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# The Impact of HPV Vaccination on HPV and Cervical Cancer in the Netherlands

De impact van HPV vaccinatie op HPV en baarmoederhalskanker in Nederland

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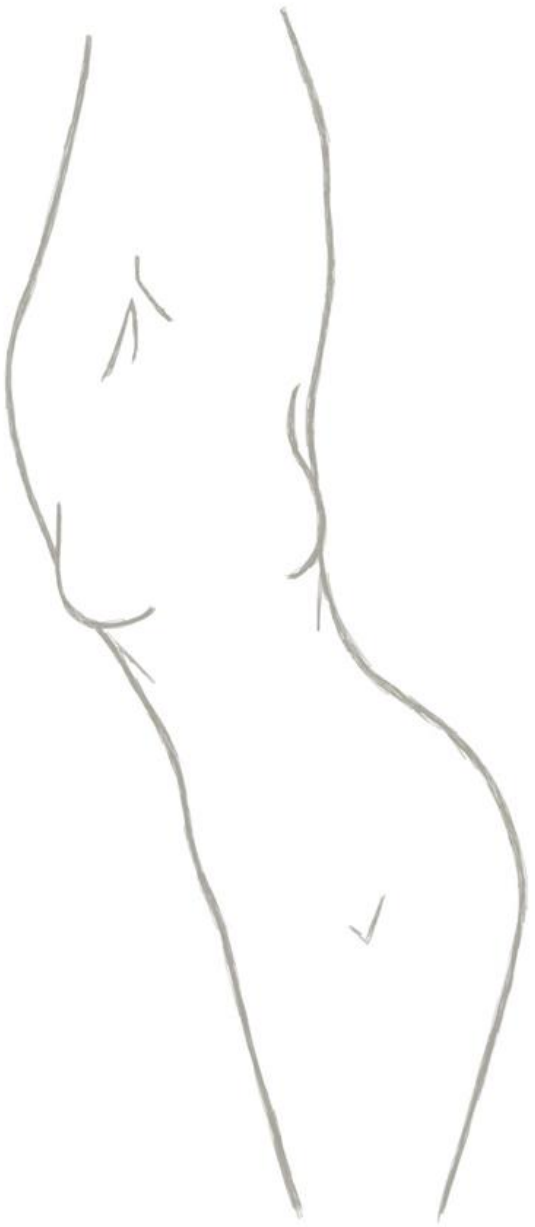
# Content

# 1

# General introduction



### 1.1 Cervical cancer epidemiology and the human papillomavirus

Cancer of the cervix uteri, caused by the human papillomavirus (HPV),[1] is the fourth most common cancer among women worldwide.[2] Globally, this type of cancer had an estimated 528,000 new cases and 266,000 deaths in 2012 (7.5% of all female cancer deaths; Figure 1.1). The largest part of the global burden, approximately 85%, occurs in the less developed countries where cervical cancer accounts for almost 12% of all female cancers. About 87% of cervical cancer deaths occur in these regions as well.

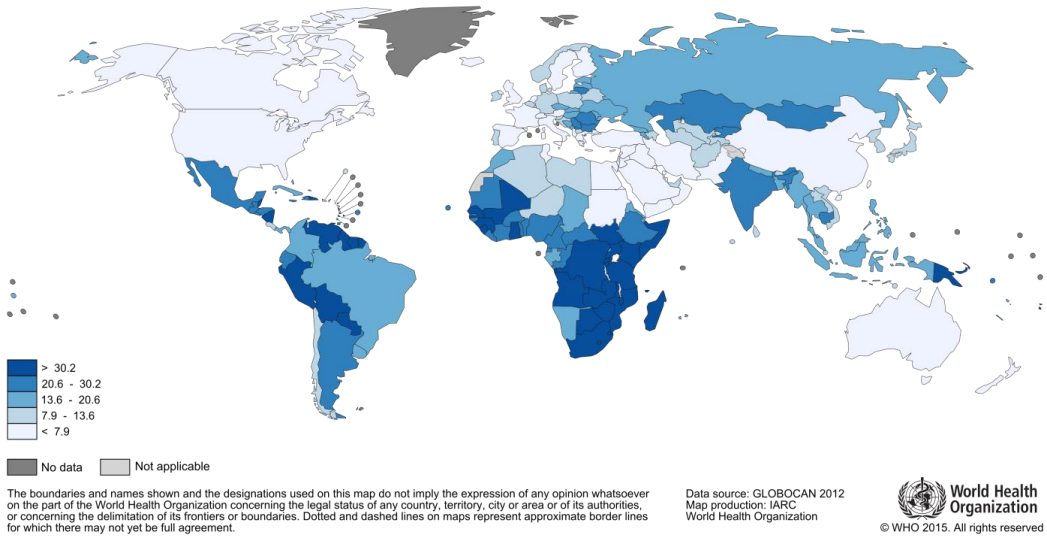



**Figure 1.1. Estimated cervical cancer incidence worldwide in 2012 (source: GLOBOCAN 2012).[2]**

In the Netherlands, cervical cancer occurs most often in women aged 30-54 years.[3] Compared to other countries, incidence and mortality are low in the Netherlands. On average, there are about 700 new cervical cancer cases each year, and around 200 deaths. Figure 1.2 shows that after a decreasing trend since 1990, incidence has again somewhat increased between 2004 and 2012.[4] Cervical cancer mortality has, however, nearly continuously decreased since 1990. These trends in incidence and mortality are likely influenced by the nationally organized screening program,[5] which has been in place since the 1980s. Factors such as the implementation of HPV vaccination in 2009 and the switch to HPV screening in 2017 are expected to influence future incidence and mortality. While HPV incidence will decrease due to HPV vaccination, the use of the more sensitive HPV DNA test may increase the number of detected HPV infections, and initially also cervical cancers. However, early

detection and subsequent removal of precancerous lesions are expected to eventually lead to a further reduction in cervical cancer incidence.[5]

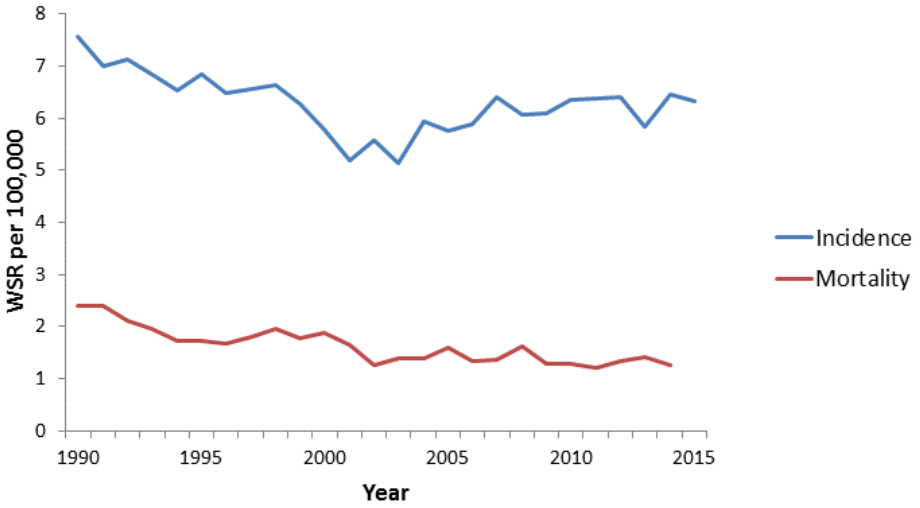



**Figure 1.2. World standardized rates (WSR) per 100,000 women of cervical cancer incidence and mortality in the Netherlands from 1990-2015 (source: Netherlands Cancer Registry).[4]**

*Human papillomavirus, natural immunity, and the etiology of cervical cancer*

In the late seventies, Harald zur Hausen postulated that cervical cancer is caused by an infection with oncogenic HPV.[6] This highly prevalent sexually transmitted virus consists of multiple types, of which over 150 types have been completely sequenced.[7] Currently, 14 HPV-types are considered high-risk for their potential to cause cervical cancer when the infection is persistent. High-risk HPV (hrHPV) prevalence reaches its peak, as high as 15% in the Netherlands, among young women aged 25-28 years (Figure 1.3).[8,9] New data recently showed that the overall hrHPV prevalence in the Netherlands might actually be twice as high as previously thought in the POBASCAM study.[10] In particular HPV types 16 and 18 are predominantly present in precancerous lesions, and approximately 80% of cervical cancer are attributable to these two types.[11] HPV is not only responsible for cervical cancer, but also linked to cancers of the vulva/vagina (for 32% of cases), penis (25%), anus (83%), oral cavity (3%), and oropharynx (11%).[12] While low-risk HPV (lrHPV) types have a lower potential for developing cervical cancer, they still contribute to disease burden through the potential development of genital warts, of which 90% can be attributed to HPV-6 and HPV-11.[13]

HPV has many mechanisms to avoid immune responses, such as hiding within host mucosal cells; minimizing the production of late proteins, thereby limiting detection opportunities by the host's immune system; and inhibition of innate immunity and cell-mediated response by early proteins.[14,15] However, a natural immune response does occur, indicated by detectable antibodies. It is still unclear

which elements of the natural immune system are important in preventing or clearing an HPV infection.[15] The large majority of HPV infections do clear naturally without progressing to cancer.[7,16] Prophylactic vaccines targeting HPV-16 and HPV-18 show some protection against other HPV-types as well, yet whether this so-called cross-protection also occurs with naturally acquired immunity is currently unknown. Reinfections associated with sexual behavior are observed as well,[16] suggesting that natural immunity can wane rapidly in some women. Understanding the role of naturally acquired immunity is crucial in predicting the impact of prevention strategies.

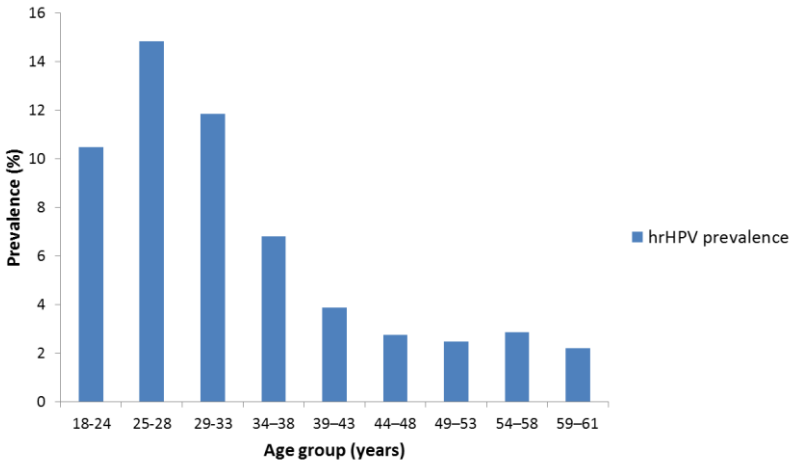



**Figure 1.3. High-risk HPV (hrHPV) prevalence in the Netherlands among women aged 18-61 years based on a study of Lenselink *et al.* and the POBASCAM study of Bulkmans *et al.*[8,9]**

HPV leads to the development of cervical cancer through different steps.[17] First, an infection of the metaplastic epithelium at the cervical transformation zone occurs. The infection can persist for a longer period of time, which can lead to the progression of the infected epithelium to cervical precancerous lesions. Only about 10% of oncogenic HPV infections persist for several years and are strongly associated with a high risk of precancerous lesions.[17] Finally, invasion takes place through the basement membrane of the epithelium, and cervical cancer develops (Figure 1.4).

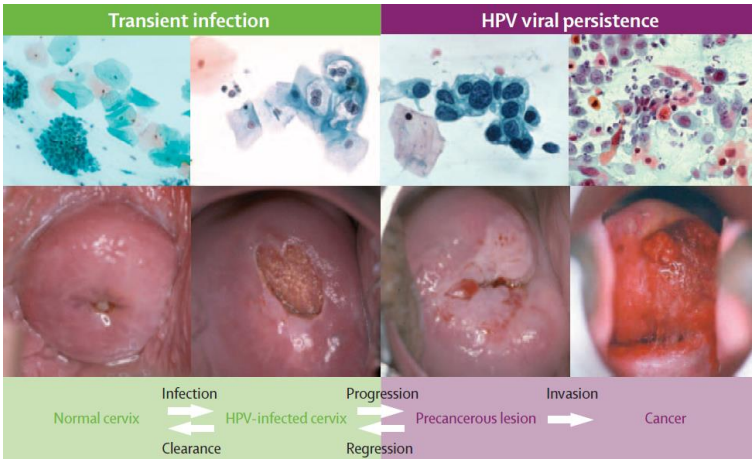



**Figure 1.4. The etiology of cervical cancer: from acquiring an HPV infection to developing precancerous lesions and cancer (figure from Schiffman *et al.*).[17]**

The precancerous lesions, or cervical intraepithelial neoplasia (CIN), are divided into three categories (CIN 1, CIN 2, and CIN 3) based on the severity of the neoplastic changes. The higher the grade of the lesion, the more severe is the replacement of the epithelium with atypical cells, and the higher the chance of progression to cervical cancer. Without screening and treatment, about 1%, 5%, and 12%, of CIN 1, CIN 2, and CIN 3, respectively, progress to cervical cancer,[18,19] a process that can take more than 15 years.[20] High risk HPV is detected in >80% of CIN 2 and CIN 3 lesions,[11,21] and virtually all invasive cervical cancers.[1] As previously mentioned, it has been estimated that approximately 80% of cervical cancers are caused by HPV types 16 and 18,[11] making them the most important high-risk types to target in prevention strategies. When an infection is acquired, early detection and treatment of CIN can prevent progression to cervical cancer.[22]

## 1.2 Cervical cancer prevention

*Cervical cancer screening*

In the Netherlands, an organized national cervical cancer screening program has been in place since the 1980s. Initially, screening was offered to women aged 35-53 years every 3 years.[23] New guidelines were introduced in 1996, in which women aged 30-60 years are invited for screening every 5 years. Screening consists of primary cytology with triage by repeat cytology or triage by a combination of repeat cytology and HPV testing.[24] Briefly, with the Papanicolaou or Pap test (also referred to as cervical smear), a brush is used to gather exfoliated cells from the histological transition zone, or outer opening of the cervix, in order to detect neoplastic abnormalities. When using conventional cytology, the collected cells are smeared on a slide and examined under a microscope. In the last decade, conventional cytology has been replaced by liquid-based cytology. The sample is

placed in a vial containing a cell preserving solution, centrifuged, and then processed into a thin layer of cells on a slide and stained, after which the sample is examined.[25]

Several randomized controlled trials have shown that screening using the hrHPV DNA test, which tests whether hrHPV is present, results in earlier detection of high-grade lesions. The hrHPV DNA test is also estimated to have a better negative predictive value for cervical cancer than cytology. New guidelines will therefore be implemented from 2017 onwards,[26] recommending primary HPV testing for women aged 30, 35, 40, 50, and 60 years. Additional HPV testing will be offered at ages 45 and 55 for women who do not attend or test positive for a hrHPV type at ages 40 and 50, respectively, and at 65 years if women test hrHPV positive at age 60 years. A self-sampling kit will be offered in this revised screening program for women who do not attend screening at the general practitioner.[26] The smears will first be tested for hrHPV DNA, and if positive, cytology triage testing on the same material and after 6 months will be carried out. Women with abnormal cytology will be referred to the gynecologist.

The severity of the cytological abnormalities determines the grading of the lesion, and thus whether treatment is recommended. CIN 1 is usually not treated given its high natural regression rate.[27] Lesions that are graded as CIN 2 or 3 have a higher progression risk to cervical cancer, and are therefore surgically removed, preferably by a large loop excision of the transformation zone (LLETZ), also referred to as loop electrosurgical excision procedure (LEEP). However, as not all CIN 2 or 3 lesions would have actually progressed to cancer, part are in fact unnecessarily treated. This overtreatment is associated with negative side effects, such as anxiety in women, increased risk of preterm birth, and, in few cases, with extremely low birth weight of infants, and perinatal mortality.[28]

*HPV vaccination*

Another area of innovation in the field is the development of several prophylactic vaccines, which followed recognition of HPV as a necessary cause for cervical cancer. First, two vaccines targeting HPV-16 and HPV-18 were licensed: the bivalent vaccine Cervarix (GlaxoSmithKline),[29] and the quadrivalent vaccine Gardasil (Merck), which additionally protects against low-risk types HPV-6 and -11.[30] More recently, the nonavalent vaccine has been developed as well (Merck), protecting against another five hrHPV types additional to the quadrivalent vaccine.[31] Several international randomized controlled trials have shown that the vaccines are efficacious and safe in girls, boys, and adults.[29,30,32,33] These trials show that highest protection is seen in young girls prior to sexual debut.[29] The exact duration of vaccine protection is not known yet, but the current follow-up of up to 10 years showed no signs of waning, suggesting long-lasting protection. While the vaccines are highly effective in preventing infection, they do not have therapeutic effects, and thus they do not accelerate infection clearance in infected individuals.[34]

Following these positive trial results, many countries have implemented HPV vaccination with either the quadrivalent or bivalent vaccine in the past years. Most vaccination programs focus on

pre-adolescent girls, although some countries (Austria, the US, Australia, Canada, and Liechtenstein) have included boys as well. Coverage among girls differs substantially between countries, ranging from 32% in the United States to >70% in Australia, and even exceeding 90% in Scotland.[35] In the Netherlands, the bivalent vaccine was offered to girls aged 13–16 years in a mass catch-up campaign in 2009, and subsequently introduced into the Dutch national immunization program with 12-year-old girls being eligible for vaccination.[36] Coverage of 58% was reached in 2013, which is much lower than the >90% coverage for other vaccinations included in this program.[37] However, the effects of vaccination are not only determined by vaccine coverage. Due to vaccination, overall HPV prevalence in the population will decrease, causing a lower infection risk for unvaccinated individuals as well.[38] This indirect protective effect of vaccination is often referred to as 'herd immunity'. Knowledge about the extent of this indirect protection in the population is crucial in estimating the cost-effectiveness of vaccination and of cervical cancer screening programs in the post-vaccination era.

The introduction of HPV vaccination and renewal of the cervical cancer screening program are expected to change the epidemiology of HPV and cervical cancer, and may increase the cost-effectiveness ratio of cervical cancer prevention. Vaccination is expected to reduce the population-level HPV prevalence and incidence. Due to herd immunity effects, also unvaccinated women will be at lower risk for developing cervical cancer. The new screening program, despite fewer lifetime screens than the current program, might therefore still be too intensive for a (partly) vaccinated population, especially if herd immunity effects are substantial. Also, the uptake and strategy of vaccination programs might change over time, influencing the impact of vaccination and therefore cervical disease burden. Ideally, when determining the cost-effectiveness of cervical cancer screening programs, both the direct and herd-immunity effects of vaccination should be considered.

### 1.3 Mathematical modeling

Mathematical modeling can be used to capture knowledge of the transmission and natural history of infectious diseases, and to estimate the epidemiological and public health impact of different types of interventions. Models are especially useful to answer research questions for which intervention trials would be impractical, unethical or might have negative consequences. Both deterministic and stochastic models can be used instead of trials to estimate the impact of different interventions and strategies. Deterministic models use fixed processes and ignore random chance.[39] Their output is solely determined by the parameter values and initial conditions, and is therefore always the same. Stochastic models incorporate random chance, and use probability distributions instead of unique parameter values. While deterministic models require less data and usually run much faster than the more complex stochastic models, several disadvantages are inherent to these types of models. Especially in disease dynamics, random chance plays a role, and deterministic models might be too simplistic to grasp these dynamics. Furthermore, they ignore individual heterogeneity, usually an

important factor in infectious disease transmission, especially those related to sexual risk behavior, and may not properly account for the complexity of transmission through sexual networks. Stochastic individual-based models incorporate randomness and individual heterogeneity, and allow for aspects to change with age and over time ('dynamic'), such as risk behavior and intervention participation. This type of models, while usually more computationally intensive, is therefore very suitable to study infectious disease dynamics and the impact of interventions.

*STDSIM for the transmission of HPV*

STDSIM is a stochastic microsimulation model which has been extensively used to model the heterosexual transmission and control of sexually transmitted infections (STIs).[40-43] The model was originally developed for sub-Saharan settings. In the model, each individual has its own characteristics that are either constant (e.g., date of birth, sex) or subject to change (e.g., number of sexual partners, infection status). The model consists of four modules: 1) demography; 2) sexual behavior; 3) STI transmission and natural history; and 4) interventions. The demography module includes all processes that determine the demographic structure of the population, i.e. fertility, mortality, and migration. The sexual behavior module simulates processes of starting and ending relationships, frequency of sexual contacts, and sexual mixing according to age preference. The module STI transmission and natural history defines the durations of disease states, transmission probabilities per sexual contact, and possible immunity. The interventions module describes the timing, attribution, and efficacy of different interventions.

All events are determined by probability distributions (see the appendices of Chapter 2), and can lead to new events (e.g., birth leads to a future event of becoming sexually active) or a cancellation of future events (e.g., death cancels all scheduled events concerning sexual activity or STI transmission for this person and to or from his/her partner).

For this thesis, we have quantified STDSIM to the Netherlands by adjusting parameters of demography and sexual behavior using Dutch demographic data and national sexual health surveys.[44-46] As self-reported data on sexual behavior can be difficult to interpret, we included the transmission of another common, short-lasting STI, chlamydia,[47] to validate the level of sexual risk behavior in our model. We then included HPV-16 and HPV-18 transmission, hysterectomies (removal of the uterus and cervix, which places the woman outside the transmission process in our model), vaccination efficacy, and vaccine uptake based on observational data.[29,32,37,48-51] More information on the structure, quantification, and model fit can be found in the appendices of Chapter 2.

*MISCAN-Cervix for the transition to disease states and cervical cancer screening*

The Microsimulation Screening Analysis (MISCAN) model is a microsimulation model originally developed to evaluate screening of disease.[52] The model produces output on the effects of screening procedures, morbidity and mortality, which can be used to explain and predict trends in cancer

incidence and mortality, and to quantify the effects of primary and secondary prevention. MISCAN-Cervix has been used extensively to model the harms and benefits of cervical cancer screening strategies and HPV vaccination in the Netherlands.[53-57] The model consists of three parts: 1) demography, 2) natural history, and 3) screening. In the demography module, a large population of women with individual life histories is simulated, based on Dutch demographic and hysterectomy data.[44,48] These women can acquire a hrHPV infection that is either transient or leads to the development of CIN in the natural history module. This process is based on age-specific probabilities assigning women to different pathways in MISCAN, which divide cervical disease into seven sequential stages: high-risk HPV infection; three pre-invasive stages (CIN 1, CIN 2, and CIN 3); and three invasive stages (International Federation of Gynecology and Obstetrics (FIGO) stages 1A, 1B, and 2 or higher). In the screening module, screening ages, triage strategies, test characteristics, and adherence to screening, triage and referral to colposcopy are defined. Finally, the number of life years spent in each disease state as well as the number of lifetime events (e.g. screening and cervical cancer diagnoses) are calculated, which can be used to determine the cost-effectiveness of screening. More information can be found in Supplements S5.2.

*Integrating STDSIM and MISCAN-Cervix*

While STDSIM and MISCAN-Cervix are both microsimulation models, the structures of these models are rather different (Table 1.1). STDSIM simulates a dynamic population of individuals that can interact by forming sexual relationships, through which HPV-16 and HPV-18 spread. The spread of HPV depends on sexual behavior, the prevalence of HPV-16 and HPV-18, the transmission probability per sexual contact, naturally acquired immunity, and intervention efficacy and uptake of the individual itself and of others. HPV-16 and HPV-18 incidence is the result of these transmission dynamics. Both direct and indirect (herd immunity) effects of interventions such as vaccination are thus inherent parts of the model. MISCAN-Cervix simulates a population of women that do not interact. Here, the emphasis is placed on cervical disease progression and how screening can detect the different stages. Infection acquisition does not occur through a sexual network, but HPV incidences in different age groups are input parameters of the model. Progression from an HPV infection to precancerous lesions and cervical cancer are subsequently modeled in detail.

From January 2017, the cervical cancer screening program in the Netherlands uses primary HPV screening. The first HPV vaccinated cohorts will reach the screening start-age (30 years of age) in the Netherlands in 2023. As mentioned above, screening should be evaluated in combination with the reduced cervical cancer risk due to vaccination. By using the age-specific HPV incidence over time estimated by STDSIM as input for MISCAN-Cervix, both the direct and indirect effects of vaccination can be incorporated in the evaluation of screening and the impact of vaccination on cervical disease.

**Table 1.1. Overview of differences and similarities between STDSIM and MISCAN-Cervix.**

| | STDSIM | MISCAN-Cervix |
|---|---|---|
| **Approach** | Microsimulation model of a population of individuals simulated simultaneously. | Microsimulation model of individuals simulated one at a time. |
| **Population** | Men and women. | Only women. |
| **Acquiring an HPV infection** | Transmission of HPV occurs through a dynamic sexual network. The transmission probability is modeled per sexual contact. Susceptibility to (re-)infection is reduced due to naturally acquired immunity after clearing an infection or interventions such as vaccination and hysterectomy. Coinfections of HPV-16 and HPV-18 can occur in the model. | Women acquire new high-risk HPV infections with age-specific incidence rates, depending on the background risk and whether the woman has had a hysterectomy. Multiple infections or lesions may be present simultaneously. |
| **Infection and cervical disease** | Only HPV-16 and HPV-18 are modeled in STDSIM. Other HPV-types and HPV-related cervical disease are not included in the model. | An HPV infection can either clear without cervical abnormalities or progress to cervical intraepithelial lesions (CIN). CIN can regress spontaneously or develop into cervical cancer. CIN 1 and CIN 2 can also occur without an HPV infection, in which case they will always regress. |
| **Interventions** | Vaccination can be offered with different efficacy and strategies (e.g. timing and target age groups). As transmission of HPV occurs through sexual contacts, both direct and herd immunity effects of vaccination are taken into account. Hysterectomy clears an existing infection immediately and prevents women from acquiring a new infection. | Screening can be implemented with different tests, start ages, intervals, test characteristics, and triage strategies. The disease stage that can be detected by screening depends on the type of screening method (i.e. cytology detects cervical abnormalities, while HPV screening detects an HPV infection). After detection of CIN or cancer, treatment is offered. |
| **Main outcomes** | HPV-16 and HPV-18 incidence and prevalence. | Prevalence of precancerous lesions, cervical cancer incidence and mortality, and life years spent in each disease state. |

### 1.4 Aim and research questions

The overall aim of this thesis is to study the transmission dynamics of HPV-16 and HPV-18 in the Netherlands, and to estimate the impact of vaccination on the HPV-16 and HPV-18 epidemic, and cervical disease burden after the renewal of the cervical cancer screening program. Improved understanding of the natural history of HPV, and especially the role of natural immunity, is crucial to accurately estimate the impact of HPV and cervical cancer prevention strategies. Thus, the first research question of this thesis is:

*1) What is the role of naturally acquired immunity following an infection in HPV transmission?*

After modeling the transmission dynamics of the two most oncogenic HPV types, we estimate the impact of the bivalent vaccine administered through different vaccination strategies in the Netherlands on the prevalence and incidence of HPV-16 and -18. This leads to the second research question:

*2) What is the impact of vaccination on HPV epidemiology in the Netherlands?*

The population-level prevalence and incidence of HPV will decrease due to vaccination in the upcoming years. It is crucial to estimate the cervical disease burden in light of different vaccination strategies and the renewal of the screening program. Thus, the final research question is:

*3) What is the impact of vaccination on cervical disease burden and its control in the Netherlands?*

### 1.5 Structure of this thesis

**Chapter 2** addresses the first research question. STDSIM is quantified to the Netherlands and used to explore the transmission dynamics of HPV-16 and HPV-18, to provide more insight into the natural history of HPV. Demographic data and national sexual health surveys are used to reproduce the Dutch population and its sexual network. Finally, HPV-16 and HPV-18 are introduced into the simulated population to estimate the transmission probabilities and acquired immunity dynamics, in order to reproduce the observed age-specific HPV-16 and HPV-18 prevalence.

Our second research question is addressed in Chapters 3 and 4. In **Chapter 3**, the impact of the current Dutch girls-only vaccination program on HPV-16 and HPV-18 is estimated using STDSIM. Alternative vaccination strategies are included as well, such as increasing coverage among girls and routine vaccination for boys. In **Chapter 4**, the girls-only program is extended by offering HPV vaccination to adults through a one-time mass campaign and in existing public health settings, i.e. during the first cervical cancer screening visit and at sexual health clinics.

Innovations in the cervical cancer screening program, i.e. the switch to primary HPV testing and fewer lifetime screens, will already take place from 2017 onwards, though the first vaccinated girls will not enter the screening program until 2023. Therefore, in **Chapter 5**, the potential harms of primary HPV screening for women who are intensively screened are assessed while considering only unvaccinated cohorts, using MISCAN-Cervix. Our final research question is subsequently addressed in Chapters 6 and 7. In **Chapter 6**, we investigated at what level of herd immunity it would be cost-effective to reduce screening intensity in unvaccinated women. Finally, by linking STDSIM with MISCAN-Cervix, the burden of cervical disease in the Netherlands is estimated under the new screening program in **Chapter 7**, assuming different vaccination scenarios.

In the general discussion, **Chapter 8**, the answers to all research questions will be summarized and discussed. Also, observational studies have shown that both HPV and HIV influence each other's acquisition. Not surprisingly, HPV and cervical cancer are highly prevalent in high endemic areas of HIV. We will therefore also perform some exploratory analyses on the association between HPV and HIV, specifically in KwaZulu-Natal, South Africa, using STDSIM. Lastly, overall conclusions will be drawn and recommendations will be provided.

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# 2

# The role of acquired immunity in the spread of human papillomavirus (HPV): explorations with a microsimulation model

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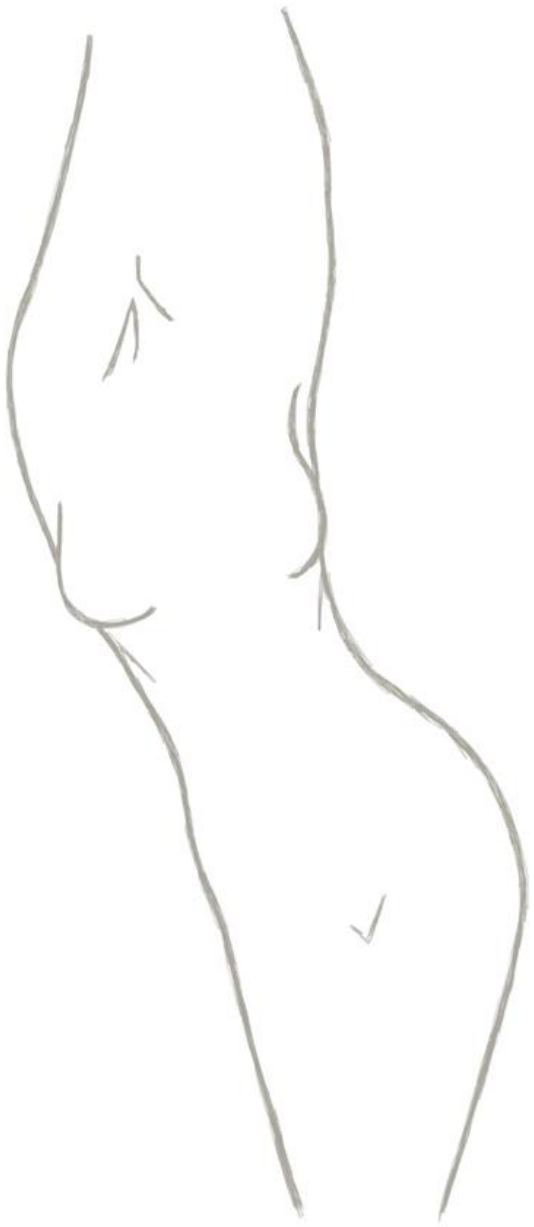

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**Abstract**

**Background**

Knowledge of the natural history of human papillomavirus (HPV), in particular the role of immunity, is crucial in estimating the (cost-) effectiveness of HPV vaccination and cervical cancer screening strategies, because naturally acquired immunity after clearing an infection may already protect part of the risk population against new HPV infections.

**Methods**

We used STDSIM, an established stochastic microsimulation model, quantified to the Netherlands. We explored different assumptions regarding the natural history of HPV-16 and HPV-18, and estimated the transmission probabilities and durations of acquired immunity necessary to reproduce age-specific prevalence.

**Results**

A model without acquired immunity cannot reproduce the age-specific patterns of HPV. Also, it is necessary to assume a high degree of individual variation in the duration of infection and acquired immunity. According to the model estimates, on average 20% of women are immune for HPV-16 and 15% for HPV-18. After an HPV-16 infection, 50% are immune for less than 1 year, whereas 20% exceed 30 years. For HPV-18, up to 12% of the individuals are immune for less than 1 year, and about 50% over 30 years. Almost half of all women will never acquire HPV-16 or HPV-18.

**Conclusions**

Acquired immunity likely plays a major role in HPV epidemiology, but its duration shows substantial variation. Combined with the lifetime risk, this explains to a large extent why many women will never develop cervical cancer.

## Introduction

Infection with human papillomavirus (HPV) is a necessary cause for developing cervical cancer,[1] the fourth most common cancer among women worldwide.[2] HPV is one of the most prevalent sexually transmitted infections (STI),[3,4] and over 118 different types have been identified.[5] At least 14 of these are considered high-risk types for cervical cancer due to their oncogenic nature after progressing for a longer period of time.[6] However, most HPV infections clear naturally. In the Netherlands, HPV prevalence in the general population (among women with normal cytology) was estimated to be 3.9% in 2010, with a peak in younger women.[7]

The bivalent vaccine Cervarix offers protection against HPV-16 and HPV-18, which account for 70–76% of the cervical cancers.[8] Cervarix was introduced in the Netherlands in 2009 for 12 year old girls with a catch-up campaign for girls aged 13–16 years, with a modest vaccine uptake of only 50%.[9] The vaccine was implemented in the national immunization program in 2010. A crucial factor in estimating the effect of vaccination is naturally acquired immunity, yet little is known about its degree and duration.[10] Understanding the transmission and immunity mechanisms of HPV is essential to adequately predict the (cost-)effectiveness of HPV vaccinations and cervical cancer screening strategies.

Several mathematical models have been developed to study the spread of HPV and immunity processes responsible for clearing an HPV infection.[11–17] Some of these models are deterministic,[13,14,17] and may not properly account for the complexity of transmission through sexual networks.[18] Also, only HPV prevalence data of limited age ranges are used,[16] or the transmission probability was estimated per sexual partnership instead of per sexual contact.[11,13,14] An exception is the study by Burchell *et al.* (2006), who estimated the median transmission probability at 40% per sex act, but ranging from a lower limit of 5% to an upper limit of 100%.[15] This wide range indicates that further research on the transmission probability per sexual contact is necessary, ideally by using more detailed data.

We explored the transmission dynamics of HPV-16 and HPV-18, especially regarding the process of acquired immunity, by reproducing the age patterns of type-specific HPV prevalence in the Netherlands,[19,20] using the established stochastic microsimulation model STDSIM. This model has been used extensively for heterosexual transmission and control of HIV and other STIs in African settings.[21–23] In the current study, we quantified the model to a Western setting for the first time. The transmission of chlamydia, [24, personal communication] of which more is known regarding its natural history, has been included in the model to validate our model fit of sexual behavior.

## Methods

*STDSIM and its quantification to the Netherlands*

STDSIM simulates the life course of individuals in a dynamic network of heterosexual contacts, in which STIs, such as HPV, can spread. Each individual has its own characteristics that are either constant (e.g., date of birth and sex) or subject to change (e.g., number of sexual partners, infection status). Events are determined by probability distributions, and can lead to new events (e.g., a birth leads to a future event of becoming sexually active) or a cancellation of future events (e.g., a death cancels all scheduled events concerning sexual activity or STI transmission for this person and to or from his/her partner). More information on the model structure can be found in the S1A Supporting Information.

We first used generally available information to quantify our model regarding demography and sexual behavior. Age- and sex-specific life expectancy and migration data[25] and age specific fertility rates[25,26] were used to quantify STDSIM such that it represents the Dutch demography. To model the sexual network structure, we used data from three national sexual health surveys.[27–29] We then simulated the transmission of chlamydia. Chlamydia is a short-lasting STI that is common among heterosexuals in the Netherlands, and was included to validate the level of risk behavior in the model. A detailed description of the model quantification for the Dutch setting and the transmission and natural history of chlamydia can be found in S1B-S1D Supporting Information.

*Transmission and natural history of HPV*

We simulated the transmission of HPV-16 and HPV-18. We assumed equal transmission probabilities per sexual contact for male-to-female and female-to-male transmission.[13,15,17] The transmission of both HPV types is independent given individual sexual risk behavior, and HPV transmission parameters were calibrated to make the model fit the observed age- and type-specific HPV prevalences.

Two important aspects distinguish the transmission of HPV from other STIs in our model. First, transmission can also occur through genital skin,[30] and previous research shows no association between condom use and HPV acquisition risk.[31] Therefore, we assumed that condoms do not have a protective effect against HPV, though they do protect against chlamydia. Second, we assumed that women who have had a hysterectomy cannot acquire an HPV infection, similar to other modeling studies.[13,14] We used age-specific data to model the fraction of women in the population who have had a hysterectomy.[32] In the model, women clear an existing HPV infection immediately after a hysterectomy, and are considered immune for future HPV infections.

We further assumed that the durations of infection and acquired immunity follow a Weibull distribution. The Weibull distribution is a continuous probability distribution, defined by a shape and scale parameter. If the shape parameter is set to 1, the distribution reduces to the exponential distribution. The shape parameters were varied with pre-set values of 0.25, 0.50, 1, 2, and 4. This allowed us to explore whether large (small shape parameter) or little (high shape parameter) individual

variation in the average duration of infection and acquired immunity would be consistent with the available data.

The mean duration of an HPV infection in women was based on the studies of Goodman *et al.*[33] and Trottier *et al.*,[34] which measured type-specific time to clearance of an incident infection in women with normal cytology within a large age range. Together, these studies resulted in a total sample size of 966 women aged 18–85 years. We first transformed the median durations reported by Goodman *et al.*[33] into mean durations, depending on the shape parameter of the Weibull distribution assumed. A weighted average of these results and mean durations as reported in Trottier *et al.*[34] was then used as the mean durations for each HPV type in our model (S2.3 Table). To obtain mean infection durations in men, we again transformed median durations based on the HPV in Men (HIM) Study of Giuliano *et al.*,[35] which included 1159 men aged 18–70 years.

In the base case analysis, we assumed that everyone acquires full immunity for some (Weibull distributed) time immediately after clearing an infection. During this period, an individual cannot acquire a new HPV infection, irrespective of whether this is due to the development of antibodies or other components of the adapted immune system. We varied the immunity duration from no immunity to effectively lifelong, and the transmission probability from 0% to 100%, to find parameter values that made the model most accurately reproduce the observed HPV prevalence trends with age (see section "Optimizing HPV parameters"). In addition, we assumed an alternative mechanism for acquired immunity based on the history of HPV infections, for which the methods and results are documented in S1E Supporting Information.

We used data on age-specific prevalence of high-risk HPV infections among women in the Netherlands from the POBASCAM study.[20] The POBASCAM study is a population-based randomized controlled trial (recruitment of women from 1999–2002) on the implementation of high-risk HPV testing in cervical screening, including 21,950 Dutch women between the ages of 29–61 years.[20] We added data from a cross-sectional study (2007) among women aged 18–29 years representative for the general population in the Netherlands, to include HPV prevalence data of young women outside the screening age.[19] Both studies only measured the overall high-risk HPV prevalence. Based on Coupé *et al.*, who also used POBASCAM data,[36] we calculated the age-specific fractions of each HPV type within the overall prevalence, and applied these fractions to the above mentioned data to obtain the type-specific HPV prevalence (S2.4 Table). We assumed a 94% HPV test sensitivity.[37,38]

*Optimizing HPV parameters*

We performed a grid search to determine combinations of transmission probabilities and mean duration of acquired immunity (Weibull distributed) for each HPV-type, and the 5 preset shape parameters of the Weibull distributions of the durations of infection and acquired immunity that result in the best fit to the type- and age-specific HPV prevalence. For each parameter combination, we ran the model 100 times. The best fit was based on the binomial log likelihood of the observed prevalence

data and model estimates summed over the age categories. The log-likelihood ratio is the difference between log-likelihoods of two different models.[39] To compare models, we performed likelihood ratio tests using the log-likelihood ratio times-2, which is approximately chi-squared distributed.

For the combinations of Weibull shapes with the best fit, we used a regression model of the transmission probability and acquired immunity duration as a metamodel.[39,40] First, we fitted the log-likelihoods of the grid to a second order polynomial regression model, as has been done by Fischer *et al.*[39] We then determined the optimal parameter combination of the transmission probability and acquired immunity duration, as well as 95% confidence intervals (CIs). We ran the model with this optimal parameter combination 1000 times, to precisely determine the predicted average age- and type-specific HPV prevalence. Finally, we performed a chi-squared test summed over the age categories to determine the goodness-of-fit of our model compared to the observed HPV prevalence.

Finally, we used the optimal model to estimate the age-specific proportion of women who are immune for HPV-16 and HPV-18, respectively. We accounted for uncertainty in the type specific transmission probability and the duration of acquired immunity by re-running the model with 200 alternative parameter combinations.[23] We randomly sampled combinations from the 95% CIs of the estimated transmission probabilities and immunity durations, and accepted them if the resulting age-specific HPV prevalence did not differ significantly from the optimal model predictions. Uncertainty ranges for the proportion of women with acquired immunity were subsequently obtained by taking the $5^{th}$ lowest value as lower bound and $5^{th}$ highest value as upper bound for each age group.

**Results**

Our model is able to accurately simulate the Dutch population (Fig. 2.1A), number of recent partners for men (Fig. 2.1B, left bars) and age difference in relationships (Fig. 2.1C and 2.1D). The model does show a larger proportion of women with 2 or more recent partners than reported in the surveys (Fig. 2.1B, right bars). However, especially for women, it is well-known that social desirability bias in self-reported sexual behavior often results in underreporting of the number of current or recent partners to make a more favorable appearance.[41,42] The modeled prevalence of chlamydia for both men and women is close to the observed prevalence levels given by Van den Broek *et al.* (Fig. 2.1E).[24, personal communication]

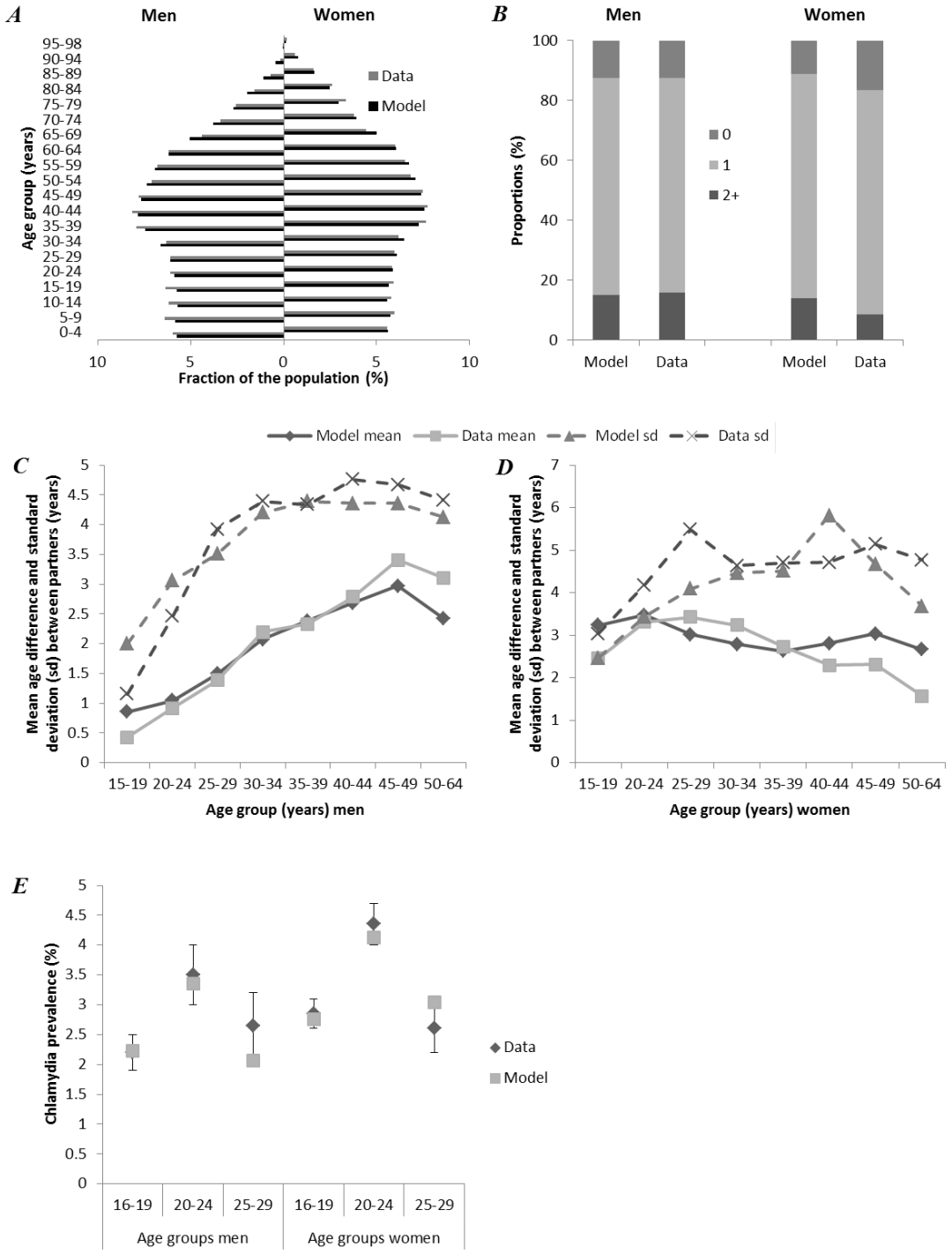


**Figure 2.1. Comparison of the model predictions with data of population composition, sexual behavior and chlamydia prevalence.** Modeled population composition per age group, compared to data of Statistics Netherlands (A).[25] Modeled number of partners in the last 6 months in men and women aged 20–64 years, compared to data of 19–64 years old in Rutgers WPF (B).[27,28] Mean and standard deviations (sd) of age differences in relationships, reported by male respondents (C) and female respondents (D). Modeled chlamydia prevalence of 15–29 years old compared to the data of Van den Broek *et al.* (2012) [24] of 16–29 years old (E).

