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The expected herd effects of HPV vaccination: How to interpret cross-sectional surveys over time

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Submitted

ABSTRACT

Background

Mass vaccination changes the infection risk of unvaccinated individuals; this is the herd effect of immunization. We study the herd effects of vaccinating girls against sexually transmitted human papillomavirus (HPV), in particular HPV-16, associated with the majority of cervical cancers.

Methods

We used a compartmental HPV-16 transmission model for the Netherlands to study how vaccination changes the HPV-16 infection hazard and the proportion susceptible to infection, assuming 60% female vaccine coverage and lifelong protection against clinically relevant infection. We assess how the HPV-16 infection prevalence and seroprevalence are expected to change over time in cross-sectional surveys.

Results

We expect similar reductions for the infection hazard, prevalence and seroprevalence within the first two decades of vaccination, but larger reductions in men than women. For the vaccine-eligible age cohorts, reductions are 74% and 58% in unvaccinated men and women, respectively, 10 years after introduction of vaccination. The reduced infection hazard leads to a build-up of susceptibles, which could lead to an increased incidence among unvaccinated women around age 30 years.

Conclusions

Changes in HPV-16 seroprevalence are a good proxy for changes in HPV-16 infection prevalence. Cross-sectional surveys repeated every decade are well suited for monitoring the herd effects of HPV vaccination.

INTRODUCTION

Infection with high-risk human papillomavirus (HPV) is the necessary cause for the development of cervical cancer, currently ranked 4th on the worldwide cancer incidence in women.¹ Over 40 HPV types are known that spread via sexual contact and preferentially infect the anogenital epithelia.² These types can be divided into low-risk types (e.g. HPV-6 and -11) that are associated with genital warts, and high-risk types (e.g. HPV-16 and -18) that are associated with various carcinomas in the anogenital region, in particular cervical cancer. Reducing the cervical cancer incidence has been the main objective for the introduction of vaccination programs against HPV-16/18. In most developed countries, a bivalent vaccine (targeting HPV-16/18) or quadrivalent vaccine (targeting HPV-16/18/6/11) is offered primarily to preadolescent girls. Vaccine uptake varies between 17% and 84% in European countries.³

The relatively low uptake of HPV vaccination leaves ample scope for the unvaccinated population (both women and men) to benefit from indirect effects of vaccination. Indirect protection of unvaccinated individuals arises when their sexual partners (or partners thereof) have had vaccination, thus shielding them from infection. The resulting reduced infection risk among these unvaccinated individuals is called the "herd effect" of vaccination.⁴ Modeling studies predict substantial herd effects after female HPV vaccination in heterosexual men,^{5,6} and for the Netherlands it was estimated that approximately 1 in 4 cervical cancers prevented will be due to herd immunity at the current female vaccine coverage of 60%.⁷

If the time between infection and clinical manifestation of vaccine-preventable disease is short, herd effects can be studied shortly after introduction of vaccination. However, the time from HPV infection to cervical cancer can take over twenty years and the herd effects from HPV-16/18 vaccination on the cancer incidence may not be discernible within the next decades.⁸ As the time between HPV infection and onset of high-grade precursor lesions (CIN2/3) is 3-5 years, a reduction in CIN2/3 incidence arises much earlier. Cervical cancer screening programs are aimed at reducing cervical cancer mortality by detecting precursor lesions, which are often free of symptoms. These programs might also be useful for monitoring herd effects of HPV vaccination in unvaccinated women. However, organized screening starts at age 30 years in the Netherlands and participation might be biased towards vaccinated women.⁹ Moreover, these programs do not provide any information about potential herd effects in men. HPV-related cancer incidence in men peaks at older age than in women due to the lack of organized screening programs for men, which complicates monitoring of their herd effects. To corroborate the existence of herd effects before their clinical impact becomes apparent, surrogate markers might be used for monitoring purposes. Candidate markers are the presence of type-specific HPV DNA, reflecting current infection, or the presence of HPV type-specific IgG antibodies in serum, reflecting past infection.

We study the expected herd effects of HPV-16 vaccination by means of a transmission model, targeting surrogate markers that are interesting for monitoring purposes. Both in terms of cost and organization, cross-sectional surveys that either test for the presence of HPV-16 DNA or antibodies specific for HPV-16 are attractive for monitoring. We study the post-vaccine change in

the proportion susceptible to infection and in the hazard of infection, and assess the observable change in the HPV-16 infection prevalence and HPV-16 seroprevalence, stratified by gender. Our predictions will aid in planning and interpreting future cross-sectional surveys, as well as in validating model predictions that assess the ultimate impact of HPV vaccination on the cervical cancer incidence.

