-2.6)
B) Vaccine protection of 20 years (instead of lifelong)								
2vHPV	3.4 (3.4-3.4)	3.3 (3.3-3.3)	3.2 (3.2-3.2)	3.1 (2.9-3.1)	3.2 (3.1-3.2)	2.9 (2.9-2.9)	2.6 (2.5-2.7)	2.5 (2.3-2.5)
9vHPV	11.1 (10.9-11.1)	10.7 (10.5-10.7)	10.3 (9.9-10.4)	10 (9.2-10.1)	9.9 (9.7-9.9)	8.7 (8.7-8.7)	7.6 (7.3-7.8)	6.8 (6.3-7.0)
C) Increased proportion of population in high risk group (30% instead of 20%)								
2vHPV	3.5 (3.5-3.5)	3.4 (3.3-3.4)	3.2 (3.1-3.3)	3 (2.6-3.1)	3.2 (3.1-3.2)	2.8 (2.7-2.9)	2.4 (2.1-2.5)	1.9 (1.2-2.1)
9vHPV	11.2 (11.2-11.2)	10.8 (10.5-11.0)	10.4 (9.9-10.5)	9.7 (8.3-10.1)	9.9 (9.8-10.0)	8.4 (7.8-8.6)	6.8 (5.1-7.2)	4.6 (1.6-5.6)
D) Decreased proportion of population in high risk group (10% instead of 20%)								
2vHPV	3.3 (3.2-3.3)	3 (2.8-3.0)	2.7 (2.4-2.8)	2.3 (1.7-2.4)	2.8 (2.8-2.8)	2.3 (2.0-2.3)	1.8 (1.5-1.9)	1.4 (1.0-1.6)
9vHPV	10.5 (10.5-10.5)	9.6 (8.9-9.4)	8.7 (7.6-8.8)	7.4 (4.9-7.7)	8.3 (8.4-8.1)	6 (5.1-6.0)	4.3 (2.7-4.5)	2.6 (1.1-3.3)
E) Increased (by 50%) overall partner change rates in the population								
2vHPV	3.4 (3.4-3.4)	3.2 (3.2-3.3)	2.9 (3.0-3.2)	2.6 (2.7-3.1)	3 (3.0-3.1)	2.5 (2.5-2.8)	2.1 (2.0-2.4)	1.6 (1.1-2.0)
9vHPV	10.8 (10.9-11.0)	10.2 (10.5-10.7)	9.4 (10.0-10.4)	8.4 (8.6-9.9)	9.1 (9.1-9.7)	7 (7.1-8.1)	5.3 (4.7-6.8)	3.4 (1.4-5.1)
F) Decreased (by 33.3%) overall partner change rates in the population								
2vHPV	3.4 (3.3-3.4)	3.3 (3.0-3.2)	3.2 (2.7-3.0)	2.9 (2.2-2.7)	3.1 (2.9-3.0)	2.7 (2.4-2.5)	2.3 (1.7-2.2)	1.8 (1.1-1.8)
9vHPV	11.1 (10.7-10.8)	10.6 (9.8-10.2)	10.2 (8.5-9.6)	9.3 (6.8-8.8)	9.6 (8.9-9.1)	8 (6.5-7.2)	6.4 (3.7-5.7)	4.2 (1.5-4.1)