Fig. 2.2 shows the best estimated HPV-16 and HPV-18 prevalence when assuming no immunity, exponential distributions, and Weibull distributions. A model without acquired immunity clearly cannot reproduce the age-specific patterns in the prevalence of HPV-16 and HPV-18 (Fig. 2.2). The prevalence is underestimated in women aged 25–33 years, while overestimated in older age groups. For both HPV-types, it is also not sufficient to assume exponential distributions for the duration of infection and acquired immunity. While the best fitting model for HPV-16 still deviates from the data for women aged 18–33 years ($\chi^2$ (5) = 15.26, $p$ =.009; S2.1F Supporting Information, S2.5 Table), it provides a significantly better fit than the model without immunity ($\chi^2$ (4) = 43.88, $p$<.001), and the model with exponential distributions ($\chi^2$ (4) = 53.24, $p$ <.001). This best fitting model had Weibull shape parameters of 0.50 and 0.25 for the duration of infection and immunity, respectively, corresponding with half of the men and over 70% of women clearing their infection within 1 year (S2.3 Table). In this model, almost 50% of the individuals are no longer immune 1 year after clearing the infection (S2.6 Table). Still, about 20% have an estimated duration of acquired immunity that lasts longer than 30 years. The corresponding estimated transmission probability is 6.9% per sexual contact (95% CI: 5.4; 8.6).

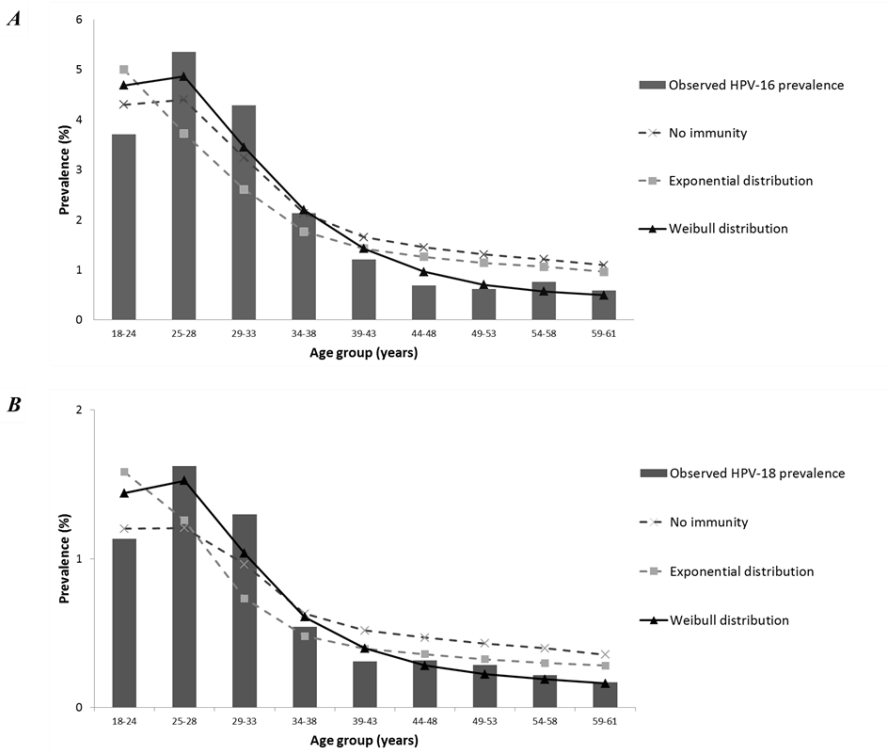


**Figure 2.2. Comparison of the observed and estimated age-specific HPV prevalence.** The estimated prevalence is given by the best fitting models of the different scenarios. These scenarios include no acquired immunity after clearing an infection (exponential distribution for the duration of infection); exponentially distributed durations; Weibull distributed durations. (A) shows the results for HPV-16; (B) for HPV-18.

For HPV-18, we found similar individual variation in the infection duration compared to HPV-16. The corresponding Weibull shape of 0.50 suggests that 62% of men and 69% of women clear their infection within 1 year (S2.3 Table). For almost 15% of men and over 9% of women, infection lasts longer than 4 years. The model with immunity fits the data significantly better than the model without immunity, in which the prevalence is underestimated in women aged 25–33 years and overestimated in women aged 34+ years (Fig. 2.2B, S2.5 Table). The model with Weibull distributions fits the data better than with exponential distributions, which shows similar deviations as the model without immunity (Fig. 2.2B, S2.5 Table). Fits using Weibull shapes of 0.50, 1, 2, and 4 are comparable, indicating that the shape parameter of the duration of immunity is less important for HPV-18 compared to HPV-16. These shape parameters correspond with 42–50% of the individuals having an estimated duration of acquired immunity longer than 30 years, while only 0–12% is immune for less than 1 year after clearing the infection (S2.6 Table). Corresponding estimated transmission probabilities for the model range from 6.7% (95% CI: 5.4; 8.3) to 9.0% (95% CI: 5.7; 13.0) per sexual contact. This model shows no significant deviations from the observed HPV-18 prevalence (S2.5 Table).

The best fitting model for HPV-16 and HPV-18 suggests that approximately half of the women in the model will have an HPV-16 infection in their lifetime (Fig. 2.3A), and 25% an HPV-18 infection (Fig. 2.3B). About 46% of women will never acquire either an HPV-16 or HPV-18 infection in our model (Fig. 2.3C). The proportion of women who are immune to HPV- 16 is higher than HPV-18, peaking at 22% of women aged 30–39 years for HPV-16 (Fig. 2.4A) and 15% of women aged 30–44 years for HPV-18 (Fig. 2.4B).

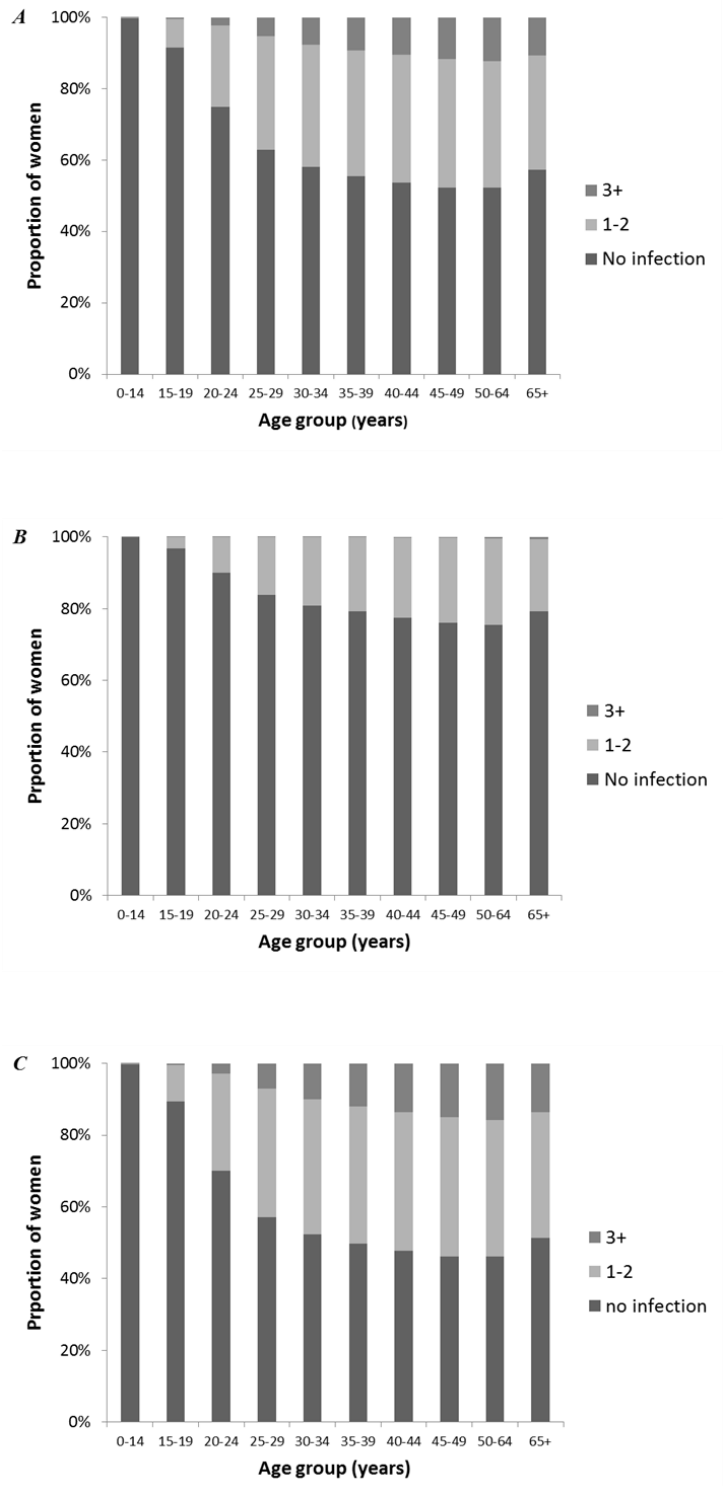


**Figure 2.3. Predicted cumulative number of HPV-16 (A), HPV-18 (B), and HPV-16/-18 (C) infections in women.** The proportion of women with no lifetime infections slightly increased in women aged 65+ compared to women aged 50–64 years. This results from a cohort effect due to a combination of historical data on fertility rates and timing of an increase in migration (1965), and will only have a minimal effect on our estimates.

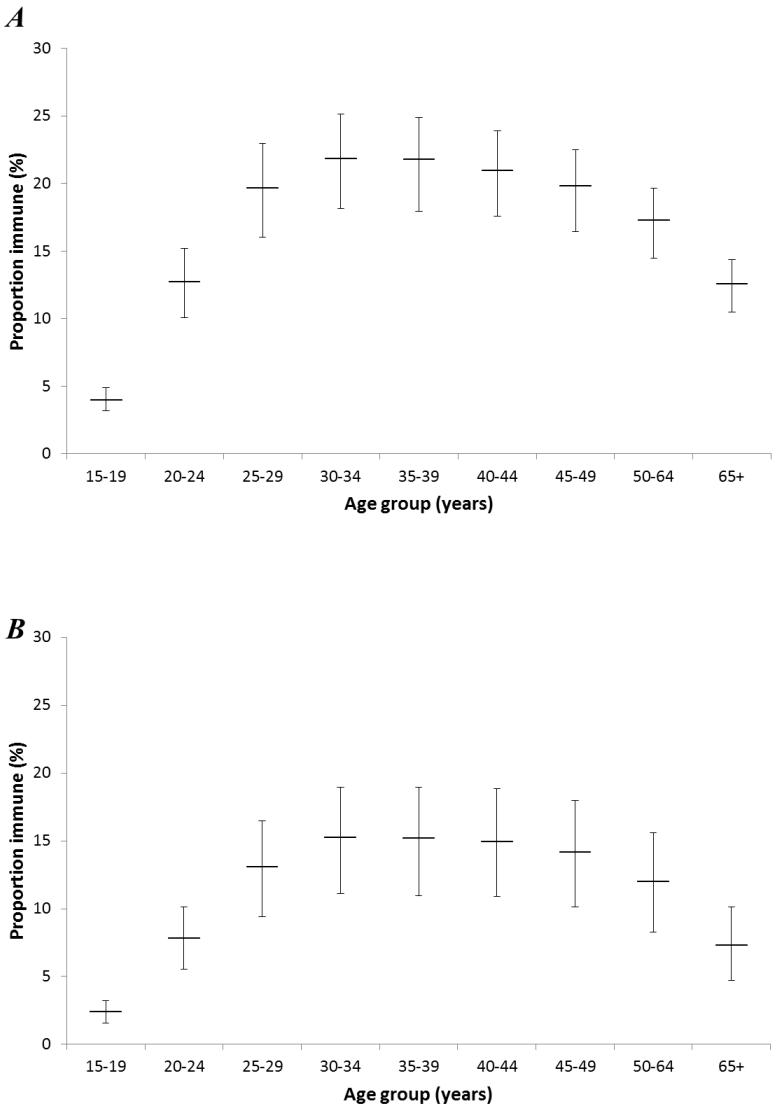


**Figure 2.4. The distribution of acquired immunity in the best fitting model for HPV-16 (A) and HPV-18 (B).** Bars reflect uncertainty ranges (see Methods).

## Discussion

In this study we quantified STDSIM to a high-income country for the first time. The model was able to accurately replicate the Dutch population and sexual network. Our estimates indicate that including a mechanism of acquired immunity is essential to adequately explain the age patterns of HPV prevalences in the Netherlands. Also, our model suggests that there is large individual variation in the duration of infection and acquired immunity. This is especially the case for HPV-16, for which, in our model, 50% of the individuals are immune only for less than a year after clearing an infection, yet 20% for longer than 30 years. For HPV-18, a higher proportion will develop long lasting acquired immunity.

Our finding that large individual variation exists in naturally acquired immunity is consistent with Mikolajczyk *et al.*,[43] who concluded that the observed distribution of antibody titers reflects individual differences in immune response. We found that, especially for HPV-16, most women only become immune for a relatively short period of time (less than 1 year) after clearing an infection. This concurs with earlier findings of an association between re-infections and sexual activity,[44] likely due to rapidly waning immunity after clearing an infection in some women. In addition, studies found that only 40–60% of previously infected individuals have detectable antibodies shortly after an infection,[45,46] further suggesting that many women were immune for a short period of time or not at all. Surprisingly, our results suggest that acquired immunity lasts longer than 30 years for about half of the people after clearing an infection of HPV-18, whereas the proportion of people with acquired immunity less than 1 year is minimal, ranging from 0.07% to 12% in the best fitting model. Baussano *et al.*[47] also found in his model that a larger proportion of individuals developed lifelong immunity for HPV-18 compared to HPV-16. It could be that, for those developing naturally occurring antibodies, the amount of protection may be different between HPV-16 and HPV-18.[48] Possible reasons behind these contrasting findings should follow from clinical research.

We also found that some degree of individual variation must be assumed in the duration of infection. This variation in infection duration could to some extent be attributable to latent undetectable infections and might be difficult to measure in observational studies. While some infections might appear as two separate infections in observational studies, they could be an ongoing long-term infection that might have been latent during follow-up visits. On the other hand, very short infections might not be detected since they could fall between follow-up visits.[49]

Our model for HPV-18 has a good model fit and does not deviate significantly from the observed prevalence data. For HPV-16, the model shows a slightly worse fit to the data. In particular, it overestimates the HPV-16 prevalence for women aged 18–24 years, and shows a small underestimation for women aged 25–33 years. This may be due to dynamics in natural history specific to HPV-16 that are difficult to capture in models. However, the differences are relatively small and are unlikely to influence our results.

Our study has some limitations. First, we ignored effects as a result of cervical cancer and cervical cancer screening on HPV transmission. Infections only clear naturally in our model and not through the removal of high-grade lesions. However, the majority of infections does not end by treatment of cervical neoplasia. Hence, the underestimation of the transmission probability per sexual contact is likely minimal. Second, the Weibull shapes in our model for the duration of infection and acquired immunity are only fitted using pre-set parameter values. Limited data did not allow a more precise assessment of shapes. Thus, individual variation in reality could somewhat differ from the best fitting model parameters chosen in our study. Third, we assumed that the durations of infection and immunity are randomly drawn. It could be that these durations depend on individual characteristics, such as age, history of HPV infections, or individual factors related to the immune system. Fourth, we

did not incorporate cross-protection of immunity between HPV-16 and HPV-18 in our model. Clinical trials have shown that the HPV-specific vaccines protect to some extent against other HPV-types as well,[50] indicating that cross-protection may also exist in naturally acquired immunity. However, the extent of cross protection of acquired immunity against HPV-16 and HPV-18 is currently unknown, and we have therefore not incorporated it in our model. A particular strength of our study is that we did not rely on HPV prevalence data based on opportunistic cervical screening for younger women (outside of the age range of the Dutch cervical cancer screening program). A representative sample was used instead, leading to more reliable age-specific patterns which are crucial in understanding the natural history of HPV.

Our model suggests that the lifetime risk of acquiring an HPV-16 or HPV-18 infection for women is about 50%. This is nearly as high as the risk of only HPV-16, indicating that many women with an HPV-18 infection will also acquire an HPV-16 infection in their lifetime. In our model, acquired immunity for HPV-16 and HPV-18 infections peaks at 22% and 15% of women respectively, and especially those with long-term acquired immunity will benefit less from vaccination as they are already protected naturally. In addition, women who develop immunity are the women with the highest risk, given their history of an HPV infection. Therefore, even though HPV vaccination will certainly decrease individual risks of cervical cancer, many women would not really need it since they will never acquire an HPV-16 or HPV-18 infection during their lifetime, and others are already protected because of naturally acquired immunity after clearing an infection. Clearly, vaccines will be most effective when targeted at young women, at an age before starting sexual relationships and being exposed to HPV for the first time. As the indirect effects of vaccination depend on the sexual network, acquired immunity, vaccine coverage, and target groups, a model is essential to further study the (cost-)effectiveness and optimal delivery strategies of HPV vaccination in preventing cervical cancer.

We also explored an alternative mechanism for acquired immunity after clearing an HPV-16 or HPV-18 infection (S2.1E Supporting Information). In this mechanism, women are not fully immune for variable duration, yet their susceptibility to re-infection reduces cumulatively after each infection. For both HPV-types, we found similar individual variation in infection duration and transmission probabilities compared to the base case mechanism. It was again necessary to assume acquired immunity after clearing an infection. Also under this mechanism, about half of the women will never acquire HPV-16 or -18. The alternative mechanism did show a worse fit to the observed prevalence data.

In conclusion, we show that, using a mathematical model, acquired immunity likely plays a major role in HPV epidemiology. While our model suggests that most people are only immune for a short period of time after clearing an HPV-16 infection, acquired immunity is long-term for most people after clearing an HPV-18 infection. The proportion of women being immune for HPV-16 and HPV-18 and lifetime risk for an HPV-16 and HPV-18 infection already explains to a large extent why most women will never develop cervical cancer.

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# 2

## Supplements

S2.1A: General model structure

S2.1B: Demography

S2.1C: Sexual behavior

S2.1D: Chlamydia

S2.1E: Alternative acquired immunity mechanism

S2.1F: Parameter values and goodness-of-fit of the best fitting models for HPV-16 and HPV-18

**S2.1A: General model structure**

STDSIM has four main modules: (1) demography, (2) sexual behavior, (3) STI transmission and natural history, and (4) interventions.[1-4] The demography module contains processes that determine the demographic structure of the simulated population, such as fertility, mortality, and migration. The sexual behavior module includes the processes of starting and ending relationships, frequency of sexual contacts, and age mixing patterns. The module of STI transmission and natural history defines the duration of disease stages, STI symptoms, transmission probabilities per sexual contact and possible immunity processes. Finally, the interventions module describes the timing, effectiveness and further consequences of treatments, as well as condom use.

Thus far, STDSIM has only been used for sub-Sahara African settings.[1-3] We quantified the model for the first time to a Western situation, by adjusting parameters of demography, sexual behavior, and chlamydia transmission, and by including HPV transmission, HPV natural history and hysterectomies based on observational data for the Netherlands. Details regarding these adjustments, as well as an alternative mechanism for acquired immunity against HPV, goodness-of-fit procedures, and parameter values for the best fitting models of HPV-16 and HPV-18 are given below.

**S2.1B: Demography**

We used data from Statistics Netherlands to reproduce an average Dutch population.[5] Model runs start in 1911 with almost 10,000 men and over 10,000 women. New individuals enter the model through birth and immigration, while deaths and emigration remove individuals from the population. New births are randomly assigned to sexually active women in the age range 15-49 years. We used age-specific fertility rates to assign births proportionally to observed fertility patterns across different age-groups.[5,6] After birth, each individual is assigned a date of death, which is drawn from a pre-defined life-table. We used life expectancy data of the Dutch population in 2008 to construct an age- and sex-specific life table representative for the general population in the Netherlands.[5] Finally, we used the average of the age- and gender-specific migration rates of the Dutch population from 2000-2008 to simulate immigration and emigration.[5] The simulated population consists of about 80,000 men and

women in 2008. The simulated population was compared to data of the population composition of the Netherlands in 2008 (Figure 2.1A).[5]

**S2.1C: Sexual behavior**

We adjusted model parameters for sexual behavior from the sub-Saharan applications based on data mentioned below to be able to reproduce the Dutch sexual network. Adjustments include the oldest age category, tendencies for more recent or concurrent partners by adjusting the promiscuity factors and steady relationship probabilities, and the age preference matrix, to correspond with the available data on Dutch sexual behavior, as described below.

People become available for a sexual relationship at the 'age of sexual debut', which is randomly drawn from a uniform distribution. The average age of sexual debut is 17 years for women and men, ranging from 12-22 years.[7-10] When an individual is available, he or she can be selected by someone from the opposite sex who is at the end of his or her availability period. The duration of this period is drawn from an exponential distribution (Table S2.1). If the individual has not been chosen, he or she will select a partner from the pool of available persons of the opposite sex at the end of his or her availability period (uniformly distributed). Each time a relationship is formed or ended, a duration until the person becomes available for a new relationship is drawn from a predefined exponential distribution. For more information on the mechanisms and formulas, see also Hontelez *et al.* (2013).[3] The age- and sex-specific promiscuity factors (Table S2.1), which reflect the tendency of individuals to form relationships, were fine-tuned individually so that the model accurately reproduces the observed number of recent partners of men (Figure 2.1B).

Two types of sexual relationships are considered: long-term ('steady') relationships such as marriage (average duration of 40 years), and short-term ('casual') relationships (average duration of 1 year), both exponentially distributed. The type of relationship depends on the age of the male partner, and is defined as the (age-specific) probability of a steady relationship (Table S2.1). Every relationship starts with a sexual contact. After each contact, the time until a new sexual contact within the relationship is drawn from an exponential distribution. The mean frequency of sexual contacts depends on the age of the male partner. The sexual contact frequency within a relationship is on average once every 2 days for individuals up to 20 years old, decreasing to once per week for individuals from 21 to 35 years and once every two weeks for people older than 35 years.[10, personal communication] The average duration of a relationship is drawn from an exponential distribution, depending on relationship type.

**Table S2.1. Sexual behavior parameters adjusted from previous STDSIM applications in order to reproduce to Dutch sexual network.**

| | | Men | Women |
|---|---|---|---|
| Age-specific promiscuity | 0-14 | 2.9 | 2.6 |
| | 15-19 | 2.9 | 3.8 |
| | 20-24 | 7.2 | 5.5 |
| | 25-29 | 6.1 | 2.6 |
| | 30-34 | 5.6 | 2.9 |
| | 35-39 | 2.3 | 0.7 |
| | 40-44 | 1.8 | 0.5 |
| | 45-49 | 1.6 | 0.3 |
| | 50-64 | 1.6 | 0.3 |
| | 65+ | 1.6 | 0.3 |
| Probability of a steady relationship | 0-14 | 0 | N/A* |
| | 15-19 | 0.05 | N/A* |
| | 20-24 | 0.3 | N/A* |
| | 25-29 | 0.4 | N/A* |
| | 30-34 | 0.5 | N/A* |
| | 35-39 | 0.8 | N/A* |
| | 40-44 | 0.9 | N/A* |
| | 45-49 | 0.95 | N/A* |
| | 50-64 | 0.95 | N/A* |
| | 65+ | 0.95 | N/A* |
| Average time to availability (exponentially distributed) | single | 1 year | 1 year |
| | casual relationship | 11 years | 20 years |
| | steady relationship | 100 years | 100 years |
| Maximum duration availability period (uniformly distributed) | | 1 year | 2.25 years |

** determined by the age of the male partner*

The probabilities of selecting a partner in a certain age class are defined in an age preference matrix (Table S2.2). When there is no partner available in that specific age class, the remaining age groups with a probability larger than 0 are used instead of resampling. The probabilities in the matrix were adjusted from sub-Saharan applications of STDSIM in order to reproduce the sexual age mixing patterns based on the national survey of the Rutgers WPF as reported by Schmid *et al*. (Figure 2.1C, 2.1D).[11] According to the data, the number of relationships between young people and much older individuals is negligible, hence we do not allow them to occur in the model at all. Per individual age group, we increased the probability of a relationship with partners with a similar age.

**Table S2.2. Age preference matrix for men and women, adjusted to reproduce the observed age differences in relationships.**

| | | **Age of partner (years)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0-14 | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-64 | 65+ |
| **Age men** | 0-14 | 0.80 | 0.20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **(years)** | 15-19 | 0.25 | 0.75 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 20-24 | 0 | 0.17 | 0.80 | 0.03 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 25-29 | 0 | 0 | 0.25 | 0.65 | 0.10 | 0 | 0 | 0 | 0 | 0 |
| | 30-34 | 0 | 0 | 0.05 | 0.35 | 0.55 | 0.05 | 0 | 0 | 0 | 0 |
| | 35-39 | 0 | 0 | 0 | 0.08 | 0.37 | 0.55 | 0 | 0 | 0 | 0 |
| | 40-44 | 0 | 0 | 0 | 0 | 0.10 | 0.45 | 0.45 | 0 | 0 | 0 |
| | 45-49 | 0 | 0 | 0 | 0 | 0 | 0.10 | 0.45 | 0.45 | 0 | 0 |
| | 50-64 | 0 | 0 | 0 | 0 | 0 | 0 | 0.10 | 0.40 | 0.50 | 0 |
| | 65+ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.05 | 0.20 | 0.75 |
| **Age women** | 0-14 | 0.85 | 0.15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **(years)** | 15-19 | 0.10 | 0.85 | 0.05 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 20-24 | 0 | 0.05 | 0.55 | 0.25 | 0.10 | 0.05 | 0 | 0 | 0 | 0 |
| | 25-29 | 0 | 0 | 0 | 0.50 | 0.35 | 0.15 | 0 | 0 | 0 | 0 |
| | 30-34 | 0 | 0 | 0 | 0 | 0.50 | 0.35 | 0.15 | 0 | 0 | 0 |
| | 35-39 | 0 | 0 | 0 | 0 | 0 | 0.45 | 0.30 | 0.25 | 0 | 0 |
| | 40-44 | 0 | 0 | 0 | 0 | 0 | 0 | 0.45 | 0.35 | 0.20 | 0 |
| | 45-49 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.50 | 0.45 | 0.05 |
| | 50-64 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.65 | 0.35 |
| | 65+ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.25 | 0.75 |

Independent from their sexual relationships, we modeled a high-risk group with more frequent one-off contacts (on average 2.25 contacts per month) to match the proportion of participants (11%) that reported to have 21 or more lifetime sexual partners in a Dutch survey.[8,10] We used the STDSIM mechanisms originally designed for commercial sex work to this end.

By allowing for variation between individuals in the age of sexual debut and the number, type and overlap of sexual contacts as described above, heterogeneity in the population was taken into account. The fit of the sexual network was checked verified using the age differences in relationships,[11] the number of recent partners[8,10] and the chlamydia prevalence (see Figure 2.1).[12, personal communication]

**S2.1D: Chlamydia**

The transmission probability of chlamydia is assumed to be 0.45 per sexual contact, based on the model of Gray *et al.*,[13] which has contact frequencies similar to the Dutch survey data. The assumed average duration of infections is 52 weeks in women[2,14-16] and 28 weeks in men.[14,17] The susceptibility to re-infection is reduced by 30% after each successive infection, based on observations on ocular chlamydia.[18] Chlamydia symptoms occur within 4 weeks (uniformly distributed) in 50% of the men and 30% of the women.[14,19] Symptomatic men and women get tested with a test specificity of 99% and sensitivity of 98%.[20] Patients receive treatment after a positive test result, leading to 100% cure of the infection, after which they become susceptible again. Their susceptibility is reduced by 30% after each successive infection, similar to individuals who naturally clear their infection. In our model, condoms have a protective effect against the transmission of chlamydia (yet do not protect against HPV, see main text) and were used in 7% of the sexual contacts in long-term relationships and 50% in short-term relationships and one-off contacts with a failure rate of 11.8%, based on the Dutch national sexual health survey.[8] Data of the chlamydia prevalence came from the Chlamydia Screening Implementation (CSI) study in three regions in the Netherlands (Amsterdam, Rotterdam, and South Limburg) for 16 to 29-year old residents from 2008-2010.[12, personal communication] We used the prevalence estimates for the Limburg area as national level estimates, as was also done by Schmid *et al.* (2013).[19]

**Table S2.3. The duration of infection when assuming different values for the shape parameter of the Weibull distribution of HPV-16 and HPV-18 infections.** The distribution is a weighted average based on the studies of Trottier *et al.*[24] and Goodman *et al.*[25] Bold numbers indicate the Weibull shape and corresponding duration of infection for the best fitting models.

| | Weibull shape | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean duration (months) | < 1 yr | 1-4 yr | >4 yr | Mean duration (months) | < 1 yr | 1-4 yr | >4 yr |
| **HPV-16** | 0.25 | 1268.4 | 49.9% | 12.5% | 37.7% | 140.5 | 69.8% | 11.8% | 18.4% |
| | **0.50** | **50.8** | **49.7%** | **25.0%** | **25.3%** | **15.6** | **71.1%** | **20.6%** | **8.4%** |
| | 1 | 17.6 | 49.4% | 44.0% | 6.5% | 12.2 | 62.7% | 35.4% | 1.9% |
| | 2 | 13 | 48.8% | 51.2% | 0.0% | 11.7 | 56.2% | 43.8% | 0.0% |
| | 4 | 12.1 | 47.7% | 52.3% | 0.0% | 11.6 | 53.7% | 46.3% | 0.0% |
| **HPV-18** | 0.25 | 655 | 55.7% | 12.7% | 31.6% | 201.8 | 66.5% | 12.2% | 21.3% |
| | **0.50** | **26.2** | **61.6%** | **23.7%** | **14.8%** | **17.2** | **69.3%** | **21.3%** | **9.4%** |
| | 1 | 9.1 | 73.3% | 26.2% | 0.5% | 12.2 | 62.7% | 35.3% | 1.9% |
| | 2 | 6.7 | 91.9% | 8.1% | 0.0% | 11.5 | 57.7% | 42.3% | 0.0% |
| | 4 | 6.3 | 100.0% | 0.0% | 0.0% | 11.3 | 57.2% | 42.8% | 0.0% |

**Table S2.4. Observed high-risk HPV (hrHPV) prevalence with the type-specific fractions and the corresponding type-specific prevalence per age group.** The observed high-risk HPV prevalence is based on the studies of Lenselink *et al.*[21] and Bulkmans *et al.*[22] By applying the fractions observed in Coupé *et al.*,[23] we obtained the type-specific HPV-16 and HPV-18 prevalence.

| Age-group (years) | Observed hrHPV prevalence (%) | Type-specific fractions | | Type-specific HPV prevalence (%) | |
|---|---|---|---|---|---|
| | | HPV-16 | HPV-18 | HPV-16 | HPV-18 |
| 18-24 | 10.50 | 0.35 | 0.11 | 3.71 | 1.13 |
| 25-28 | 14.83 | 0.36 | 0.11 | 5.35 | 1.62 |
| 29-33 | 11.87 | 0.36 | 0.11 | 4.28 | 1.3 |
| 34-38 | 6.82 | 0.31 | 0.08 | 2.13 | 0.54 |
| 39-43 | 3.87 | 0.31 | 0.08 | 1.21 | 0.31 |
| 44-48 | 2.76 | 0.25 | 0.12 | 0.69 | 0.32 |
| 49-53 | 2.49 | 0.25 | 0.12 | 0.62 | 0.29 |
| 54-58 | 2.86 | 0.27 | 0.08 | 0.76 | 0.22 |
| 59-61 | 2.22 | 0.27 | 0.08 | 0.59 | 0.17 |

**S2.1E: Alternative acquired immunity mechanism**

In our study, we also explored the possibility of an alernative mechanism for acquiring immunity after clearing an HPV infection, instead of a certain period of full immunity with Weibull distributed duration. In this alternative mechanism, we assumed that the susceptibility to re-infection decreases cumulatively after clearing each new infection. This way, the number of past infections directly influences the degree of protection. In this mechanism, we only estimated the Weibull shape of the duration of infection, the transmission probability per sexual contact, and the proportion of reduced susceptibility. To determine the best fitting model, we varied immunity from no immunity to 100% reduced susceptibility after each infection, and the transmission probability from 0% to 100% per sexual contact.

When assuming this mechanism, our results show again that a model with acquired immunity fits the HPV prevalence data for HPV-16 ($\chi^2 = 42.74$, $p < .001$) and HPV-18 ($\chi^2 = 10.64$, $p = .014$) much better than a model without acquired immunity, which underestimates the prevalence in women aged 25-33 years and overestimates the prevalence in women older than 39 years (Figure S2.1, Table S2.5). Again, a model with a Weibull distribution for the duration of infection instead of an exponential distribution fits better for HPV-16 ($\chi^2 = 47.04$, $p <.001$), which shows large overestimations of the prevalence in women aged 18-28 years, and underestimations in women older than 29 years (Figure S2.1A). The corresponding Weibull shape for the duration is 0.50, equal to the base case mechanism. In this model, the susceptibility for re-infection is reduced by 58% after each infection (Table S2.6). The corresponding transmission probability is 5.3% (95% CI = 4.6; 6.1) per sexual contact. While this is the best fitting model, it still shows an overestimation in women aged 18-24 years and underestimation in women aged 25-33 years and older than 54 years ($\chi^2 = 19.14$, $p = .004$).

For HPV-18, a model with a Weibull shape of 0.50 yields the best model fit to the observed data based on visual assessment and Pearson's chi squared value (Figure S2.1B, Table S2.5), though the difference with a model with an exponentially distributed infection duration is not significant ($\chi^2 = 7.06$, $p = .07$). In this model, the susceptibility for re-infection is reduced by 80% after each infection (Table S2.6). The corresponding transmission probability is 4.8% (95% CI= 4.2; 5.6) per sexual contact. The model shows no significant deviations from the data ($\chi^2 = 5.99$, $p=.42$).

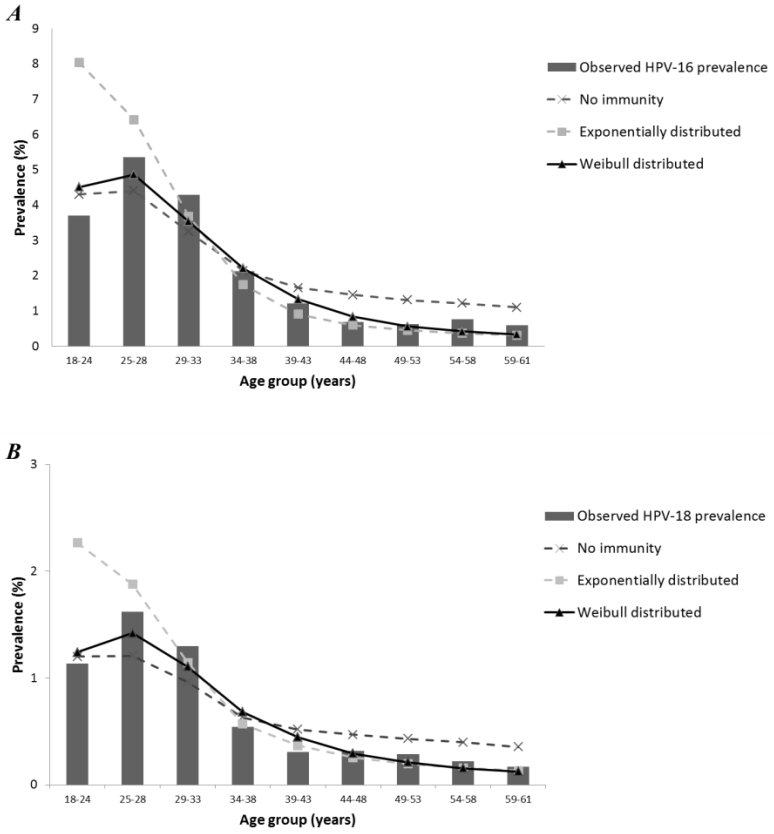


**Figure S2.1. Comparison of the observed and estimated age-specific HPV prevalence.** The estimated prevalence is given by the best fittings model when assuming no immunity (exponential distribution for the duration of infection) or different scenarios when assuming cumulatively decreasing susceptibility to re-infection after each infection (58% for HPV-16 and 80% for HPV-18). These scenarios include an exponentially distributed duration of infection and a Weibull distributed duration of infection (Weibull shape 0.50). ***(A)*** shows the results for HPV-16; ***(B)*** for HPV-18.

**Table S2.5. Parameter values and goodness-of-fit for the best fitting HPV-16 and HPV-18 models of the different scenarios and both acquired immunity mechanisms.** The scenarios include no acquired immunity; exponentially distributed durations (Weibull shape = 1); and Weibull distributed durations.

| | Wb inf | Wb imm | Log-likelihood | -2*Log-likelihood ratio | | -2*Log-likelihood ratio | | $\chi^2$ | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Compared to no immunity | p-value | Compared to exponential distribution | p-value | | |
| **HPV-16** | 1 | No imm | -53.97 | | | | | | |
| | 1 | 1 | -58.65 | 9.36 | 0.053 | | | | |
| | 0.50 | 0.25 | -32.03 | 43.88 | <.001 | 53.24 | <.001 | 15.26 | 0.009 |
| | 0.50 | AM | -32.60 | 42.74 | <.001 | 47.04 | <.001 | 19.14 | 0.004 |
| | 1 | AM | -56.12 | 4.3 | 0.23 | | | | |
| **HPV-18** | 1 | No imm | -27.41 | | | | | | |
| | 1 | 1 | -27.68 | 0.54 | 0.97 | | | | |
| | 0.50 | 0.50 | -21.70 | 11.43 | 0.022 | 11.97 | 0.018 | 4.80 | 0.44* |
| | 0.50 | 1 | -21.59 | 11.63 | 0.02 | 12.18 | 0.016 | 4.77 | 0.44* |
| | 0.50 | 2 | -21.69 | 11.45 | 0.022 | 11.99 | 0.017 | 5.08 | 0.41* |
| | 0.50 | 4 | -22.50 | 9.82 | 0.044 | 10.37 | 0.035 | 6.09 | 0.30* |
| | 0.50 | AM | -22.09 | 10.64 | 0.014 | 7.06 | 0.07 | 5.99 | 0.42* |
| | 1 | AM | -25.62 | 3.58 | 0.31 | | | 11.18 | 0.08* |
| | 4 | AM | -25.62 | 3.58 | 0.31 | | | 10.48 | 0.11* |

*Wb inf = Weibull shape infection duration; Wb imm = Weibull shape immunity duration; No imm = no immunity; AM = alternative mechanism; * indicates that the model does not differ significantly from the data, based on the chi-squared test.*

*The log-likelihood ratio test has 4 degrees of freedom for the base case immunity mechanism, and 3 degrees of freedom for the alternative mechanism. The chi-squared test has 5 degrees of freedom for the base case mechanism, and 6 degrees of freedom for the alternative mechanism.*

These results suggest that women need to clear about two subsequent HPV-16 infections in order to arrive at a similar level of acquired immunity (83%) after clearing one HPV-18 infection. Our best fitting model implies that around 45% will have an HPV-16 infection in their lifetime, and 20% an HPV-18 infection, similar to the base case immunity mechanism (Figure S2.2). Half of the women will never acquire an HPV-16 or -18 infection.

**S2.1F: Parameter values and goodness-of-fit of the best fitting models for HPV-16 and HPV-18**

We performed a two-dimensional grid search to determine combinations of transmission probabilities and mean duration of acquired immunity (or susceptibility reduction for the alternative mechanism) for each HPV-type, and the 5 pre-set shape parameters of the Weibull distributions of the durations of both infection and acquired immunity. In the models without immunity, we only fitted the transmission probability and Weibull shape for the duration of infection. The goodness-of-fit of the models was based on the log-likelihood, which we used in a likelihood ratio test to determine the best fitting model compared to the observed data (Table S2.4).[21-23] Table S2.5 shows the optimal parameter combinations and corresponding log-likelihoods when assuming no acquired immunity after clearing an infection; exponentially distributed durations; and Weibull distributed durations. For the best fitting models, we calculated Pearson's chi-squared values to determine the model fit compared to the observed prevalence data (Table S2.5). The corresponding duration of infection and immunity are shown below in Tables S2.3,[24,25] and S2.6, respectively.

**Table S2.6. Parameter values and the distribution of immunity durations for the best fitting HPV-16 and HPV-18 models under the base case and alternative immunity mechanism.** Scenarios include no acquired immunity; exponentially distributed duration (Weibull shape = 1); and Weibull distributed duration.

| | Wb inf | Wb imm | p | i | <1 year immune | >30 year immune |
|---|---|---|---|---|---|---|
| **HPV-16** | 1 | No immunity | 3.1% | - | - | - |
| | 1 | 1 | 19.4% | 3.96 years | 22.3% | 0.0% |
| | **0.50** | **0.25** | **6.9%** | **111.65 years** | **49.4%** | **20.3%** |
| | **0.50** | **AM** | **5.3%** | **58.40%** | - | - |
| | 1 | AM | 6.8% | 25.30% | - | - |
| **HPV-18** | 1 | No immunity | 3.4% | - | - | - |
| | 1 | 1 | 13.4% | 11.46 years | 8.4% | 7.3% |
| | **0.50** | **0.50** | **6.7%** | **115.18 years** | **12.3%** | **48.6%** |
| | **0.50** | **1** | **7.7%** | **43.25 years** | **2.3%** | **50.0%** |
| | **0.50** | **2** | **7.6%** | **28.67 years** | **0.1%** | **42.3%** |
| | **0.50** | **4** | **9.0%** | **28.12 years** | **0.0%** | **41.7%** |
| | **0.50** | **AM** | **4.8%** | **79.70%** | - | - |
| | 1 | AM | 7.6% | 40.80% | - | - |
| | 4 | AM | 8.6% | 30.80% | - | - |

*Wb inf = Weibull shape infection duration; Wb imm = Weibull shape immunity duration; p = transmission probability per sexual contact; i = mean immunity duration; AM = alternative mechanism. Bold numbers indicate the best fitting models. All women that clear an HPV infection will become immune. The percentages of women being immune for <1 year and >30 years are shown; the remaining women are immune for a period of 1-30 years.*

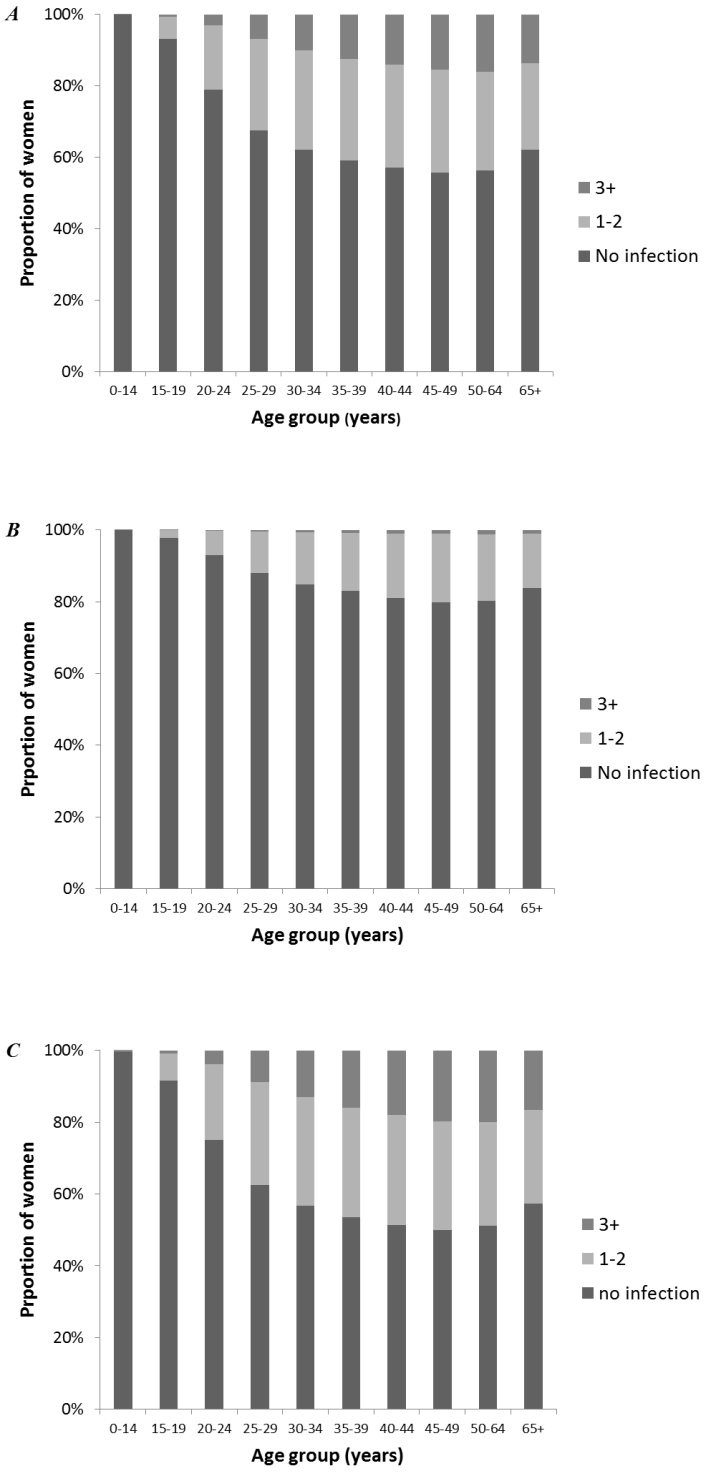


**Figure S2.2. Predicted cumulative number of HPV-16 *(A)*, HPV-18 *(B)*, and HPV-16/-18 infections in women.** The proportion of women with no lifetime infections slightly increased in women aged 65+ compared to women aged 50-64 years. This results from a cohort effect due to a combination of historical data on fertility rates and timing of an increase in migration (1965), and will only have a minimal effect on our estimates.