METHODS

The infection hazard, often called the force of infection (FOI) in infectious disease terminology, is the rate at which a susceptible individual acquires an infection. After introduction of vaccination, the FOI and the age-specific proportions of susceptible individuals will change. A decrease in FOI leads to a slower depletion of the susceptible population and therefore to a change in the proportion infected or with naturally acquired immunity. Both factors influence the post-vaccine HPV incidence in the general population. Consequently, changes in observable infection endpoints such as the (cumulative) incidence, HPV infection prevalence and seroprevalence, will reflect a combination of the change in FOI and proportion susceptible.

It is often not feasible to assess susceptibility to infection, in particular for HPV; various tests are available for detecting current infection, but a reliable marker of natural immunity against infection does not exist. Using a transmission model, we can assess the changes of the conceptual outcomes (the FOI and proportion susceptible) and thereby interpret the changes in observational measures.

Dynamic model of HPV transmission

To inform on the vaccine-induced change in the proportion susceptible, the force of infection, and the HPV-16 infection prevalence, we used a susceptible-infectious-recovered-susceptible (SIRS) model for HPV-16 transmission in the Dutch heterosexual population published before.¹⁰ In short, this model was calibrated on data of clinically relevant cervical HPV DNA prevalence and clearance from a large population-based screening intervention study conducted prior to introduction of vaccination.^{11, 12} It has a separate compartment for virgins and distinguishes three levels of sexual activity. The sexual contact network matches two large surveys on sexual behavior in the Netherlands.^{13, 14} It assumes that partnerships are primarily formed between couples of similar age, but men have a wider age-preference than women. The transmission probability of HPV-16 infection was estimated at 80% per heterosexual partnership, independent of sex. The average duration of an incident infection is 8 months for both men and women. We assumed that most men cleared infection within a year, but that 45% of the infections in women persisted for longer duration. These persistent infections are cleared at reduced rate or they progress to precancerous lesions, which can be detected and treated through the cervical screening program. The model assumed a similar loss of natural immunity in men and women, which was estimated at 4% per year.

To project post-vaccine changes in the HPV-16 seroprevalence, we developed a link function between the HPV-16 incidence from the transmission model and the subsequent serological response, as follows. The age-specific proportions seropositive and seronegative in the Dutch population were described by a two-state dynamic model. Everyone is seronegative at young age. After HPV-16 infection, a proportion ϕ of newly infected individuals move to the seropositive compartment. Subsequently the seropositive status is lost at rate γ :

$$\begin{aligned} \frac{dS_n}{da} &= -\phi I(a) + \gamma S_p(a) \\ \frac{dS_p}{da} &= \phi I(a) - \gamma S_p(a). \end{aligned} \quad (1)$$

Here, S_n denotes the proportion of seronegative and S_p the proportion of seropositive persons. The age-specific HPV-16 incidence $I(a)$ is input from the transmission model. Note that we do not assume that seropositivity is correlated with natural immunity. The solution of Equation 1 denotes the age-specific HPV-16 seroprevalence, which is a function of parameters $\{\phi, \gamma\}$. These parameters were assumed to be sex-specific. We estimated $\{\phi, \gamma\}$ by fitting a mixture model with

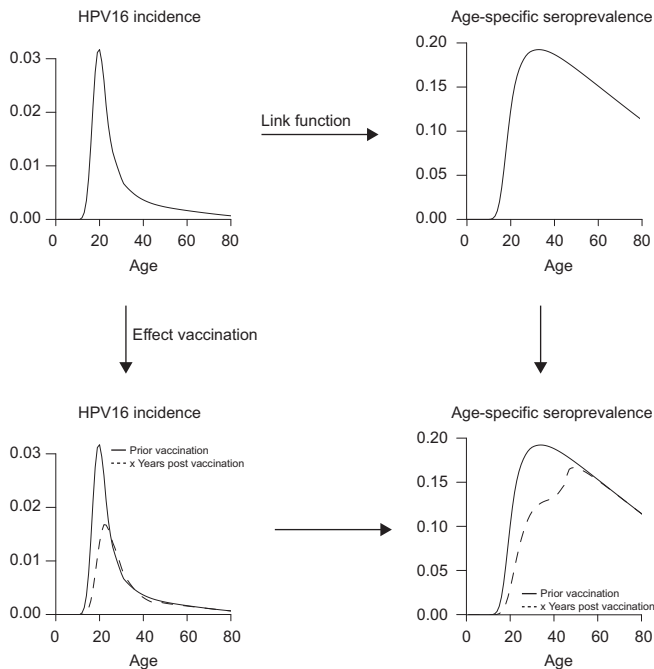


Figure 1. Schematic explanation of the model-based projections of the HPV-16 seroprevalence prior to and after implementation of vaccination. The HPV-16 seroprevalence is obtained by projecting a link function onto the HPV-16 incidence function that is obtained from a HPV-16 transmission model. The herd effects of vaccination on the seroprevalence are obtained by projecting the link function onto the HPV-16 incidence post vaccination as predicted by the transmission model.

the age-specific HPV-16 seroprevalence as mixing proportions, to serological concentrations of HPV-16 antibodies collected prior to introduction of vaccination in the Netherlands.^{15, 16} The HPV-16 seroprevalence post vaccination is obtained by projecting the link function on the HPV-16 incidence post vaccination as predicted by the transmission model (Figure 1). We refer to the Appendix for the sex-specific seroprevalence figures (Appendix Figure 1) and for technical details regarding the modeling of the serological process and parameter estimation. In short, we estimated that 76% of women and 60% of men seroconvert after an incident HPV-16 infection. Seropositivity is lost at a rate of 2% per year in women and at 0.8% per year in men.