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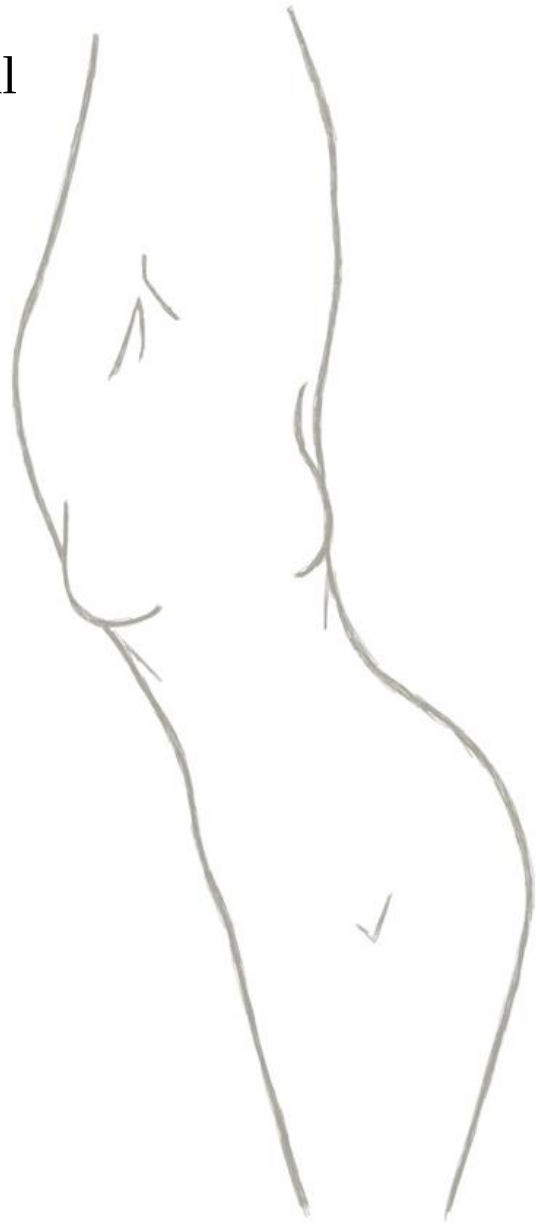
# 3

# The estimated impact of natural immunity on the effectiveness of human papillomavirus vaccination



Vaccine (2015)

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**Abstract**

**Background**

Mathematical modelling is used to estimate the effectiveness of HPV vaccination. These estimates depend strongly on herd immunity and thus on naturally acquired immunity, a mechanism of which little is known. We estimated the impact of different vaccination strategies on HPV-16 and HPV-18 transmission and cervical cancer incidence in the Netherlands, considering different acquired immunity mechanisms.

**Methods**

We used the STDSIM microsimulation model, and considered two mechanisms for acquired immunity after infection: (I) full immunity with variable duration; (II) cumulatively decreasing susceptibility to reinfection. Girls aged 13–16 years received vaccination (94.7% efficacy for HPV-16 and 92.3% for HPV-18) during a once-off catch-up campaign with 50% coverage, followed by annual vaccination of 12-year-old girls (60% coverage). Alternative vaccination scenarios included increased coverage, including boys, and lower vaccine efficacy.

**Results**

HPV-16 incidence reduced by 64% under mechanism I and 75% under mechanism II; HPV 18 incidence reduced by 58% and 73%, respectively, and these reductions lead to 48–56% fewer cervical cancer cases. Increasing coverage can lead to over 96% reduction in HPV incidence. Vaccinating boys reduced incidence by 79–89% for HPV-16 and 83–98% for HPV-18 in women.

**Conclusions**

Effectiveness estimates of HPV vaccination differ slightly between different acquired immunity mechanisms, yet these differences are unlikely to affect policy decisions. Offering vaccination to boys as well may be considered to further reduce cancer incidence.

## Introduction

Human papillomavirus (HPV) vaccination has been implemented in many countries over the past years, focusing mainly on girls. Coverage among girls differs substantially between countries, ranging from 32% in the United States to >70% in Australia, and even exceeding 90% in Scotland.[1,2] The bivalent vaccine protects against high-risk HPV-16 and HPV-18 infections that account for approximately 80% of the cervical cancers,[3,4] while the quadrivalent vaccine protects against HPV-16, HPV-18, HPV-6, and HPV-11.[5] The bivalent vaccine was offered to girls aged 13–16years in a mass catch-up campaign in 2009 in the Netherlands,[6] and subsequently introduced in the Dutch national immunization program with 12-year-old girls being eligible for vaccination. Coverage of 58% was reached in 2013, which is much lower than the >90% coverage for other vaccinations included in this programme.[7] However, by reducing HPV prevalence in the population, vaccination not only protects those vaccinated, but (indirectly) unvaccinated individuals as well.[8] This is often called herd immunity, also in HPV modelling studies.[8–11]

Mathematical modelling has been used to estimate cost-effectiveness of HPV vaccination.[9–14] These mathematical models require realistic assumptions for the transmission and infection clearance of HPV, as well as the extent and duration of acquired immunity after infection clearance. However, there is still much uncertainty regarding acquired immunity after infection clearance, and a better understanding of this process is crucial to model the effectiveness of different vaccination strategies accurately.[15] Explorative modelling studies have shown that the proportion of people developing lifelong immunity affects the predicted effectiveness of HPV vaccination.[9,12] However, these studies only varied the proportion of individuals developing lifelong immunity, and hence did not compare different biological mechanisms.

Another important aspect is the extent to which heterogeneity in sexual networks and behaviour is included in the modelling. Deterministic models may not properly account for the complexity of transmission through sexual networks.[10,13,14] The established individual-based simulation model STDSIM is well-designed to capture sexual networks and their dynamics and has recently been used to model the spread of HPV in the Netherlands.[16]

In this study, we determined the impact of the current HPV vaccination programme on HPV transmission dynamics and cervical cancer incidence in the Netherlands with the STDSIM microsimulation model[16] and accounting for two different biological mechanisms of acquired immunity. In addition, we estimated the potential impact of alternative vaccination scenarios and strategies, including different coverage levels and the inclusion of boys.

## Methods

*STDSIM to model HPV transmission and control*

We used STDSIM, an established stochastic microsimulation model to study the spread and control of sexually transmitted infections (STIs).[16–19] The model simulates the life course of individuals in a dynamic heterosexual network, in which STIs, such as HPV, can spread. Each individual has its own characteristics that are either constant (e.g. sex) or subject to change (e.g. infection status). Events are determined by probability distributions, and can lead to new events (e.g. birth leads to a future event of becoming sexually active) or cancellations of future events (e.g. death cancels all scheduled events for this person). More detailed information on the model can be found elsewhere.[16–19]

We have previously quantified STDSIM to the Netherlands to model the spread of HPV-16 and HPV-18, which has been extensively described elsewhere.[16] Briefly, we reproduced the Dutch population and its sexual network, based on demographic data[20,21] and national sexual health surveys.[22–24] We then introduced HPV-16 and HPV-18 in the population to estimate the transmission probabilities and acquired immunity dynamics necessary to reproduce the observed age-specific patterns in HPV-16 and HPV-18 prevalence.[25–27] The two mechanisms of acquired immunity after infection clearance used here originate from the previous study by Matthijsse *et al.*[16] In the first mechanism, we assumed that everyone acquires full immunity with a variable duration (Weibull distributed; mechanism I). In the second mechanism, we assumed that susceptibility to reinfection decreases cumulatively after each subsequent infection (mechanism II).

*Vaccination scenarios*

The base case scenario in our analysis was similar to the vaccination strategy and observed uptake in the Netherlands: a mass vaccination campaign for 13–16-year-old girls in 2009 (50% coverage), and subsequent annual vaccination of 12-year-old girls (60% coverage).[6,7] Vaccine efficacy was set at 94.7% for HPV-16 and 92.3% for HPV-18,[4] modelled as reduced susceptibility to infection.[28] We modelled this protection to be lifelong, since no evidence of waning has emerged from clinical trials.[29] Furthermore, vaccine efficacy is also still substantial in women previously exposed to HPV-16 and/or HPV-18,[30] hence we assumed that vaccine efficacy is independent of infection status of the girls at the moment of vaccination. Infection clearance is not accelerated by the vaccine in our model.[30]

We developed several alternative scenarios to further investigate the potential impact of HPV vaccination. First, we ran the model under different assumptions regarding vaccination coverage from 2016 onwards, ranging from 30% (as was the coverage in the United States) to 100%. Second, we examined the impact of including boys in the vaccination programme from 2016 onwards, using base case target ages and coverage levels for both girls and boys. As bivalent vaccine efficacy estimates for boys are unavailable, efficacy for boys was assumed to be equal to the quadrivalent vaccine efficacy for boys (78.7% for HPV-16; 96.0% for HPV-18).[31] Third, a preliminary report on a recent longitudinal observational study in the Netherlands showed that vaccine effectiveness against incident

HPV-16/18 infections among 14–16-year-old girls was only 73%, considerably lower than the efficacy reported in trials.[32] We therefore developed two conservative scenarios for vaccine efficacy (70% and 80% for both HPV-16 and HPV-18) within the base case scenario. For these lower vaccine efficacies, we also determined the minimum coverage level for girls necessary to reach similar incidence reduction as obtained by the base case scenario.

All scenarios had the vaccine assigned independently of sexual risk behaviour,[33] and accounted for the two acquired immunity mechanisms described above.

*Vaccination impact*

We calculated the impact of the base case and alternative vaccination scenarios as the relative decrease in HPV-16 and HPV-18 incidence in all women when a steady state is reached compared to the pre-vaccination incidence in 2008. This was also done separately for vaccinated and unvaccinated women, to determine herd immunity effects of HPV vaccination. Furthermore, we looked at HPV-16 and HPV-18 prevalence after vaccination when a steady state is reached.

Based on estimated age-specific HPV 16 and HPV-18 incidence reductions, we also estimated potential effects of the vaccination scenarios on cervical cancer incidence by applying the proportional decrease in age-specific HPV incidence to reported pre-vaccination cervical cancer incidence rates in the Netherlands, assuming that the preventable proportion is the proportion of cancers that are HPV-16 or HPV-18 positive.[34] We used the average number of incident cases in women per age group from 2004 to 2008 (i.e. before the introduction of HPV vaccination).[35] We then calculated the proportion of these cancers caused by HPV-16 and HPV-18 by applying estimates from Guan *et al.*,[3] who determined the positivity for HPV types in HPV-positive invasive cervical cancer in Western Europe. In cancers with multiple HPV types present, we assumed that multiplicity of HPV infections occurs at random and that all high risk HPV types prevalent in a cancer are equally likely to have caused the cancer. We also calculated 95% binomial proportion confidence intervals (CIs) of the corrected HPV prevalences using the Clopper-Pearson method. The proportion of cervical cancers caused by HPV-16 and HPV-18 are 62.5% (95% CI: 60.4–64.5%) and 17.2% (95% CI: 15.7–18.8%), respectively. We assumed an average lag time of 20 years between acquiring an HPV infection and cervical cancer, based on the estimated duration to clinical cervical cancer in the MISCAN model.[36]

*Simulations*

Model runs started in 1911 with almost 10,000 men and over 10,000 women, and ended in 2100 with approximately 60,000 men and 60,000 women. Incidence estimates were averaged over 1000 model runs to correct for stochastic variation in model runs. In addition, we determined the impact of uncertainty in the proportion of cervical cancers attributable to HPV-16 and HPV-18 on the estimated cervical cancer incidence reductions. We randomly sampled 80 alternative proportion combinations from the 95% CIs of the estimated proportions of HPV-16 and HPV-18 in cervical cancers[3] and re-

calculated the cervical cancer incidence with these combinations of proportions.[16,19] Uncertainty ranges (UR) for the estimated cervical cancer incidence reductions were subsequently obtained by taking the 2nd lowest cervical cancer incidence value as lower bound and 2nd highest value as upper bound for each vaccination scenario.

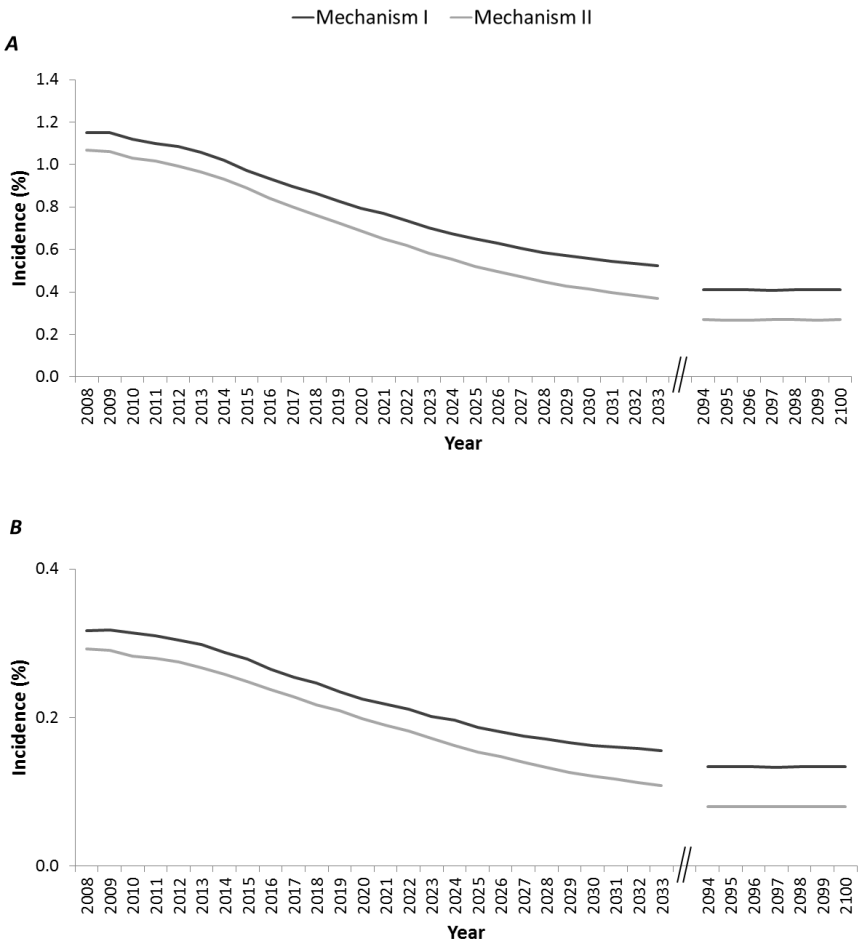


**Fig. 3.1. Estimated trends in HPV-16 (A) and HPV-18 (B) incidence for all women over the period 2008–2100 under both acquired immunity mechanisms following vaccination from 2009 onwards.** Mechanism I assumes full immunity with a variable duration after clearing an infection; mechanism II assumes cumulatively decreasing susceptibility to reinfection after each infection.

## Results

Fig. 3.1 shows trends in incidence of HPV-16 (3.1A) and HPV-18 (3.1B) over the years following vaccination in the base case scenario, with incidence reductions for both HPV-16 and HPV-18 slightly higher in mechanism II. Our model predicted that HPV-16 incidence is reduced by 15% under mechanism I, and 17% under mechanism II five years after the implementation of vaccination. These

reductions are 12% and 15%, respectively, for HPV-18. After 10 years, incidence reductions under mechanism I and II are 31% and 36% for HPV-16, and 29% and 32% for HPV-18, respectively. For both HPV-types, a large part of the total reduction has already been accomplished after 20 years. HPV-16 incidence is predicted to reduce by 52% under mechanism I, and 61% under mechanism II. HPV-18 incidence is predicted to reduce by 49% (mechanism I) and 59% (mechanism II). Steady state is achieved approximately 70 years after the start of vaccination for both HPV-types, with HPV-16 incidence 64% (mechanism I) and 75% (mechanism II) lower compared to the pre-vaccination steady state. For HPV-18, incidence is reduced by 58% under mechanism I and 73% under mechanism II. Similar to incidence reductions, HPV prevalence in the post-vaccination steady state is lower under mechanism II than under mechanism I for both HPV-16 (Fig. 3.2A) and HPV-18 (Fig. 3.2B). Largest reductions in prevalence occurred in women aged 25–33 years, with HPV-16 prevalence 70% (mechanism I) and 80% (mechanism II) lower, and HPV-18 65% (mechanism I) and 80% (mechanism II) lower compared to pre-vaccination prevalence.

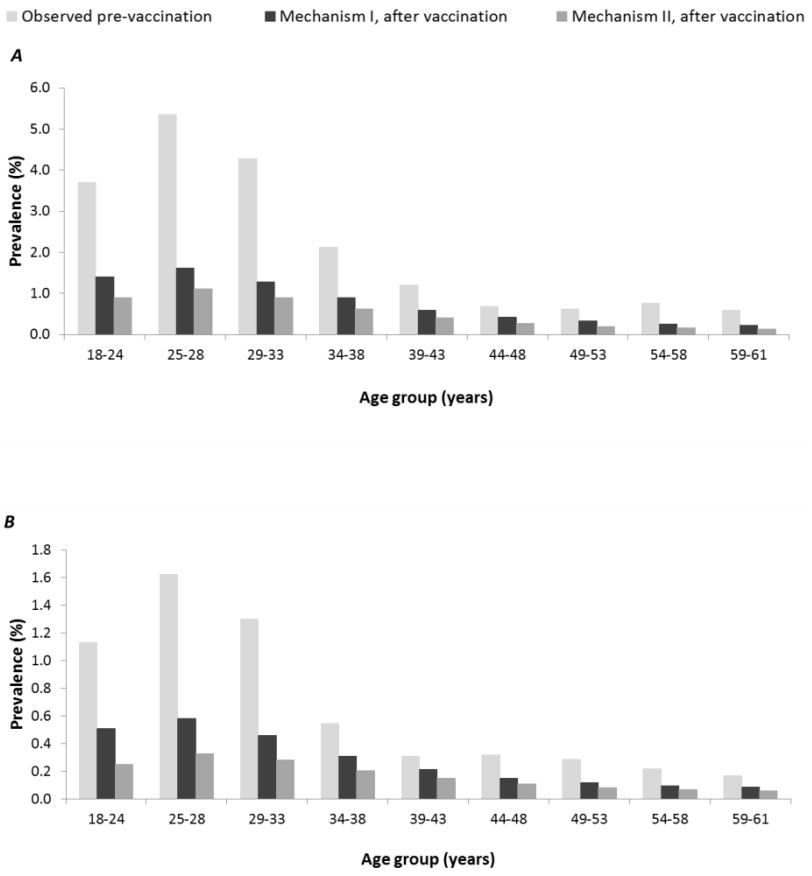


**Fig. 3.2. Age-specific prevalence of HPV-16 (A) and HPV-18 (B) in pre-** [25–27] **and post-vaccination steady state under both acquired immunity mechanisms.** Mechanism I assumes full immunity with a variable duration after clearing an infection; mechanism II assumes cumulatively decreasing susceptibility to reinfection after each infection.

Increasing coverage has a strong effect on incidence reductions under both acquired immunity mechanisms for both HPV-16 (Fig. 3.3A) and HPV-18 (Fig. 3.3B). In addition, the effect of herd immunity increases with higher coverage levels, resulting in substantial incidence reductions for unvaccinated women (Fig. 3.3C and D). Even if the coverage level would be as low as 30% from 2016 onwards, incidence reductions would be 36% (mechanism I) and 44% (mechanism II) for HPV-16, and 30% (mechanism I) and 40% (mechanism II) for HPV-18. When complete coverage is accomplished, elimination of both types is achieved under mechanism II, and approximated under mechanism I (96% reduction). Offering vaccination to boys and girls at similar coverage levels compared to the base case reduced incidence by 79% (mechanism I) and 89% (mechanism II) for HPV-16, and 83% (mechanism I) and 98% (mechanism II) for HPV-18 (Fig. 3.4).

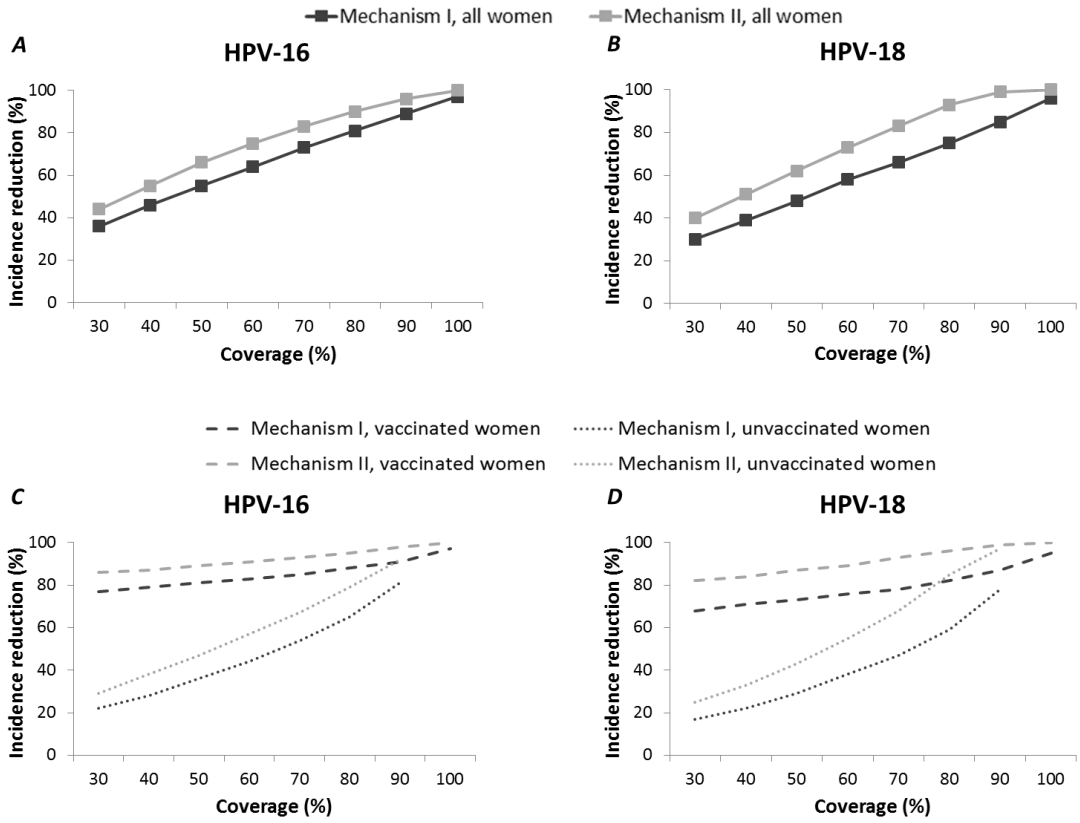


**Fig. 3.3. Estimated reductions in HPV-16 and HPV-18 incidence for all women (A and B), and stratified by vaccination status (C and D) for different coverage levels, in post-vaccination steady state under both acquired immunity mechanisms.** Mechanism I assumes full immunity with a variable duration after clearing an infection; mechanism II assumes cumulatively decreasing susceptibility to reinfection after each infection.

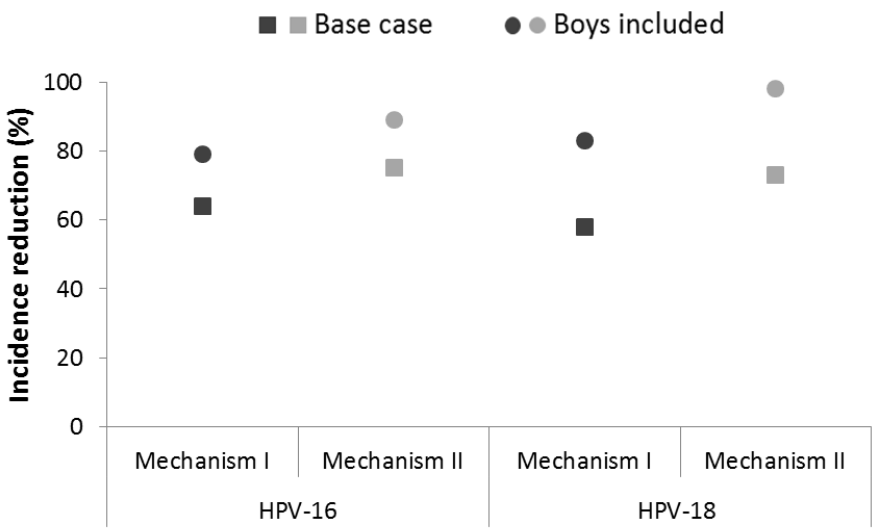


**Fig. 3.4. Estimated reductions in HPV-16 and HPV-18 incidence for all women if boys are included in the vaccination programme, in post-vaccination steady state under both acquired immunity mechanisms.** Mechanism I assumes full immunity with a variable duration after clearing an infection; mechanism II assumes cumulatively decreasing susceptibility to reinfection after each infection. Vaccination coverage for both boys and girls is 50% during the catch-up campaign and 60% onwards.

Lower vaccine efficacy leads to substantially lower impact of HPV vaccination compared to the base case assumption of efficacy found in clinical trials (Fig. 3.5). Even with full coverage, vaccine efficacy of 70% cannot achieve base case incidence reduction levels under mechanism I for both HPV-16 (Fig. 3.5A) and HPV-18 (Fig. 3.5B). While for HPV-16 this result also holds under mechanism II, full coverage is sufficient for HPV-18 to match the base case incidence reduction. Vaccine efficacy of 80% can still match incidence reductions observed in the base case for HPV-16 with a coverage level of 90% under mechanism II (Fig. 3.5C). For HPV-18, similar incidence reductions as the base case scenario are only possible when either full coverage under mechanism I or 80% coverage under mechanism II is achieved (Fig. 3.5D).

Table 3.1 shows associated predicted reductions in cervical cancer incidence in post-vaccination steady state under both acquired immunity mechanisms. Our model predicts that incidence is reduced by 48% (95% UR: 47–49%) under mechanism I and 56% (95% UR: 55–58%) under mechanism II in the base case scenario. Increasing coverage leads to fewer cervical cancer cases compared to the base case scenario, with a maximum reduction of 74% (95%UR: 72–77%) under mechanism I, and 79% (95% UR: 77–81%) under mechanism II (Table 3.1). Including boys also leads to substantial incremental reductions in cervical cancer incidence under current coverage levels,

reducing by 61% (95% UR: 60–63%) under mechanism I and 70% (95% UR: 68–72%) under mechanism II (Table 3.1). Under both mechanisms, coverage among girls needs to exceed 80% to outweigh the inclusion of boys in the base case scenario. The effect of different acquired immunity mechanisms on cervical cancer incidence is more profound when assuming lower vaccine efficacy.

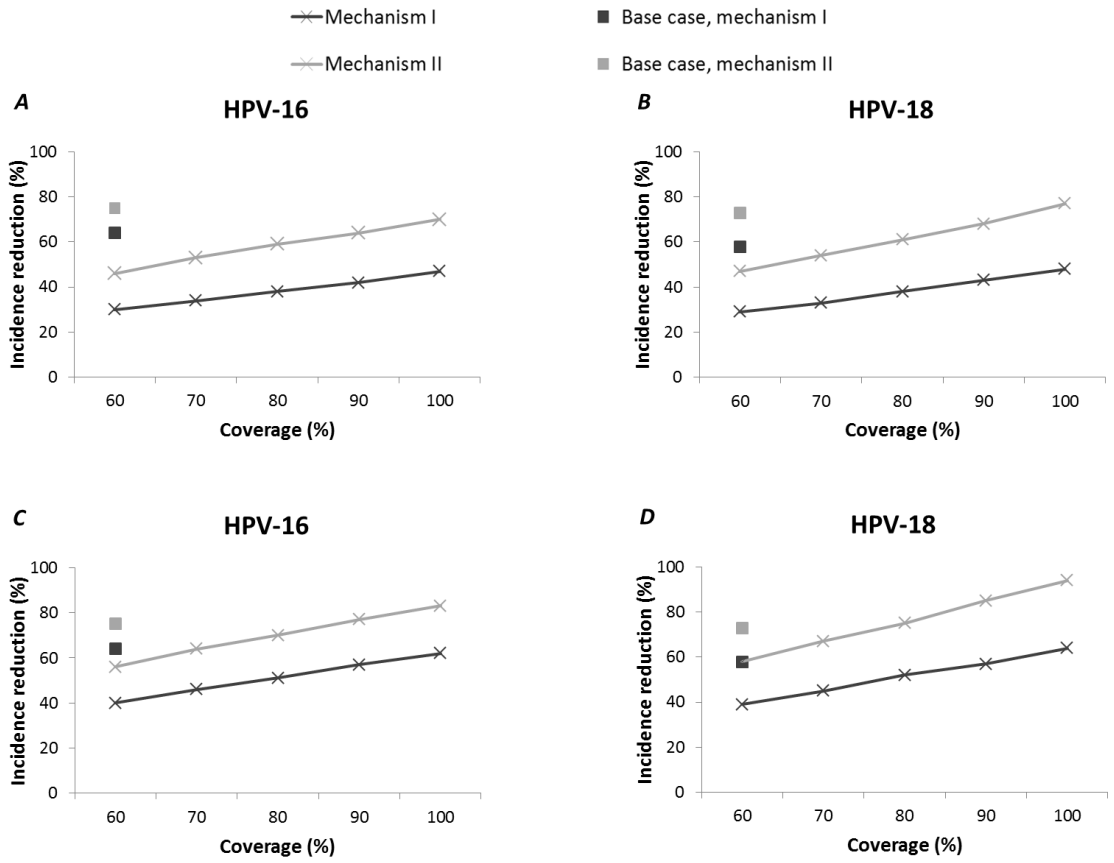


**Fig. 3.5. Estimated reductions in HPV-16 and HPV-18 incidence for all women if vaccine efficacy is only 70% (A and B) or 80% (C and D), in post-vaccination steady state under both acquired immunity mechanisms.** Mechanism I assumes full immunity with a variable duration after clearing an infection; mechanism II assumes cumulatively decreasing susceptibility to reinfection after each infection.

**Table 3.1. Estimated reductions (%) and 95% uncertainty ranges (UR)[a] in new cervical cancer cases in post-vaccination steady state compared to pre-vaccination incidence under both acquired immunity mechanisms.[b]**

| | Mechanism I | | Mechanism II | |
|---|---|---|---|---|
| | % | (95% UR) | % | (95% UR) |
| **Coverage (%)** | | | | |
| 30 | 24 | (24-25) | 29 | (28-30) |
| 40 | 33 | (32-34) | 40 | (39-41) |
| 50 | 40 | (39-41) | 48 | (46-49) |
| 60 (base case)[c] | 48 | (47-49) | 56 | (55-58) |
| 70 | 54 | (53-56) | 64 | (62-65) |
| 80 | 61 | (60-63) | 70 | (68-72) |
| 90 | 68 | (66-70) | 76 | (74-78) |
| 100 | 74 | (72-77) | 79 | (77-81) |
| **Inclusion of boys[c]** | 61 | (60-63) | 70 | (68-72) |
| **Lower vaccine efficacy (%)** | | | | |
| 70 | 20 | (20-21) | 32 | (31-33) |
| 80 | 29 | (28-30) | 40 | (38-41) |

[a] *Uncertainty ranges (UR) reflect the uncertainty in the proportion of cervical cancer attributable to HPV-16 and HPV-18.*

[b] *Mechanism I assumes full immunity with a variable duration after clearing an infection; mechanism II assumes cumulatively decreasing susceptibility to reinfection after each infection.*

[c] *Vaccination coverage is 50% during the catch-up campaign, and 60% onwards.*

**Discussion**

Our results showed that HPV and cervical cancer incidence reduce substantially following vaccination under both acquired immunity mechanisms. Vaccination effects are larger for HPV-16 than for HPV 18, and largest under mechanism II. In addition, the impact of different acquired immunity mechanisms are more profound for HPV-18 compared to HPV-16, with the inclusion of boys, and when assuming lower vaccine efficacy. Finally, our results showed that including boys in the vaccination programme can substantially improve HPV transmission control. Under both immunity mechanisms, coverage of girls needs to exceed 80% to outweigh the inclusion of boys with 60% coverage.

These results provide decision makers in the field of HPV with assurance that, while little is known about the actual acquired immunity processes following infection clearance,[37] decisions regarding vaccination strategies based on model estimates seem robust to different assumptions on

acquired immunity. Nevertheless, coverage levels in most countries remain low, and our results show that this leads to sub-optimal reductions in cervical cancer incidence despite the effects of herd immunity. The relatively low coverage levels of HPV vaccination should be taken into account when updating the screening programmes following the introduction of HPV vaccination. However, by redirecting more resources to substantially improve vaccination programme uptake, it may be possible to eliminate both HPV-16 and HPV-18, thereby making current screening programmes outdated.

Consistent with Brisson *et al.*[38] and Bogaards *et al.*,[10] we found larger vaccine effectiveness for HPV-18 compared to HPV-16. Our results of a reduction of 48–56% in cervical cancer incidence in the current vaccination programme in the Netherlands (60% coverage) and 68–76% with 90% vaccine coverage are similar to results by Bogaards *et al.*,[10] who found incidence reductions of 47% and 68% for coverage levels of 50% and 90%, respectively. Horn *et al.*[13] estimated that vaccination would reduce new cervical cancer cases by 37% at a vaccine coverage of 50%, which is similar to our estimates with 50% coverage under mechanism I (40% reduction), yet more conservative than under mechanism II (48% reduction). Adding boys to the current vaccination programme in our model leads to a further reduction in cervical cancer incidence by 13 percentage points under mechanism I and 14 percentage points under mechanism II compared to the base case, only slightly lower compared to the 19% additional reduction found by Horn *et al.*[13] While there is ample room for improvement in female coverage rates,[11] a coverage of more than 80% among girls needs to be achieved in order to outweigh the inclusion of boys under current coverage levels in our model. This is consistent with results of Baussano *et al.*,[39] who reported that vaccinating boys under coverage levels of 65% leads to incremental benefits compared to girls-only vaccination, yet this diminishes when coverage of 90% among girls can be achieved. Such high coverage might be feasible now that fewer vaccine doses are recommended.[40]

Several other modelling studies found differences in effectiveness estimates of HPV vaccination between different acquired immunity assumptions.[9,12] In our model, mechanism II (i.e. cumulatively decreasing susceptibility to reinfection after each infection) is biologically similar to the efficacy mechanism of the vaccine. Hence, the reduced susceptibility due to the vaccine is boosted with the lifelong reduced susceptibility following an infection if the woman were to acquire and clear an infection before or after vaccination. This means that women can effectively develop lifelong full immunity. In mechanism I, full immunity following an infection is only reached for a certain variable duration, regardless of vaccination. Afterwards, the maximum immunity they can achieve will decrease again to the maximum effectiveness of the vaccine (94.7% for HPV-16 and 92.3% for HPV 18) if a woman is vaccinated, or to fully susceptible if a woman is not vaccinated.

The main strength of our study is that STDSIM allows us to model both HPV-types simultaneously and both acquired immunity mechanisms in combination with vaccination. In addition, the model is able to capture both direct and indirect effects of vaccination as we can track incidence in vaccinated and unvaccinated individuals over time. Furthermore, we model HPV transmission and

vaccination within a realistic sexual network, essential to accurately estimate the impact of interventions. Finally, we also look at the decline in HPV incidence before a steady state is reached, important for future cost-effectiveness studies.

Our study also comes with limitations. First, we assumed equal vaccine effectiveness for girls that have (had) an infection at the moment of vaccination. Slightly lower efficacy estimates have been found in these women, yet these measurements suffered from limited statistical power.[30] Since these estimates still show comparable and substantial efficacy, and given the young age of our target groups (hence limited previous exposure to HPV), we believe that including this phenomenon would only have a minimal effect on our estimates. Second, we do not model HPV progression to cervical cancer explicitly in our model. However, while a relatively simple calculation for the effect on cervical cancer is used, we believe that we correctly assumed that there is a pretty straightforward relationship between type-specific HPV and cervical cancer incidence, both in situations with and without screening. Comparative effects of different scenarios and acquired immunity mechanisms are therefore still of value. Third, our relatively simple assumption that each HPV type is equally likely to have caused the cancer in case of multiple infections could have underestimated the proportion of cancers caused by HPV-16 and HPV-18. While unfortunately not much data is available, this underestimation is likely to be minimal. The true proportions of cancers caused by HPV-16 and HPV-18, which we estimated to be 62.5% and 17.2% respectively, must be lower than the type-specific HPV prevalence without correction for multiple infections. Based on data of Guan *et al.*,[3] these type-specific HPV prevalences were 66.9% for HPV-16 and18.4% for HPV-18, so that the underestimation could not have been larger than 4.4 and 1.2 percentage points, respectively. Finally, our reduction estimates of cervical cancer incidence may be slightly underestimated, since we do not take cross-protection of the vaccine into account. However, cross-protection efficacy appears to be lower than efficacy for vaccine-sensitive HPV-types.[41] Furthermore, cross-protected HPV-types account for a much smaller proportion of cervical cancer incidence,[3] hence our underestimation is likely to be minimal.

In conclusion, HPV vaccination will substantially reduce HPV and cervical cancer incidence, despite relatively poor coverage. Increasing coverage and including boys in the vaccination programme will further improve transmission control, potentially leading to elimination of HPV-16 and HPV-18. Although expanding knowledge on acquired immunity mechanisms is important to accurately estimate the cost-effectiveness of HPV and cervical cancer prevention interventions, policy decisions regarding vaccine uptake strategies seem robust to different acquired immunity assumptions.

**Acknowledgement**

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# 4

# Public health benefits of routine human papillomavirus vaccination for adults in the Netherlands: a mathematical modeling study

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**Abstract**

**Background**

Expanding routine human papillomavirus (HPV) vaccination to adults could be an effective strategy to improve prevention of HPV infection and cervical cancer.

**Methods**

We evaluated the following adult vaccination strategies for women only and for both women and men in addition to the current girls-only vaccination program in the Netherlands, using the established STDSIM microsimulation model: one-time mass campaign, vaccination at the first cervical cancer screening visit, vaccination at sexual health clinics, and combinations of these strategies.

**Results**

The estimated impact of expanding routine vaccination to adult women is modest, with the largest incremental reductions in the incidence of HPV infection occurring when offering vaccination both at the cervical cancer screening visit and during sexually transmitted infection (STI) consultations (about 20% lower after 50 years for both HPV-16 and HPV-18). Adding male vaccination during STI consultations leads to more-substantial incidence reductions: 63% for HPV-16 and 84% for HPV-18. The incremental number needed to vaccinate among women is 5.48, compared with 0.90 for the current vaccination program.

**Conclusions**

Offering vaccination to adults, especially at cervical cancer screening visits (for women) and during STI consultations (for both sexes), would substantially reduce HPV incidence and would be an efficient policy option to improve HPV prevention and subsequently avert cervical and possibly male HPV-related cancers.

## Introduction

Human papillomavirus (HPV) vaccination, targeting the most oncogenic HPV types for cervical cancer, HPV-16 and HPV-18,[1,2] has been implemented in many countries. Vaccination programs using either the bivalent or quadrivalent vaccine focus mainly on young girls (and, in some countries, also boys) prior to sexual debut. The United Kingdom has had a relatively high vaccination coverage (about 86% among girls),[3] but most countries experience suboptimal coverage levels, varying from 32%, in the United States, to about 70%, in Australia.[4] The low uptake, together with the limited target age group, has led to HPV transmission control not reaching its full potential in most countries. Recent findings from the multinational Vaccine Immunogenicity and Efficacy (VIVIANE) study showed that the bivalent vaccine is efficacious against HPV-16/18 infections in women aged >25 years,[5] sparking the debate about whether adult women should also be offered HPV vaccination to further improve cervical cancer prevention.[5-8] In addition, recent findings of the Mid-Adult Males (MAM) study indicated that the quadrivalent vaccine is safe and induces HPV antibodies in vaccinated men aged 27–45 years.[9] Vaccination strategies also targeting adults could therefore improve HPV transmission control, especially in cohorts too old to have been covered by current vaccination programs or those in countries with poor coverage.[5-8]

Thus far, it has not been studied how adult vaccination should be implemented. An effective and efficient strategy to roll out HPV vaccination for adult women could be by using existing public health programs, in particular cervical cancer screening and sexual health services.[6,10,11] In addition, a one-time mass campaign could target women who were too old for vaccination when the current girls-only program was initiated. Inclusion of boys and men in HPV vaccination strategies could further improve transmission control, with the additional benefit of protecting them against HPV-related cancers that can affect males.[11-13]

Here, we used the established STDSIM model to estimate the impact of extending the current girls-only Dutch vaccination program with vaccination for women and men up to 45 years of age. We previously used this model to estimate the impact of the current Dutch vaccination strategy and found that the incidence of HPV-16 and HPV-18 infection will eventually decline by 64% and 58%, respectively, compared with the pre-vaccination incidence.[13] In the current study, we extended this model to simulate different HPV vaccination strategies integrated within existing public health services for cervical cancer screening and sexual health in the Netherlands, as well as a one-time mass vaccination campaign for adults.

## Methods

*Model structure and quantification*

STDSIM simulates the life course of individuals in a dynamic heterosexual network, in which sexually transmitted infections (STIs)such as HPV can spread. Same-sex partnerships are not included in our

model. Each individual has characteristics that are either constant (e.g., date of birth and sex) or subject to change (e.g., number of sexual partners and infection status). Events are determined by probability distributions and can lead to new events (e.g., birth leads to a future event of becoming sexually active) or to the cancellation of future events (e.g., a death cancels all scheduled events concerning sexual activity for this person). STDSIM can simulate several interventions simultaneously.

We have previously quantified STDSIM to reproduce sexual behavior dynamics and the spread of HPV-16 and HPV-18 in the Netherlands.[14] Briefly, we reproduced the Dutch population and its sexual network, using demographic data[15, 16] and national sexual behavior surveys.[17-19] To validate the modeling of sexual risk behavior in the model, we simulated the transmission of chlamydia and compared our results to prevalence data from the Chlamydia Screening Implementation study.[20] We then introduced HPV-16 and HPV-18 in the simulated population to estimate the transmission probabilities and acquired immunity dynamics necessary to reproduce the observed age-specific HPV 16 and HPV-18 prevalences.[21–23] Complete information of the model structure can be found elsewhere,[14,24] and the parameter quantification and model validation for the Dutch setting is described in detail by Matthijsse *et al.*[13,14] and are briefly described in Supplementary Materials 4.1A–4.1D.

*Assumptions about vaccine efficacy*

We used the same assumptions for the impact of HPV vaccination of girls and boys in the Netherlands as in our previous study.[13] Efficacy of vaccination for girls aged <25 years was set to 94.7% for HPV-16 and 92.3% for HPV-18 and modeled as a lifelong reduced susceptibility to infection.[1,25] Efficacy for boys was assumed to be equal to the recently reported quadrivalent vaccine efficacy for boys (i.e., 78.7% for HPV-16 and 96.0% for HPV-18).[26]

Vaccine efficacy for women aged >24 years was obtained from the VIVIANE study, which showed an efficacy of 77.4% for both HPV types.[5] This efficacy is thus 18.3% lower for HPV-16 and 16.1% lower for HPV-18, compared with that for young girls. We used the same relative reductions to men aged >24 years, resulting in a vaccine efficacy of 64.5% for HPV-16 and 80.6% for HPV-18. We simulated vaccine efficacy to be independent of HPV status at the time of vaccination, as vaccine efficacy is still substantial in women previously exposed to HPV-16 and HPV-18.[5,13,27] Infection clearance is not accelerated by the vaccine in our model.