Herd effects of HPV vaccination

Our base-case scenario reflects the Dutch situation, with a vaccine coverage of 60% among 12-year-old girls and among 13-16-year-old girls in the year of vaccine introduction. We assumed that vaccination provides lifelong protection against clinically relevant HPV-16 infections. We report sex- and age-specific reductions of the FOI, the proportion susceptible, the HPV-16 infection prevalence and the seroprevalence over time. Reductions are relative to the pre-vaccine situation for all outcomes.

Sensitivity analysis

We performed univariate sensitivity analyses to gain insight into the influence of model parameters on the reduction of the FOI fifty years after introduction of vaccination. To assess the effect of infection persistence, we assumed a similar natural history in women as in men. In that case, HPV-16-specific model parameters are independent of sex and different reductions in men and women can be attributed to the sexual contact network or the sex that has been targeted for vaccination. We also evaluated the effect of the loss of natural immunity by assuming a rate of 41% per year instead of 4.1% per year. In addition, we assessed the effect of the sex that is targeted for vaccination: we ran all scenarios with female-only and with male-only vaccination. We did not change the other model parameters in sensitivity analyses, hence the models do no longer match the observed pre-vaccine HPV infection prevalence and seroprevalence.

RESULTS

Effects of HPV vaccination on the HPV-16 FOI and proportion susceptible

The HPV vaccination program is expected to lead to a substantial change in the HPV-16 FOI of women (Figure 2). The age-specific reduction of the FOI is largest around adolescence, and changes over calendar time. Fifty years after the introduction of HPV vaccination, a small increase in FOI is expected for women around age 30 years. The proportion susceptible in the unvaccinated population shows an increase between age 13 and 35 years because fewer persons are infected or have natural immunity against HPV-16. The HPV-16 incidence is obtained by multiply-

ing the FOI with the proportion susceptible, hence the incidence will increase if the increase in proportion susceptible is stronger than the reduction in FOI. Indeed, we expect an increase in incidence for women in their late twenties - early thirties, starting approximately 20 years after introduction of vaccination (Figure 3).

For men we expect a larger reduction in FOI as compared to women (Figure 2). An increase in FOI over calendar time is not expected. The age-specific reduction in FOI is sufficiently large to outweigh the increase in the proportion susceptible, therefore we do not expect an increase in HPV-16 incidence among men (Figure 3).

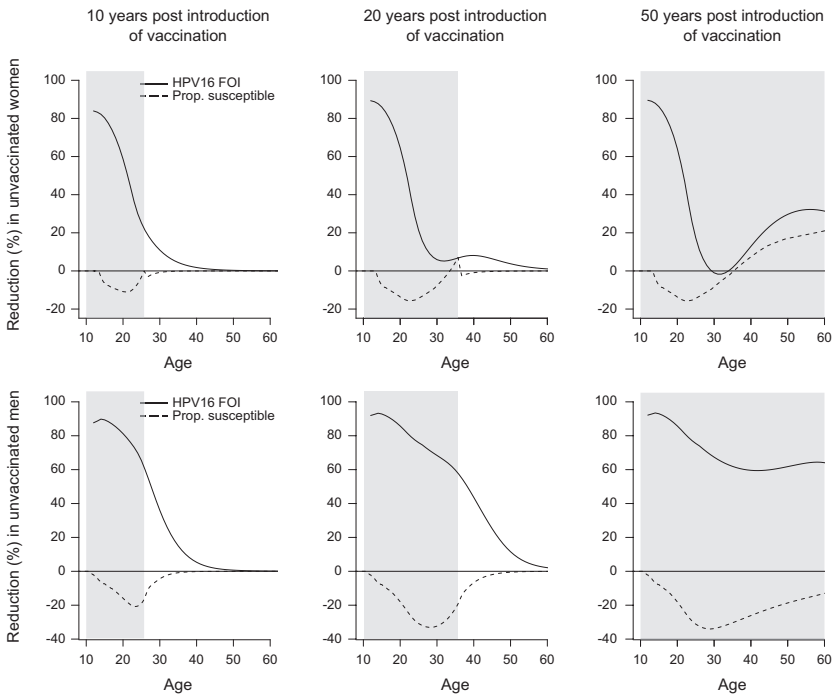


Figure 2. The predicted age-specific reduction in the HPV-16 force of infection (solid line) and the proportion susceptible to HPV-16 infection 10, 20 and 50 years after the introduction of HPV-16/18 vaccination to the Dutch national immunization program. All reduction figures are relative to the pre-vaccination era. The shaded area denotes the vaccinated age cohorts.

Effects of HPV vaccination on HPV-16 infection prevalence and seroprevalence

Vaccination will reduce the HPV-16 infection prevalence and seroprevalence in unvaccinated women and men (Figure 4). Within the first two decades of vaccination, very similar age-specific reductions are expected for the FOI, infection prevalence and seroprevalence, both in women and in men (Figure 2 and Appendix Figure 2). However, these endpoints diverge after several decades of vaccination. After 10 years of vaccination, reductions are 58% in unvaccinated women and 74%

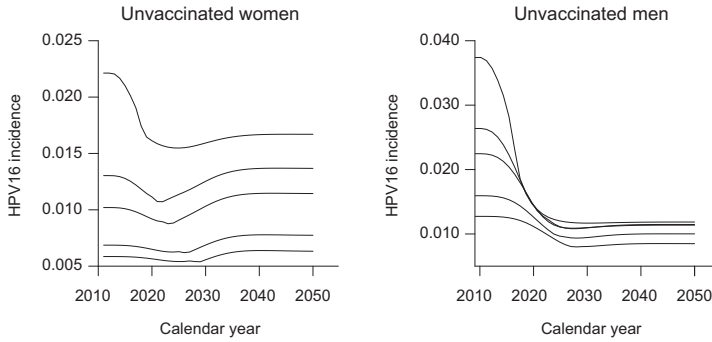


Figure 3. Change in the incidence of HPV-16 infections for unvaccinated women and men by age group (from top to bottom: 22, 25, 27, 30 and 32 years old) after the implementation of HPV-16/18 vaccination within the Dutch national immunization program in 2009.

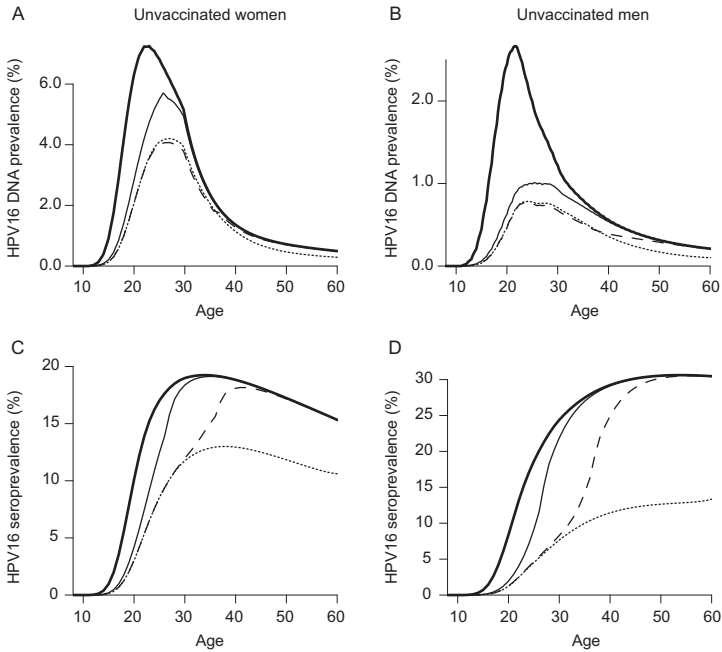


Figure 4. Cross-sectional figures of the HPV-16 infection prevalence (A) and seroprevalence (C) in unvaccinated women, and the HPV-16 infection prevalence (B) and the seroprevalence (D) in men after introduction of HPV-16/18 vaccination within the Dutch national immunization program. The thick black lines present the pre-vaccine situation, the thin lines denote the situation 10 years (fine solid line), 20 years (dashed line), and 50 years (dotted line) post vaccination.

in unvaccinated men in the age group 10-26 years, both in the HPV-16 infection prevalence and seroprevalence. Fifty years after the introduction of HPV-16 vaccination, the reduction in HPV-16 infection prevalence in unvaccinated women declines with age up to around age 30 years, after which it increases again (Table 1). Note that a relatively large reduction of approximately 40% is expected for women above age 50 years, but the absolute prevalence of HPV-16 infection is low in this age group (Figure 4). Although for unvaccinated women a small increase in HPV-16 incidence is expected, this will not result in an increased HPV-16 infection prevalence. This is partly due to the fact that organized screening in the Netherlands starts at age 30 years, which suppresses HPV infection prevalence by detection and treatment of precancerous lesions above age 30 years. The reduction in seroprevalence shows a similar decline with age as the infection prevalence, but it stabilizes from age 35 years onwards. The majority of persons who acquire an HPV-16 infection in their life will have been infected before age 35 years, hence the seroprevalence will not change much thereafter. For men we expect a larger reduction for all infection outcomes compared with women. Note that the shapes of the age-specific reductions in infection prevalence and seroprevalence are comparable between men and women (Appendix Figure 2).