*Vaccination strategies*

We first modeled the current vaccination program as implemented in the Netherlands: a mass campaign for 13–16-year-old girls in 2009 with a coverage of 50% and annual vaccination of 12-year old girls at 60% coverage.[13,28,29] We then simulated the addition of several adult vaccination strategies to the current girls-only strategy from 2016 onward. In strategies targeting both men and women,

routine vaccination for boys was included from 2016 onward, assuming the same target age groups and uptake as for girls. The following 5 individual strategies were simulated (Supplementary Figure S4.5), as well as various combinations of these strategies.

Mass campaign (females)

This is a one-time mass campaign conducted in 2016 for women aged 24–45 years to capture those who fell outside the age ranges of the original catch-up campaign in 2009. Coverage rates are equal to the age-specific attendance rates of the Dutch cervical cancer screening program.[30]

Screening (females)

Vaccination is offered to all 30-year-old women attending cervical cancer screening for the first time from 2016 onward.[30] We assumed that all women accepted the vaccination, but they were not offered a new vaccination if they had already been vaccinated in the past.

STI consultation (females)

All girls and women aged 15–29 years attending sexual health clinics for STI testing are offered HPV vaccination. Attendance rates were derived from Statistics Netherlands[15] and the National Public Health Compass.[31] In the model, we tuned the clinic visit rates to reproduce the observed attendance rates in the Netherlands, and we assumed that women with ≥2 recent sex partners are 3 times more likely to go for a consultation than women with 1 recent sex partner. The resulting visit rates in the model were 2.75%, 5.10%, and 2.15% for ages 15–19 years, 20–24 years, and 25–29 years, respectively, for those with 1 recent sex partner and 8.25%, 15.30%, and 6.45%, respectively, for those with ≥2 recent sex partners. We assumed that all girls and women at the sexual health clinics accepted vaccination, but they did not receive another vaccination if they had already been vaccinated in the past.

Mass campaign (females and males)

This is a one-time mass campaign for men and women aged 24–45 years in 2016, assuming the same coverage rates for men as for women[32] in the first strategy involving a mass campaign for females only.

STI consultation (females and males)

Males and females aged 15–29 years attending sexual health clinics for STI testing from 2016 onward are offered HPV vaccination. Similar to the third strategy, consisting of STI consultation for females only, we tuned the visit rates in the model to reproduce the attendance rates derived from Statistics Netherlands and the National Public Health Compass.[15, 31] For men aged 15–19 years, 20–24 years, and 25–29 years, the resulting visit rates are 1.50%, 2.80%, and 1.65%, respectively, for those with 1

recent sex partner and 4.50%, 8.40%, and 4.95%, respectively, for those with ≥2 recent sex partners. We assumed that all adults at the sexual health clinics accepted vaccination, but they did not receive another vaccination if they had already been vaccinated in the past.

*Impact calculations*

The impact of strategies was calculated by estimating the relative reduction in the incidence of HPV-16 and HPV-18 infection in all women 10, 20, 50, and 70 years after the introduction of the vaccination program. In addition, we compared the efficiency of the programs by determining the incremental number needed to vaccinate (NNV) to prevent 1 new infection in all women from 2008 2029 and 2008–2079.

*Sensitivity analysis*

In contrast to the base case analysis, we also ran the model assuming that the vaccine has no protective effect in individuals with an HPV infection at the time of vaccination. We further varied the vaccine efficacy for adults by using the limits of the 95% confidence interval of the VIVIANE study, resulting in vaccine efficacies for women ranging from 49.7% to 91.1% for both HPV types.[5] For men, we used the same relative reduction percentages, leading to an efficacy of 41.3% for HPV-16 and 51.7% for HPV-18 as lower bounds, and 75.7% and 94.8%, respectively, as upper bounds. Also, as an alternative scenario, we varied the expected uptake of the vaccination strategies, assuming that only half of the attending adults would accept the vaccine (instead of all attending adults). Finally, Huijsmans *et al.*[33] recently showed that HPV prevalence in the Netherlands could be twice as high as the earlier data our model fit was based upon.[22] Therefore, we reanalyzed the impact of our most efficient strategies in a model with doubled HPV prevalence prior to vaccination. The overall prevalence among women was doubled in the model by increasing sexual risk behavior.

**Table 4.1. Incident human papillomavirus 16 (HPV-16) and HPV-18 infections for all women 10, 20, 50, and 70 years after the introduction of the current vaccination program (in 2009) under different adult vaccination strategies (all starting by 2016).**

| Vaccination strategy (sex) | Incident infections per 100 life years, by HPV-types[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | HPV-16 | | | | HPV-18 | | | |
| | 10 y | 20 y | 50 y | 70 y | 10 y | 20 y | 50 y | 70 y |
| **Current vaccination program** | 0.84 | 0.58 | 0.44 | 0.41 | 0.24 | 0.17 | 0.14 | 0.13 |
| **Inclusion of women** | | | | | | | | |
| 1 Mass campaign (F) | 0.72 (15%) | 0.53 ( 9%) | 0.43 ( 1%) | 0.41 ( 0%) | 0.20 (18%) | 0.15 (10%) | 0.14 ( 2%) | 0.14 ( 0%) |
| 2 Screening (F) | 0.81 ( 3%) | 0.52 ( 9%) | 0.38 (12%) | 0.36 (13%) | 0.23 ( 4%) | 0.15 (11%) | 0.12 (14%) | 0.11 (15%) |
| 3 STI consultations (F) | 0.81 ( 3%) | 0.54 ( 6%) | 0.40 ( 9%) | 0.37 (10%) | 0.23 ( 3%) | 0.16 ( 5%) | 0.13 ( 8%) | 0.12 ( 8%) |
| 4 Mass + STI (F) | 0.69 (17%) | 0.50 (14%) | 0.39 (11%) | 0.37 (11%) | 0.19 (20%) | 0.14 (16%) | 0.13 (10%) | 0.12 ( 8%) |
| 5 Screening + STI (F) | 0.79 ( 6%) | 0.50 (14%) | 0.35 (20%) | 0.32 (22%) | 0.23 (6%) | 0.14 (15%) | 0.11 (21%) | 0.10 (23%) |
| 6 Screening + mass (F) | 0.70 (16%) | 0.49 (15%) | 0.38 (13%) | 0.36 (13%) | 0.20 (19%) | 0.14 (18%) | 0.12 (16%) | 0.11 (15%) |
| **Inclusion of women, boys and men** | | | | | | | | |
| 7 Mass campaign (F+M) | 0.64 (24%) | 0.40 (30%) | 0.26 (40%) | 0.24 (41%) | 0.15 (36%) | 0.09 (49%) | 0.06 (61%) | 0.05 (62%) |
| 8 STI consultations (F+M) | 0.75 (10%) | 0.44 (24%) | 0.24 (45%) | 0.20 (50%) | 0.20 (19%) | 0.10 (38%) | 0.05 (65%) | 0.04 (71%) |
| 9 Mass + STI (F+M) | 0.62 (27%) | 0.37 (35%) | 0.23 (48%) | 0.20 (50%) | 0.15 (38%) | 0.08 (53%) | 0.04 (69%) | 0.04 (71%) |
| 10 Screening (F) + STI (F+M) | 0.73 (13%) | 0.40 (31%) | 0.19 (56%) | 0.15 (63%) | 0.19 (22%) | 0.09 (47%) | 0.04 (75%) | 0.02 (84%) |
| 11 Screening (F) + mass (F+M) | 0.63 (25%) | 0.37 (36%) | 0.21 (52%) | 0.18 (56%) | 0.15 (37%) | 0.08 (54%) | 0.04 (74%) | 0.03 (80%) |

*HPV-16 and HPV-18 infection incidence prior to vaccination was 1.16 and 0.32 infections/100 life-years, respectively. The corresponding incidence graphs are shown in Supplementary Figures 3 and 4. Abbreviations: STI, sexually transmitted infection.*

[a] *The relative percentage reduction in incidence as compared to the current vaccination program (girls only) is shown between parentheses.*

**Results**

For all strategies, most of the incidence reduction has occurred within 50 years following vaccination (Table 4.1), and after approximately 70 years equilibrium is reached (Supplementary Figures S4.3 and S4.4). For strategies concerning only women, the most substantial incidence reductions over time are achieved through a combined strategy of offering vaccination to adult women at the first cervical cancer screening visit and during STI consultations (Table 4.1). The incidences of both HPV-16 and HPV-18 are then reduced by approximately 20% as compared to the incidence under the current vaccination program. While strategies including a one-time mass campaign generate substantial incremental reductions 10 years after the introduction of the current vaccination program (e.g., 15% for HPV-16), the effects wear off over time, and the incidence is about the same as under the current program in the long run. Including also boys and men is projected to lead to substantial incremental reductions in HPV infection incidence among women in all strategies, especially for HPV-18 (Table 4.1). A combined strategy of offering vaccination to women at their first cervical cancer screening visit and to both men and women at STI consultations would lead to the largest incidence reductions over time (63% for HPV-16 and 84% for HPV-18).

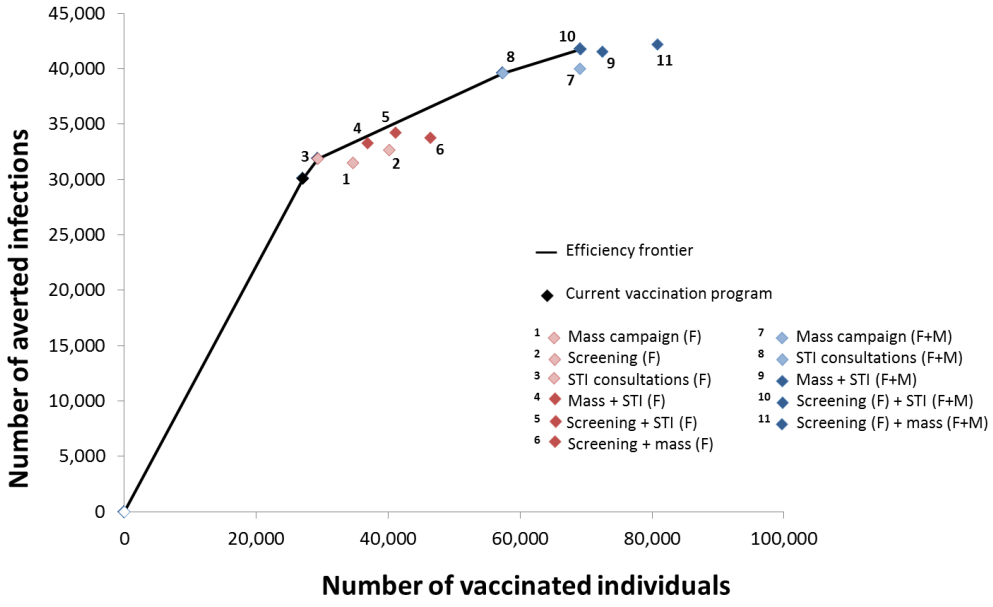


**Figure 4.1. Estimated cumulative number of averted infections and vaccinated individuals for the current vaccination program and all adult vaccination strategies considered from 2008–2079 in the Netherlands.** In strategies targeting both men and women, routine vaccination for boys was included from 2016 onward. Numbers are scaled to a simulated population of 100 000 people in 2016. Values of the corresponding number needed to vaccinate are given in Supplementary Table S4.1. *Abbreviations*: STI, sexually transmitted infection.

The NNV to prevent 1 infection for the current vaccination program as compared to no vaccination is 0.90, when considering 2008–2079 (Figure 4.1 and Supplementary Table S4.1). The most efficient adult vaccination strategies are vaccination during STI consultations for women alone (incremental NNV = 1.27), vaccination during STI consultations for both men and women (incremental NNV = 3.63), and the combination of vaccination during the first cervical cancer screening visit and STI consultations for both men and women (incremental NNV = 5.48). Estimated trends in HPV-16 and HPV-18 infection incidence under these most efficient strategies are shown in Figure 4.2. Less efficient are the strategies of mass campaigns and cervical cancer screening, offered either individually or combined. When considering a shorter time frame, 2008–2029, the incremental NNVs are obviously higher, but the order of efficiencies is similar (Supplementary Table S4.1).

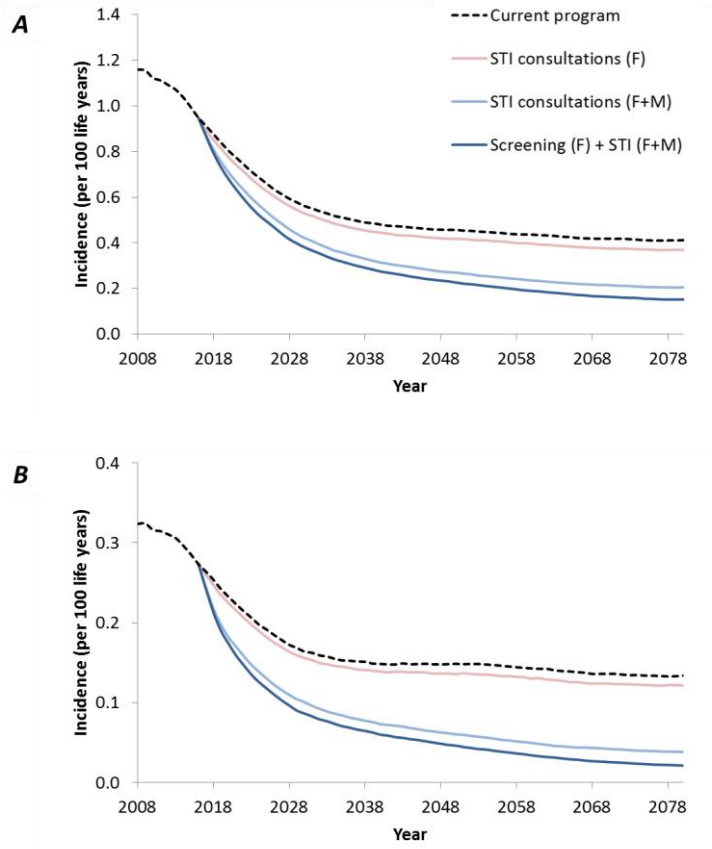


**Figure 4.2. Model-estimated trends in incident human papillomavirus type 16 (HPV-16; A) and HPV-18 (B) infections for all women for the period 2008 (before vaccination) until 2080 when vaccinating adults under the 3 most efficient vaccination strategies by 2016.** *Abbreviations*: STI, sexually transmitted infection.

**Table 4.2. Incident human papillomavirus type 16 (HPV-16) infections for all women 70 years after the introduction of the current vaccination program in the sensitivity analyses.**

| | Incident HPV-16 infections per 100 life-years[a] | | | | |
|---|---|---|---|---|---|
| | **Base case** | **Ineffective in infected individuals** | **Lower vaccine efficacy[b]** | **Higher vaccine efficacy[c]** | **Reduced vaccine acceptability[d]** |
| **Inclusion of women only** | | | | | |
| 1 Mass campaign (F) | 0.41 (0%) | 0.41 (0%) | 0.41 (0%) | 0.41 (0%) | 0.41 (0%) |
| 2 Screening (F) | 0.36 (13%) | 0.37 (11%) | 0.39 (5%) | 0.33 (21%) | 0.39 (6%) |
| 3 STI consultations (F) | 0.37 (10%) | 0.37 (9%) | 0.37 (10%) | 0.37 (10%) | 0.39 (5%) |
| 4 Mass + STI (F) | 0.37 (11%) | 0.37 (10%) | 0.37 (10%) | 0.37 (10%) | 0.39 (5%) |
| 5 Screening + STI (F) | 0.32 (22%) | 0.33 (19%) | 0.35 (15%) | 0.29 (29%) | 0.36 (12%) |
| 6 Screening + mass (F) | 0.36 (13%) | 0.37 (11%) | 0.39 (5%) | 0.32 (21%) | 0.39 (6%) |
| **Inclusion of also boys and men** | | | | | |
| 7 Mass campaign (F+M) | 0.24 (41%) | 0.24 (41%) | 0.24 (41%) | 0.24 (42%) | 0.24 (41%) |
| 8 STI consultations (F+M) | 0.20 (50%) | 0.20 (50%) | 0.20 (50%) | 0.20 (50%) | 0.22 (46%) |
| 9 Mass + STI (F+M) | 0.20 (50%) | 0.20 (50%) | 0.20 (50%) | 0.20 (50%) | 0.22 (46%) |
| 10 Screening (F) + STI (F+M) | 0.15 (63%) | 0.16 (62%) | 0.18 (56%) | 0.13 (69%) | 0.19 (53%) |
| 11 Screening (F) + mass (F+M) | 0.18 (56%) | 0.19 (54%) | 0.21 (48%) | 0.16 (62%) | 0.21 (48%) |

*Results for HPV-18 are shown in Supplementary Table S4.2. Abbreviations: STI, sexually transmitted infection.*

[a] *The relative percentage reductions as compared to the estimated HPV-16 infection incidence per 100 life-years (0.41) under the current vaccination program in the base case are shown in parentheses.*

[b] *Vaccine efficacy was reduced to 49.7% for HPV-16 in women (instead of 77.4%) and to 41.3% in men (instead of 64.5%).*

[c] *Vaccine efficacy was increased to 91.1% and 75.7% for HPV-16 in women and men, respectively.*

[d] *Vaccine acceptability was reduced by 50%.*

The sensitivity analysis shows that reductions in the incidence of HPV infection are only slightly lower as compared to the base case when assuming that vaccination is ineffective in HPV positive women, yet the order of effective strategies remains the same (Table 4.2 and Supplementary Table S4.2). Assuming lower and higher vaccine efficacies for adults particularly affects the incidence reductions in strategies that incorporate vaccination at the first cervical cancer screening visit (Table 4.2 and Supplementary Table S4.2). The maximum difference in incidence reduction is 9 percentage points (i.e., the HPV-18 incidence is reduced by 6% as compared to the current vaccination program, instead of 15%). In all other strategies, vaccine efficacy has a limited impact on the estimated incidence reduction. Assuming lower vaccine acceptability affects mostly the incidence reduction under the combined strategy of vaccination at the first cervical cancer screening and at STI consultations for both men and women, with a difference of about 10 percentage points. The incidences of HPV-16 and HPV-18 are still estimated to decrease by 53% and 75%, respectively (instead of 63% and 84%, respectively, compared with the current vaccination program (Table 4.2 and Supplementary Table S4.2). When the prevalences of HPV-16 and HPV-18 are twice as high prior to vaccination, the estimated relative reductions in incidence are slightly higher, compared with our base case analysis (Supplementary Table S4.3).

**Discussion**

Using STDSIM and vaccination efficacy estimates from the VIVIANE study, we have presented the first estimations of the impact of extending routine HPV vaccination to adult women, boys, and men through existing public health programs. Compared with the current, girls-only program, the incidences of HPV-16 and HPV-18 infection are estimated to decrease in the long run by 63% and 84%, respectively, when offering vaccination both at the first cervical cancer screening visit for women (aged 30 years) and at STI consultations for men and women (aged 15–29 years). For this strategy, the incremental NNV to prevent 1 HPV infection is 5.48, which is 6 times higher than the NNV of 0.90 for the current program.

There are 3 important limitations associated with these results. First, there is still large uncertainty about the vaccine efficacy for adults, yet the sensitivity analysis in which we varied the efficacy shows that this hardly affects our main findings. Still, observational studies are needed to determine the efficacy of the bivalent vaccine for adult men. Second, we made rather simple assumptions regarding vaccine uptake levels for adults based on cervical cancer screening and STI consultation rates, which might be too optimistic. However, while halving vaccine acceptability would lead to lower estimated incidence reductions, significant incremental benefits are still to be expected. Furthermore, an HPV prevalence of approximately 5% is rather low as compared to that in other countries and to recent results by Huijsmans *et al.*,[33] possibly affecting the generalizability of our study. Our sensitivity analysis showed that doubling HPV prevalences as compared to the base case

resulted in a slightly higher impact of the most efficient strategies, yet differences were small. Finally, we did not include cervical intraepithelial neoplasia (CIN), cervical cancer, and treatment of women with CIN or cervical cancer in our model. By removing precancerous lesions, treatment could shorten the duration of the underlying HPV infection. However, this is to some extent taken into account in our model because we calibrated the natural history of HPV on prevalence data from a screened population.[14,22]

We appreciate that a 70-year time horizon might be less relevant for policy makers as uncertainties of predictions are increased with longer time horizons, owing to the emergence of factors such as new technical developments (better vaccines) or development of resistance. However, our results emphasize the need to consider both short- and long-term predictions in assessing HPV vaccination strategies. Our short-term incidence reductions (10 years and 20 years after the start of the current program) indicate that a one-time mass campaign for adults will have the largest incremental impact on HPV infection incidence. However, this impact diminishes over time as the vaccinated cohort ages, whereas the strategies with a relatively modest short-term impact are predicted to become more effective after 50 and 70 years since implementation.

Three other studies have modeled the impact of vaccinating women outside the age range of the vaccination program.[34–36] However, these models were limited by not considering natural immunity[35] and herd immunity,[34–36] both important factors in determining the effects of interventions on sexually transmitted infections.[37] Still, consistent with Bogaards *et al.*,[34] we found that the mechanism of vaccine efficacy with regard to HPV status at the time of vaccination does not influence the effectiveness estimates of HPV vaccination. This could be due to the low observed HPV prevalence in older age groups, so that assumptions about effectiveness in HPV positive women have a minor impact on model predictions.

Our results clearly suggest that implementing adult vaccination by using the most efficient of our selected strategies for women only or for women, boys, and men will have a substantial impact on HPV incidence and thus cervical cancer incidence. Starting from the observation that 62.5% and 17.2% of cervical cancers are caused by HPV-16 and HPV-18, respectively,[38] and using the reported average lag time of 20 years between acquiring an HPV infection and developing cervical cancer, cervical cancer incidence would decline by about 51% when vaccinating adult women at STI consultations and by 69% when vaccinating women at cervical cancer screening and both sexes at STI consultations, compared with 48% under the current vaccination program (for details on the underlying calculations, see the article by Matthijsse *et al.*).[13] In addition, vaccination will also offer some protection against vaginal and oropharyngeal cancer, against anal and penile cancers when boys and adult men will be included,[12] and against genital warts if the quadrivalent vaccine is used.[26] While the new nonavalent vaccine would protect against 5 additional high-risk HPV types,[39] the estimated cervical cancer reductions would only slightly increase, as the extra genotypes in the nonavalent

vaccine are less oncogenic than HPV-16 and HPV-18[38] and will therefore protect against relatively fewer cancers.

Most modeling studies have estimated that HPV vaccination of preadolescent girls is cost-effective, as presented in 3 overviews.[40-42] One modeling study concluded that girls-only vaccination in the Netherlands would not be cost-effective,[43] yet it was performed using the previous recommendations of 3 vaccine doses instead of 2 and before the vaccine price reductions. Although the health gain associated with HPV vaccination of boys mainly consists of reduced cervical cancer risk for women, boys can still benefit substantially through reductions in other HPV-related cancers.[12] This would especially be the case for men who have sex with men, who would benefit marginally from reduced transmission in the general population. The incremental NNV of offering vaccination to women at sexual health clinics in our study is 1.27, only slightly higher than the NNV of the current vaccination program. This indicates that HPV vaccination of adults is less efficient than HPV vaccination of girls. However, since vaccinating girls is cost-effective, even slightly less efficient adult vaccination strategies are likely to still satisfy the usual criteria for cost-effectiveness. Also, modeling studies usually assume lifelong vaccine protection. If this protection would not last for a lifetime, vaccination of adults could provide the necessary booster for the vaccine, thereby reinforcing the cost-effectiveness of adult vaccination. Cost-effectiveness may be further enhanced if the recommended number of vaccine doses could be reduced, especially when the similar protection recently found after only 1 dose as compared to the full 3-dose vaccination schedule would also apply for a longer time horizon than the current follow-up of 4 years.[44,45] Finally, the additional reductions in cervical cancer incidence due to extending the eligible age range for HPV vaccination warrant reevaluation of the current cervical cancer screening program, possibly leading to cost savings if fewer screenings turn out to be sufficient for a similar population effect.

The use of existing public health programs to provide HPV vaccination, as we assumed for most strategies, offers 2 important advantages. First, the need for large upfront investments is reduced by using existing infrastructures. Second, the familiarity of existing public health programs might enhance acceptability of the vaccine. Most women aged >26 years have positive attitudes about receiving HPV vaccination,[32] and a recent study among women aged 26–77 years showed that many would want to be vaccinated against HPV, even if they had to pay for the vaccine out of pocket.[46] This might even become less of an obstacle now that vaccine prices are decreasing. A meta-analysis of 22 studies examining HPV vaccine acceptability among men found a moderate level of acceptance.[47] Most influential correlates of acceptability that can be targeted in campaigns are perceived HPV vaccine benefits and healthcare provider recommendation.[47]

We conclude that rolling out adult HPV vaccination within existing public health infrastructures is likely to be an effective and efficient strategy to further and more quickly reduce HPV infection incidence in the Netherlands, as an addition to the current girls-only vaccination program. In particular, offering vaccination to women at the first cervical cancer screening visit and to

both men and women during STI consultations seems a very promising strategy to improve HPV transmission control, specifically for cohorts too old to have been covered by current vaccination programs or in countries with suboptimal coverage. Future research should study vaccine acceptability among adults in different public health settings. In any case, even with modest adult vaccination uptake in the general population, incremental and especially faster benefits can be achieved, and our results strongly suggest that the Netherlands, as well as other countries with routine HPV vaccination, should consider rolling out adult vaccination to further enhance cervical cancer prevention.

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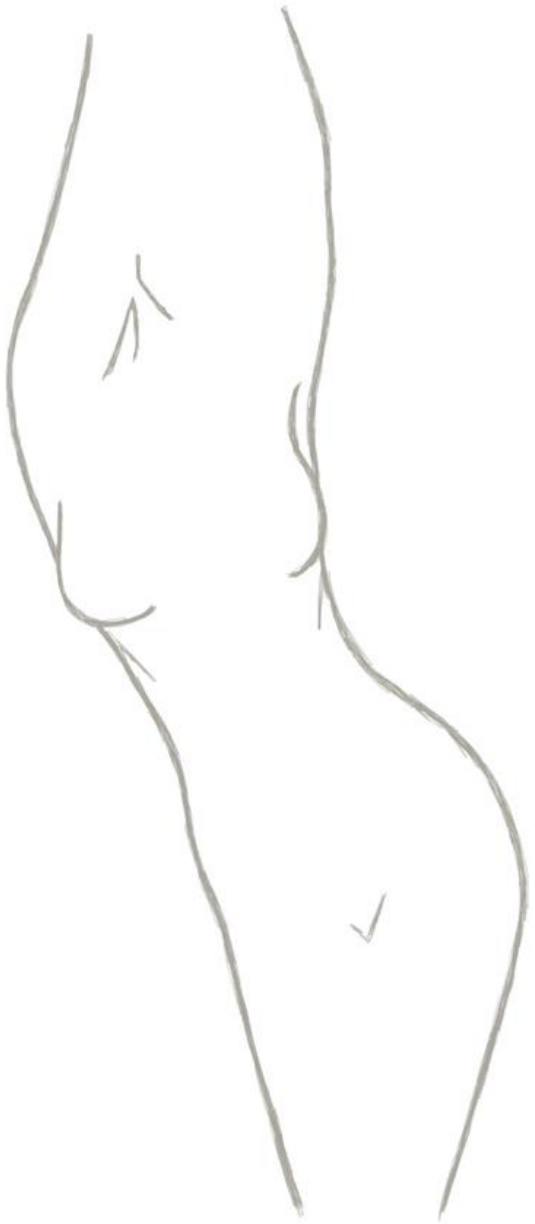
# 4

## Supplements



## S4.1 Description of the STDSIM model

For this study, we have used the STDSIM model previously quantified to the Netherlands.[1,2] Sections S4.1A-S4.1C have in nearly the same form also been published in the supplements of Matthijsse *et al.*[1]

### *S4.1A General model structure*

STDSIM has four modules: (1) demography, (2) sexual behavior, (3) STI transmission and natural history, and (4) interventions.[3-6] The demography module contains processes that determine the demographic structure of the simulated population, such as fertility, mortality, and migration. The sexual behavior module includes the processes of starting and ending relationships, frequency of sexual contacts, and age mixing patterns. The module of STI transmission and natural history defines the duration of disease stages, STI symptoms, transmission probabilities per sexual contact and possible immunity processes. Finally, the interventions module describes the timing, effectiveness and further consequences of treatments, as well as condom use.

We previously quantified the model to the Netherlands by adjusting parameters of demography and sexual behavior, and by including HPV transmission, HPV natural history and hysterectomies based on observational data for the Netherlands.[1] We do not assume a protective effect of condoms on HPV transmission, given inconsistent results in literature regarding this protective effect, and the fact that genital skin transmission can occur as well.[7,8] Below we give a brief summary of the structure, quantification, and the fit of the model to the Dutch setting. The full model is published in Matthijsse *et al.*[1]

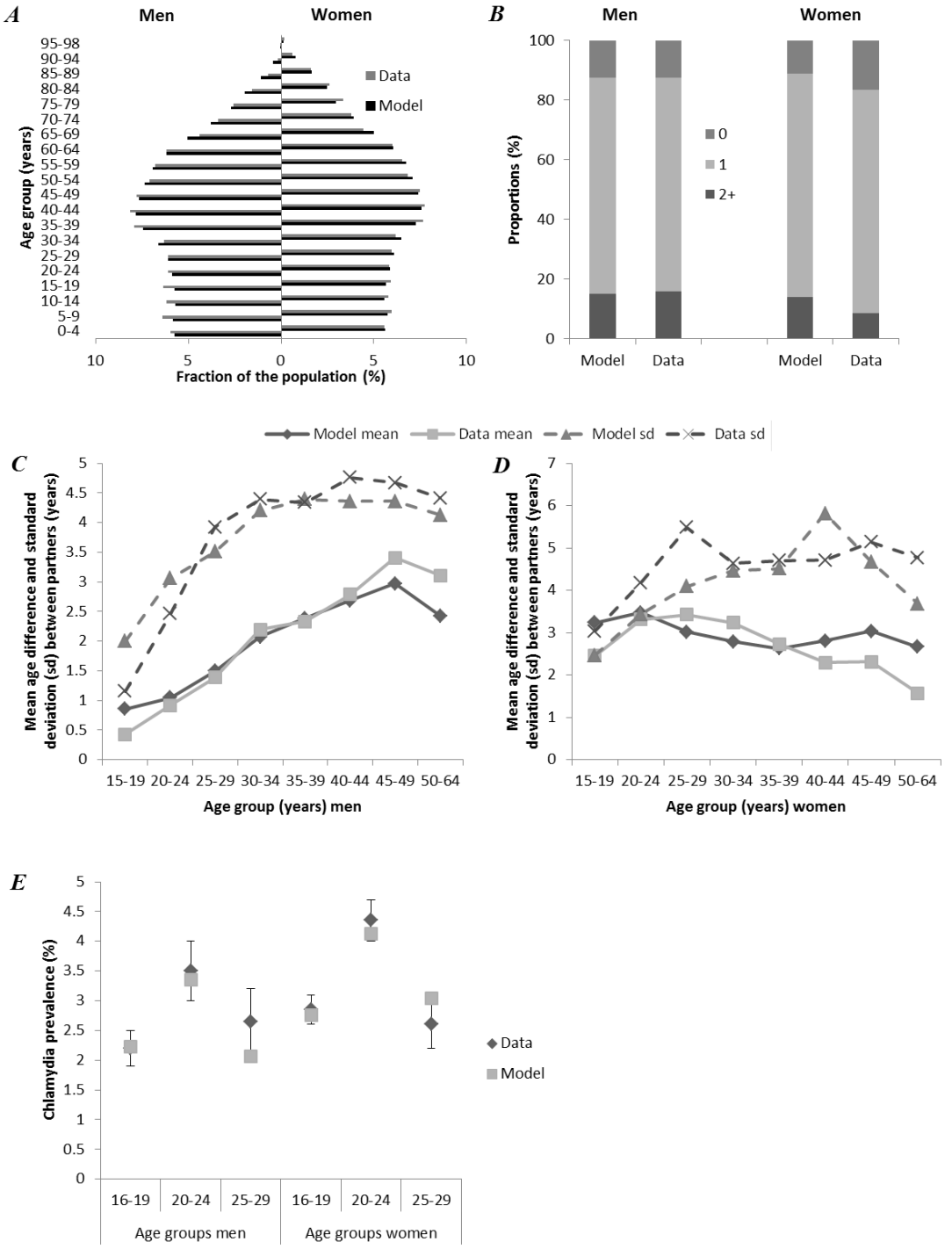



**Figure S4.1. Comparison of the model predictions with data of population composition, sexual behavior, and chlamydia prevalence.[1]** Modeled population composition per age group, compared to data of Statistics Netherlands *(A)*.[9] Modeled number of partners in the last 6 months of men and women aged 20-64 years compared to data of 19-64 year-old men and women in Rutgers WPF (B).[12,13] Mean and standard deviation (sd) of age differences in relationships, reported by male respondents *(C)* and female respondents *(D)*. Modeled chlamydia prevalence of 15-29 years old compared to the data of Van den Broek *et al.*[20] of 16-29 years old *(E)*.

*S4.1B Demography*

We used data from Statistics Netherlands to reproduce an average Dutch population.[1,9] All model runs start in 1911 with almost 10,000 men and over 10,000 women. New individuals enter the model through birth and immigration, while deaths and emigration remove individuals from the population. New births are randomly assigned to sexually active women in the age range 15-49 years. We used age-specific fertility rates to assign births proportionally to observed fertility patterns across different age-groups.[1,9,10] After birth, each individual is assigned a date of death, which is drawn from a pre-defined life-table. We used life expectancy data of the Dutch population in 2008 to construct an age- and sex-specific life table representative for the general population in the Netherlands.[1,9] Finally, we used the average of the age- and gender-specific migration rates of the Dutch population from 2000-2008 to simulate immigration and emigration.[9] The simulated population consists of about 80,000 men and nearly the same number of women in 2008. The simulated population was compared to data of the population composition of the Netherlands in 2008 (Figure S4.1A).[9]

*S4.1C Sexual behavior*

The fitting procedure of sexual behavior in STDSIM to reproduce a sexual network representative of the Netherlands is elaborately described in Matthijsse *et al.*[1] In the model, people become available for a sexual relationship at the 'age of sexual debut', which is randomly drawn from a uniform distribution. The average age of sexual debut is 17 years for women and men, ranging from 12-22 years.[11-13] When a person is available, he or she can be selected by someone from the opposite sex to form a relationship with. This 'period of availability' has a pre-set duration of 1 year for men and 2.25 years for women, and if the person has not been selected at the end of his or her availability period, he or she will select a partner from the opposite sex out of the pool of available people. This approach guarantees that both males and females determine the partner-selection process.[14] Each time a relationship is formed or ended, a duration until the person becomes available for a new relationship is drawn from the predefined distribution of durations until availability. This mechanism of partnership formation fulfills two requirements: 1) there should be a pool of potential partners at any moment, and 2) there should be a minimum rate of partner acquisition. Being available during (at most) a pre-set period ensures a pool of potential partners, and taking the initiative to find a partner at the end of this period ensures a minimum rate of partner acquisition.

Two types of sexual relationships are considered in STDSIM: long-term ('steady') relationships such as marriage (average duration of 40 years), and short-term ('casual') relationships (average duration of 1 year), both exponentially distributed.[1] The type of relationship depends on the age of the male partner, and is defined as the (age-specific) probability of a steady relationship. While this assumption is a simplification of real life, this structure is of little importance when modeling sexual behavior in Western settings given the small observed age differences between partners, and the therefore likely similar relationship preferences between men and women. Every relationship starts

with a sexual contact. After each contact, the time until a new sexual contact within the relationship is drawn from an exponential distribution.

Independent from their sexual relationships, a high-risk group with more frequent one-off contacts (on average 2.25 contacts per month) was included in the model to match the proportion of participants (11%) that reported to have 21 or more lifetime sexual partners in a Dutch survey.[11,12]

All underlying dynamics and formulas of sexual behavior, relationship formation, and mixing are described in detail in Hontelez *et al.*[5] All parameter values to reproduce the Dutch sexual network are described in Matthijsse *et al.*[1] Figure S4.1 shows the predicted number of recent partners for men (Figure S4.1B) and the age difference in relationships (Figures S4.1C and S4.1D) compared to data from the Netherlands. In addition, we independently verified the transmission dynamics by simulating the transmission of chlamydia through the network (transmission probability of 0.45 per sexual contact;[1,15] average duration of infection of 52 weeks in women;[1,4,16-18] and 28 weeks in men),[1,16,19] and we found that the model closely reproduced observed chlamydia prevalence levels (Figure S4.1E).

*S4.1D The natural history of HPV-16 and HPV-18*

The fitting procedure of the natural history of HPV-16 and HPV-18 is described in detail by Matthijsse *et al.*[1] The best fitting model for HPV-16 assumes a Weibull distribution with a shape parameter of 0.50 (out of chosen values 0.25, 0.50, 1, 2, and 4) for the duration of infection with a mean of 50.8 months for men and 15.6 months for women, and a Weibull shape of 0.25 for the duration of immunity with a mean of 112 years for both men and women. This corresponds with half of the men and over 70% of the women clearing their infection within 1 year. In this model, almost 50% of the individuals are no longer immune 1 year after clearing the infection. Still, about 20% have an estimated duration of acquired immunity that lasts longer than 30 years. The corresponding estimated transmission probability is 6.9% (95% CI: 5.4-8.6) per sexual contact. For HPV-18, the best fitting model assumes a Weibull shape of 0.50 for the duration of infection with a mean of 26.2 months for men and 17.2 months for women, suggesting that over 60% of the men and almost 70% of the women clear their infection within 1 year. The mean duration of 43 years with a Weibull shape of 1 for the duration of immunity for HPV-18 suggests that, after clearing an HPV-18 infection, about 2% is immune for less than 1 year, and half of the individuals are immune for more than 30 years. The corresponding transmission probability is 7.7% (95% CI: 5.2-10.6) per sexual contact. Figure S4.2 shows that the observed and estimated HPV-16 and HPV-18 prevalence prior to vaccination match rather well.

For the current study, HPV-16 and -18 incidence and prevalence estimates were averaged over 2,000 runs of the STDSIM model to minimize stochastic variation. Each model run started 100 years prior to the introduction of the vaccine with almost 10,000 men and over 10,000 women, and ended 100 years after the introduction.

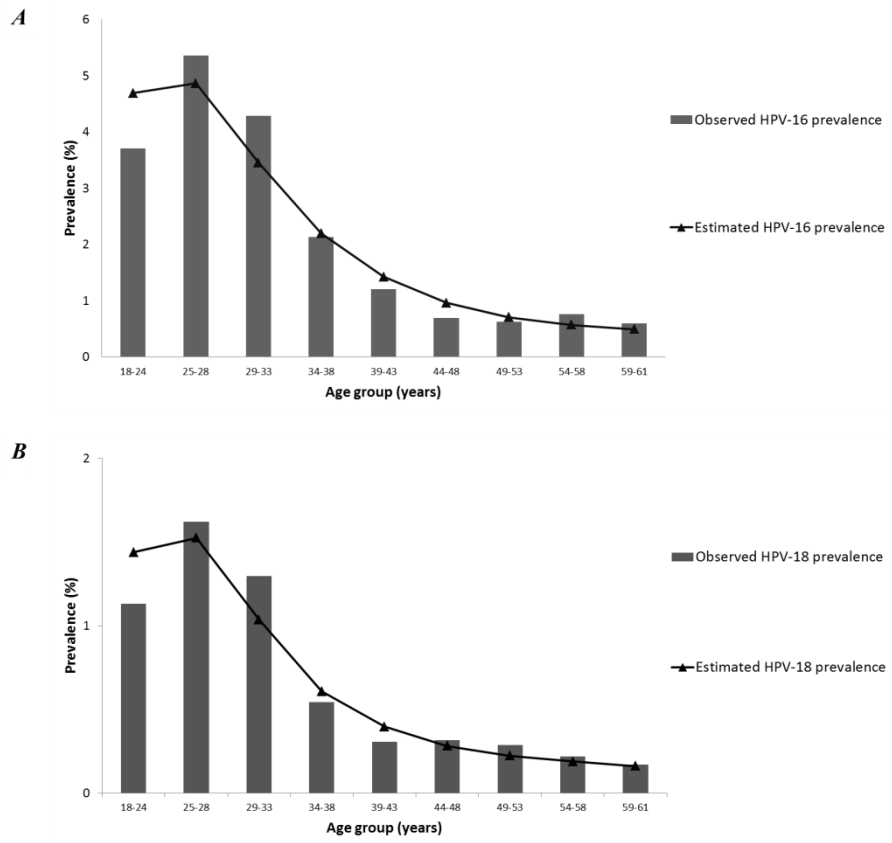



**Figure S4.2. Comparison of the observed and estimated age-specific HPV prevalence prior to vaccination.**[1] *(A)* shows the results for HPV-16; *(B)* for HPV-18.

## S4.2 Supplementary figures and tables with results

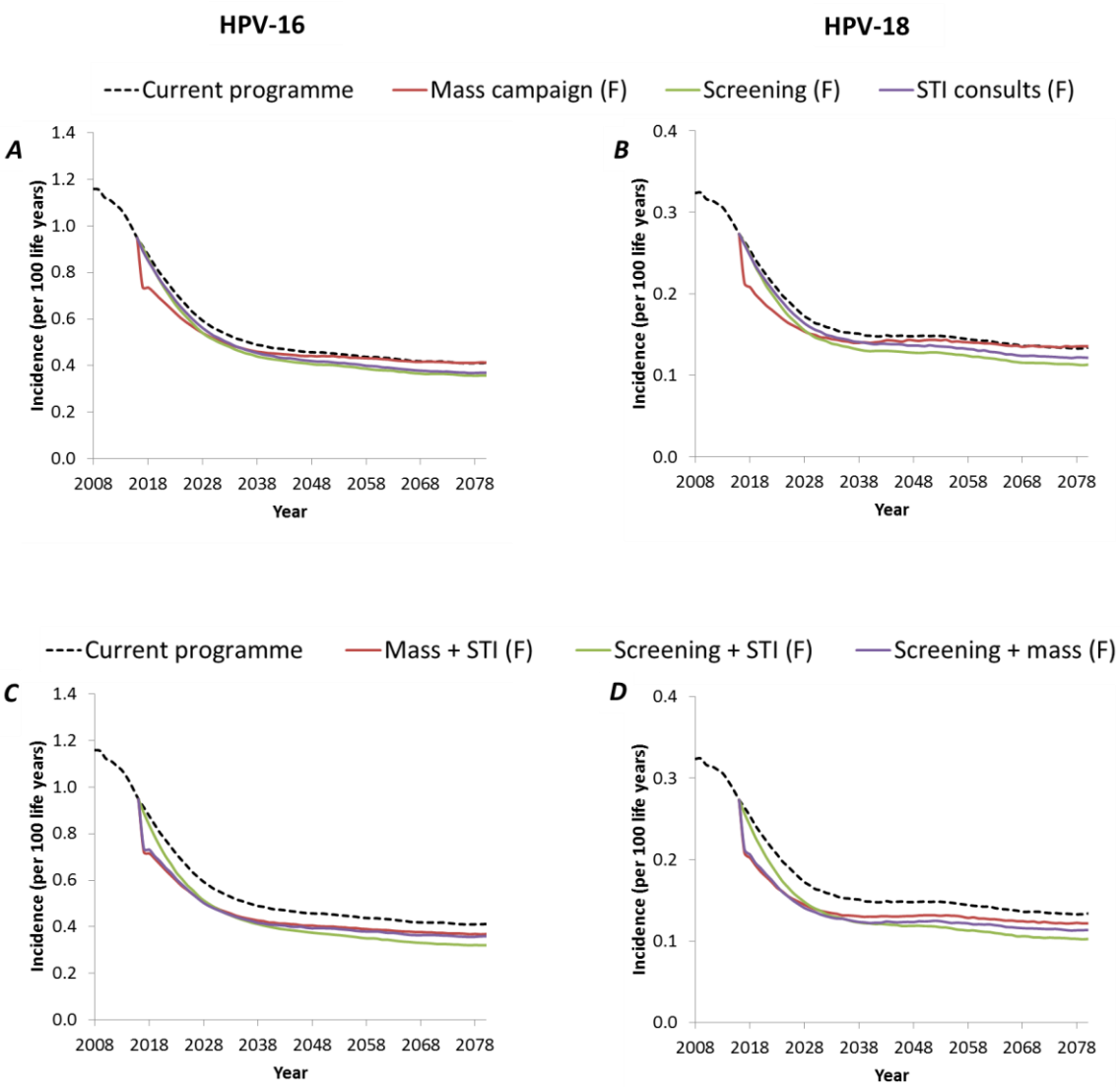



**Figure S4.3. Estimated trends in HPV-16 (left) and HPV-18 (right) incidence for all women over the period 2008 (pre-vaccination) until 2080, when vaccinating adult women starting by 2016, through different vaccination strategies alone (A and B) or combined (C and D).**

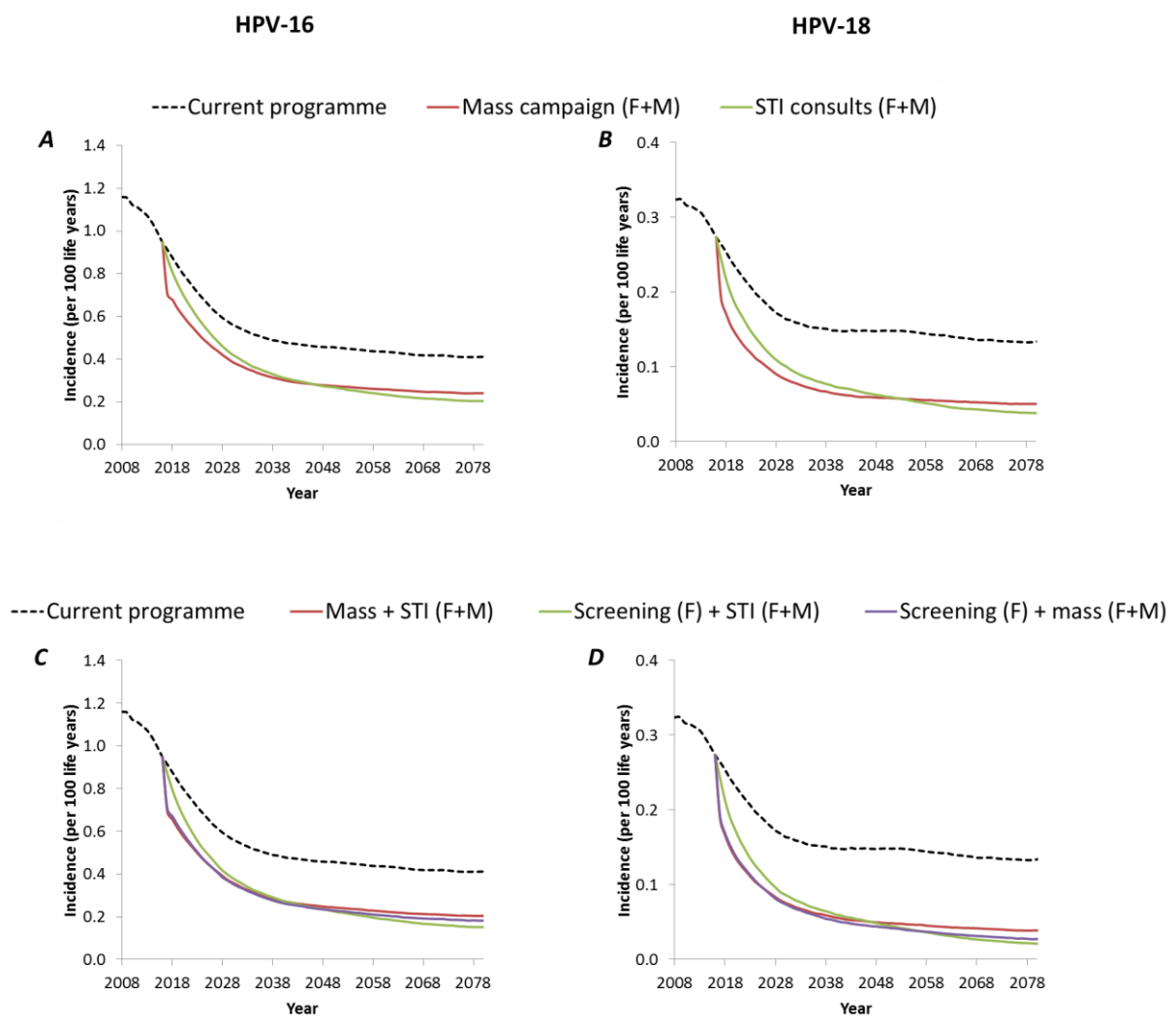



**Figure S4.4. Estimated trends in HPV-16 (left) and HPV-18 (right) incidence for all women over the period 2008 (pre-vaccination) until 2080 when boys and adult men are included by 2016 in the different vaccination strategies alone (A and B) or combined (C and D).**

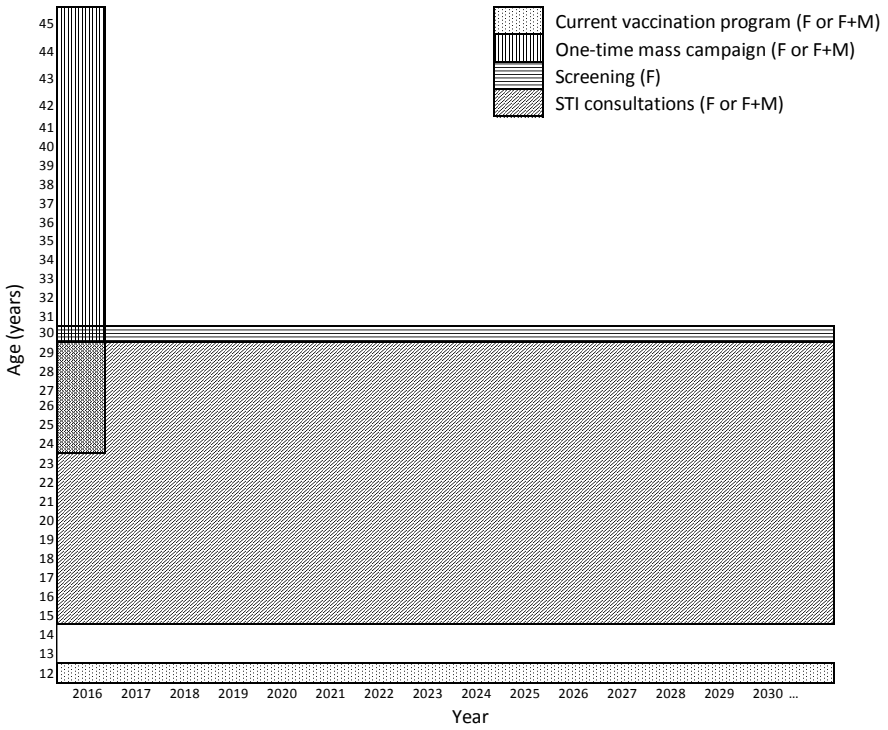



**Figure S4.5. Graphic representation of the scenarios in which adults are vaccinated from 2016 onwards in addition to the current girls-only vaccination program. In strategies targeting both men and women, routine vaccination for boys was included from 2016 onwards.**

**Table S4.1. Vaccinated individuals, averted HPV infections* and (incremental) number needed to vaccinate (NNV) under the current vaccination program and the most efficient adult vaccination strategies.**

| | 2008-2029 | | | 2008-2079 | | |
|---|---|---|---|---|---|---|
| | **Vaccinated individuals (thousands)** | **Averted infections (thousands)** | **(Incremental) NNV** | **Vaccinated individuals (thousands)** | **Averted infections (thousands)** | **(Incremental) NNV** |
| Current vaccination programme | 7.5 | 4.0 | 1.87 | 27.1 | 30.1 | 0.90 |
| STI consults (F) | 8.1 | 4.2 | 2.57 | 29.3 | 31.9 | 1.27 |
| STI consults (F+M) | 15.7 | 5.1 | 8.90 | 57.4 | 39.6 | 3.63 |
| Screening (F) + STI (F+M) | 19.5 | 5.4 | 12.26 | 69.2 | 41.8 | 5.48 |

** These numbers are rounded and scaled to a simulated population of 100,000 people in 2016.*

**Table S4.2. HPV-18 incidence per 100 life years for all women 70 years after the introduction of the current vaccination program in the sensitivity analyses.** The relative reductions compared to the estimated HPV-18 incidence per 100 life years (0.13) under the current vaccination program in the base case are shown in parentheses.

| | **Base case** | **Ineffective in infected individuals** | **Lower vaccine efficacy*** | **Higher vaccine efficacy‡** | **Reduced vaccine acceptability§** |
|---|---|---|---|---|---|
| *Inclusion of adult women only* | | | | | |
| 1 Mass campaign (F) | 0.136 (0%) | 0.134 (0%) | 0.134 (0%) | 0.134 (0%) | 0.135 (0%) |
| 2 Screening (F) | 0.112 (15%) | 0.114 (14%) | 0.125 (6%) | 0.103 (22%) | 0.124 (6%) |
| 3 STI consults (F) | 0.122 (8%) | 0.122 (8%) | 0.122 (8%) | 0.122 (8%) | 0.128 (4%) |
| 4 Mass + STI (F) | 0.122 (8%) | 0.122 (9%) | 0.121 (9%) | 0.122 (8%) | 0.128 (4%) |
| 5 Screening + STI (F) | 0.102 (23%) | 0.102 (23%) | 0.113 (15%) | 0.093 (30%) | 0.117 (12%) |
| 6 Screening + mass (F) | 0.113 (15%) | 0.114 (15%) | 0.124 (6%) | 0.102 (23%) | 0.124 (7%) |
| *Inclusion of also boys and men* | | | | | |
| 7 Mass campaign (F+M) | 0.050 (62%) | 0.051 (62%) | 0.050 (62%) | 0.050 (62%) | 0.050 (62%) |
| 8 STI consults (F+M) | 0.038 (71%) | 0.038 (71%) | 0.038 (71%) | 0.038 (71%) | 0.043 (68%) |
| 9 Mass + STI (F+M) | 0.039 (71%) | 0.039 (71%) | 0.039 (70%) | 0.039 (71%) | 0.044 (67%) |
| 10 Screening (F) + STI (F+M) | 0.022 (84%) | 0.021 (84%) | 0.028 (79%) | 0.017 (87%) | 0.034 (75%) |
| 11 Screening (F) + mass (F+M) | 0.027 (80%) | 0.028 (79%) | 0.037 (72%) | 0.022 (84%) | 0.039 (71%) |

** Vaccine efficacy was reduced to 49.7% for HPV-18 in women (instead of 77.4%), and 52.7% in men (instead of 80.6%).*
*‡ Vaccine efficacy was increased to 91.1% and 94.8% for HPV-18 in women and men, respectively.*
*§ Vaccine acceptability was reduced by 50%.*

**Table S4.3. Relative incidence reduction achieved under the most efficient vaccination strategies for base case and doubled HPV-16 and HPV-18 prevalence levels.** The relative incidence reductions (%) for HPV-16 and HPV-18 concern a comparison between incidences for the adult vaccination strategy compared to the current girls-only vaccination in the long run, i.e. 70 years after the introduction of the current vaccination program in 2009. The doubled prevalence was derived in the model by increasing the sexual risk behavior (see methods section). For HPV-16, the base case and doubled prevalences are 1.53% and 3.06% respectively. For HPV-18, these are 0.47% and 0.94%.

| **Vaccination strategy** | **Relative incidence reduction (%)** | | | |
|---|---|---|---|---|
| | **HPV-16** | | **HPV-18** | |
| | **Base case (prev. = 1.53%)** | **Double (prev. = 3.06%)** | **Base case (prev. = 0.47%)** | **Double (prev. = 0.94%)** |
| **STI consultations (F)** | 10% | 12% | 8% | 12% |
| **STI consultations (F+M)** | 50% | 60% | 71% | 80% |
| **Screening + STI (F+M)** | 63% | 68% | 84% | 89% |

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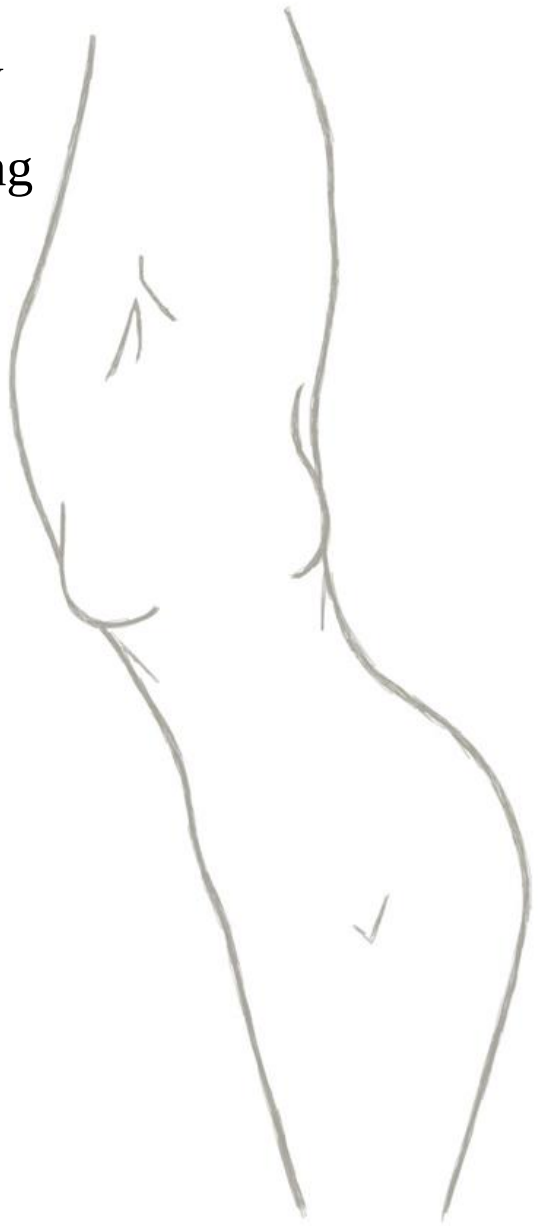
# 5

# The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study

Cancer Causes & Control (2016)



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Inge M.C.M. de Kok
Suzette M. Matthijsse
Marjolein van Ballegooijen

**Abstract**

**Background**

It is well acknowledged that HPV testing should not be performed at young age and at short intervals. Cytological screening practices have shown that over-screening, i.e., from a younger age and at shorter intervals than recommended, is hard to avoid. We quantified the consequences of a switch to primary HPV screening for over-screened women, taking into account its higher sensitivity but lower specificity than cytology.

**Methods**

The health effects of using the HPV test instead of cytology as the primary screening method were determined with the MISCAN-Cervix model. We varied the age women start screening and the interval between screens. In the sensitivity analyses, we varied the background risk of cervical cancer, the HPV prevalence, the discount rate, the triage strategy after cytology, and the test characteristics of both cytology and the HPV test.

**Results**

For women screened 5 yearly from age 30, 32 extra deaths per 100,000 simulated women were prevented when switching from primary cytology to primary HPV testing. For annual screening from age 20, such a switch resulted in 6 extra deaths prevented. It was associated with 9,044 more positive primary screens in the former scenario versus 76,480 in the latter. Under all conditions, for women screened annually, switching to HPV screening resulted in a net loss of quality-adjusted life years.

**Conclusion**

For over-screened women, the harms associated with a lower test specificity outweigh the life years gained when switching from primary cytology to primary HPV testing. The extent of over-screening should be considered when deciding on inclusion of primary HPV screening in cervical cancer screening guidelines.

## Introduction

In several Western countries, cytological screening has considerably reduced the cervical cancer incidence and mortality over the past four decades.[1] Nevertheless, even in countries with a nationwide screening program, women still die from cervical cancer. Although most deaths occur after age 30 and in women who did not adequately participate in screening, some deaths occur at young age and in women who recently received a negative test result (which suggests it was false negative).[2–4] Therefore, clinicians may tend to screen more frequently than recommended.[5]

Ever since infection with the human papillomavirus (HPV) was found to be a necessary condition for developing cervical cancer,[6,7] testing for the presence of high-risk HPV types (i.e., carcinogenic types) has received much attention. A summary of meta-analyses estimated that the HPV test has a 23 % (95% CI: 13–33 %) higher sensitivity, but a 6 % (95% CI: 4–8 %) lower specificity than cytology for detecting high-grade lesions and cervical cancer.[8] Cost-effectiveness analyses based on these findings have shown that in well-controlled screening situations primary HPV screening is likely to be more effective, as well as more cost-effective than primary cytology.[9,10] Therefore, many countries are considering a switch from primary cytology to primary HPV screening. In the USA, co-testing (i.e., cytology combined with HPV testing) is already recommended, and Australia and the Netherlands are preparing a switch from primary cytology to primary HPV screening.[11–13]

For primary cytology, it is known that over-screening, here defined as screening from a younger age or at shorter intervals than recommended, is neither required to detect progressive lesions in an early phase nor desired as it detects many regressive lesions. Unavoidably, it also involves more false-positive test results, adding to the psychological stress women may experience from having a positive test and being referred for colposcopy.[14] In addition, the costs of over-screening are substantial, amounting to approximately 0.5–1 billion USD per year for the US healthcare system, while yielding little or no health gains.[15]

Because of its lower specificity to detect clinically relevant lesions, avoiding over-screening is even more essential for HPV screening than for cytology screening. The vast majority of HPV infections clear spontaneously, especially at young age.[16] Detecting these infections leads to unnecessary triage situations or referrals to colposcopy. For over-screened women, switching to HPV (co-)testing may therefore do more harm than good.

Guidelines driven by rational decision making tend to restrict cytology screening—and HPV screening even more so. The US guidelines currently recommend cervical screening in women aged 21–65 years with an interval of 3 or 5 years (dependent on both age and test).[17] In European guidelines, primary HPV screening is recommended for women aged ≥35 and discouraged for those below the age of 30.[18] In the Netherlands, primary HPV screening will be offered from age 30 to 65 every 5–10 years, and in Australia from age 25 to 69 every 5 years.[11,13] Unfortunately, also for HPV screening, having well-considered screening policy recommendations will not guarantee that women are screened accordingly.

A recent US study showed that over 68 % of physicians would recommend another cytological test in 1 or 2 years where the guidelines recommend a 3-year interval.[19] After a negative co-test, 67–94 % of clinicians recommended a shorter screening interval than suggested by US guidelines.[20] Several European countries also have reported considerable over-screening.[21] In summary, large proportions of women are being over-screened with cytology, and this is likely to continue when HPV screening is implemented.

Notwithstanding these facts, HPV testing is, for good reasons, increasingly often included in primary screening recommendations. However, despite its lower specificity, we are unaware of intensified efforts to minimize the level of over-screening. In this study, we aim to quantify the harms and benefits of introducing primary HPV screening for women with diverse screening behaviors, age of first screen ranging from 20 to 30 years, and screening interval from 1 to 5 years. These scenarios cover both recommended schedules and observed levels of over-screening. The results of this study show the effects of introducing HPV screening for over-screened women, as well as for those who adhere to guidelines. Although the model was based on Dutch data, the resulting outcomes are important for all over-screened women, regardless of where they live. Since it seems too early to draw conclusions on the effect of switching to HPV screening in over-screened women who have been vaccinated, this analysis only considers unvaccinated cohorts.

## Methods

Health effects of different screening scenarios were estimated using the MISCAN-Cervix model, which is described in more detail in the model profile (see Supplements S5.2).[22]

### *MISCAN-Cervix model*

MISCAN-Cervix is a microsimulation model in which a large study population with individual life histories is generated. In all of the analyses presented here, we simulated a 20-year-old cohort of 100 million women with life expectancy as observed in the Netherlands,[23] which was not affected by HPV vaccination (neither directly nor through herd immunity). A fraction of these women will acquire HPV infections and/or develop cervical intraepithelial neoplasia (CIN) lesions. If these precursors progress to cervical cancer, the result may be death. Screening can detect the disease, which can then be treated at an earlier stage. As a result, cervical cancer death may be prevented or postponed.

In the model, the disease development is in seven sequential stages: high-risk HPV infection, three pre-invasive stages (CIN grades 1, 2, and 3), and three invasive stages (International Federation of Gynecology and Obstetrics (FIGO) stages 1A, 1B, and 2 or worse). While pre-invasive and FIGO 1A stages can be diagnosed only by screening, because at these stages the women are assumed to be symptom-free, FIGO 1B or worse can also be clinically diagnosed. Because precursors are usually not progressive,[24] over 90 % of modeled HPV infections clear without ever resulting in neoplasia and most

pre-invasive lesions regress spontaneously. In the hypothetical situation without competing other cause mortality, undetected preclinical invasive neoplasia will always progress to clinical cancer. CIN grades 1 and 2 can develop in the absence of a high-risk HPV infection; in that case, the lesion will always regress. CIN grade 3 or worse can only develop if a high risk HPV infection is present.

*Triage strategies*

For primary HPV screening and primary cytology, we used a cost-effective triage strategy, as published previously.[9] Primary cytological test results classified as atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion are immediately followed by an HPV test using the same material. A positive primary HPV test is immediately followed by cytology using the same material. If no cytological abnormalities are found, another cytological test is performed after 6 months.

Although the latter strategy will also be implemented in the Dutch screening program in 2017, triage strategies were not selected based on guidelines or current practice. Instead, we decided to select strategies based on cost-effectiveness, such that inefficiencies in triage strategies would not dilute or exaggerate the effect of switching to HPV screening. The triage practices of over-screened women are unknown and might be very heterogeneous. It seems unlikely that women, who do not follow primary screening guidelines, do follow the exact triage recommendations. We therefore chose to simulate a relatively simple triage strategy for both primary tests and to focus on the number of positive primary tests (i.e., those that require follow-up) instead of on the number of triage tests.

*Screening scenarios*

We simulated 12 cohorts with different screening behaviors, varying the age at which women start screening (20, 25, or 30 years) and the frequency with which they get tested (every 1, 2, 3, or 5 years). In all scenarios, screening was assumed to end at or before the age of 65.[17,25] The resulting outcomes are only relevant for women having the screening behavior as modeled and should not be translated to an entire population.

*Assumptions for screening and treatment*

Table 5.1 presents the base case assumptions for screening. We assumed the sensitivity of cytology (that is, the probability that the result is at least ASCUS) to be 40% for true stage CIN grade 1, 50% for CIN grade 2, and 75% for CIN grade 3 or cancer.[26] In the model calibration, the sensitivity of testing for at least high-grade squamous intraepithelial lesion (HSIL), the cytological cutoff for referral to colposcopy, and therefore for detection, was estimated to be 4% for CIN grade 1, 18% for CIN grade 2, 56 % for CIN grade 3, and 60% for cervical cancer. Furthermore, the specificity of cytology was estimated to be 97.6% based on Dutch data.[27] Based on the observed difference in CIN grade 3 or cancer detection rates between cytology and the HPV test, we assumed the sensitivity of the HPV test

to be 94% for a high-risk HPV infection.[28] As we assumed that cervical cancer can only develop if an HPV infection is present, the sensitivity for cervical cancer is also 94%. The overall sensitivity for CIN lesions is lower and depends on the age-specific prevalence of HPV infections in CIN lesions. In the model, the specificity for detecting high-risk HPV infections was assumed to be 100%. A probable (but unknown) lack of specificity was accounted for by the inclusion of fast clearing infections, in concordance with HPV clearing studies.[29,30]

**Table 5.1. Base case model inputs and variations in the sensitivity analyses.**

| Parameter | Base case value | Alternative value(s) |
|---|---|---|
| Background risk of cervical cancer mortality | 5 per 100,000 life years | 10 per 100,000 life years |
| HPV prevalence in women without CIN grade 2 or worse [a] | Low | High [b] |
| Sensitivity of cytology | | |
| *Probability of at least ASCUS (at least triage) for:* | | |
| CIN grade 1 | 40% [26] | 32% |
| CIN grade 2 | 50% [26] | 40% |
| CIN grade 3 or worse | 75% [26] | 60% |
| *Probability of at least HSIL (referral for colposcopy) for:* | | |
| CIN grade 1 | 4% [c] | 3% |
| CIN grade 2 | 18% [c] | 14% |
| CIN grade 3 | 56% [c] | 45% |
| Cervical cancer | 60% [c] | 48% |
| Specificity of cytology (CIN grade 1 or worse) | 97.6% [c] | 95.2% |
| Sensitivity of HPV test [d] | 94% [28] | 85%, 100% [8] |
| Specificity of HPV test | 100% [e] | Not varied as such [f] |
| Discounting | 3% [31] | 0%, 5% |

*HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; ASCUS = atypical squamous cells of undetermined significance; HSIL = high grade squamous intraepithelial lesion.*

[a] *Depends on age, age-dependency was not varied.*

[b] *The number of false-positive referrals to colposcopy and CIN grade 1 lesions was doubled.*

[c] *Value was determined in model calibration.*

[d] *Probability to detect an HPV infection, regardless of whether a CIN lesion or cancer is present.*

[e] *A possible lack of specificity was modeled by including fast-clearing HPV infections.*

[f] *As a lower specificity of the HPV test corresponds with a higher prevalence of harmless HPV infections in the model, this parameter was not varied.*

Detection and management of pre-invasive lesions, including treatment if necessary, were assumed to lead to a 100% cure rate. However, new HPV infections and recurring CIN lesions after CIN treatment cannot be excluded. For invasive cancer, we determined age-specific and stage-specific survival probabilities based on data from the Netherlands Cancer Registry.[31] Since cancers detected by screening are usually at a less advanced stage than clinically diagnosed ones, women have a higher chance to survive them. If an invasive cancer is screen-detected, the probability to die from cervical cancer is reduced by 89.4%, 50%, and 20% when detected in FIGO stages 1A, 1B, and 2 or worse, respectively.

Table 5.2 presents the utility losses assumed in the base case scenario. A small (psychological) loss in quality of life is assumed for attending a screen (including waiting for the result) and for being in triage (including attending follow-up screenings). Larger losses in quality of life are assumed for being diagnosed and treated for CIN or cancer and for having a terminal stage of cervical cancer. We based the utility losses on nationally and internationally published data.[32–35]

**Table 5.2. Model inputs regarding the utility loss due to screening, treatment and terminal care.**

| | **Disutility** | **Duration** | **Quality-adjusted time lost** |
|---|---|---|---|
| **Screening** [35] | | | |
| Primary screening | 0.005 | 2 weeks | 2 hours |
| Being in triage | 0.005 | 0.5 year[a] | 22 hours |
| False-positive referral | 0.005 | 0.5 year | 22 hours |
| **Treatment of pre-invasive lesions** [34] | | | |
| CIN grade 1 | 0.03 | 0.5 year | 6 days |
| CIN grade 2 or 3 | 0.07 | 1 year | 26 days |
| **Cancer treatment** [33,34] **and terminal care** [36] | | | |
| FIGO stage 1 | 0.062 | 5 years | 4 months |
| FIGO stage 2+ | 0.280 | 5 years | 17 months |
| Terminal care | 0.740 | 1 year | 9 months |

*CIN = cervical intraepithelial neoplasia; FIGO = International Federation of Gynecology and Obstetrics.*

[a] *Time between primary and triage test is 6 months*

*Base case analysis*

For every scenario, we first estimated health effects of both primary cytology and primary HPV testing as compared to the situation without screening. Then, differences in health effects between these two interventions were explored. A first indication of the harm–benefit balance of introducing primary

HPV testing is given by the number of additional positive primary screens (i.e. at least ASCUS for cytology screening and HPV positive for HPV screening) that is required to prevent one additional cervical cancer death. As women with a positive primary screen require follow-up in terms of triage or colposcopy, we refer to this outcome measure as ‘‘Number Needed to Follow-up’’ or NNF.

Comparing the life years lost to cervical cancer between the two interventions yields the number of life years gained by switching to the more sensitive primary HPV testing. Similarly, the difference in total disutility due to screening and treatment caused by these interventions can be computed. As the number of quality-adjusted life years (QALYs) gained combines these positive and negative effects of screening, this outcome measure was used to compare the total health effects of primary HPV screening with those of primary cytology. Health effects were discounted to the year in which all women are 20 years old, using an annual rate of 3%.[36]

*Sensitivity analyses*

Some model parameters may have a non-negligible level of uncertainty, while others differ among countries or geographical regions. In one-way sensitivity analyses, we varied these types of parameters, covering for high-income countries, if they would influence the difference in health effects between primary HPV screening and primary cytology (Table 5.1).

Among Dutch women, the assumed background risk of dying from cervical cancer is relatively low (5 deaths per 100,000 life years). We have doubled this risk to determine the effects for countries with a higher risk.

To observe the effect of a higher prevalence of harmless HPV infections, we have doubled the number of referrals that did not result in the detection of a clinically relevant lesion (i.e. CIN grade 2 or worse). Detecting more harmless HPV infections implicitly corresponds with a lower clinically relevant specificity of HPV testing.

Presumably, the high level of quality assurance in the Netherlands contributes to a relatively high quality of cytology compared to less controlled situations. To explore the impact of switching to HPV testing for settings with a lower quality of cytology, the sensitivity of cytology in both primary and triage testing was reduced by 20% in one of the sensitivity analyses. In another sensitivity analysis, the lack of specificity of cytology in both primary and triage testing was doubled from 2.4% to 4.8%.

Some uncertainty exists about the sensitivity of the HPV test, which may also vary between tests and situations. A summary of meta-analyses found that the relative sensitivity of the HPV test as compared to cytology is 1.23 (95% CI: 1.13–1.33). Based on this confidence interval, the sensitivity of the HPV test was assumed to be 85% in one of the sensitivity analyses and 100% in another.[8] As these are assumed probabilities to detect an HPV infection, and women with a CIN lesion are not necessarily HPV infected, the sensitivity for CIN lesions is still lower than 100% in the latter scenario.

In another sensitivity analysis, the triage strategy after a positive cytological test was adjusted to reflect current Dutch screening guidelines. According to these guidelines, women with HSIL are directly referred for colposcopy and women with ASCUS or low-grade intraepithelial lesion (LSIL) are invited for cytology and HPV triage after 6 months. Women testing HSIL or ASCUS/LSIL and HPV positive at this point in time will be referred for colposcopy, and women testing either ASCUS/LSIL or HPV positive will be invited for another cytological test at 18 months.

Lastly, as reported discount rates vary from 0% to 5%, we also present the health effects when using an annual discount rate of 0% and of 5%.

## Results

*Base case analysis*

For the 12 different screening scenarios considered, Table 5.3 shows the impact of replacing primary cytology with primary HPV screening. The numbers are based on the undiscounted results of primary cytology and primary HPV screening compared to the situation without screening, as displayed in Supplementary Tables S5.1 and S5.2, respectively. Although in practice, it is very unlikely that the start age is well controlled, while the screening interval is not, we first discuss the effects of switching to HPV testing in women who start screening at age 30 and have repeated testing at intervals that are either recommended or shorter than recommended. Then, we discuss the effects of switching for women who are not only screened more frequent than recommended, but also from a younger age.

*Frequent screening from age 30*

For 5-yearly screening starting at age 30, replacing primary cytology with primary HPV screening reduced the number of cervical cancer deaths by 32 per 100,000 simulated women, which was a reduction of 27% (Fig. 5.1; Table 5.3). This reduction was achieved at the expense of 9,044 more positive primary screens per 100,000 women (+34%), resulting in 2,572 more referrals to colposcopy (+29%). With annual screening in the same age range, switching to primary HPV screening would prevent only 7 extra deaths per 100,000 women (-9%), while positive primary screens would increase by 14,271 (+14%) and referrals to colposcopy by 3,477 (+19%). The (discounted) NNF was 769 in the first scenario versus 11,880 in the latter, more intensive one (Table 5.4).

**Table 5.3. The impact of replacing primary cytology with primary HPV screening for 12 different screening scenarios.**

| Screen interval | Start age | # Primary screens[a] | # Positive primary screens | # Referrals to colposcopy | # False-positive referrals (no CIN detected) | # CIN 1 | # CIN 2 | # CIN 3 | # Cervical cancer cases | # Cervical cancer deaths |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 years | 30 | +1,014 (+0%) | +9,044 (+34%) | +2,572 (+29%) | +308 (+42%) | +1,651 (+59%) | +722 (+36%) | -71 (-2%) | -114 (-29%) | -32 (-27%) |
| | 25 | +1,455 (+0%) | +17,741 (+54%) | +3,743 (+31%) | +497 (+50%) | +2,311 (+58%) | +1,040 (+36%) | -63 (-2%) | -116 (-32%) | -32 (-27%) |
| | 20 | +1,807 (+0%) | +22,293 (+59%) | +4,747 (+33%) | +581 (+51%) | +3,079 (+60%) | +1,282 (+37%) | -153 (-3%) | -117 (-33%) | -32 (-27%) |
| 3 years | 30 | +1,352 (+0%) | +11,375 (+30%) | +2,932 (+26%) | +442 (+40%) | +2,247 (+55%) | +652 (+25%) | -384 (-12%) | -67 (-20%) | -19 (-16%) |
| | 25 | +2,136 (+0%) | +24,759 (+52%) | +4,332 (+28%) | +754 (+49%) | +3,185 (+54%) | +950 (+25%) | -530 (-12%) | -66 (-24%) | -18 (-18%) |
| | 20 | +2,909 (+0%) | +32,648 (+58%) | +5,698 (+30%) | +931 (+51%) | +4,403 (+56%) | +1,184 (+25%) | -792 (-17%) | -65 (-27%) | -17 (-19%) |
| 2 years | 30 | +1,980 (+0%) | +12,642 (+23%) | +3,220 (+24%) | +609 (+38%) | +2,756 (+49%) | +437 (+14%) | -566 (-18%) | -41 (-15%) | -12 (-13%) |
| | 25 | +3,204 (+0%) | +31,715 (+47%) | +4,780 (+25%) | +1,072 (+47%) | +3,891 (+49%) | +631 (+14%) | -798 (-19%) | -39 (-19%) | -11 (-14%) |
| | 20 | +4,023 (+0%) | +45,199 (+59%) | +6,316 (+27%) | +1,373 (+51%) | +5,367 (+50%) | +734 (+13%) | -1,142(-26%) | -39 (-18%) | -12 (-13%) |
| 1 year | 30 | +3,719 (+0%) | +14,271 (+14%) | +3,477 (+19%) | +1,093 (+35%) | +3,113 (+34%) | -140 (-4%) | -584 (-22%) | -18 (-8%) | -7 (-9%) |
| | 25 | +6,113 (+0%) | +51,316 (+43%) | +5,361 (+21%) | +2,046 (+47%) | +4,330 (+34%) | -200 (-4%) | -811 (-23%) | -17 (-10%) | -7 (-9%) |
| | 20 | +8,211 (+0%) | +76,480 (+55%) | +7,259 (+22%) | +2,675 (+50%) | +6,096 (+35%) | -400 (-6%) | -1,108(-35%) | -17 (-10%) | -6 (-9%) |

*Numbers are differences between primary cytology and primary HPV screening, shown separately in Supplementary Tables S5.1 and S5.2.*

*CIN = cervical intraepithelial neoplasia.*

*The table shows undiscounted numbers per 100,000 simulated women, with percentage changes between brackets.*

*[a] As compared to primary cytology, the number of primary screens is slightly higher for HPV screening (i.e. less than 1%) because it detects more (progressive) CIN lesions, resulting in fewer women being diagnosed with cervical cancer. Whereas women who have been diagnosed with a CIN lesion are assumed to be referred back to routine screening, those with cervical cancer are not.*

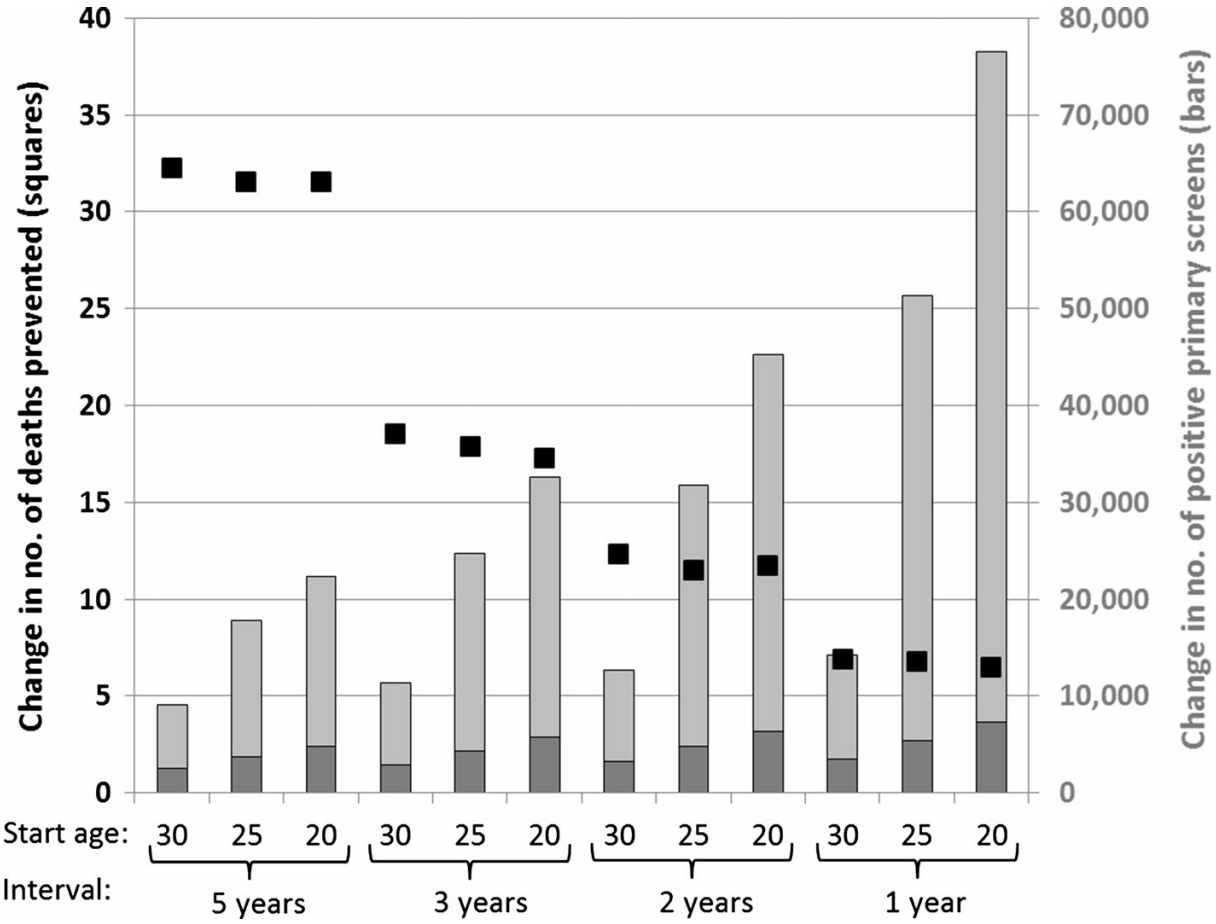


**Fig. 5.1 Simulated increase in lifetime number of deaths from cervical cancer prevented (left axis) and positive primary screens (right axis) when primary cytology is replaced with primary HPV screening.** The increase in positive primary tests is split up in referrals to colposcopy (dark grey) and non-referrals to colposcopy (light grey). Undiscounted results for different start ages and intervals of screening are given per 100,000 women.

**Table 5.4. Number of additional positive primary screens per additionally prevented cervical cancer death (NNF) when primary cytology is replaced with primary HPV screening, for the base case and eight sensitivity analyses.**

| Screening interval | Start age | Base case | Background risk of cervical cancer mortality ↑ | HPV prevalence in CIN 1 or less[a] ↑ | Sensitivity of cytology ↓ | Specificity of cytology ↓ | Sensitivity of HPV test ↑ | Sensitivity of HPV test ↓ | Cytology triaged as in Dutch program | No discounting | 5 % discounting |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 years | 30 | 769 | 399 | 887 | 503 | NA[b] | 805 | 761 | 657 | 280 | 1,256 |
| | 25 | 1,589 | 811 | 1,788 | 993 | 502 | 1,628 | 1,638 | 1,360 | 562 | 2,692 |
| | 20 | 2,065 | 1,057 | 2,352 | 1,309 | 747 | 2,117 | 2,108 | 1,772 | 706 | 3,603 |
| 3 years | 30 | 1,889 | 969 | 2,202 | 1,190 | NA[b] | 2,047 | 1,690 | 1,532 | 613 | 3,223 |
| | 25 | 4,443 | 2,289 | 4,997 | 2,712 | 1,009 | 4,725 | 4,213 | 3,645 | 1,385 | 7,927 |
| | 20 | 6,444 | 3,275 | 7,324 | 3,827 | 1,980 | 6,907 | 6,088 | 5,282 | 1,886 | 12,056 |
| 2 years | 30 | 3,865 | 2,006 | 4,531 | 2,545 | NA[b] | 4,360 | 3,197 | 2,983 | 1,027 | 7,182 |
| | 25 | 10,526 | 5,341 | 11,779 | 6,443 | 1,346 | 11,521 | 9,381 | 8,140 | 2,760 | 20,582 |
| | 20 | 15,405 | 7,764 | 17,331 | 9,506 | 4,229 | 16,723 | 13,750 | 11,941 | 3,850 | 32,252 |
| 1 year | 30 | 11,880 | 6,220 | 13,731 | 9,024 | NA[b] | 14,088 | 8,562 | NA[c] | 2,073 | 27,408 |
| | 25 | 36,576 | 18,503 | 39,954 | 28,544 | NA[b] | 40,654 | 30,861 | NA[c] | 7,570 | 86,763 |
| | 20 | 60,133 | 29,372 | 65,790 | 45,416 | NA[b] | 66,783 | 50,634 | NA[c] | 11,788 | 156,829 |

*HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; NA = not applicable*

*Numbers were discounted with an annual rate of 3%, unless stated otherwise.*

*[a] The number of women with a false-positive result or CIN grade 1 was doubled to account for a higher HPV prevalence among these women.*

*[b] The number of positive primary screens decreased with switching to HPV screening.*

*[c] The current Dutch screening program involves triage testing at 18 months after the primary test, which, for annual screening, interferes with the next screening round.*

**Table 5.5. Simulated change in number of QALYs gained and percentage change when primary cytology is replaced with primary HPV screening, for the base case and eight sensitivity analyses.**

| Screen interval | Start age | Base case | Background risk of cervical cancer mortality ↑ | HPV prevalence in CIN grade 1 or less[a] ↑ | Sensitivity of cytology ↓ | Specificity of cytology ↓ | Sensitivity of HPV test ↑ | Sensitivity of HPV test ↓ | Cytology triaged as in Dutch program | No discounting | 5 % discounting |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 years | 30 | +116 (+4%) | +319 (+5%) | +101 (+3%) | +265 (+9%) | +115 (+4%) | +130 (+4%) | +80 (+2%) | +175 (+20%) | +667 (+5%) | +27 (+2%) |
| | 25 | +57 (+2%) | +258 (+4%) | +34 (+1%) | +203 (+7%) | +58 (+2%) | +63 (+2%) | +37 (+1%) | +124 (+15%) | +591 (+4%) | -26 (-2%) |
| | 20 | +16 (+1%) | +214 (+3%) | -19 (-1%) | +153 (+5%) | +16 (+1%) | +17 (+1%) | +3 (+0%) | +98 (+13%) | +559 (+4%) | -70 (-6%) |
| 3 years | 30 | +4 (+0%) | +105 (+2%) | -16 (-0%) | +83 (+3%) | +4 (+0%) | +4 (+0%) | -2 (-0%) | +72 (+8%) | +254 (+2%) | -27 (-2%) |
| | 25 | -67 (-2%) | +24 (+0%) | -99 (-3%) | -6 (-0%) | -66 (-2%) | -75 (-2%) | -59 (-2%) | +16 (+2%) | +157 (+1%) | -89 (-7%) |
| | 20 | -125 (-4%) | -37 (-1%) | -175 (-6%) | -71 (-2%) | -124 (-4%) | -138 (-4%) | -111 (-4%) | -15 (-2%) | +88 (+1%) | -147 (-13%) |
| 2 years | 30 | -52 (-2%) | +2 (+0%) | -76 (-2%) | -19 (-1%) | -52 (-2%) | -57 (-2%) | -49 (-1%) | +34 (+4%) | +56 (+0%) | -55 (-4%) |
| | 25 | -133 (-4%) | -86 (-1%) | -172 (-5%) | -114 (-4%) | -132 (-4%) | -144 (-4%) | -117 (-4%) | -20 (-2%) | -55 (-0%) | -125 (-10%) |
| | 20 | -196 (-6%) | -148 (-2%) | -257 (-9%) | -189 (-6%) | -195 (-6%) | -210 (-7%) | -174 (-6%) | -41 (-7%) | -112 (-1%) | -191 (-19%) |
| 1 year | 30 | -127 (-4%) | -106 (-2%) | -155 (-5%) | -128 (-4%) | -125 (-4%) | -135 (-4%) | -115 (-4%) | NA[b] (-) | -154 (-1%) | -99 (-8%) |
| | 25 | -238 (-8%) | -218 (-3%) | -283(-10%) | -254 (-8%) | -237 (-8%) | -253 (-8%) | -214 (-7%) | NA[b] (-) | -290 (-2%) | -197 (-19%) |
| | 20 | -334 (-12%) | -315 (-5%) | -407(-15%) | -360(-13%) | -332(-12%) | -354 (-13%) | -303(-11%) | NA[b] (-) | -390 (-3%) | -293 (-36%) |

*HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; NA = not applicable.*

*The table shows numbers per 100,000 simulated women, with percentage changes between brackets. Numbers were discounted with an annual rate of 3 %, unless stated otherwise.*

[a] *The number of women with a false-positive result or CIN grade 1 was doubled to account for a higher HPV prevalence among these women.*

[b] *The current Dutch screening program involves triage testing at 18 months after the primary test, which, for annual screening, interferes with the next screening round.*

*Frequent screening from age 20*

With annual screening starting at the age of 20 instead of 30, switching from primary cytology to primary HPV screening resulted in similar benefits (i.e. six additional deaths prevented per 100,000 women (-9%)). However, the number of women with a positive screen test increased by 76,480 instead of by 14,271 per 100,000 women. The NNF equaled 60,133, which was more than 5 times the NNF of switching in case of annual screening from age 30 and more than 78 times the NNF of switching in case of 5-yearly screening from age 30.