For women, the reduction in HPV-16 infection prevalence and seroprevalence is mainly limited to the vaccinated age cohorts (Appendix Figure 2 and Table 1) because most sexual partnerships are formed between persons of similar age. The contacts for men are assumed to have a wider age range than the contacts of women, and therefore the spillover in herd effects towards unvaccinated age groups is substantially larger.

Sensitivity analysis

Sensitivity analyses were employed to determine the influence of model parameters on the vaccine-induced reduction in the FOI (Appendix Figure 3). The reduction in the FOI became larger if we did not allow for infection persistence in women, but this effect was particularly strong in the female FOI. In case we assumed a short duration of natural immunity, a stabilizing reduction in the FOI from age 30 years onwards was observed, and the rebound in female FOI reduction was no longer present. For men the reduction in FOI was only sensitive to the sex targeted for vaccination, with lower reductions if men were targeted for vaccination. For both men and women it holds that largest reductions in FOI are observed in the opposite sex that is targeted for vaccination (Appendix Figure 3).

DISCUSSION

We investigated the expected herd effects of vaccination against sexually transmitted HPV-16 by means of a transmission model. Assuming 60% female vaccine coverage, substantial effects are expected in prevalence of HPV-16 infection and HPV-16 seropositivity, both in unvaccinated women and men. These effects appear already within 10 years after introduction of vaccination and are mostly restricted to vaccine-eligible cohorts. Cross-sectional surveys provide an ideal

Table 1. Average reduction in HPV-16 infection prevalence and seroprevalence in unvaccinated women and men by age group. All reductions are relative to the pre-vaccine era and are calculated for 10, 20 and 50 years after the introduction of HPV vaccination to the national immunization program (NIP) assuming 60% vaccine coverage in 12-year old girls.

Unvaccinated women	10 years post introduction of HPV vaccination to the NIP ⁵		20 years post introduction of HPV vaccination to the NIP		50 years post introduction of HPV vaccination to the NIP	
	Reduction in HPV-16 infection prevalence	Reduction in HPV-16 seroprevalence	Reduction in HPV-16 infection prevalence	Reduction in HPV-16 seroprevalence	Reduction in HPV-16 infection prevalence	Reduction in HPV-16 seroprevalence
10-20 years	73%	74%	81%	82%	82%	82%
20-30 years	24%	25%	44%	50%	42%	50%
30-40 years	2%	1%	15%	19%	15%	33%
40-50 years	0%	0%	4%	1%	26%	31%
50-60 years	0%	0%	1%	0%	39%	31%
Unvaccinated men						
10-20 years	84%	84%	89%	90%	89%	90%
20-30 years	50%	43%	63%	74%	62%	75%
30-40 years	11%	2%	37%	42%	35%	64%
40-50 years	1%	0%	19%	5%	41%	59%
50-60 years	0%	0%	4%	0%	50%	58%

The shaded area denotes that the complete age group (gray) or a part of the age group (light gray) has been targeted for female vaccination.

⁵NIP; national immunization program

opportunity to study herd effects of HPV vaccination before a reduction in HPV-related cancer becomes manifest.

We studied two surrogate markers of the impact of HPV vaccination for monitoring indirect effects in unvaccinated individuals. Projected reductions in the HPV-16 infection prevalence and HPV-16 seroprevalence were very similar for the first twenty years following the introduction of a preadolescent HPV vaccination program. Monitoring for changes in HPV-16 infection prevalence could be integrated with HPV-based screening. The Netherlands will be the first country to adapt their organized screening program on the basis of HPV DNA test results on cervical smears, starting in 2016. However, screening only starts at the age of 30 years in the Netherlands, meaning that the first vaccine-eligible women will not be invited for participation until 2023. For the Dutch situation, monitoring the effects of vaccination sooner by means of HPV infection prevalence is hampered by the lack of pre-vaccine prevalence figures from the general Dutch population that could serve as a benchmark. Alternatively, these effect can be monitored by means of consecutive Dutch serological surveys, which has been done previously for other vaccine-preventable infections.^{17, 18} These surveys are repeated at 10-yearly intervals and cover a representative part of the Dutch population. In case of HPV, a benchmark of the pre-vaccine seroprevalence

figures is available and the subsequent serological survey scheduled for 2016/2017 will provide information of the herd effects on the short term. In addition, this survey provides information on vaccine-induced antibody levels, a proxy of vaccine protection, in vaccinated women.