*Changes in QALYs*

Table 5.5 shows the QALYs gained (or lost) by switching from primary cytology to primary HPV screening for the diverse screening behaviors. Under base case assumptions, a substantial number of QALYs were gained for women who were screened every 5 years from age 30. For more intensively screened women, the benefit of switching to HPV screening was uncertain. For women screened annually or biennially from any age, or triennially from age 20 or 25, replacing primary cytology with primary HPV testing even resulted in a net health loss.

*Sensitivity analyses*

In all sensitivity analyses, primary HPV screening prevented more cervical cancer deaths than did primary cytology. In most scenarios, this occurred at the expense of more positive screens, and the NNF increased quite rapidly with the intensity of the screening scenario (Table 5.4). Only when the specificity of cytology was assumed to be lower (95.2% instead of 97.6%), for some levels of over-screening, the number of positive screens decreased with the shift to primary HPV testing. The discount rate appeared to have the largest impact on the NNF.

In the sensitivity analyses, switching to primary HPV testing resulted in fewer QALYs gained in the case of more intensive screening. Overall, for a given level of over-screening, whether QALYs were gained or lost did not vary substantially among the sensitivity analyses. Generally, switching was favorable for women screened every 5 years and unfavorable for those screened annually or biennially. However, when the background risk of cervical cancer mortality was increased, when cytology was triaged as is currently recommended in the Dutch screening program or when health effects were not discounted, switching to HPV screening also resulted in QALYs gained for women screened biennially from age 30. For women screened every 5 years from age 20, QALYs were lost when the HPV prevalence was increased and when results were discounted at an annual rate of 5%.

**Discussion**

Even in countries with carefully constructed screening guidelines, women may be over-screened. As for over-screened women the risk of cervical cancer is already strongly reduced with primary

cytology, the gains of switching to primary HPV screening are expected to be relatively small. Indeed, our analysis predicted that while switching would prevent 32 deaths per 100,000 women who are screened every 5 years, only 6–7 deaths would be averted in those screened annually. In the latter group, the increase in positive tests and subsequent follow-up procedures even resulted in a net loss in health.

Because the same conclusion was reached in all of the sensitivity analyses, it is likely generalizable to other developed countries. The lower the ratio of HPV prevalence to cervical cancer mortality risk, the less harmful the HPV testing will be for over-screened women. The sensitivity analysis in which we doubled the lifetime risk of dying from cervical cancer showed that it would still be harmful if this ratio would be twice as low as in the Netherlands though. In countries with an even lower HPV prevalence to cervical cancer mortality risk ratio, switching to HPV testing might be beneficial for over-screened women. In the USA, however, both HPV prevalence and cervical cancer mortality are comparable to the Netherlands.[37,38] In most European countries, cervical cancer mortality is higher,[39] but HPV prevalence is also (up to) twice as high.[38]

Obviously, the goal of a cancer screening program is to decrease the disease's incidence and mortality rate. Because in every simulated scenario switching from primary cytology to primary HPV screening reduced the number of cervical cancer cases and deaths, one could argue that primary HPV screening should always be preferred. This would indeed be true if being in triage, being referred for colposcopy, and being treated for CIN would not be associated with losses in quality of life. However, the health-related burden of these events is a drawback of screening that should not be overlooked.[40,41]

A number of randomized controlled trials (RCTs) have compared primary cytology screening to either HPV screening alone or HPV screening combined with cytology.[42–45] In these RCTs, HPV screening resulted in a higher detection rate of CIN lesions and an improved protection against cervical cancer.[46] CEAs based on these findings showed that primary HPV screening with an interval of at least 3 years is cost-effective for women above age 30.[9,47] We showed that the effectiveness is questionable if this cannot be guaranteed. In this regard, data from a US population based registry showed that recommending 3-yearly cytology screening resulted in a median time between two consecutive smears of 1.87 years in 2011.[48] There is no reason to assume that guidelines regarding primary HPV screening would be followed more closely. In fact, a study from 2010 found a lower adherence to guidelines after a negative co-test as compared to after a negative cytological test.[19] Although co-testing is intended for women who want to extend their screening interval from 3 to 5 years, many clinicians provide it on an annual basis.[19]

Switching to HPV screening could be considered more effective for women with that level of over-screening for which HPV screening was associated with a net health benefit, but this would not necessarily be more cost-effective. However, the decision to include primary HPV screening in national screening guidelines should take into account its population-level cost-effectiveness. If only a

relatively small number of women are over-screened, then switching to HPV screening may well be (very) cost-effective on a population level. In the Netherlands, given the small number of smears taken outside the screening program,[49] it is expected to be cost-effective.

*Strengths and limitations*

Even though earlier research showed that primary HPV screening is more cost-effective than primary cytology for women who adhere to screening guidelines,[10,50] this is the first study to quantify its harms and benefits for over-screened women. As over-screening practices are likely to remain, these results are relevant to any country considering recommending primary HPV screening, either alone or as a co-test.

Our study also has some limitations. First of all, our model is based on Dutch data. Although it might have been better to adjust the model for every single country, we did vary those country-specific parameters that would influence the conclusion. For example, we increased the HPV prevalence level to estimate effects for high HPV prevalence countries such as Denmark.[51] We did not modify the prevalence age distribution as the peak between the ages of 20 and 30 has also been observed in other European countries and in the USA.[51,52]

Although we varied test characteristics to explore the effect of switching to HPV screening for different settings, the ranges considered are not representative for low- and middle-income countries, where sustaining cytology programs of sufficient quality is often difficult.[53,54] As the test characteristics are only one of many factors that may be different in those countries, separate analyses are needed for these situations.

Meta-analyses have shown that removal of CIN lesions carries an increased risk of having preterm births.[55,56] We did not include this potential harm because estimates of the impact on a woman's quality of life are unavailable. If we would have accounted for this in our analyses, in over-screened women even more QALYs would have been lost by switching to primary HPV screening.

Although there are numerous possible triage strategies for cytology and HPV testing, in the base case analysis we only considered two that were found to be cost-effective in a previous analysis.[9] In a sensitivity analysis, we did explore the impact of switching from the less efficient cytology screening strategy that is currently recommended in the Netherlands to the cost-effective HPV screening strategy that will be implemented in 2017. When these less efficient cytology practices were assumed, switching to HPV testing was obviously more beneficial. Nevertheless, it still resulted in a net health loss for women screened biennially from age 20 to 25 or triennially from age 0 (effects for annually screened women were not evaluated for this triage strategy). If future triage practices would be much more efficient than current ones, then switching to HPV testing might be considered beneficial for over-screened women, but this would be due to more efficient triage procedures rather than to an improved performance of the primary test.

Lastly, we did not consider a co-testing strategy, which is already recommended in the USA for women aged 30–65 years.[12,17,57] Co-testing results in more screen positives than does primary HPV screening because HPV negative smears can still be cytology positive. From results of an RCT performed in the Netherlands, where women aged 30–60 years are screened every 5 years, we calculated that the number of screen positives would be 33% higher with co-testing than with primary HPV screening.[28] As a consequence, the number of screen-detected CIN grade 3 lesions or cancer would be 7% higher. In an RCT performed in the UK, in which women aged 20–64 years were screened with an interval of 2–4 years, the number of screen positives would have been 46% higher with co-testing as compared to primary HPV screening, while the number of screen-detected clinically relevant lesions (at least CIN grade 3) would have been only 3% higher.[58] For intensively screened women, co-testing can potentially prevent slightly more cervical cancer cases than primary HPV screening, but the utility loss associated with the additional positive screens probably outweighs these minor gains. Therefore, co-testing is expected to be even more harmful than primary HPV screening alone for over-screened women.

*Conclusion*

We determined the pros and cons of replacing primary cytology with primary HPV screening for women who are over-screened, i.e. from a younger age and with a shorter screening interval than recommended. Although in all scenarios more deaths would be averted by screening primarily with the HPV test, the negative effects outweighed the benefits. We may conclude that irrespective of costs, it is disputable to recommend primary HPV screening, either alone or as a co-test, as long as a substantial part of the population is still over-screened. A well-organized and structurally monitored screening program, in which primary tests taken outside the program are not reimbursed by the government, could help minimizing the number of tests taken outside the program, thereby limiting the level of over-screening.[21,59] One may consider to first further develop strategies to reduce over-screening or at least give it high priority when issuing guidelines including primary HPV screening.

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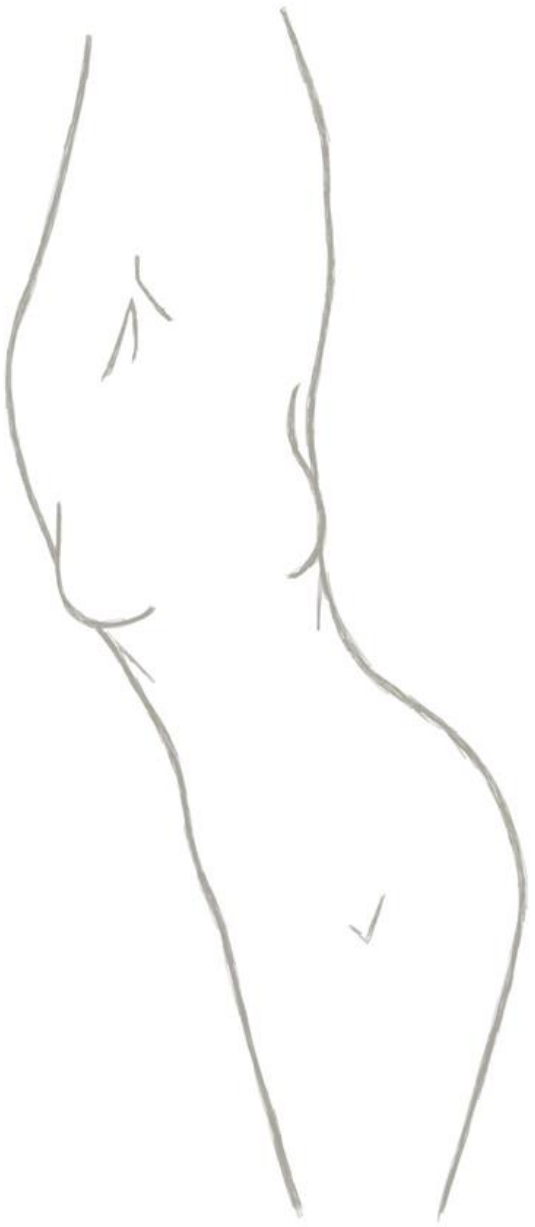
# 5

## Supplements



## S5.1 Supplementary figures and tables with results

## S5.2 MISCAN-Cervix model profile

S5.2A Model structure

S5.2B Demography

S5.2C Natural history

S5.2D Screening

S5.2E Effectiveness

## S5.1 Supplementary figures and tables with results

**Supplementary Table S5.1. Effects of primary cytology for 12 different screening scenarios; undiscounted numbers per 100,000 simulated women.**

| Screening interval | Start age | # Primary screens | # Positive primary screens | # Referrals | # False-positive referrals (no CIN detected) | # CIN 1 | # CIN 2 | # CIN 3 | # Cervical cancer cases | # Cervical cancer deaths |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 years | 30 | 739,525 | 26,923 | 8,868 | 742 | 2,819 | 2,015 | 3,174 | 398 | 121 |
| | 25 | 840,937 | 32,721 | 12,139 | 988 | 3,980 | 2,893 | 4,177 | 358 | 116 |
| | 20 | 941,786 | 37,492 | 14,305 | 1,148 | 5,144 | 3,451 | 4,465 | 352 | 115 |
| 3 years | 30 | 1,118,531 | 38,434 | 11,168 | 1,108 | 4,106 | 2,609 | 3,268 | 332 | 114 |
| | 25 | 1,315,382 | 47,706 | 15,619 | 1,540 | 5,868 | 3,778 | 4,377 | 269 | 100 |
| | 20 | 1,511,580 | 56,297 | 19,192 | 1,838 | 7,934 | 4,722 | 4,658 | 244 | 91 |
| 2 years | 30 | 1,674,942 | 54,320 | 13,581 | 1,609 | 5,634 | 3,110 | 3,172 | 272 | 96 |
| | 25 | 1,971,111 | 66,941 | 19,192 | 2,259 | 8,003 | 4,489 | 4,238 | 209 | 82 |
| | 20 | 2,183,094 | 76,854 | 23,484 | 2,703 | 10,818 | 5,618 | 4,321 | 215 | 90 |
| 1 year | 30 | 3,346,636 | 99,553 | 18,556 | 3,116 | 9,033 | 3,658 | 2,708 | 222 | 79 |
| | 25 | 3,858,503 | 118,972 | 25,785 | 4,380 | 12,625 | 5,236 | 3,530 | 176 | 75 |
| | 20 | 4,368,263 | 138,478 | 32,507 | 5,377 | 17,425 | 6,540 | 3,159 | 166 | 75 |

*CIN = cervical intraepithelial neoplasia.*

**Supplementary Table S5.2. Effects of primary HPV screening for 12 different screening scenarios; undiscounted numbers per 100,000 simulated women.**

| Screening interval | Start age | # Primary screens | # Positive primary screens | # Referrals | # False-positive referrals (no CIN detected) | # CIN 1 | # CIN 2 | # CIN 3 | # Cervical cancer cases | # Cervical cancer deaths |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 years | 30 | 740,539 | 35,968 | 11,440 | 1,050 | 4,470 | 2,737 | 3,103 | 283 | 89 |
| | 25 | 842,392 | 50,462 | 15,881 | 1,485 | 6,290 | 3,933 | 4,113 | 242 | 84 |
| | 20 | 943,593 | 59,784 | 19,052 | 1,730 | 8,223 | 4,733 | 4,312 | 234 | 84 |
| 3 years | 30 | 1,119,883 | 49,809 | 14,100 | 1,550 | 6,353 | 3,261 | 2,883 | 265 | 95 |
| | 25 | 1,317,518 | 72,465 | 19,951 | 2,294 | 9,053 | 4,729 | 3,847 | 204 | 82 |
| | 20 | 1,514,489 | 88,945 | 24,890 | 2,769 | 12,327 | 5,907 | 3,866 | 179 | 74 |
| 2 years | 30 | 1,676,921 | 66,962 | 16,802 | 2,218 | 8,391 | 3,546 | 2,605 | 231 | 83 |
| | 25 | 1,974,315 | 98,656 | 23,801 | 3,330 | 11,894 | 5,121 | 3,440 | 170 | 71 |
| | 20 | 2,187,117 | 122,053 | 29,800 | 4,075 | 16,185 | 6,351 | 3,179 | 176 | 79 |
| 1 year | 30 | 3,350,355 | 113,824 | 22,033 | 4,209 | 12,146 | 3,519 | 2,124 | 205 | 72 |
| | 25 | 3,864,616 | 170,288 | 31,145 | 6,426 | 16,955 | 5,036 | 2,719 | 158 | 68 |
| | 20 | 4,376,474 | 214,958 | 39,766 | 8,052 | 23,521 | 6,140 | 2,051 | 149 | 68 |

*CIN = cervical intraepithelial neoplasia.*

## S5.2 MISCAN-Cervix model profile

In this appendix, we describe the model inputs of the Microsimulation Screening Analysis (MISCAN) model for cervical cancer.[1] This model can be used to assess the harms and benefits of different screening programs for cervical cancer, as well as human papillomavirus (HPV) vaccination. The model has been used previously for cost-effectiveness analyses of cervical cancer screening and HPV vaccination.[2-5]

### *S5.2A Model structure*

Figure S5.1 shows the structure of MISCAN-Cervix. The model consists of the following 4 parts: demography, natural history, screening, and effectiveness. The assumptions used in each of these parts are described below.

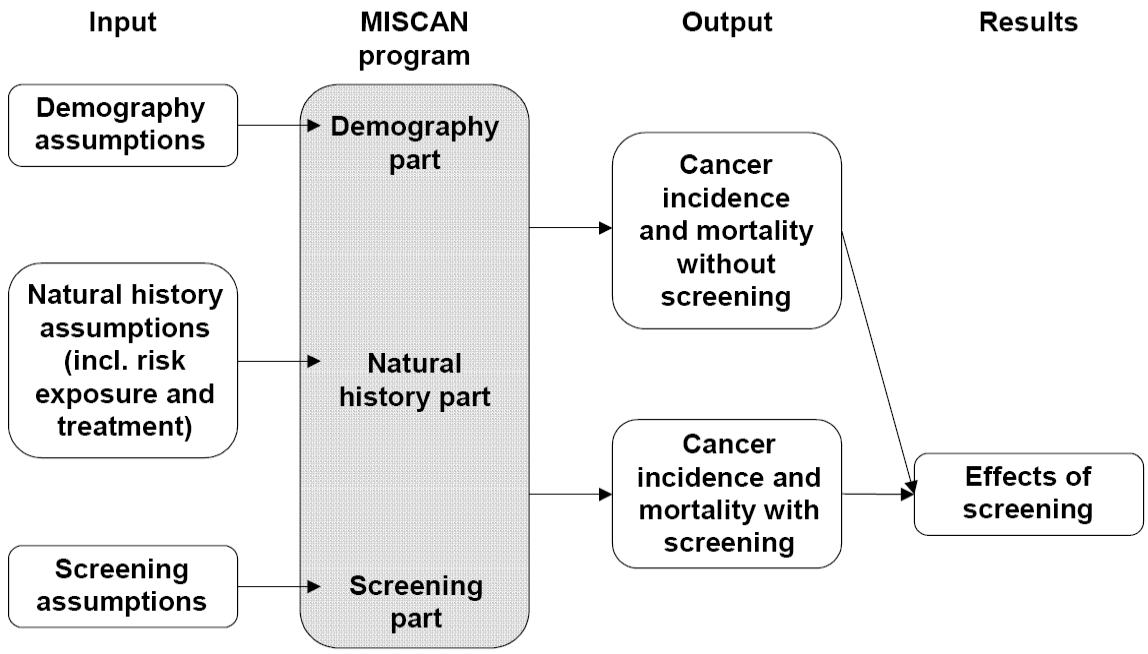



**Figure S5.1. Structure of the MISCAN-Cervix model**

### *S5.2B Demography*

The MISCAN model generates a simulated population, which in this analysis corresponds with the 1990 Dutch birth cohort. General characteristics of the simulated population (i.e. those not related to the disease) are based on demographic and hysterectomy data; mortality from other causes was estimated using the observed age-specific mortality in the Netherlands in 2011.[6,7]

For each woman, a time of death from other causes (i.e. causes other than cervical cancer) is generated; this time of death is independent of the cervical cancer disease model. In the model, a woman's lifetime cannot exceed 100 years. The time of death from other causes is generated using a life table for women from Statistics Netherlands.[7] The assumed hysterectomy rates vary by age. These rates are based on data from Statistics Netherlands and Information Centre for Health Care and are presented in Table S5.3.[8,9]

**Table S5.3. Model assumptions for the age-specific probability of having had a hysterectomy for reasons other than cervical cancer.** Linear interpolation is used to determine the probability of having had a hysterectomy at intermediate ages. Source: Information Centre for Health Care.[8,9]

| Age | Cumulative probability of having had a hysterectomy |
|---|---|
| 20 | 0 |
| 25 | 0.0002 |
| 30 | 0.0017 |
| 35 | 0.0076 |
| 40 | 0.0213 |
| 45 | 0.0432 |
| 50 | 0.0735 |
| 55 | 0.0916 |
| 60 | 0.1009 |
| 65 | 0.1102 |
| 70 | 0.1217 |
| 75 | 0.133 |
| 80 | 0.1419 |
| 85 | 0.1468 |

*S5.2C Natural history*

During her lifetime, each woman has an age-specific risk of acquiring high-risk HPV infections (i.e. an infection caused by an HPV type that can cause cancer and that can be detected by the HPV test) and CIN lesions without a (detectable) high-risk HPV infection. Most HPV infections clear or regress naturally, some HPV infections can progress to CIN 1, CIN 2, CIN 3, cervical cancer, and death from cervical cancer.

The age-specific incidence of HPV infections that progress to cervical cancer was calibrated to the age-specific incidence of cervical cancer, which was obtained from the Dutch Cancer Registry. The age-specific incidence of pre-invasive lesions that do not progress to cervical cancer was calibrated so that the simulated detection rates of CIN lesions fit the observed detection rates in the

Netherlands. The observed detection rates were obtained from the Dutch Network and National Database for Pathology (PALGA) for the period 2000-2007. The incidence of high-risk HPV infections that do not progress to CIN was calibrated so that the simulated prevalence of all high-risk HPV infections fits the observed high-risk HPV prevalence.[10,11]

In MISCAN-Cervix, 6 disease pathways are distinguished. Each instance of these disease pathways represents an HPV infection or a 'lesion' (i.e. CIN of a certain grade or a stage of cervical cancer). Each disease pathway starts as either an HPV infection or as an HPV negative CIN 1 lesion. The natural history (i.e. in the situation without screening) of these 6 disease pathways is shown in Figure S5.2 and can be described as follows:

A) HPV infections that clear naturally without ever leading to CIN
B) HPV infections that progress to CIN 1 and then regress
C) HPV infections that progress to CIN 1 and CIN 2 and then regress
D) HPV infections that progress to CIN 1, CIN 2, and CIN 3 and then regress
E) HPV negative CIN 1 lesions that regress naturally or become HPV negative CIN 2 and then regress naturally
F) HPV infections that progress to CIN 1, CIN 2, CIN 3, preclinical FIGO 1A (micro-invasive) cervical cancer, and preclinical FIGO 1B cervical cancer. Preclinical FIGO 1B cervical cancer can either become clinically detected FIGO 1B cervical cancer or progress to preclinical FIGO 2+ cervical cancer and then to clinical FIGO 2+ cervical cancer. Clinically detected cervical cancer can progress to death from cervical cancer or remain in that state forever (if the woman is cured from cervical cancer).

A woman can acquire multiple lesions and HPV infections during her lifetime, and multiple lesions and HPV infections may be present at the same time. In each simulated life history (i.e. between ages 0 and 100), the number of lesions of each type follows a Poisson distribution. The annual probability of acquiring an HPV infection or CIN lesion is age-dependent and depicted in Figures S5.3A (regressive disease pathways) and S5.3B (progressive disease pathway). The transitions and sojourn times of the HPV infections or lesions are simulated based on a continuous-time semi-Markov process. The sojourn times of most states in the model have either an exponential or a Weibull probability distribution (Table S5.4).

In the model, women who do not have cervical cancer have an age-specific probability of getting a hysterectomy for reasons other than cervical cancer. A hysterectomy is assumed to remove all prevalent HPV infections and CIN lesions. Women with a hysterectomy will no longer acquire HPV infections or CIN lesions and are also no longer invited for screening tests.

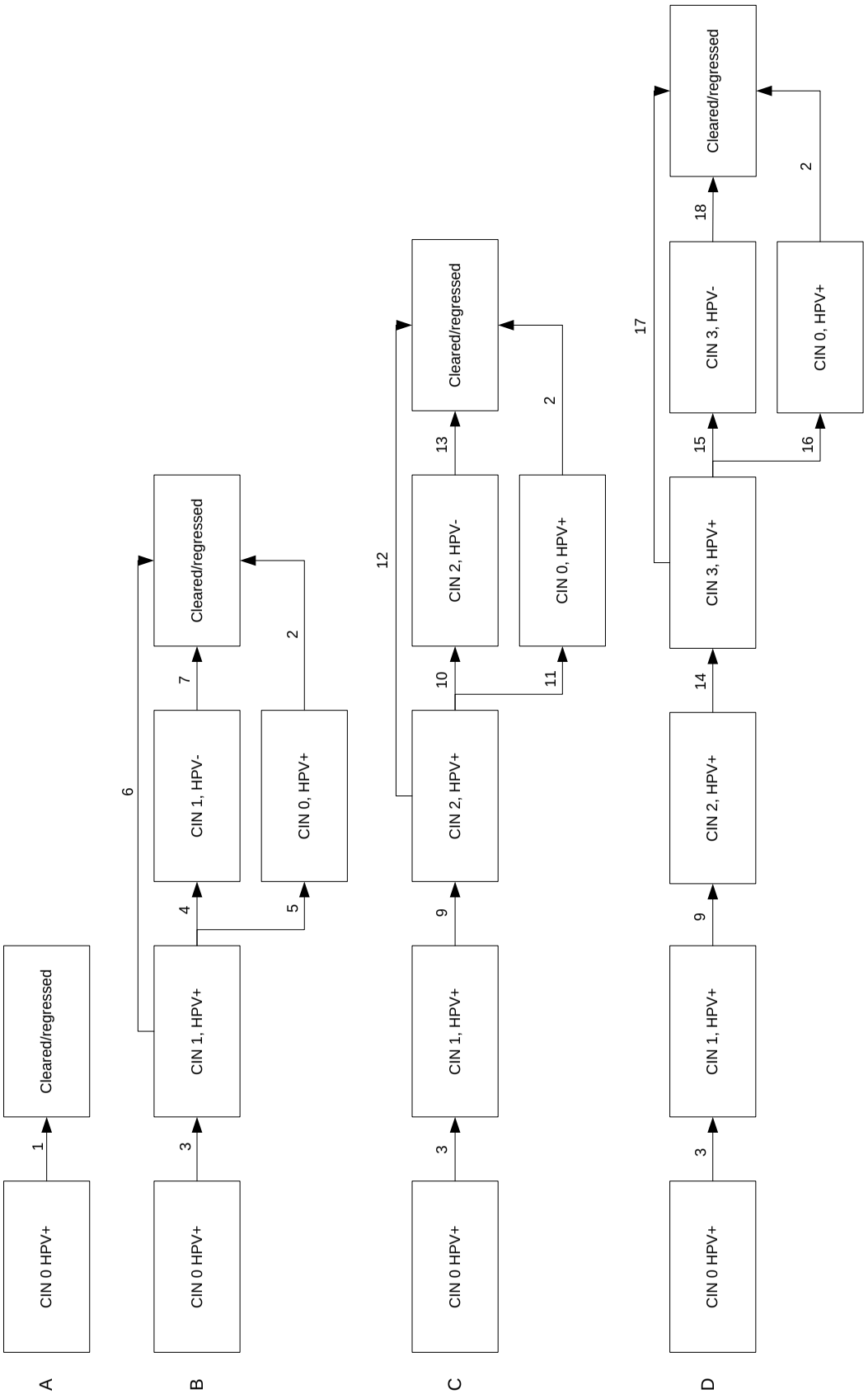



**Figure. S5.2 Schematic representation of the MISCAN model, with disease pathways A through F.**

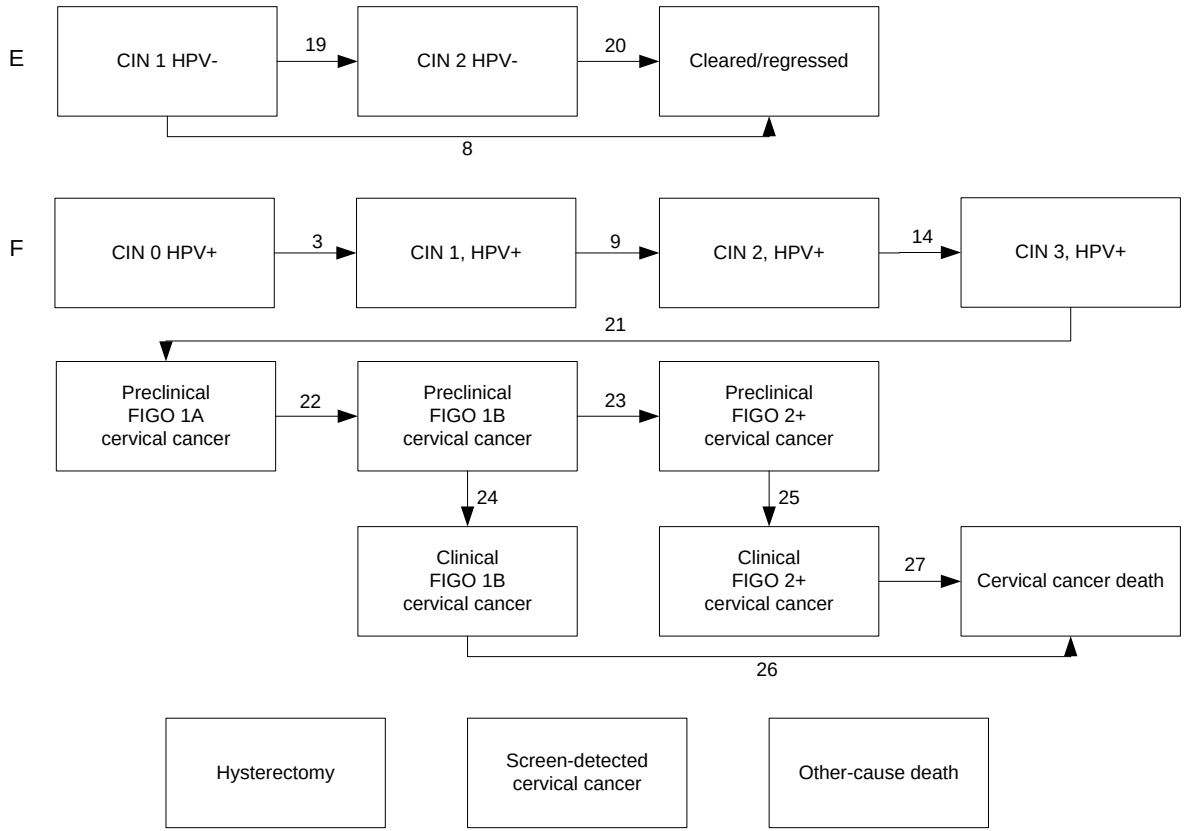



**Fig. S5.2 (continued) Schematic representation of the MISCAN-cervix model, with disease pathways A through F**

*Notes: There are six disease pathways (types A through F) in MISCAN. All lesions start as either an HPV infection without CIN (disease pathways A, B, C, D, and F) or as a CIN 1 lesion without HPV infection (disease pathway E). Cleared/regressed denotes the absence of CIN and HPV infection; CIN 0 denotes the absence of CIN and cervical cancer. All cervical cancer states are HPV positive. The arrows between the states show which types of transitions can occur; the numbers refer to the duration distributions shown in Table 5. In every state before death, a transition to "Other-cause death" can occur, and in every state before cancer, a transition to "Hysterectomy" can occur (connecting arrows not shown); in these cases, the transition applies to all HPV infections and CIN lesions of that person simultaneously*.

**Table S5.4. Transitions and duration distributions used in MISCAN-Cervix.**

| Transition number[a] | Disease pathway[a] | From state | To state | Probability of transition | Type of distribution | Mean duration (years) | Weibull shape parameter |
|---|---|---|---|---|---|---|---|
| 1 | A | CIN 0 HPV+ | Cleared/regressed | 1 | Exponential | 1 | 1 |
| 2 | B, C, D | CIN 0 HPV+ | Cleared/regressed | 1 | Exponential | 1 | 1 |
| 3 | B, C, D, F | CIN 0 HPV+ | CIN 1 HPV+ | 1 | Exponential | 1 | 1 |
| 4 | B | CIN 1 HPV+ | CIN 1 HPV- | 0.4 | Exponential | 1.5 | 1 |
| 5 | B | CIN 1 HPV+ | CIN 0 HPV+ | 0.3 | Exponential | 1.5 | 1 |
| 6 | B | CIN 1 HPV+ | Cleared/regressed | 0.3 | Exponential | 1.5 | 1 |
| 7 | B | CIN 1 HPV- | Cleared/regressed | 1 | Exponential | 1 | 1 |
| 8 | E | CIN 1 HPV- | Cleared/regressed | 1 | Exponential | 1.5 | 1 |
| 9 | C, D, F | CIN 1 HPV+ | CIN 2 HPV+ | 1 | Exponential | 1.5 | 1 |
| 10 | C | CIN 2 HPV+ | CIN 2 HPV- | 0.4 | Exponential | 2 | 1 |
| 11 | C | CIN 2 HPV+ | CIN 0 HPV+ | 0.3 | Exponential | 2 | 1 |
| 12 | C | CIN 2 HPV+ | Cleared/regressed | 0.3 | Exponential | 2 | 1 |
| 13 | C | CIN 2 HPV- | Cleared/regressed | 1 | Exponential | 1 | 1 |
| 14 | D, F | CIN 2 HPV+ | CIN 3 HPV+ | 1 | Exponential | 2 | 1 |
| 15 | D | CIN 3 HPV+ | CIN 3 HPV- | 0.4 | Weibull | 3.1 | 1.67 |
| 16 | D | CIN 3 HPV+ | CIN 0 HPV+ | 0.3 | Weibull | 3.1 | 1.67 |
| 17 | D | CIN 3 HPV+ | Cleared/regressed | 0.3 | Weibull | 3.1 | 1.67 |
| 18 | D | CIN 3 HPV- | Cleared/regressed | 1 | Exponential | 1 | 1 |
| 19 | E | CIN 1 HPV- | CIN 2 HPV- | 1 | Exponential | 1.5 | 1 |
| 20 | E | CIN 2 HPV- | Cleared/regressed | 1 | Exponential | 2 | 1 |
| 21 | F | CIN 3 HPV+ | Preclinical FIGO 1A | 1 | Weibull | 11.8 | 1.67 |
| 22 | F | Preclinical FIGO 1A | Preclinical FIGO 1B | 1 | Exponential | 3.2 | 1 |
| 23 | F | Preclinical FIGO 1B | Preclinical FIGO 2+ | Age-specific[b] | Exponential | 0.5 | 1 |
| 24 | F | Preclinical FIGO 1B | Clinical FIGO 1B | Age-specific[b] | Exponential | 0.5 | 1 |
| 25 | F | Preclinical FIGO 2+ | Clinical FIGO 2+ | 1 | Exponential | 1.3 | 1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 26 | F | Clinical FIGO 1B | Cervical cancer death | Age-specific[c] | Piecewise uniform | Age-specific[d] | - |
| 27 | F | Clinical FIGO 2+ | Cervical cancer death | Age-specific[c] | Piecewise uniform | Age-specific[d] | - |

[a] *See Figure S5.3.*

[b] *Transition probability depends on age; see Table 5.3A.*

[c] *Transition probability depends on age; see Table 5.3B.*

[d] *See Table 5.3C for the duration distribution.*

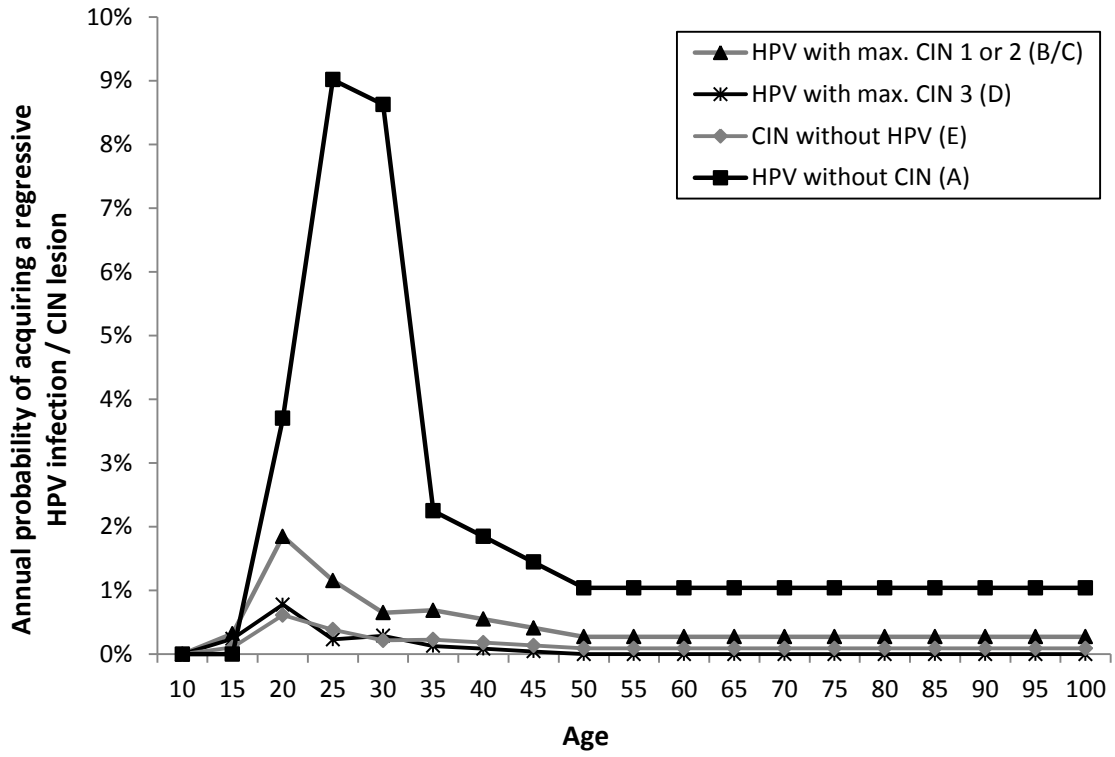



**Figure S5.3A. Annual probability of acquiring a regressive HPV infection or CIN lesion.**

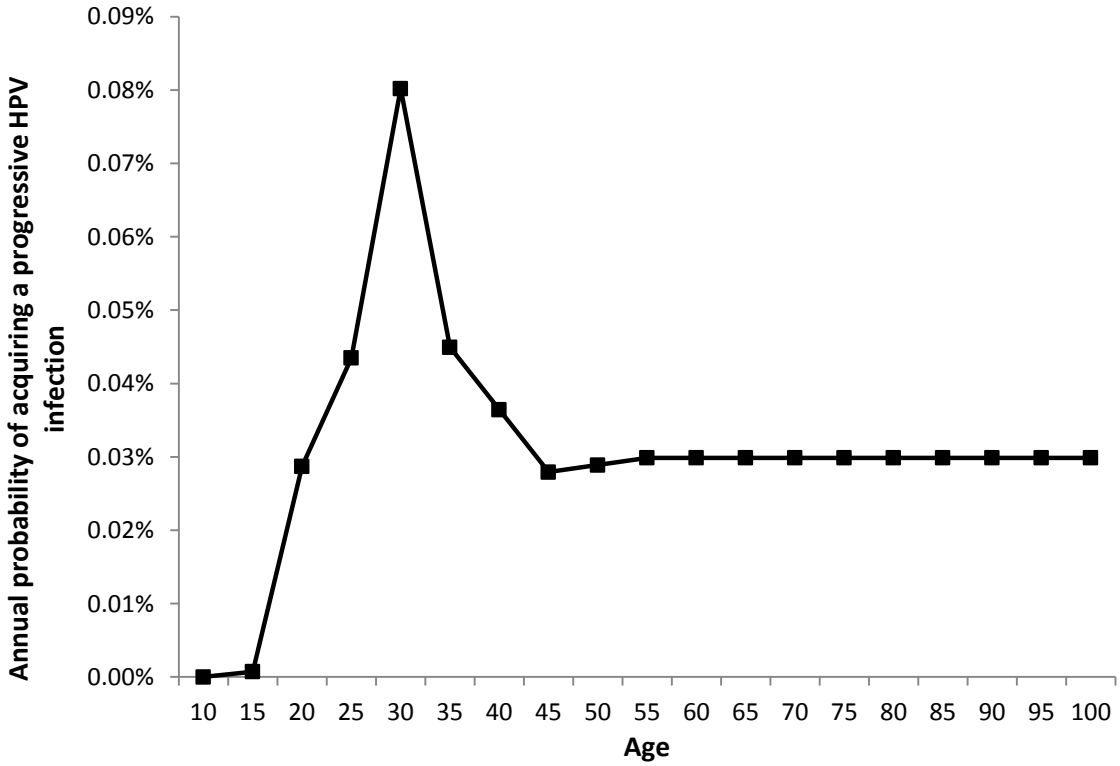



**Figure S5.3B. Annual probability of acquiring a progressive HPV infection.**

The assumptions for the probability and the duration of survival after a clinically detected (i.e. detected because of symptoms) cervical cancer are based on data from the Dutch Cancer Registry for the period 1989-2009. As these data include both adenocarcinoma and squamous cell carcinoma, the survival we estimated is a weighted average of these two types of cervical cancer. We assumed that all cervical cancer mortality occurs in the first 10 years after diagnosis. The assumed probability of long term survival depends on age and stage (FIGO 1B or FIGO 2+); in the model, FIGO 1A cervical cancer cannot be clinically detected. Table S5.5A shows what percentage of clinically detected cancers is detected in stages FIGO 1B and FIGO 2+. The model assumptions for the long-term survival probabilities are shown in Table S5.5B and the assumed duration distributions are shown in Table S5C.

**Table S5.5A. Age-specific probability that cervical cancer is detected in stages FIGO 1B and FIGO 2+, given that it is clinically detected.** Percentages in the table are estimated in the model calibration. Linear interpolation is used to determine the probabilities at intermediate ages.

| Age | Clinical detection in stage: | |
|---|---|---|
| | FIGO 1B | FIGO 2+ |
| 0 | 25.4% | 74.6% |
| 25 | 25.4% | 74.6% |
| 40 | 35.0% | 65.0% |
| 55 | 61.4% | 38.6% |
| 70 | 75.4% | 24.6% |
| 100 | 75.4% | 24.6% |

**Table S5.5B. Model assumptions for the age-specific probability that clinical FIGO 1B and FIGO 2+ cervical cancer will lead to death from cervical cancer (i.e. 100% - probability of long-term survival), in the absence of other-cause mortality.** Linear interpolation is used to determine the probabilities at intermediate ages. Source: observed age-specific and stage-specific survival for the periods 1989-2002 and 2003-2009, obtained from the Dutch Cancer Registry.

| Age | Clinical FIGO 1B | Clinical FIGO 2+ |
|---|---|---|
| 0 | 9.7% | 45.5% |
| 30 | 9.7% | 45.5% |
| 45 | 10.8% | 51.1% |
| 60 | 22.9% | 55.4% |
| 80 | 34.5% | 68.7% |
| 100 | 34.5% | 68.7% |

**Table S5.5C. Model assumptions for the duration distribution of clinical FIGO 1B and FIGO 2+ cervical cancer, if the transition to death from cervical cancer occurs.** The values in this table represent the percentages of cervical cancer deaths that occur within a given number of years after the moment of clinical diagnosis. It is assumed that no cervical cancer mortality occurs more than 10 years after clinical diagnosis. Source: observed age-specific and stage-specific survival for the periods 1989-2002 and 2003-2009, obtained from the Dutch Cancer Registry.

| Years after detection | Clinical FIGO 1B | Clinical FIGO 2+ |
|---|---|---|
| 1 | 10.4% | 37.6% |
| 2 | 36.5% | 64.6% |
| 3 | 47.9% | 78.1% |
| 4 | 61.5% | 84.5% |
| 5 | 78.3% | 88.5% |
| 6 | 84.4% | 90.5% |
| 7 | 90.3% | 93.3% |
| 8 | 93.1% | 96.4% |
| 10 | 100% | 100% |

*S5.2D Screening*

Screening can change the life histories of women. In the current analysis, we compare the effects of primary cytology and primary HPV screening for different screening scenarios, in which we varied:

- the start age of screening: 20, 25 or 30 years
- the screening interval: 1, 2, 3 or 5 years.

As we were only interested in the effects of primary HPV screening for women who are intensively screened, we assumed that all women were screened accordingly. The compliance to triage testing and referrals to colposcopy was also assumed to be 100%.

When an HPV test is applied, each HPV infection prevalent at the time of screening has a probability of producing a positive test (i.e. the sensitivity). If the HPV test is positive, cytological inspection determines whether the woman is referred to colposcopy or invited for cytological triage after 6 months. When the primary test is cytology, the woman is directly referred to colposcopy if the result is a high-grade squamous intraepithelial lesion (HSIL) or worse. If the cytological result is abnormal but less than HSIL, an HPV test determines whether the woman is referred to colposcopy or sent back to the routine program. For the assumed characteristics of the HPV test and cytology, see Table 5.1 of the main manuscript.

If a woman is referred to colposcopy, all prevalent CIN lesions are assumed to be diagnosed and successfully removed. HPV infections without CIN are not treated. For screen-detected cervical cancer, a stage-specific improvement (compared to the situation without screening) in the probability of cure is assumed.

*The effects of early detection on survival*

In the model, detection of cervical cancer by screening prevents death from cervical cancer in some but not all cases. However, if death from cervical cancer is not prevented, the time of death from cervical cancer is not changed by screening.

For screen-detected invasive cancers, survival was modelled as a reduction in the risk of dying compared with that risk in the situation without screening, when the cancer would have become clinical. This improvement of prognosis (89.4%, 50% and 20% for FIGO 1A, 1B and 2+ respectively) was calibrated to reproduce recently observed stage specific survival given observed screening (Dutch Cancer Registry).

### *S5.2E Effectiveness*

For each simulated woman who is alive, MISCAN-Cervix can determine the state, which can be Normal, HPV infected, CIN 1, CIN 2, CIN 3, FIGO 1A, FIGO 1B, and FIGO 2+. A woman can have multiple HPV infections or CIN lesions at the same time. Her state is determined by the most severe disease stage present, using the order HPV infection, CIN 1, CIN 2, CIN 3, FIGO 1A cervical cancer, FIGO 1B cervical, and FIGO 2+ cervical cancer; if no HPV infections or CIN lesions are present, the woman's state is Normal.

The model produces the number of life years spent in each state as well as the number of certain events (e.g. screenings and cervical cancer diagnoses) in a lifetime. For each of these events, Table 5.2 of the main manuscript presents the amount of quality-adjusted time lost. To calculate the total disutility of a screening scenario, a sum is taken over all the numbers of events multiplied by their associated quality-adjusted time lost.

In the current analysis, the number of life years gained is calculated as the difference in total years lived by the population between primary cytology and primary HPV screening. To determine the number of QALYs gained (or lost) by switching to primary HPV screening, we computed the difference in the total number of QALYs between both situations.

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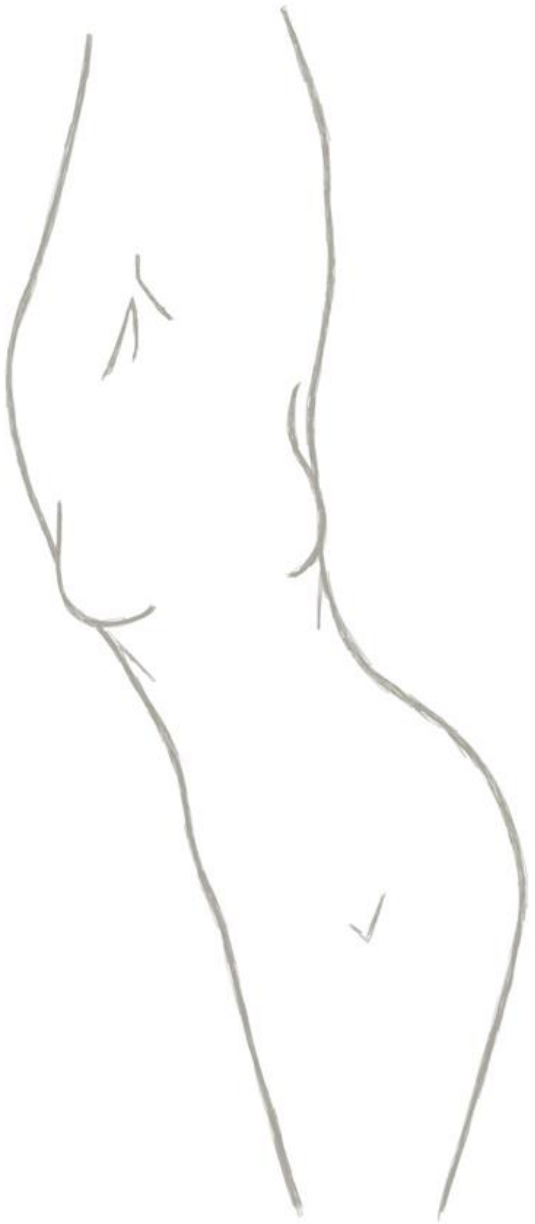
# 6

# Cervical cancer screening in partly HPV vaccinated cohorts - a cost-effectiveness analysis

PLoS ONE (2016)



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**Abstract**

**Background**

Vaccination against the oncogenic human papillomavirus (HPV) types 16 and 18 will reduce the prevalence of these types, thereby also reducing cervical cancer risk in unvaccinated women. This (measurable) herd effect will be limited at first, but is expected to increase over time. At a certain herd immunity level, tailoring screening to vaccination status may no longer be worth the additional effort. Moreover, uniform screening may be the only viable option. We therefore investigated at what level of herd immunity it is cost-effective to also reduce screening intensity in unvaccinated women.

**Methods**

We used the MISCAN-Cervix model to determine the optimal screening strategy for a pre-vaccination population and for vaccinated women (~80% decreased risk), assuming a willingness-to-pay of €50,000 per quality-adjusted life year gained. We considered HPV testing, cytology testing and co testing and varied the start age of screening, the screening interval and the number of lifetime screens. We then calculated the incremental cost-effectiveness ratio (ICER) of screening unvaccinated women with the strategy optimized to the pre-vaccination population as compared to with the strategy optimized to vaccinated women, assuming different herd immunity levels.

**Results**

Primary HPV screening with cytology triage was the optimal strategy, with 8 lifetime screens for the pre-vaccination population and 3 for vaccinated women. The ICER of screening unvaccinated women 8 times instead of 3 was €28,085 in the absence of herd immunity. At around 50% herd immunity, the ICER reached €50,000.

**Conclusion**

From a herd immunity level of 50% onwards, screening intensity based on the pre-vaccination risk level becomes cost-ineffective for unvaccinated women. Reducing the screening intensity of uniform screening may then be considered.

## Introduction

Infection with the human papillomavirus (HPV) has been identified as a necessary cause for cervical cancer.[1] Both the bivalent vaccine (targeting HPV-types 16/18), which is used in the Netherlands, and the quadrivalent vaccine (targeting HPV-types 6/11/16/18) are effective in preventing the two highly oncogenic types 16 and 18,[2,3] that are found in roughly 80% of invasive cervical cancers.[4] Recently, a nonavalent vaccine has been approved,[5] targeting seven oncogenic (and two non-oncogenic) HPV types and thereby potentially preventing almost 90% of cervical cancers worldwide.[6]

In the Netherlands, a catch-up campaign targeted all 13- to 16-year-old girls in 2009. Since 2010, all 12-year-old girls are offered vaccination. The three-dose vaccination coverage has steadily increased from 49% in the 1993 birth cohort to 61% in the 2000 birth cohort.[7,8] In these partly vaccinated cohorts, the prevalence of HPV-16/18 infections is lower than in the pre-vaccination population. Therefore, unvaccinated women in those cohorts will be at lower risk for developing cervical cancer. While this indirect protective effect of vaccination, so-called herd immunity, will be limited at first, it is expected to increase over time.[9] It can be estimated by the percentage reduction in HPV-16/18 prevalence among unvaccinated women who were offered vaccination, as compared to totally unvaccinated cohorts. In the Netherlands, primary HPV screening will be implemented in 2016. From then, it could be relatively easy to monitor HPV-16/18 prevalence in unvaccinated women.

In many developed countries, vaccinated cohorts are approaching the start age of cervical cancer screening. Especially in settings where both vaccinated and unvaccinated women are well represented, it is unclear what screening strategy should be offered. In the youngest vaccinated cohorts (with limited herd immunity), vaccinated women are at much lower risk than unvaccinated women and screening based on vaccination status is likely more cost-effective than current uniform screening.[10-13] However, vaccinated women may not accept being offered less screening, solely because they adhered to vaccination guidelines. Screening based on vaccination status also requires the linkage of the screening invitational system with vaccination registries, which may not be (fully) possible in all settings.

As long as the follow-up of HPV vaccinated women in trials and population-based settings is not long enough to observe (statistical) differences in cervical cancer rates between vaccinated and unvaccinated cohorts, countries are reluctant to reduce the screening frequency. In the U.S., the same screening protocol is recommended for both vaccinated and unvaccinated women.[14,15] European guidelines even state that HPV vaccines cannot replace or modify current routine cervical cancer screening protocols.[16]

What is merely realized, is that women at reduced risk (due to either vaccination or herd immunity) could also be harmed by too intensive screening. These women will be offered more screening tests than needed, which increases their probability of being referred to the gynecologist in the absence of clinically relevant lesions. Women with abnormal cytology or HPV positive test results

commonly experience fear, self-blame, distress and anxiety about cervical cancer, which reduces their quality of life.[17,18] The ethical justification of continuing screening optimized to unvaccinated women instead of to those who adhered to vaccination guidelines, is therefore questionable. Moreover, it is probably very inefficient and cost-ineffective to do so. To avoid this inefficiency, screening should be optimized to vaccinated women as soon as unvaccinated women are substantially protected via herd immunity. We investigated at what level of herd immunity this would be justified for unvaccinated women.

## Materials and Methods

Using the MISCAN-Cervix model, we determined two optimal screening strategies: one for a pre-vaccination cohort, and one for a vaccinated cohort. To determine the level of herd immunity for which it would be cost-effective to replace the first strategy by the second, both strategies were applied to an unvaccinated cohort, assuming different levels of herd immunity.

### *MISCAN-Cervix model*

The MISCAN-Cervix model, which is described in more detail in the model profile (see Supplements S5.2 of Chapter 5 in this thesis), was used to estimate costs and effects of different screening strategies.[19] In all of the analyses presented here, we simulated a cohort of 1 million women. While none of these women were assumed to be affected by vaccination when determining the optimal screening strategy for the pre-vaccination population, all of them were assumed to be vaccinated when determining the optimal screening strategy for vaccinated women. Both these optimal strategies were then applied to unvaccinated women assuming various herd immunity levels.

A fraction of these women will acquire HPV infections and/or develop cervical intraepithelial neoplasia (CIN) lesions. If these precursors progress to cervical cancer, women may die from the disease. If the population undergoes screening, the disease can be detected and treated in an earlier stage. As a result, cervical cancer death may be prevented or postponed.

The population at risk for cervical cancer was simulated based on demographic and hysterectomy data;[20,21] mortality from other causes was estimated using the observed age-specific mortality in the Netherlands in 2013.[20] The age-specific incidence of HPV infections that progress to cervical cancer was calibrated to the age-specific incidence of cervical cancer, which was obtained from the Netherlands Cancer Registry (NCR).[22] The age-specific incidence of pre-invasive lesions that do not progress to cervical cancer was calibrated so that the simulated detection rates of CIN lesions fit the observed detection rates in the Netherlands. These observed detection rates were obtained from the Dutch Network and National Database for Pathology (PALGA) for the period 2000–2007.[23] The incidence of high-risk HPV-infections that do not progress to CIN was calibrated

so that the simulated prevalence of all high-risk HPV-infections fits the observed high-risk HPV prevalence.[24,25]

In the model, disease is subdivided into seven sequential stages: high-risk HPV-infection, three pre-invasive stages (CIN grade 1, 2 and 3), and three invasive stages (International Federation of Gynecology and Obstetrics (FIGO) stages 1A, 1B and 2+).[26] Pre-invasive and FIGO 1A stages can be diagnosed by screening only, because no symptoms will develop, whereas stages 1B and 2+ can also be clinically diagnosed. Because precursors are usually not progressive;[27] in the model, most HPV-infections will clear without ever resulting in neoplasia, and lesions in pre-invasive stages can regress spontaneously. In the hypothetical situation without competing other-cause mortality, undetected preclinical invasive neoplasia will always progress to clinical cancer. CIN grades 1 and 2 can develop in the absence of a high-risk HPV infection; in that case the lesion will always regress. CIN grade 3 or worse can only develop if a high-risk HPV-infection is present.[28]

*Screening policies*

We simulated four different screening policies: (A) primary HPV screening with reflex cytology triage and cytology triage after six months (future Dutch screening program), (B) primary cytology with reflex HPV triage, (C) combined primary HPV and cytology (i.e. co-testing) with HPV triage after 12 months, and (D) primary cytology with cytology and HPV triage after six months and cytology triage after 18 months (current Dutch screening program). Policies (A) and (B) were already found to be cost-effective in case of no herd immunity;[29] policies (C) and (D) are included because of their resemblance with current practice in the U.S. and in the Netherlands, respectively.

*Screening schedules*

Screening schedules differed by start age, screening interval and number of screens in a lifetime. Possible start ages were 25, 30, 35, 40 and 45 years. The screening interval varied from 5 to 20 years and the number of lifetime screens ranged from 1 to 12. Because screening women older than 80 years is not likely to be beneficial,[30] all strategies ended at or before the age of 80. In this way, 312 screening schedules were created.

*Assumptions for screening and treatment*

As we aimed to optimized screening for women who adhere to screening guidelines, we assumed full attendance in both primary screening and triage testing (S6.1 Table). The sensitivity of cytology (the probability that the result is at least atypical squamous cells of undetermined significance (ASCUS)) was assumed to be 40% for CIN grade 1, 50% for CIN grade 2 and 75% for CIN grade 3 or cancer.[31] In the model calibration, the sensitivity of detecting at least high-grade squamous intraepithelial lesion (HSIL) was estimated to be 4% for CIN grade 1, 18% for CIN grade 2, 56% for CIN grade 3 and 60% for cervical cancer. The specificity of cytology was estimated at 97.6%. Based on the observed

difference in CIN grade 3 or cancer detection rates between cytology and the HPV test, we assumed the sensitivity of the HPV test to be 85% for a high-risk HPV-infection.[32] Although contamination and cross-reactivity may cause HPV tests to produce positive results in the absence of high-risk HPV infections, we assumed the specificity for the presence of HPV to be 100% and modelled a possible lack in specificity by including fast-clearing infections.

Detection of pre-invasive lesions and their associated management, including treatment if necessary, were assumed to lead to a 100% cure rate. A woman can, however, acquire new HPV-infections and develop CIN lesions after CIN treatment. For invasive cancer, we determined age-specific and stage-specific survival probabilities based on data from the NCR.[33] Since cancers detected by screening are found in an earlier stage than clinically diagnosed ones, women have a higher chance of survival. Using the NCR data, we estimated that if an invasive cancer is screen-detected, the probability to die from cervical cancer is reduced by 89.4%, 50% and 20% for FIGO stages 1A, 1B and 2+, respectively.[33]

*Assumptions for costs and utility losses*

The estimated costs are based on a societal perspective, and are reported in 2013 euros (S6.2 Table). Screening costs include the costs for the invitational system and quality assurance, time and travel costs of the woman being screened, costs of smear taking, costs of evaluating the smear, costs of repeat tests after an inadequate test result, and costs of registration in PALGA. Diagnosis costs for women referred for colposcopy, treatment costs for detected pre-invasive lesions, treatment costs for invasive cervical cancer and costs of palliative care were derived from previous cost studies performed in the Netherlands.[34] A small (psychological) loss in quality of life was assumed for attending screening (including waiting for the result) and for being in triage (including attending follow-up screenings).[35] Larger losses in quality of life were assumed for being diagnosed and treated for CIN or cancer, and for having a terminal stage of cervical cancer.[36,37] Both costs and health effects were discounted with an annual rate of 3%.

*Assumptions for vaccination*

We assumed the efficacy of the bivalent vaccine as observed in the PATRICIA trial,[42,43] which is 25.3% for HPV-infections without cytological abnormalities,[38] and 35.0%, 54.8% and 93.2% for CIN grade 1, 2 and 3 respectively (Table 6.1).[2] As vaccination trials have not showed any waning in vaccine efficacy until now,[39] the protection from vaccination was assumed to be lifelong. Due to limited follow-up of the trials, a reduction in cervical cancer incidence has not been observed yet. However, studies do give estimates of the type-specific reduction in HPV prevalence.[40,41] In combination with the HPV-type distribution observed in cervical cancer cases in western Europe,[4] the vaccine efficacy for cervical cancer was estimated at 83.4%. In this calculation we assumed that all cervical cancers are caused by a single oncogenic HPV-type, thereby avoiding overestimating the

effect of the vaccine. We further assumed that all oncogenic types are equally likely to be co-infected with other oncogenic types, and decreased all type-specific HPV-positivity rates with the same percentage (6.6%) to account for multiple infections.

In the absence of herd immunity, unvaccinated women were assumed to have the cervical cancer risk as is currently observed in the Netherlands.[42] Full herd immunity was assumed to be equally effective as vaccination in preventing both HPV-infections, CIN lesions and cervical cancer. When the herd immunity level was assumed to be e.g. 25%, then 25% of the infections, lesions and cancers that would have been prevented by vaccination, were averted in unvaccinated women.

**Table 6.1. Vaccination assumptions for base case analysis and sensitivity analyses.**

| | **Vaccine type** | **Vaccine duration**[†] | **Vaccine efficacy** | | | | |
|---|---|---|---|---|---|---|---|
| | | | **HPV-infections without CIN** | **CIN 1** | **CIN 2** | **CIN 3** | **Cervical cancer** |
| **Directly observed from PATRICIA trial (base case)** | Bivalent | Lifelong | 25.3% | 35.0% | 54.8% | 93.2% | 83.4%[¥] |
| **Directly observed from FUTURE trial** | Quadrivalent | Lifelong | 21.4%[‡] | 29.7% | 42.9% | 45.5% | 77.8%[¥] |
| **Indirectly based on PATRICIA trial*** | Bivalent | Lifelong | 51.4% | 33.5% | 55.4% | 62.2% | 83.4% |
| **Indirectly based on FUTURE trial*** | Quadrivalent | Lifelong | 38.2% | 26.1% | 47.5% | 53.9% | 77.8% |

*HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia.*

** Vaccine efficacy is calculated by combining the reduction in type-specific HPV-infections observed in the trial, with the HPV-type distribution observed in HPV-infections without cytological abnormalities (in the Netherlands),[43] and in CIN grade 1, 2, and 3, and cervical cancer (in western Europe).[4]*

*[†] Trials do not (yet) show that vaccine efficacy wanes; we assumed that if it would, vaccine boosters would be offered.*

*[¥] Because the follow-up of the trials is too short to give (meaningful) estimates for cervical cancer, we used the estimates from the indirect approach.*

*[‡] Observed vaccine efficacy for high-risk HPV-infections combined with ASC-US (atypical squamous cells of undetermined significance), trial results do not include efficacy for high-risk HPV-infections only.*

*Analyses and outcomes*

For a pre-vaccination and a vaccinated cohort, we simulated the screening strategies described earlier and determined their discounted costs and effects as compared to no screening. For both cohorts, the optimal screening strategy was determined as follows. We first excluded all dominated screening strategies, i.e. those strategies that were more costly and less effective than (combinations of) other

strategies. We then ranked the efficient strategies based on the number of quality-adjusted life years (QALYs) gained and calculated their incremental cost-effectiveness ratio (ICER), i.e. the additional costs per additional QALY gained compared to the next less effective, efficient strategy. For each cohort, the optimal screening strategy was then defined as the strategy with an ICER just below the willingness-to-pay threshold of €50,000 per QALY gained, which is a commonly used threshold in cost-effectiveness analyses for cervical cancer screening.[29,44]

The two optimal screening strategies were applied to unvaccinated women assuming herd immunity levels of 0%, 25%, 50%, 75% and 100%. For all these levels, the ICER of screening optimized to the pre-vaccination cohort as compared to screening optimized to the vaccinated cohort was calculated. If the ICER reached above €50,000 per QALY gained, screening optimized to the pre-vaccination risk level was no longer considered cost-effective for unvaccinated women.

*Sensitivity analyses*

In the sensitivity analyses, we varied the following parameters:

Vaccine efficacy

1. First, we used the vaccine efficacy from two randomized efficacy trials in which the quadrivalent vaccine was used (FUTURE I[45] and FUTURE II).[46] The efficacy found in these trials was lower than for the bivalent vaccine, i.e. 29.7%, 42.9% and 45.5% for CIN grade 1, 2 and 3 lesions, respectively.[47] Because in these trials HPV testing was only used when cytological abnormalities were observed, the reduction in HPV-infections in women without cytological abnormalities is not known. Instead, we used the reduction in HPV-positive women with ASCUS, which was 21.4%.[47] Again, the efficacy for cervical cancer was estimated using the type-specific reduction in HPV prevalence[41,48] and the HPV-type distribution in cervical cancer,[4] which resulted in an estimate of 77.8%.
2. Second, we estimated the efficacy for all disease stages by using the type-specific reduction in HPV prevalence observed in the PATRICIA trial and the HPV-type distribution observed in the Netherlands (for HPV-infections without cytological abnormalities)[43] and in western Europe (for CIN lesions and cervical cancer).[4] This resulted in an assumed vaccine efficacy of 51.4% for HPV-infections, and of 33.5%, 55.4% and 62.2% for CIN grade 1, 2 and 3 respectively. For cervical cancer, the efficacy remained at its base case value of 83.4%.
3. Finally, this indirect approach of combining the type-specific reduction in HPV prevalence with the HPV-type distribution in HPV-infections, CIN lesions and cervical cancer was also used to determine the vaccine efficacy for the quadrivalent vaccine. The assumed vaccine efficacy was 38.2% for HPV-infections, 26.1%, 47.5%, 53.9% for CIN grade 1, 2 and 3 respectively and 77.8% for cervical cancer.

Background risk for cervical cancer in unvaccinated women.

Instead of assuming an equal background risk for vaccinated and unvaccinated women, we included two sensitivity analyses in which the background risk in unvaccinated women was assumed 50% higher and 50% lower than in vaccinated women.

**Results**

*Base case analysis*

For a pre-vaccination cohort, 6-yearly primary HPV screening in the age range 30–72 years is most cost-effective (S6.3 Table). This corresponds to 8 screens in a lifetime. The optimal strategy for vaccinated women is also primary HPV screening, but in a smaller age range (35–59 years) and with a longer interval (every 12 years), corresponding with 3 lifetime screens (S6.4 Table).

Health effects

As compared to screening 3 times, screening 8 times reduces cervical cancer deaths with 161 per 100,000 unvaccinated women in the absence of herd immunity, and with 28 in case of full herd immunity (Table 6.2). It thereby yields 388 and 34 more QALYs gained when assuming 0% and 100% herd immunity, respectively (Table 6.3). However, it also requires more screen tests, more referrals for colposcopy and more CIN treatments. For one additionally prevented death, the required additional number of referrals for colposcopy increased from 34 for 0% herd immunity to 118 for 100%.

Costs and cost-effectiveness

Screening 8 times instead of 3 increases total costs with approximately €10.9 and €11.1 million assuming no and full herd immunity, respectively. Consequently, the ICER of screening 8 times instead of 3 increased from €28,085 per QALY gained in the absence of herd immunity to €35,042, €47,530, €77,541, and €322,234 for 25%, 50%, 75% and 100% herd immunity, respectively. From Fig 6.1, the estimated herd immunity level for which screening 8 times would cost approximately €50,000 per QALY gained when compared to screening 3 times, is 52%.

**Table 6.2. Undiscounted health effects for unvaccinated women of primary HPV screening at ages 30–72 every 6 years (optimal for unvaccinated women without herd immunity) and at ages 35–59 every 12 years (optimal for vaccinated women), as compared to no screening.** For different levels of herd immunity, results are given per 100,000 unvaccinated women.

| Herd immunity level | Screening strategy | # Primary screens | # Triage screens | # Referrals for colposcopy | # False-positive referrals (no CIN) | # CIN grade 1 | # CIN grade 2 | # CIN grade 3 | # Cases prevented | # Deaths prevented |
|---|---|---|---|---|---|---|---|---|---|---|
| 0% | 30-72, 6y | 717,049 | 55,427 | 10,188 | 873 | 3,805 | 2,360 | 3,029 | 1,416 | 589 |
| | 35-59, 12y | 277,073 | 20,127 | 4,718 | 271 | 1,479 | 1,014 | 1,782 | 982 | 423 |
| 25% | 30-72, 6y | 716,804 | 51,324 | 8,969 | 823 | 3,630 | 2,080 | 2,340 | 1,123 | 471 |
| | 35-59, 12y | 277,153 | 18,450 | 4,085 | 257 | 1,421 | 889 | 1,383 | 776 | 338 |
| 50% | 30-72, 6y | 716,579 | 47,130 | 7,756 | 770 | 3,468 | 1,802 | 1,648 | 832 | 348 |
| | 35-59, 12y | 277,233 | 16,752 | 3,447 | 242 | 1,357 | 765 | 985 | 579 | 248 |
| 75% | 30-72, 6y | 716,354 | 42,929 | 6,535 | 723 | 3,286 | 1,528 | 953 | 537 | 225 |
| | 35-59, 12y | 277,308 | 15,054 | 2,803 | 229 | 1,290 | 632 | 589 | 372 | 161 |
| 100%* | 30-72, 6y | 716,113 | 38,739 | 5,472 | 678 | 3,121 | 1,254 | 252 | 230 | 98 |
| | 35-59, 12y | 277,386 | 13,352 | 2,156 | 213 | 1,228 | 511 | 176 | 158 | 70 |

*CIN = cervical intraepithelial neoplasia.*

**We assumed that with full herd immunity, unvaccinated women have the same cervical cancer risk as vaccinated women.*

**Table 6.3. Base case costs and QALYs gained as compared to no screening (both 3% discounted) of screening optimized to a pre-vaccinated cohort and of screening optimized to a vaccinated cohort, and incremental cost-effectiveness of the former strategy as compared to the latter.** For different levels of herd immunity, results are given per 100,000 unvaccinated women.

| Herd immunity level | Screening strategy | | | Costs | Incremental costs | QALYs gained | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|---|
| | Age range | Interval | No. of screens | | | | | |
| 0% | 35-59 | 12y | 3 | €4,458,721 | | 1,488 | | |
| | 30-72 | 6y | 8 | €15,357,002 | + €10,898,282 | 1,876 | + 388 | €28,085 |
| 25% | 35-59 | 12y | 3 | €5,062,986 | | 1,184 | | |
| | 30-72 | 6y | 8 | €15,991,074 | + €10,928,088 | 1,495 | + 312 | €35,042 |
| 50% | 35-59 | 12y | 3 | €5,756,793 | | 868 | | |
| | 30-72 | 6y | 8 | €16,731,153 | + €10,974,359 | 1,098 | + 231 | €47,530 |
| 75% | 35-59 | 12y | 3 | €6,457,603 | | 556 | | |
| | 30-72 | 6y | 8 | €17,474,531 | + €11,016,928 | 698 | + 142 | €77,541 |
| 100%* | 35-59 | 12y | 3 | €7,181,587 | | 231 | | |
| | 30-72 | 6y | 8 | €18,277,092 | + €11,095,505 | 265 | + 34 | €322,234 |

*QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio*

**We assumed that with full herd immunity, unvaccinated women have the same cervical cancer risk as vaccinated women.*

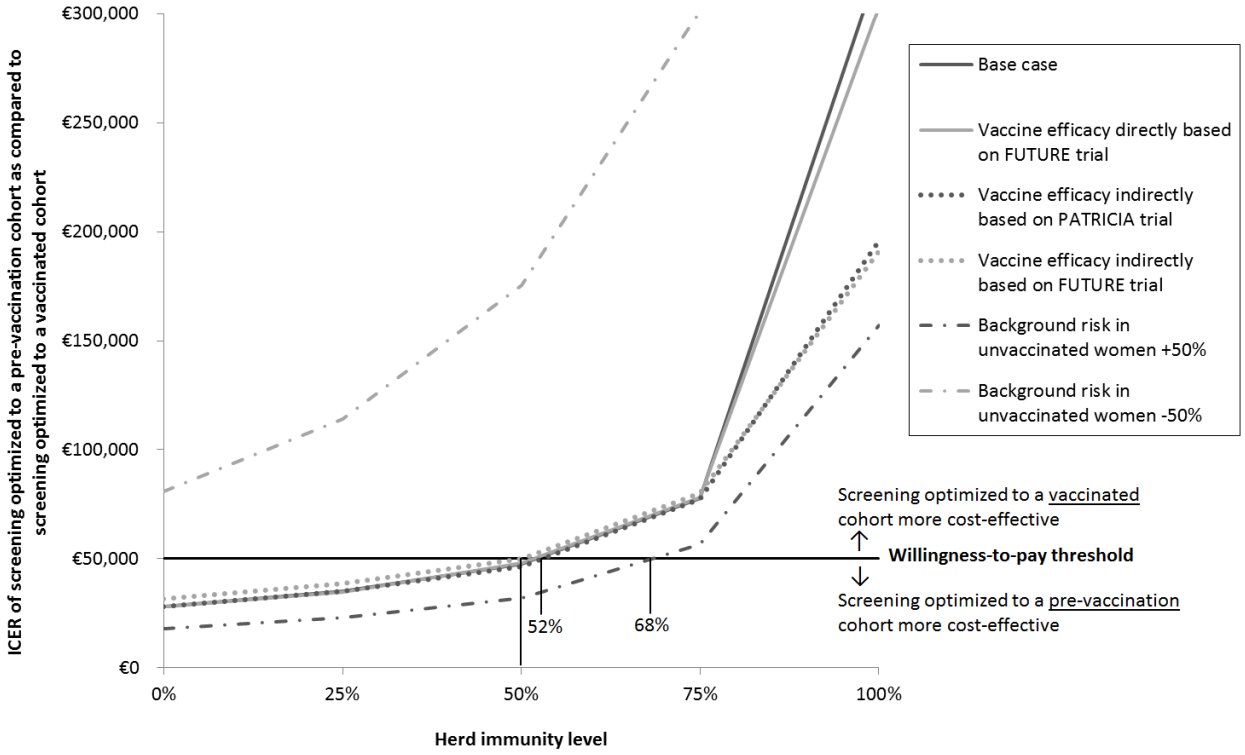


**Fig 6.1. Incremental cost-effectiveness ratio (ICER) of screening optimized to a pre-vaccination cohort as compared to screening optimized to a vaccinated cohort, for unvaccinated women who benefit from different herd immunity levels, under both base case assumptions and sensitivity analyses.**

*Sensitivity analyses*

When vaccine efficacy was calculated indirectly from the FUTURE trial, the optimal screening strategy for vaccinated women involved an additional screening round at age 71 (S6.5 Table). In all other sensitivity analyses, the optimal strategy for vaccinated women was unchanged (S6.6 and S6.7 Tables).

Similar to the base case analysis, the ICER of using the strategy optimized to the pre-vaccination cohort instead of to the vaccinated cohort, increased with increasing level of herd immunity (Table 6.4). In sensitivity analyses with different efficacy assumptions, screening optimized to the pre-vaccination population can be considered cost-effective as long as the herd immunity level is below 50%-52%. When unvaccinated women would have a 50% lower background risk for cervical cancer, screening can be optimized to vaccinated women, regardless of the herd immunity level. If instead, unvaccinated women have a 50% higher background risk, screening optimized to the pre vaccination population should be continued until the herd immunity reaches above ~68%.

**Table 6.4. Results sensitivity analyses: incremental cost-effectiveness ratio of screening optimized to a pre-vaccination cohort, as compared to screening optimized to a vaccinated cohort.**

| Herd immunity level | Vaccine efficacy* | | | Background risk in unvaccinated women | |
|---|---|---|---|---|---|
| | Directly observed from FUTURE trial | Indirectly based on PATRICIA trial | Indirectly based on FUTURE trial | +50% | -50% |
| 0% | € 28,085 | € 28,085 | € 31,450 | € 17,828 | € 80,972 |
| 25% | € 35,050 | € 34,675 | € 38,631 | € 22,950 | € 114,122 |
| 50% | € 46,471 | € 48,097 | € 49,747 | € 31,998 | € 175,596 |
| 75% | € 77,153 | € 78,139 | € 80,122 | € 56,390 | € 301,129 |
| 100%† | € 195,881 | € 303,352 | € 191,000 | € 157,043 | QALYs lost‡ |

*QALYs = quality-adjusted life years.*

** For vaccine efficacy assumptions, see Table 6.1.*

*† We assumed that with full herd immunity, unvaccinated women have the same cervical cancer risk as vaccinated women.*

*‡ For unvaccinated women at 50% reduced cervical cancer risk, QALYs were lost when screening was optimized to the pre-vaccination risk level instead of to the risk level in vaccinated women.*

**Discussion**

For both a pre-vaccination and a vaccinated cohort, primary HPV screening is more cost-effective than primary cytology or co-testing. The optimal number of lifetime screens varied from 8 for the pre-vaccination cohort, to only 3 for the vaccinated cohort. For unvaccinated women, the adverse effects and costs of screening become more important as the herd immunity level increases. Offering these women 8 instead of 3 lifetime screens incrementally required 34 colposcopy referrals per prevented death for 0% herd immunity, which increased to 118 referrals for 100% herd immunity. The ICER of screening 8 times instead of 3 increased from €28,085 per QALY gained in the absence of herd immunity to €322,234 at full herd immunity. Screening optimized to the risk level in vaccinated women becomes more cost-effective than screening optimized to the pre-vaccination risk level when the herd immunity reaches above 50%-55%.

To foresee whether and when the herd immunity will reach this level, countries need to monitor the HPV-16/18 prevalence in unvaccinated women, starting with a reliable pre-vaccination baseline measurement. A recent cross-sectional study among women aged 18–24 years in Australia, in whom vaccination coverage was 55%-74% for 1–3 doses,[49] showed a reduction in HPV-16/18 prevalence of 93% and 35% in vaccinated and unvaccinated women, respectively, compared to the pre-vaccination prevalence.[50] From these early data, the estimated herd immunity level would equal (0.35 / 0.93 ≈) 38%.

We have not incorporated vaccination coverage as a separate parameter in our analyses, the reason for which is as follows. Vaccination coverage plays a role in two ways: first, it determines how many unvaccinated women there are (which is important when evaluating how to screen them), and second, it is one of the main determinants of herd immunity. Mathematical models have been created to estimate the level of herd immunity given vaccination coverage.[51-53] These models have been helpful in decision analyses concerning vaccination (also in boys), by estimating its indirect effect in the unvaccinated. However, when it comes to screening decisions that depend on current or near future herd immunity, it seems more appropriate to seek guidance from actual measurements (of HPV prevalence in the unvaccinated) than from model based predictions of herd immunity levels. Indeed, the exact relation between coverage and herd immunity will only become established based on such measurements.

The manuscript primarily focused on the effect of decreasing the screening frequency of uniform screening for unvaccinated women. For vaccinated women, this adjustment would be cost effective by definition. Meanwhile, it is important to point out that the harms of screening the vaccinated 8 times instead of 3 were smaller than the life years gained (Table 6.3), meaning that unadjusted screening did not result in a net loss in health for vaccinated women.

We optimized the screening strategy to the pre-vaccination risk level and to the risk level in vaccinated women. For partly vaccinated cohorts, it could be beneficial to have a screening strategy that is a compromise of these two strategies. In fact, when ignoring the costs and efforts related to restructuring screening guidelines, it would likely be cost-effective to reduce the screening frequency gradually while the herd immunity level increases. Adjusting national screening guidelines every few years is not a very workable solution though. Likewise, it could be cost-effective to tailor screening to vaccination status. Our results have shown that as soon as the herd immunity level reaches 50%, then it is beneficial (in terms of cost-effectiveness) for unvaccinated women to replace screening optimized to the pre-vaccination risk level with screening optimized to the risk level in vaccinated women. If this already happens within a few years, then establishing tailored screening by e.g. developing a vaccination registry that is linked to the screening invitational system, may not be worthwhile. The (lack of) accumulation of herd immunity over time is crucial in deciding whether the establishment of tailored screening would be worth these additional efforts. We performed our analyses under the assumption that it is most realistic that countries will continue screening all women uniformly, and that a once-only adjustment is made as soon as this seems justified for unvaccinated women.

Notable limitations are the following. First, we assumed that the efficacy of the vaccine has a lifelong duration. Although until now, HPV vaccination trials have shown a sustained efficacy,[2,3] it is possible that the efficacy will wane in the future. If the protection would fade away and offering vaccination boosters would not be an option, then screening optimized to vaccinated women would probably be more intensive than in the current analyses, and unvaccinated women could be screened accordingly from a lower herd immunity level onwards. Second, as the follow-up of the vaccination

trials is too limited to give (meaningful) estimates of the vaccine efficacy for cervical cancer, we had to estimate this efficacy indirectly. The decrease in CIN grade 3 lesions does indicate that the vaccine is likely to prevent clinically relevant lesions, and therefore also cancer.[2,47] If the decrease in cervical cancer risk would be smaller than estimated, vaccinated women would also require more intensive screening, again meaning that unvaccinated women could be screened accordingly from a lower herd immunity level. Third, we assumed an equal background risk for vaccinated and unvaccinated women. Because reasons for refusing vaccination may vary widely (e.g. lack of knowledge about HPV, low perceived risk of infection, concerns about safety, religious values),[54] the background risk in unvaccinated women could both be higher or lower as compared to vaccinated women. In the sensitivity analyses we showed that even if the background risk in unvaccinated women would be 50% higher, then unvaccinated women could already be screened as vaccinated women from ~68% herd immunity onwards. Finally, we have not modeled the effects of the nonavalent vaccine, because its use is still limited compared to the bivalent and quadrivalent vaccine. If vaccination with this more potent vaccine would lead to a less intensive optimal screening strategy for vaccinated women, the herd immunity level at which unvaccinated women could be screened accordingly would be higher.

To our knowledge, this is the first study evaluating at what herd immunity level a once-only uniform (equal for vaccinated and unvaccinated women) screening adaptation becomes, considering risks, benefits and costs, an option. Because vaccinated women are approaching the age at which cervical cancer screening starts, the results of this study will be relevant in the near future. It shows, that as long as stepwise adjustment or dichotomized screening based on vaccination status are considered unfeasible, one may wait until the HPV-16/18 prevalence amongst unvaccinated women drops below 50% of the pre-vaccination level, before considering adjusting screening. Meanwhile, also the necessary evidence for a decrease in cervical cancer risk in vaccinated women should become available.

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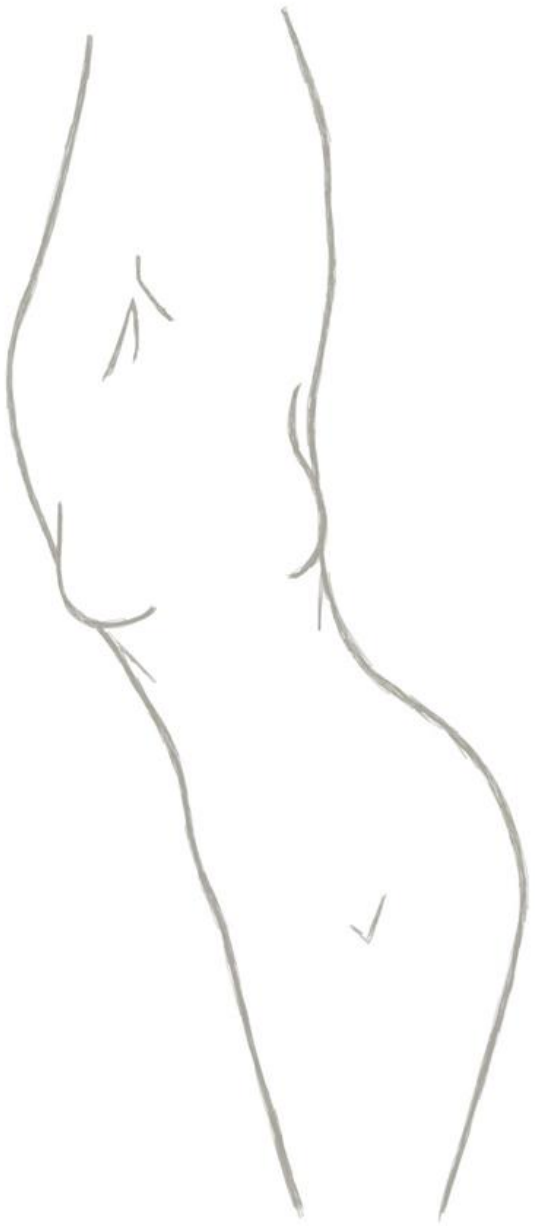
# 6

## Supplements



For this study, we have used the Microsimulation Screening Analysis (MISCAN) model for cervical cancer.[1] This model can be used to assess the harms and benefits of different screening programs for cervical cancer, as well as human papillomavirus (HPV) vaccination. The model has been used previously for cost-effectiveness analyses of cervical cancer screening and HPV vaccination.[2-6] Please see the **supplements S5.2A-S5.2C** of Chapter 5 for the MISCAN-Cervix model profile. Below, we described our assumptions regarding screening and the cost-effectiveness analyses specific to this study.

**Screening**

Screening can change the life histories of women. In the current analysis, we considered screening strategies in which we varied:

- the start age: 25, 30, 35, 40, and 45 years
- the number of screens: 1, 2, …, 11, 12 screens
- the interval: 5, 6, …, 19, and 20 years
- the policy: *A.* primary HPV screening with cytology triage (t=0 and t=6),
  *B.* primary cytology with HPV triage (t=0),
  *C.* primary co-testing with HPV triage (t=12), and
  *D.* primary cytology with cytology (t=6 and t=18) and HPV triage (t=6), where t = the time in months since primary screening.

As we were interested in optimizing screening for those who adhere to screening guidelines, both the screening uptake and the compliance to triage testing and referrals to colposcopy were assumed to be 100%.

When an HPV test is applied, each HPV infection prevalent at the time of screening has a probability of producing a positive test (i.e. the sensitivity). If the HPV test is positive, cytological inspection determines whether the woman is referred to colposcopy or invited for cytological triage after 6 months (policy A). When the primary test is cytology, the woman is directly referred to colposcopy if the result is a high-grade squamous intraepithelial lesion (HSIL) or worse. For abnormal cytological results less than HSIL, an HPV test determines whether the woman is referred to colposcopy or sent back to the routine program, when following policy B. In policy D, these women are invited for another cytological test after 6 months. Again, if the result is HSIL or worse, women are referred to the gynecologist. For abnormal results less than HSIL, an HPV test is used to determine whether the woman is referred for colposcopy (positive HPV test) or invited for another cytological test after 12 months from then (negative HPV test). If the cytological result is normal, women are only invited for another cytological test after 12 months if the smear tests positive on the presence of high-risk HPV infections. For policy D, we assumed that all primary testing includes both cytology and

HPV testing. Women with HSIL or worse or with ASCUS/LSIL combined with a positive HPV test are directly referred for colposcopy. Those with an ASCUS/LSIL result testing negative on HPV and those with a normal cytological result testing positive on HPV, are invited for another HPV test after 12 months. HPV-positive women are then referred for colposcopy, and HPV-negative women return to the routine program. For the assumed test characteristics of the HPV test and cytology, see Supplemental Table S6.1.

If a woman is referred to colposcopy, all prevalent CIN lesions are assumed to be diagnosed and successfully removed. HPV infections without CIN are not treated. For screen-detected cervical cancer, a stage-specific improvement (compared to the situation without screening) in the probability of cure is assumed.

*The effects of early detection on survival*

In the model, detection of cervical cancer by screening prevents death from cervical cancer in some but not all cases. However, if death from cervical cancer is not prevented, the time of death from cervical cancer is not changed by screening.

For screen-detected invasive cancers, survival was modelled as a reduction in the risk of dying compared with that risk in the situation without screening, when the cancer would have become clinical. This improvement of prognosis (89.4%, 50% and 20% for FIGO 1A, 1B and 2+, respectively) was calibrated to reproduce recently observed stage specific survival given observed screening (Netherlands Cancer Registry).

**Cost-effectiveness**

For each simulated woman who is alive, MISCAN-Cervix can determine the state, which can be Normal, HPV infected, CIN 1, CIN 2, CIN 3, FIGO 1A, FIGO 1B, and FIGO 2+. A woman can have multiple HPV infections or CIN lesions at the same time. Her state is determined by the most severe disease stage present, using the order HPV infection, CIN 1, CIN 2, CIN 3, FIGO 1A, FIGO 1B, and FIGO 2+ cervical cancer. If no HPV infections or CIN lesions are present, the woman's state is Normal.

The model produces the number of life years spent in each state as well as the number of certain events (e.g. screenings and cervical cancer diagnoses) in a lifetime. For each of these events, Supplemental Table S6.2 presents the amount of quality-adjusted time lost and the associated costs. To calculate the total disutility of a screening strategy, a sum is taken over all the numbers of events multiplied by their associated quality-adjusted time lost. A similar approach is used to determine the costs of a screening strategy.

In the current analysis, we optimized screening for a pre-vaccination cohort, and a vaccinated cohort. We calculated the costs and effects of all screening strategies mentioned earlier, and

determined the optimal strategy based on a willingness-to-pay threshold of €50,000 per quality-adjusted life year (QALY) gained. We then compared the costs and effects of these two strategies in unvaccinated women who benefit from 0%, 25%, 50%, 75% and 100% herd-immunity, where 100% herd-immunity was assumed to be equally effective as vaccination. Both vaccination and herd-immunity only provided protection against high-risk HPV-types 16 and 18.