In the post-vaccine era, the prevalence of cervical disease will decrease for vaccinated and unvaccinated women alike. As a result, the benefit of organized cervical cancer screening will decrease, and the screening burden should follow suit to safeguard efficiency of the screening program. A natural way of reducing the screening burden is by extending the screening interval. A new design of the organized screening program depends to a large extent on the effects of vaccination in the unvaccinated population. A question of particular relevance is whether screening algorithms should be developed that depend on vaccination status. From 2016 onwards, the screening interval will be extended from 5 to 10 years for women who test hrHPV-negative at age 40 or 50 years. Note that this program change has not specifically been designed for the vaccinated cohorts. In the post-vaccine era, it is unlikely that the screening interval for 40- or 50-year-old hrHPV-negative women will be further lengthened. Alternatively, the screening interval could be extended for women that test hrHPV-negative at age 30 years. However, we showed for unvaccinated women that although the hazard of infection decreases, an increase of the susceptible population could outweigh these benefits, resulting in an increased HPV-16 incidence around the age of 30 years. This increase would not favor a screening interval extension for unvaccinated women of this age as this could result in an increase in lifetime cancer risk. This exemplifies the importance of accounting for herd effects. Further research on the optimal screening program for the vaccinated age cohorts is required.

Herd effects could also be of importance for deciding whether boys should be included into national immunization programs, currently targeting girls only. Our results confirmed that large reductions in infection outcomes are expected for heterosexual men when only young women are vaccinated. Note that our results for men apply mostly to penile infections, and that the effects of vaccination cannot be directly translated to a homosexual population where anal HPV infection and seroprevalence rates are high.¹⁹ The population of men who have sex with men (MSM) suffer from a relatively large burden of HPV-related disease, but this population will benefit only partially from herd effects that arise from female vaccination. Monitoring herd effects in MSM is of particular importance at high vaccine coverage among girls, as the incremental benefits of vaccinating boys will then be driven by prevention of HPV-induced diseases in MSM. For this purpose, cross-sectional surveys specifically targeting MSM are desirable. In the Netherlands, these surveys are carried out at two-year intervals in sexual clinics of the municipal health services.¹⁹

Because our projections are based on a variety of model and parameter assumptions, the precise reduction figures may turn out to be different. We expect larger herd effects in men than in women given that vaccine is currently offered to preadolescent girls only in the Netherlands. Sensitivity analyses confirmed that the largest herd effects are invariably expected in the opposite sex that is targeted for vaccination, i.e. among partners of the vaccinated individuals. Thus men have a strong indirect benefit if their sexual partners are vaccinated, whereas the herd effects in unvaccinated women will be weaker, which was also pointed out in previous research.²⁰ Our

analysis also predicts that herd effects in unvaccinated women will be mainly restricted to those that were initially eligible for vaccination. Men have a wider age preference for their partners,^{13,14} and as a consequence, herd effects will also be noticeable in older age cohorts.

A limitation of our approach is that we could not correct for boosting of antibody concentrations upon repeated encounters with HPV in the analysis of the serological data.²¹ The parameter estimates describing the serological response after infection reflect the net effect of boosting, seroconversion and waning. If persons are re-infected at older age and antibody concentrations are boosted, antibody concentrations may wane faster than we have estimated. The reduction profiles for the seroprevalence will be different, depending on the age at which the boosting infections would occur prior to and post-vaccination. Our parameter estimates of seroconversion and seroreversion in women correspond to what is reported in the literature.^{22,23} However, empirical figures may also be influenced by intermittent boosting, which can only be accounted for if detailed personal information on sexual behavior is available.

We assumed that the vaccine provides lifelong protection against incident HPV-16 infection but it has only been proven efficacious up to 9.4 years of follow-up.²⁴ The herd effects will change and become of importance to a larger part of the population if vaccination does not provide lifelong protection. In that case, also the vaccinated persons that have lost their vaccine-induced immunity may benefit from reduced circulation of HPV-16 in the population. The effect of waning vaccine protection on the change in infection dynamics should be further investigated. Cross-sectional serological surveys will provide relevant information in this regard by monitoring the level of antibody concentrations in vaccinated women. Although these levels are a proxy and not a correlate for vaccine protection, a decline in antibody levels could hint at imperfect vaccine protection. To this end, serological surveys need to be integrated with studies targeting infection outcomes in vaccinated women.

To summarize, herd effects constitute a substantial part of the overall benefit of mass immunization programs for infectious diseases, and HPV vaccination provides a unique opportunity to study these herd effects in detail. In this paper we have shown that the expected herd effects on HPV-16 infection outcomes are substantial. Our estimates could be useful in deciding which infection markers to use and which age groups to target for monitoring purposes. Cross-sectional studies provide information on the change in infection dynamics after the introduction of HPV vaccination. They are well-suited for inferring herd effects on the short term from which projections of the expected change in cervical cancer incidence can be made.

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APPENDIX

To describe the vaccine-induced change in the HPV-16 seroprevalence, we developed a link function between the HPV-16 incidence from the transmission model, which has been published before,¹ and subsequent serological response. We assumed that all individuals started seronegative. After an incident HPV infection, we assumed a proportion to seroconvert. Subsequently, the seropositive status was lost at a certain rate. Note that we did not assume that the seropositivity is correlated with natural immunity. We used the age-specific HPV-16 incidence in the pre-vaccine era from the transmission model. The parameters of the link function (proportion seroconversion and waning seropositivity) were estimated using pre-vaccine serological data. The effect of HPV vaccination on the age-specific HPV incidence was assessed by the transmission model. The link function was projected onto this HPV incidence to obtain the seroprevalence in the post-vaccine era. This process is schematically explained in Figure 1 of the main text.

Cross-sectional pre-vaccine serological data

We analyzed HPV-16 specific antibody concentrations in serum, collected in a cross-sectional population-based survey conducted in the Netherlands in 2006/2007, before the introduction of HPV vaccination. All sera were tested for IgG type-specific antibodies against L1 virus-like-particles (VLP) with a VLP-based multiplex immunoassay.² This assay measures the antibody response to seven high-risk HPV types. For HPV-16 this test has a lower limit of detection of 0.08 luminex units per milliliter (LU/ml). We used the antibody concentration against HPV-16 of 3,875 randomly selected women, and 3,304 randomly selected men aged 0-79 years. Pre-vaccine seroprevalence figures have been published before.³

Model of serological response after infection

Currently it is assumed that after natural infection a proportion of individuals seroconverts and shows a detectable antibody response, i.e., becomes seropositive. Over time, the level of antibody concentrations will wane until the point of seroreversion is reached and only the assay-noise can be detected. We included the process of seroconversion and seroreversion in a two-state dynamic model in order to describe the age-specific HPV-16 seroprevalence (the proportion of persons belonging to the seropositive compartment) in the Dutch population. After an HPV-16 infection, a proportion ϕ of newly infected individuals moves to the seropositive compartment. Subsequently the seropositive status is lost at rate γ :

$$\begin{aligned}\frac{dS_n}{da} &= -\phi I(a) + \gamma S_p(a) \\ \frac{dS_p}{da} &= \phi I(a) - \gamma S_p(a).\end{aligned}\quad (1)$$

Here, S_n denotes the number of seronegative and S_p the number of seropositive persons. The age-specific HPV-16 incidence, $I(a)$, is given by multiplying the force of infection ($\lambda(a)$) with the

number susceptible: $l(a) = \lambda(a)S(a)$. Note that in case of HPV, it is generally assumed that seropositivity is not a correlate of protection for future infections, hence compartment S_p from the serological model does not coincide with the immune compartment R from the transmission model.

Parameter estimation in the pre-vaccination setting

We modeled the antibody concentrations from the pre-vaccine serological survey by a two-component mixture model, representing individuals being seronegative or seropositive, analogous to the method published before.³ In short, each individual with observed log-concentration y_i and age a_i contributed to the likelihood:

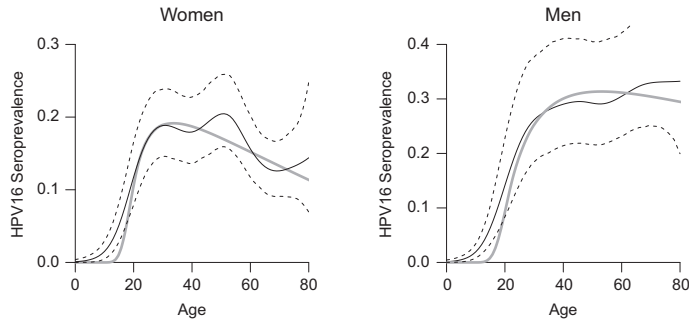
$$f(y_i) = (1 - p(a_i))f_0(y_i|\mu_0, \sigma_0) + p(a_i)f_1(y_i|\mu_1, \sigma_1).$$

The component densities f_0 and f_1 are assumed to be Normally distributed with unknown mean and variance and represent the seronegative and seropositive component respectively. If the observed log-concentration was left-censored (i.e., below the detection limit of the serological assay), the contribution to the likelihood was assumed to come from a cumulative normal distribution. The age-specific mixing proportions $p(a_i)$ represent the seroprevalence, and are given by the solution of the differential equation from the seropositive compartment in Equation 1. Due to the complexity of the transmission model, a numerical solution was obtained for the age-specific HPV-16 incidence $l(a)$ using the posterior median of the transmission model parameters.

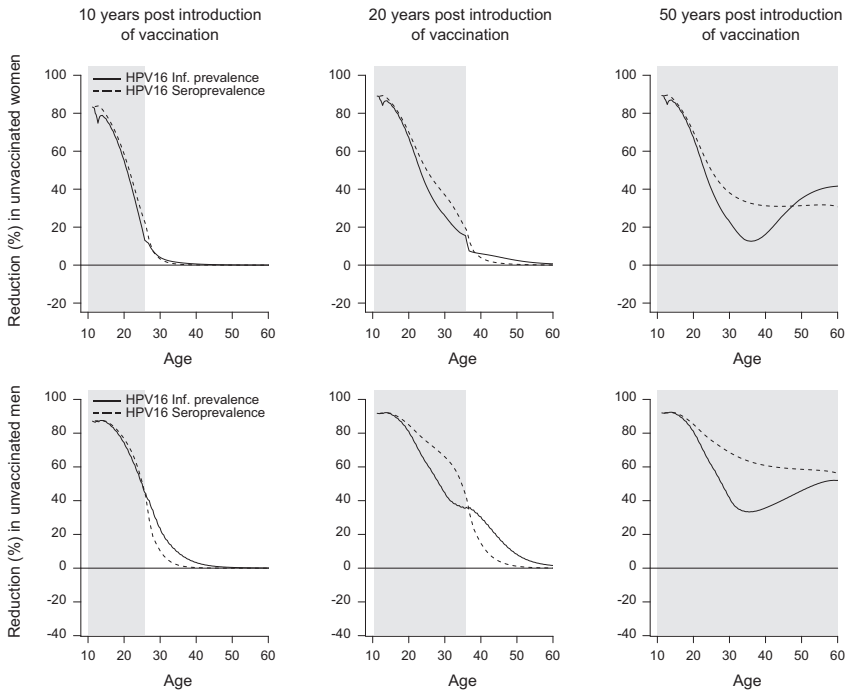
The mixture model was fit to the cross-sectional pre-vaccine serological data. The parameters φ and γ , describing the link between incident infection and seroresponse, were estimated simultaneously with the parameters of the component densities through Markov Chain Monte Carlo by a Metropolis Hastings algorithm. All analyses were performed using the statistical software R version 3.0.1.⁴ Per sex, we ran four chains of 25,000 iterations and inspected visually for convergence and mixing of the chains. For each parameter we report its posterior median and 95% credible interval (CI).

Results: Serological parameter estimates and sex-specific seroprevalence figures

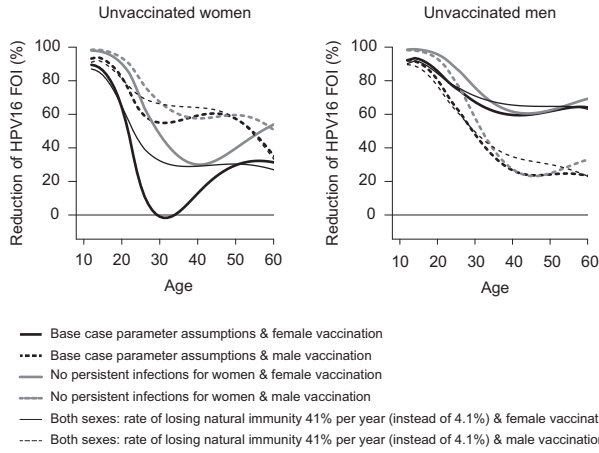
Prior to vaccination, we estimate a similar increase in male- and female-seroprevalence around the late teens, corresponding to the mode of sexual activity (Appendix Figure 1). For women, the seroprevalence decreases after age 33 years, while male seroprevalence remains increasing and eventually reaches a higher seroprevalence level compared to women. From age 52 years, we see a slowly decreasing trend in male seroprevalence as well. We estimate that 76% (95% CI: 59%, 95%) of the women seroconvert after infection, and lose their seropositive status at a rate of 2% (95% CI: 1.2%, 2.9%) per year. For men these numbers are somewhat lower, though not markedly different; 60% (95% CI: 43%, 91%) of men seroconvert after infection and seropositivity is lost at a rate of 0.8% (95% CI: 0.1%, 1.6%) per year. Both the age-specific seroprevalence (Appendix Figure 1) and the component densities are comparable with the estimates from a statistical model published before.



Appendix Figure 1. Pre-vaccine HPV-16 seroprevalence for women (left) and men (right). Gray lines denote the estimated seroprevalence using the link with the transmission model, black lines are the estimated seroprevalence figures and 95% credible interval obtained from the statistical model as published before.³



Appendix Figure 2. The predicted age-specific reduction in the HPV-16 infection prevalence (solid line) and the HPV-16 seroprevalence 10, 20 and 50 years after the introduction of HPV-16/18 vaccination to the Dutch national immunization program. All reduction figures are relative to the pre-vaccination era. The shaded area denotes the vaccinated age cohorts.



Appendix Figure 3. Scenario analysis of model assumptions on the reduction of the HPV-16 force of infection (FOI) 50 years after the introduction of HPV vaccination to the national immunization program. We investigate the effect of 1: assuming that infections do not persist for women, 2: a different rate of losing natural immunity, and 3: the effect of which sex is vaccinated.

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