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**Table S6.1. Base case assumptions for screening.**

| Parameter | Value |
|---|---|
| **Attendance** | 100% |
| | |
| **Cytology** | |
| *Probability of at least ASC-US for:* | |
| CIN grade 1 | 40% |
| CIN grade 2 | 50% |
| CIN grade 3 or worse | 75% |
| *Probability of at least HSIL for:* | |
| CIN grade 1 | 4% |
| CIN grade 2 | 18% |
| CIN grade 3 | 56% |
| Cervical cancer | 60% |
| Specificity (CIN grade 1 or worse) | 97.6% |
| | |
| **HPV test** | |
| Sensitivity for high-risk HPV-infection | 85% |
| Specificity for high-risk HPV-infection | 100%* |

*ASC-US = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial lesion; HPV = human papillomavirus.*

**Potential false-positive HPV test results were modelled as HPV-infections with a short duration.*

**Table S6.2. Base case assumptions for costs and utilities.**

| | Costs (€) | Utilities | | |
|---|---|---|---|---|
| | | Disutility | Duration | Quality-adjusted time lost |
| **Invitation** | 4.91 | - | - | - |
| **Primary screening** | | | | |
| Cytology | 66.95 | 0.005 | 2 weeks | 2 hours |
| HPV-test | 63.63 | 0.005 | 2 weeks | 2 hours |
| Cytology + HPV-test | 96.32 | 0.005 | 2 weeks | 2 hours |
| **Reflex triage** | | | | |
| Cytology | 32.69 | - | - | - |
| HPV-test | 29.38 | - | - | - |
| **Triage after 6, 12 or 18 months** | | | | |
| Cytology | 64.41 | 0.005 | Time since last test | Depends on interval |
| HPV-test | 61.1 | 0.005 | Time since last test | Depends on interval |
| **Diagnosis and treatment of pre-invasive stages** | | | | |
| False-positive referral | 300 | 0.005 | 0.5 year | 22 hours |
| CIN grade 1 | 936 | 0.03 | 0.5 year | 6 days |
| CIN grade 2 | 1,386 | 0.07 | 1 year | 26 days |
| CIN grade 3 | 1,623 | 0.07 | 1 year | 26 days |
| **Diagnosis and treatment of cancer** | | | | |
| FIGO 1A | 5,314 | 0.062 | 5 years | 4 months |
| FIGO 1B | 12,601 | 0.062 | 5 years | 4 months |
| FIGO 2+ (screen-detected) | 12,420 | 0.28 | 5 years | 17 months |
| FIGO 2+ (clinically detected) | 11,599 | 0.28 | 5 years | 17 months |
| **Terminal care** | 28,220 | 0.74 | 1 year | 9 months |

*HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia; FIGO = International Federation of Gynecology and Obstetrics.*

*Costs are in 2013 prices. €1.00 (£0.85; $1.37).*

**Table S6.3. Cost-effective strategies for a pre-vaccination cohort under base case assumptions.**

| Strategy | | | | Cost-effectiveness (3% discounted) | | |
|---|---|---|---|---|---|---|
| **Policy** | **Age range** | **Interval** | **# of screens** | **QALYs gained** | **Costs** | **ICER** |
| Primary HPV with cytology triage | 45 | - | 1 | 817 | € 3,656 | - |
| Primary HPV with cytology triage | 40 - 59 | 19 | 2 | 1,192 | € 595,896 | € 1,851 |
| Primary HPV with cytology triage | 40 - 57 | 17 | 2 | 1,210 | € 654,022 | € 3,093 |
| Primary HPV with cytology triage | 40 - 66 | 13 | 3 | 1,355 | € 1,225,940 | € 3,971 |
| Primary HPV with cytology triage | 35 - 71 | 12 | 4 | 1,545 | € 2,777,862 | € 8,138 |
| Primary HPV with cytology triage | 35 - 65 | 10 | 4 | 1,602 | € 3,247,901 | € 8,226 |
| Primary HPV with cytology triage | 35 - 71 | 9 | 5 | 1,662 | € 4,013,836 | € 12,866 |
| Primary HPV with cytology triage | 35 - 75 | 8 | 6 | 1,706 | € 4,888,675 | € 19,898 |
| Primary HPV with cytology triage | 35 - 70 | 7 | 6 | 1,726 | € 5,505,034 | € 30,264 |
| Primary HPV with cytology triage | 30 - 72 | 7 | 7 | 1,820 | € 8,797,780 | € 35,292 |
| **Primary HPV with cytology triage** | **30 - 72** | **6** | **8** | **1,857** | **€ 10,423,560** | **€ 43,175** |
| Primary HPV with cytology triage | 30 - 78 | 6 | 9 | 1,865 | € 10,849,457 | € 55,738 |
| Primary HPV with cytology triage | 30 - 75 | 5 | 10 | 1,890 | € 13,024,210 | € 85,673 |
| Primary HPV with cytology triage | 30 - 80 | 5 | 11 | 1,893 | € 13,420,746 | € 138,221 |
| Primary HPV with cytology triage | 30 - 74 | 4 | 12 | 1,897 | € 16,495,407 | € 865,290 |

*QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio; HPV = human papillomavirus.*

**Table S6.4. Cost-effective strategies for a vaccinated cohort under base case assumptions.**

| Strategy | | | | Cost-effectiveness (3% discounted) | | |
|---|---|---|---|---|---|---|
| **Policy** | **Age range** | **Interval** | **No. of screens** | **QALYs gained** | **Costs** | **ICER** |
| Primary HPV with cytology triage | 45 | - | 1 | 115 | € 1,618,507 | - |
| Primary HPV with cytology triage | 40 | - | 1 | 137 | € 2,005,709 | € 17,306 |
| Primary HPV with cytology triage | 40 - 57 | 17 | 2 | 178 | € 3,057,518 | € 25,930 |
| Primary HPV with cytology triage | 40 - 55 | 15 | 2 | 181 | € 3,143,604 | € 29,183 |
| Primary HPV with cytology triage | 35 - 50 | 15 | 2 | 198 | € 3,855,345 | € 39,937 |
| Primary HPV with cytology triage | 35 - 65 | 15 | 3 | 217 | € 4,656,004 | € 42,850 |
| **Primary HPV with cytology triage** | **35 - 59** | **12** | **3** | **226** | **€ 5,081,409** | **€ 45,286** |
| Primary HPV with cytology triage | 35 - 55 | 10 | 3 | 233 | € 5,408,214 | € 52,823 |
| Primary HPV with cytology triage | 35 - 65 | 10 | 4 | 242 | € 6,238,514 | € 88,735 |
| Primary HPV with cytology triage | 35 - 67 | 8 | 5 | 252 | € 7,594,621 | € 138,443 |
| Primary HPV with cytology triage | 35 - 75 | 8 | 6 | 254 | € 8,139,809 | € 257,058 |
| Primary cytology with HPV triage | 30 - 72 | 6 | 8 | 262 | € 13,056,727 | € 593,680 |
| Primary cytology with HPV triage | 30 - 78 | 6 | 9 | 263 | € 13,534,997 | € 862,056 |
| Primary cytology with HPV triage | 30 - 75 | 5 | 10 | 263 | € 15,697,980 | € 5,376,727 |

*QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio; HPV = human papillomavirus.*

**Table S6.5. Cost-effective strategies for a vaccinated cohort when vaccine efficacy is indirectly based on the FUTURE trial.**

| Strategy | | | | Cost-effectiveness (3% discounted) | | |
|---|---|---|---|---|---|---|
| **Policy** | **Age range** | **Interval** | **# of screens** | **QALYs gained** | **Costs** | **ICER** |
| Primary HPV with cytology triage | 40 - 53 | 13 | 2 | 123 | € 3,475,978 | - |
| Primary HPV with cytology triage | 40 - 66 | 13 | 3 | 147 | € 4,199,297 | € 29,996 |
| Primary HPV with cytology triage | 35 - 59 | 12 | 3 | 176 | € 5,354,578 | € 40,512 |
| **Primary HPV with cytology triage** | **35 - 71** | **12** | **4** | **189** | **€ 5,955,460** | **€ 47,493** |
| Primary HPV with cytology triage | 35 - 75 | 10 | 4 | 197 | € 6,465,406 | € 57,658 |
| Primary HPV with cytology triage | 35 - 71 | 9 | 5 | 209 | € 7,359,065 | € 74,476 |
| Primary HPV with cytology triage | 35 - 75 | 8 | 6 | 216 | € 8,312,103 | € 149,656 |
| Primary HPV with cytology triage | 30 - 78 | 8 | 7 | 229 | € 10,955,327 | € 203,002 |
| Primary HPV with cytology triage | 30 - 72 | 6 | 8 | 234 | € 13,466,715 | € 457,539 |
| Primary HPV with cytology triage | 30 - 78 | 6 | 9 | 235 | € 13,922,136 | € 639,319 |
| Primary cytology with HPV triage | 30 - 75 | 5 | 10 | 236 | € 16,060,457 | € 1,680,746 |

*QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio; HPV = human papillomavirus.*

**Table S6.6. Cost-effective strategies for a vaccinated cohort when vaccine efficacy is directly observed from the FUTURE trial.**

| Strategy | | | | Cost-effectiveness (3% discounted) | | |
|---|---|---|---|---|---|---|
| **Policy** | **Age range** | **Interval** | **# of screens** | **QALYs gained** | **Costs** | **ICER** |
| Primary HPV with cytology triage | 45 | - | 1 | 178 | €1,448,046 | - |
| Primary HPV with cytology triage | 40 | - | 1 | 216 | €1,850,074 | € 10,678 |
| Primary HPV with cytology triage | 40 - 58 | 18 | 2 | 273 | €2,776,309 | € 16,067 |
| Primary HPV with cytology triage | 40 - 54 | 14 | 2 | 280 | €2,946,291 | € 25,127 |
| Primary HPV with cytology triage | 35 - 65 | 15 | 3 | 334 | €4,455,547 | € 27,861 |
| Primary HPV with cytology triage | 35 - 61 | 13 | 3 | 341 | €4,728,923 | € 44,804 |
| **Primary HPV with cytology triage** | **35 - 59** | **12** | **3** | **344** | **€4,877,601** | **€ 48,674** |
| Primary HPV with cytology triage | 35 - 71 | 12 | 4 | 355 | €5,477,508 | € 52,364 |
| Primary HPV with cytology triage | 35 - 65 | 10 | 4 | 364 | €5,984,606 | € 53,712 |
| Primary HPV with cytology triage | 35 - 71 | 9 | 5 | 378 | €6,872,248 | € 67,009 |
| Primary HPV with cytology triage | 35 - 75 | 8 | 6 | 384 | €7,816,679 | € 156,284 |
| Primary cytology with HPV triage | 30 - 78 | 6 | 9 | 395 | €13,392,036 | € 480,256 |
| Primary cytology with HPV triage | 30 - 75 | 5 | 10 | 395 | €15,537,380 | € 37,371,197 |

*QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio; HPV = human papillomavirus.*

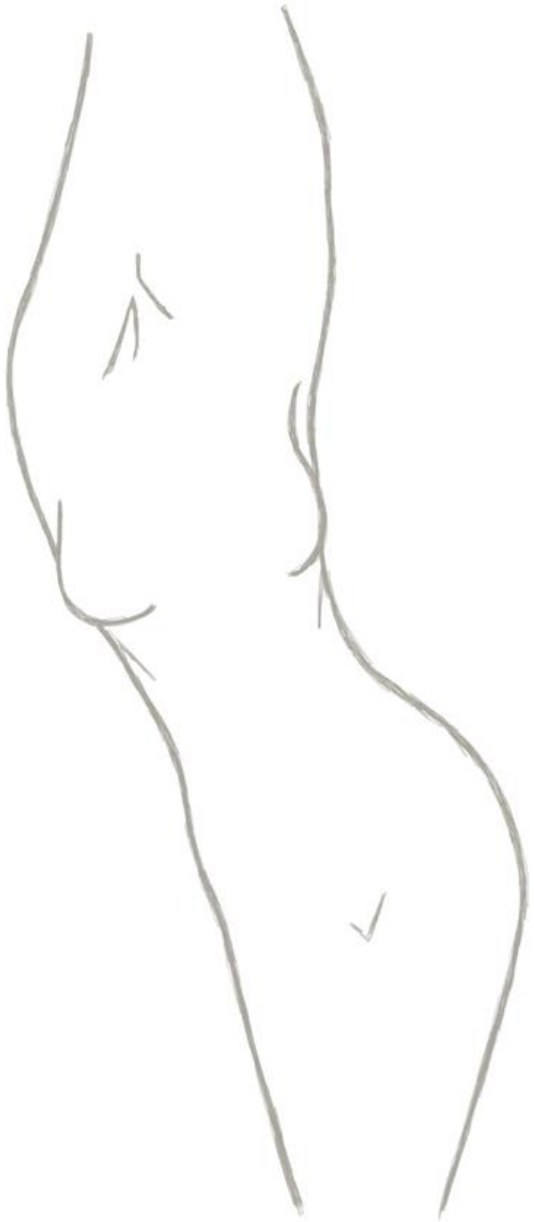
**Table S6.7. Cost-effective strategies for a vaccinated cohort when vaccine efficacy is indirectly based on the PATRICIA trial.**

| Strategy | | | | Cost-effectiveness (3% discounted) | | |
|---|---|---|---|---|---|---|
| **Policy** | **Age range** | **Interval** | **# of screens** | **QALYs gained** | **Costs** | **ICER** |
| Primary HPV with cytology triage | 45 | - | 1 | 129 | €1,515,666 | - |
| Primary HPV with cytology triage | 40 | - | 1 | 152 | €1,908,685 | 17,332 |
| Primary HPV with cytology triage | 40 - 57 | 17 | 2 | 196 | €2,904,752 | 22,669 |
| Primary HPV with cytology triage | 40 - 55 | 15 | 2 | 198 | €2,990,397 | 49,102 |
| **Primary HPV with cytology triage** | **35 - 59** | **12** | **3** | **237** | **€4,931,273** | **49,180** |
| Primary HPV with cytology triage | 35 - 55 | 10 | 3 | 243 | €5,243,447 | 56,753 |
| Primary HPV with cytology triage | 35 - 65 | 10 | 4 | 255 | €6,030,039 | 66,648 |
| Primary HPV with cytology triage | 35 - 75 | 10 | 5 | 259 | €6,543,607 | 131,391 |
| Primary HPV with cytology triage | 35 - 75 | 8 | 6 | 264 | €7,863,497 | 259,251 |
| Primary cytology with HPV triage | 30 - 78 | 6 | 9 | 269 | €13,401,036 | 1,028,756 |

*QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio; HPV = human papillomavirus.*

# 7

# The health impact of HPV vaccination in the situation of primary HPV screening: a mathematical modeling study



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## Abstract

### Background

Human papillomavirus (HPV) vaccination and the implementation of primary HPV screening will lead to a lower cervical disease burden in the Netherlands. For evaluation and further improvement of prevention, it is important to estimate the magnitude and timing of benefits in the first vaccinated cohorts, accounting for vaccination uptake and indirect vaccination effects through reduced HPV transmission.

### Methods

We evaluated the impact of the current girls-only vaccination program and alternative vaccination strategies on cervical disease burden among the first four vaccinated five-year birth cohorts, given the primary HPV screening that will be offered to them. To this end, we linked the existing microsimulation models STDSIM and MISCAN-Cervix. Alternative vaccination strategies include: improved vaccination uptake, including routine vaccination of boys, and offering adult vaccination at sexual health clinics. Outcomes include HPV incidences, the number of diagnosed precancerous lesions, cervical cancer incidence and mortality, and the (incremental) number needed to vaccinate (NNV) to gain 1 life year.

### Results

HPV-16 and HPV-18 incidence reductions achieved under the current vaccination program are estimated to reduce clinically detected cancers and cancer deaths by 35% and screen-detected cancers by almost 40%, compared to no vaccination. The NNV to gain 1 life year is 45. The most efficient strategies are: (1) improving coverage of girls (NNV = 42), and (2) improving coverage among both sexes (incremental NNV = 155). Compared to no vaccination, cervical cancer incidence and mortality are estimated to reduce by 50% when improving coverage among girls, and 60% when improving coverage among both sexes.

### Conclusions

While the current program already substantially reduces cervical cancer incidence and mortality, prevention can be further improved by increasing vaccination uptake and extending vaccination to boys. As not all cervical cancer deaths will be prevented, screening participation should still be encouraged.

## Introduction

Cervical cancer is the fourth most common cancer among women worldwide,[1] with the human papillomavirus (HPV) as its necessary cause. Over the past years, several countries have implemented vaccination against the most oncogenic types HPV-16 and HPV-18. While clinical trials indicated that the currently licensed bivalent, quadrivalent, and nonavalent vaccines are highly effective against HPV-16 and HPV-18 infection,[2-4] coverage levels in most countries remain rather disappointingly low.[5] However, by reducing HPV prevalence in the population, unvaccinated women are (indirectly) protected as well (i.e. herd immunity).[6,7] We recently estimated that HPV-16 and HPV-18 incidence in the Netherlands will substantially decline by about 60% under continuation of the current girls-only vaccination program.[7] Alternative vaccination strategies, such as efforts to increase vaccination coverage among girls, the inclusion of boys, or vaccinating men at sexual health clinics, have also been explored and in some countries even implemented.[8,9] This will further decrease cervical disease burden in the future.

Mathematical models have been used to estimate HPV incidences and the associated cervical disease burden following vaccination, as well as to determine the most cost-effective cervical cancer screening strategy in the post-vaccination era.[8,10-22] To estimate the impact of vaccination for these screening programs, a comprehensive modeling approach that combines a sexual network model for accurately predicting vaccination effects on HPV transmission and a detailed model of cervical disease natural history and screening is crucial. However, most models do not simulate HPV transmission through a sexual network,[10-19] and therefore cannot properly capture herd immunity effects. Also, the existing models did not vary vaccination strategies over time under their most cost-effective strategies, while the vaccination programs might change as a result of the ongoing debates on whether to include boys and adults in addition to girls.[8,20-22]

In 2017, the cervical cancer screening program in the Netherlands will be renewed by offering primary HPV screening instead of cytology to women starting at age 30, and by offering fewer lifetime screens. The costs and effects of this screening program for unvaccinated women were previously estimated with the MISCAN-Cervix model.[23,24] In the current study, we integrated two established and comprehensive microsimulation models of HPV transmission (STDSIM) and cervical cancer development (MISCAN-Cervix), both developed at Erasmus MC. With this new modeling framework, we estimated the cervical disease burden for the first cohorts who have received HPV vaccination under the new cervical cancer screening program, while taking both the direct and indirect effects of HPV vaccination into account. In addition, we determined the change in cervical cancer burden under various foreseeable extensions of the current girls-only vaccination program.

## Methods

*STDSIM model*

STDSIM is an established stochastic microsimulation model of the spread and control of sexually transmitted infections (STIs).[25-27] The model simulates the life course of individuals in a dynamic heterosexual network, in which STIs such as HPV can spread. Each individual has its own characteristics that are either constant (e.g. date of birth and sex) or subject to change (e.g., number of sexual partners, infection status). Events are determined by probability distributions, and can lead to new events (e.g. birth leads to a future event of becoming sexually active) or a cancellation of future events (e.g. death cancels all scheduled events concerning sexual activity or STI transmission). More detailed information on the model can be found in Hontelez *et al.*[26]

We have previously quantified STDSIM to the Netherlands to model the spread of HPV-16 and HPV-18. Briefly, we reproduced the Dutch population and its sexual network, based on demographic and sexual data.[28-30] As sexual data can be difficult to interpret, we simulated the transmission of chlamydia to validate the level of sexual risk behavior.[31] We then introduced HPV-16 and HPV-18 in the population to estimate the transmission probabilities and acquired immunity dynamics necessary to reproduce the age-specific patterns in HPV-16 and HPV-18 prevalence.[32-34] Complete information on the model structure, the parameter quantification, and model validation for the Dutch setting, is described in detail by Matthijsse *et al*.[27]

*MISCAN-Cervix model*

MISCAN-Cervix simulates the individual life histories of a population of women, based on Dutch demographic and hysterectomy data.[28,35] Women can acquire a high-risk HPV infection that either clears naturally or leads to the development of pre-invasive cervical lesions. These lesions regress or develop into invasive cervical cancer. Death can follow from cervical cancer or from other causes. Multiple infections can occur at the same time, which are independent of each other. Interventions such as hysterectomy and screening can affect these life histories. Pre-invasive stages and FIGO (International Federation of Gynecology and Obstetrics) 1A cases can only be detected by screening, since they are assumed to be asymptomatic, whereas FIGO 1B or worse can also be clinically diagnosed.[36]

The model divides cervical disease into seven sequential stages: high-risk HPV infection, three pre-invasive stages (cervical intraepithelial neoplasia (CIN) grade 1, 2, and 3), and three invasive stages (FIGO stages 1A, 1B, and 2 or worse; supplementary Figure S5.2). Age-specific onset parameters set the probability of women to acquire an HPV infection and develop lesions or cancer. In the model, most HPV infections are transient. Lesions in pre-invasive stages can also regress. While CIN 1 and CIN 2 can develop without an HPV infection (in which case they will always regress in our model), CIN 3 and cervical cancer can only develop in the presence of a high-risk HPV infection. More information can be found in De Kok *et al.*,[37] Van Rosmalen *et al.*,[24] and Naber *et al.*[36]

*Integrated modeling framework*

Using STDSIM, we estimated the relative reduction in incidence of HPV-16 and HPV-18 for every vaccination strategy over time and for different cohorts, as compared to no vaccination. To determine the effect of vaccination on cervical precancerous lesions and cancer, we subsequently used these estimates from the STDSIM model as input for the MISCAN-Cervix model.[38]

In previous studies with the MISCAN-Cervix model, the probabilities to acquire an HPV infection and develop a lesion or cancer accounted for all high-risk HPV types.[24,36,37] While we maintained the original overall values of these probabilities for a pre-vaccination cohort, we divided them into separate probabilities for HPV-16, HPV-18, and the other high-risk types, to reproduce the observed attributable proportions of HPV-16 and HPV-18 in high-risk HPV prevalence, lesions and cervical cancer. The observed attributable proportions of HPV-16 in CIN 1, CIN 2, CIN 3, and invasive cervical cancer are 15.4%, 37.6%, 47.2%, and 62.5%, respectively, after correcting for double infections (Supplementary table S7.1).[36,39] For HPV-18, these proportions are 7.8%, 7.4%, 4.7%, 17.2%, respectively. Of the transient high-risk HPV infections, 25.4% is attributable to HPV-16 and 8.2% to HPV-18.[34] In an unvaccinated population, the estimated proportion of HPV-16 and HPV-18 in transient high-risk HPV infections, precancerous lesions, and invasive cervical cancers in MISCAN-Cervix correspond well with the observed proportions, except for an underestimation of CIN 2 attributable to HPV-16 and a slight overestimation in CIN 1 and CIN 3 attributable to HPV-18 (Supplementary table S7.1).

With the integrated modeling framework we simulated a population of 10 million women consisting of four birth cohorts in MISCAN-Cervix with the following birth years: 1993-1997, 1998-2002, 2003-2007, and 2008-2012. These birth cohorts were chosen because they will be the first vaccinated cohorts to enter the national screening program in the Netherlands. The trends in relative reductions in age-specific incidence of HPV-16 and HPV-18 from STDSIM per birth cohort, which incorporates both the direct and indirect effects of vaccination, were then applied to the age-specific onset parameters in the MISCAN-Cervix model (Supplementary figure S7.1). We used the HPV reductions per birth cohorts as the indirect effects of vaccination are larger for younger than for older cohorts through reduced HPV transmission. We assumed that the incidence reduction per cohort for women aged 65+ is the same as for women aged 50-64 years.

*Vaccination strategies*

We used largely the same assumptions to model the impact of HPV vaccination as in our previous studies.[7,9] Briefly, we modeled the current vaccination strategy and observed vaccination uptake in the Netherlands: i.e. a catch-up campaign for girls aged 13-16 years in 2009 (coverage of 50%), and annual vaccination of girls aged 12 years (coverage of 60%). Vaccine efficacy is set at 94.7% for HPV-16 and at 92.3% for HPV-18.[3,40] We assumed vaccine efficacy to be independent of HPV status

at the time of vaccination, as vaccination still has a substantial protective effect in women previously exposed to HPV-16 and HPV-18.[41,42] Infection clearance is not accelerated by the vaccine in our model.

The alternative vaccination strategies represent foreseeable changes of the current girls-only program in various ways from 2017 onwards. First, we increased routine vaccination coverage among girls up to 80% and 100%, as the familiarity of the vaccine has increased and more girls might be inclined to get vaccinated in the future. Second, since some countries offer gender-neutral vaccination,[7] we included routine vaccination for boys, assuming the same target age groups and uptake as for girls (i.e. 60%, 80%, and 100% coverage). However, as bivalent vaccine efficacy estimates for boys are unavailable, efficacy for boys was assumed to be equal to the quadrivalent vaccine efficacy for boys (78.7% for HPV-16; 96.0% for HPV-18).[43] Finally, we included adult vaccination at sexual health clinics for women and for both men and women aged 15-29 years, because our previous study showed that these strategies would be highly efficient to further improve HPV incidence reductions.[9,28,44] For the adult vaccination strategies, we assumed an efficacy of 77.4% against both HPV-types for women older than 24 years.[42] For men older than 24 years, vaccine efficacy was assumed to be 64.5% for HPV-16 and 80.6% for HPV-18.[9,42] In the last strategy, where the vaccine is offered to both sexes during STI consultations, routine vaccination for boys is included as well.

*Cervical cancer screening*

We subsequently simulated the new cervical cancer screening program, in which primary HPV screening with reflex cytology and cytology triage after 6 months will be offered to women aged 30, 35, 40, 50, and 60 years. Additional HPV testing will be offered at age 45 and 55 for women who either have a positive HPV test or do not attend screening at ages 40 and 50, respectively. Women who attended screening at age 60 and tested positive for HPV will also be invited at age 65. We assumed that 10% of the population never attends screening and has a higher background risk than the 90% potential attenders.[24] Attendance among the potentially attending women for primary testing and compliance with colposcopy referrals and triage testing is based on the current screening program (see also Supplementary table S7.2), and is independent of vaccination status in our model.[45] In the new screening program, a self-sampling kit is offered to women who do not attend screening at the general practitioner. Gök *et al.* estimated that the effect of mailing self-sampling kits to all non-attendees of the Dutch cervical cancer screening program would generate an extra 5.2% attendance.[46] Since the self-sampling kit will be offered using opt-in (instead of opt-out as in the PROHTECT trial), we assumed that 3% of the non-attenders would opt-in for the self-sampling kit.[47]

We used the same specificity and sensitivity of cytology for detecting precancerous lesions and invasive cancer for testing at least atypical squamous cells of undetermined significance (ASC-US) as in our previous study, i.e. a sensitivity of 40% for CIN 1, 50% or CIN 2, and 75% for CIN 3

and cervical cancer, and a specificity of 98%.[36,48] For the HPV test, we assumed a 94% sensitivity for detecting high-risk HPV infections, regardless of whether a CIN lesion or cancer was also present (although a woman with cancer is always infected with HPV).[24,27] In our model, CIN treatment leads to full recovery. Subsequently, women can acquire new HPV infections and develop CIN lesions and/or invasive cancer. For invasive cancer, survival probabilities depend on the woman's age and cancer stage (FIGO 1B or FIGO 2+) at diagnosis, based on data from the Dutch Cancer Registry.[49] After receiving treatment for cancer, women are no longer at risk for HPV or cervical disease. The survival probabilities by age and stage can be found in Table S5.5B in the appendices of Chapter 5.

*Model outcomes*

STDSIM provides us with the estimated age-specific HPV-16 and HPV-18 incidence and vaccinated individuals over time. MISCAN-Cervix determines the most severe state of each woman (i.e. from least to most severe: normal, HPV infected, CIN 1, CIN 2, CIN 3, FIGO 1A, FIGO 1B, and FIGO 2+) and the number of life years spent in each state (see also supplements S5.2 of this thesis). For the current study, the main outcomes are the relative reductions in HPV-16 and HPV-18 incidence over time, and the numbers of diagnosed CIN 1, CIN 2, CIN 3 and cervical cancer, and cancer-related deaths. We also estimated the (incremental) number needed to vaccinate (NNV) to gain one life year, in order to determine the most efficient vaccination strategies.

*Sensitivity analyses*

Huijsmans *et al.*[50] recently showed that HPV prevalence in screening eligible women in the Netherlands could be twice as high compared to the earlier data our model fit was based upon.[32] Therefore, we re-analyzed the impact of the current vaccination program in the models with doubled HPV prevalence prior to the implementation of vaccination in the sensitivity analyses. The overall prevalence among women was doubled by increasing sexual risk behavior in STDSIM as well as by doubling the onsets of transient infections in MISCAN. Also, we varied the attendance of the screening program by assuming a 20% higher and lower attendance (Supplementary table S7.1), as we cannot be sure that screening attendance of the new program will be the same as of the current program.

**Results**

Figure 7.1 shows the estimated relative reductions in the incidence of HPV-16, HPV-18, cervical cancer, and diagnosed CIN per birth cohort under the current vaccination program compared to no vaccination. For all cohorts, the relative incidence reductions were larger for HPV-16 than HPV-18 infections. The younger the birth cohort, the larger the health impact of HPV vaccination. The larger reductions in HPV incidence and corresponding age patterns for younger cohorts are attributable to

higher levels of herd immunity, as HPV transmission reduces over time. Also, almost all girls in cohort 1 have been offered HPV vaccination by means of the catch-up campaign given their age, which had a lower coverage rate than the annual vaccination of 12-year-old girls (i.e. 50% compared to 60%). Cohort 1 therefore has relatively fewer vaccinated girls than the younger cohorts, as the younger cohorts all received vaccination according to the annual vaccination of 12-year-old girls. While for the younger cohorts a trend by age is visible (ranging from over 50% in cervical cancer incidence for women younger than 25 years to almost 40% for women aged 65+), the reductions for the oldest cohort (cohort 1) are quite stable over all ages (between 22% and 25% reduction over all ages). A slight increase in the reduction of CIN lesions is visible at the last screening age. As the percentage of CIN attributable to HPV-16 and HPV-18 slightly increase with age in the model, the impact of the vaccine on CIN is larger at these ages.

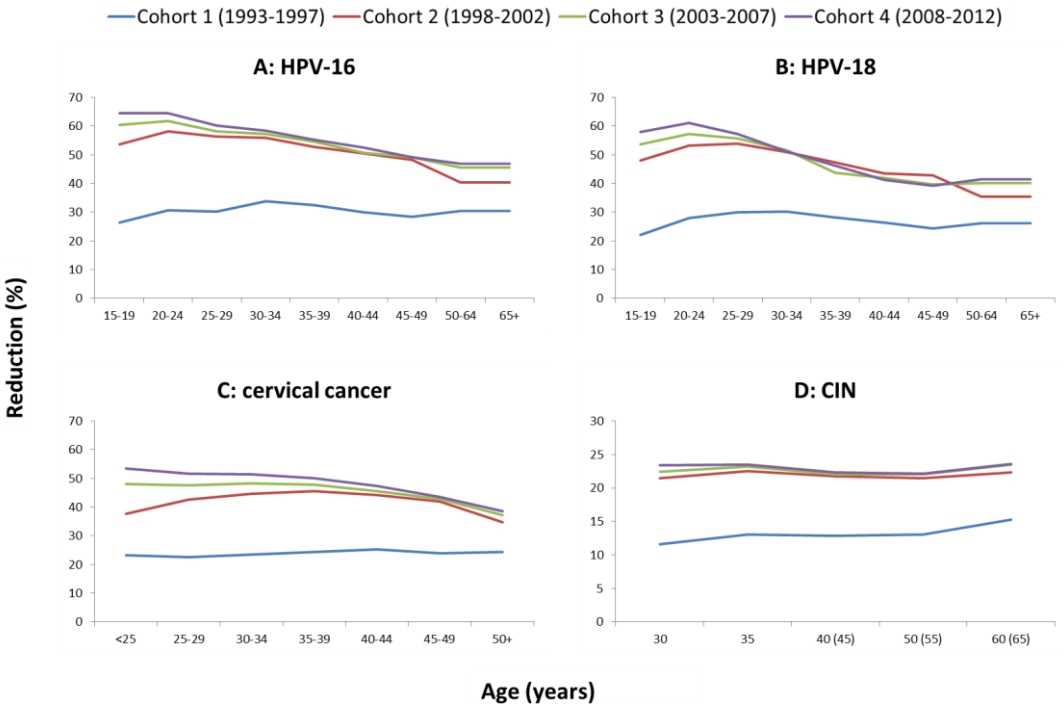


**Figure 7.1. Relative reductions by age group in the incidence of HPV-16 (A), HPV-18 (B), cervical cancer (C), and CIN (D) for the first four successive 5-year birth cohorts (vaccinated and unvaccinated women) that underwent the current girls-only vaccination program, compared to no vaccination.** Cohort 1 is born between 1993-1997; cohort 2 between 1998-2002; cohort 3 between 2003-2007; and cohort 4 between 2008-2012. The ages in parentheses on the x-axis of Figure 1D depict the additional screen ages 45 and 55 if women did not attend screening or tested HPV positive at ages 40 and 50, respectively, and at age 65 if women attended and tested positive at age 60.

Our models predict that the HPV-16 and HPV-18 incidence reductions will lead to a 35% lifetime reduction in clinically detected cancers and cervical cancer deaths, and almost 40% in screen-detected cancers, compared to no vaccination (Table 7.1). Somewhat larger health gains are accomplished when coverage of HPV vaccination among girls increases to 80% and 100%, i.e. 43% reduction in cervical cancer cases and cancer deaths under 80% coverage, and over 50% reduction in cancer cases and deaths under full coverage. However, even when vaccine uptake among girls can be increased from 60% to 80%, the health gains are still lower as compared to expanding the target group to males. Including males by offering adult vaccination at STI clinics for both sexes (which also incorporates routine boys vaccination) and solely including routine boys vaccination with current uptake levels are predicted to reduce the number of cervical cancer deaths by 49% and 45%, respectively, as compared to 43% when coverage among girls is increased to 80%. Including boys with increased uptake of 80% for both sexes leads to larger reductions in cervical cancer cases (54%) and deaths (56%) than full coverage among girls (51% and 52%, respectively). As expected, the largest health gains are accomplished when full coverage can be achieved for routine girls and boys vaccination, with reductions of 61% and 64% in cancer cases and deaths, respectively.

Under the current vaccination program, vaccinating 45 girls (NNV = 51,070/1,134) will save one life year by preventing cervical cancer death, when compared to no vaccination (Figure 7.2). Most efficient strategies are: achieving full coverage among girls (NNV = 42); and achieving full coverage of routine vaccination for both sexes (incremental NNV = 155). Less efficient are routine vaccination for both sexes with 60% and 80% coverage, and vaccination during STI consultations for both sexes. When the strategies with full coverage are excluded from the analyses, improving coverage to 80% in girls and both sexes become the most efficient strategies.

The sensitivity analyses in Table 7.2 show that, while the absolute disease burdens with and without vaccination differ, the relative health impact of the current vaccination program is nearly similar under alternative levels of cervical cancer screening attendance and with a higher baseline HPV prevalence. The largest difference in health impact between the base case and sensitivity analyses was found when we assumed a higher baseline HPV prevalence, and there was only a 3 percentage points difference in the relative reduction in cervical cancer deaths and life years lost.

**Table 7.1. Health impact of the current girls-only vaccination program and alternative vaccination strategies on cervical disease per 100,000 women.** The relative lifetime change as compared to no vaccination are shown between parentheses. In the alternative vaccination strategies, boys, and adult women and men are included in the vaccination strategies in addition to girls. Vaccination at STI consultations for adult males and females also includes routine vaccination for boys.

| Strategy | False-positive referrals | CIN 1 | CIN 2 | CIN 3 | Clinically detected cases | Screen-detected cancers | Cervical cancer deaths | Life years lost |
|---|---|---|---|---|---|---|---|---|
| No vaccination | 543 | 2,473 | 1,655 | 2,413 | 444 | 136 | 193 | 3,089 |
| Current program (60% cov.) | 458 (-16%) | 2,121 (-14%) | 1,361 (-18%) | 1,778 (-26%) | 289 (-35%) | 83 (-39%) | 126 (-34%) | 1,979 (-36%) |
| *Improved coverage among girls* | | | | | | | | |
| Girls (80% cov.) | 448 (-17%) | 2,061 (-17%) | 1,318 (-20%) | 1,696 (-30%) | 256 (-42%) | 76 (-44%) | 110 (-43%) | 1,772 (-43%) |
| Girls (100% cov.) | 431 (-21%) | 2,006 (-19%) | 1,276 (-23%) | 1,619 (-33%) | 215 (-52%) | 70 (-49%) | 92 (-52%) | 1,555 (-50%) |
| *Inclusion of also boys and adults* | | | | | | | | |
| Boys (60% cov.) | 443 (-18%) | 2,037 (-18%) | 1,310 (-21%) | 1,682 (-30%) | 246 (-45%) | 74 (-46%) | 105 (-45%) | 1,715 (-44%) |
| Boys (80% cov.) | 430 (-21%) | 1,976 (-20%) | 1,258 (-24%) | 1,596 (-34%) | 201 (-55%) | 67 (-51%) | 85 (-56%) | 1,469 (-52%) |
| Boys (100% cov.) | 416 (-23%) | 1,922 (-22%) | 1,222 (-26%) | 1,526 (-37%) | 168 (-62%) | 60 (-56%) | 70 (-64%) | 1,285 (-58%) |
| STI consultations (F) | 454 (-16%) | 2,093 (-15%) | 1,336 (-19%) | 1,732 (-28%) | 274 (-38%) | 80 (-42%) | 119 (-38%) | 1,885 (-39%) |
| STI consultations (F+M) | 438 (-19%) | 2,004 (-19%) | 1,286 (-22%) | 1,631 (-32%) | 231 (-48%) | 70 (-49%) | 98 (-49%) | 1,621 (-48%) |

*CIN = cervical intraepithelial neoplasia; cov. = coverage; STI = sexually transmitted infections; F = females; M = males*

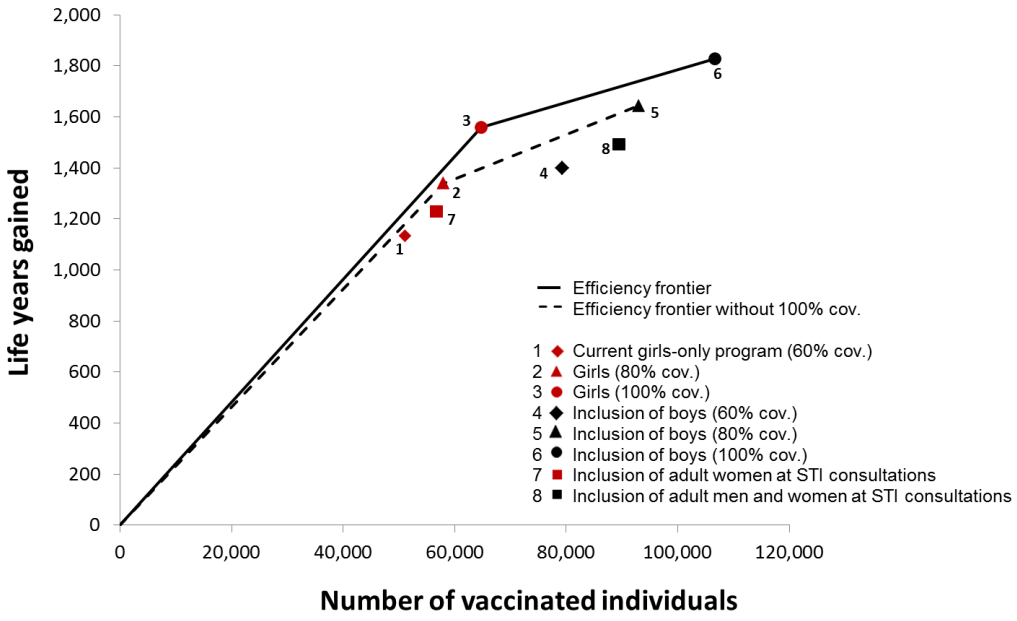


**Figure 7.2. Estimated number of life years gained and corresponding number of vaccinated individuals for the current vaccination program and alternative strategies as compared to no vaccination program.** The current vaccination program has been implemented in 2009. The alternative vaccination strategies commence from 2017 onward, in addition to the current program. Numbers are scaled to a population of 100,000 women in 2017.

*Cov. = coverage; STI = sexually transmitted infection.*

**Table 7.2. Health impact of the current girls-only vaccination program under alternative levels of cervical cancer screening attendance and with doubled baseline HPV prevalence.** Results are shown per 100,000 women. The relative change as compared to no vaccination are shown between parentheses. Alternative levels of attendance include either 20% higher or lower than the observed attendance in the current screening program.

| | False-positive referrals | CIN 1 | CIN 2 | CIN 3 | Clinically detected cases | Screen-detected cancers | Cervical cancer deaths | Life years lost |
|---|---|---|---|---|---|---|---|---|
| *Base case* | | | | | | | | |
| No vaccination | 543 | 2,473 | 1,655 | 2,413 | 444 | 136 | 193 | 3,089 |
| Current program | 458 (-16%) | 2,121 (-14%) | 1,361 (-18%) | 1778 (-26%) | 289 (-35%) | 83 (-39%) | 126 (-34%) | 1,979 (-36%) |
| *Higher attendance* | | | | | | | | |
| No vaccination | 637 | 2,836 | 1,896 | 2,647 | 389 | 121 | 174 | 2,542 |
| Current program | 531 (-17%) | 2,438 (-14%) | 1,556 (-18%) | 1,961 (-26%) | 256 (-34%) | 72 (-40%) | 115 (-34%) | 1,619 (-36%) |
| *Lower attendance* | | | | | | | | |
| No vaccination | 451 | 2,059 | 1,371 | 2,097 | 566 | 144 | 240 | 4,222 |
| Current program | 379 (-16%) | 1,765 (-14%) | 1,129 (-18%) | 1,536 (-27%) | 362 (-36%) | 88 (-39%) | 156 (-35%) | 2,666 (-37%) |
| *Higher baseline HPV prevalence* | | | | | | | | |
| No vaccination | 950 | 2,528 | 1,679 | 2,423 | 446 | 137 | 195 | 3,185 |
| Current program | 808 (-15%) | 2,172 (-14%) | 1,375 (-18%) | 1,786 (-26%) | 285 (-36%) | 82 (-40%) | 123 (-37%) | 1,950 (-39%) |

*CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; vacc. = vaccination*

**Discussion**

Using a comprehensive modeling framework, linking the established STDSIM and MISCAN-Cervix models, we have estimated the health impact of the current girls-only vaccination program and various alternative vaccination strategies under the new cervical cancer screening program in the Netherlands. HPV-16 and HPV-18 incidence reductions achieved under the current girls-only vaccination are predicted to lead to substantial reductions in cervical disease burden, with an estimated reduction of 35% in clinically detected cancers and cervical cancer deaths, and almost 40% in screen-detected cancers, compared to no vaccination. The NNV of the current girls-only program is 45. Largest health gains will be accomplished when full coverage can be achieved for routine vaccination of both girls and boys. For this strategy, the incremental NNV to gain one life year is 155, compared to the most efficient strategy of full coverage among girls (NNV = 42).

The larger reductions in HPV incidence and corresponding age patterns for younger cohorts are attributable to higher levels of herd immunity. This was also demonstrated in the study of Bogaards *et al.*, in which they concluded that the reduction of hazard in unvaccinated women increases with birth cohort year.[51] For even younger cohorts than the ones included in our study, the HPV incidence reductions will be more substantial than in the youngest simulated birth cohort, and will therefore have more health gains due to vaccination.

We have estimated the reduction in cervical cancer due to HPV vaccination before, but in a crude way.[7] In the current study, the estimated reduction in (screen- and clinically detected) cancers is smaller than the incidence reduction we found in our earlier study under the current vaccination program (36% versus 48%, respectively). Three distinctions between the studies are important to consider when interpreting this difference. First, in the previous study we used a relatively simple calculation for the reduction in cancers instead of a detailed microsimulation model. Second, primary screening methods differ between both studies. While the previous study uses incidence data from a population with primary cytology screening, we simulated here the new program with primary HPV screening, which is expected to prevent more cervical cancer cases itself.[23] Third, in the previous study, we used the incidence reduction when a steady state is achieved (approximately 70 years following the introduction of HPV vaccination), while here we estimated the lifetime health impact of the four earliest vaccinated cohorts. As the impact of HPV vaccination on HPV incidence has not reached its full potential prior to the steady state, the cancer incidence reductions are smaller than for younger, i.e. steady state, birth cohorts.

Including also routine vaccination for boys with 80% coverage was predicted to prevent more deaths than reaching full coverage among girls (56% reduction versus 53%). However, including boys appears less efficient when looking at Figure 7.2, due to the larger increase in vaccinations needed. We appreciate that full coverage of the vaccination program, either for only girls or both sexes, might be unrealistic. We therefore also explored the efficiency of the vaccination strategies when excluding the scenarios of full coverage (Figure 7.2). In that situation the most efficient strategies include

increasing coverage to 80% for girls (NNV = 43) and for both sexes (incremental NNV = 115). These results indicate that including boys is an efficient strategy to further improve cervical disease prevention, and that the higher the uptake, the more efficient this strategy will be.

Even though the models are quantified to data from the Netherlands, these results are generalizable to developed settings with a higher prevalence of HPV or cervical disease. While a higher prevalence of HPV-related cervical disease would lead to a higher absolute number of referrals and treatments, the relative reductions due to vaccination will not change substantially, as long as the proportion of cervical disease attributable to HPV-16 and -18 remains the same. This is supported by the sensitivity analysis with the higher HPV baseline prevalence (by increasing the prevalence of transient infections), in which indeed absolute numbers differ from those in the base case analysis, yet the relative reductions due to vaccination are similar.

Our study has four limitations that are noteworthy. First, in our model, we underestimated the proportion of CIN 2 attributable to HPV-16, and slightly overestimated the proportion of CIN 1 and CIN 3 attributable to HPV-18, compared to the observed proportions.[39] These discrepancies are small though, and less relevant than the associated cancer cases and deaths, which were estimated well. Also, they apply to all strategies, so that the comparative effects of different scenarios are still of value. Second, it is still uncertain if the attendance rate of the screening program will be influenced by the switch to primary HPV screening and the opt-in procedure of the self-sampling kit. However, our sensitivity analyses showed that alternative attendance rates do not influence the health impact estimates substantially. Third, our estimates of the health impact are conservative, as we did not take cross-protection of the bivalent vaccine or additional protective effects of the nonavalent vaccine into account. Finally, we calculated the health impact of vaccination under the screening program that will be implemented from 2017 onwards. As the cost-effectiveness of this program before implementation was determined in unvaccinated women,[23] it could very well be the case that a less intensive screening program is more cost-effective for a partly vaccinated population, and this would lead to different health impact estimates.

We conclude that, already for the first vaccinated birth cohorts, the current vaccination program will lead to substantial reductions in cervical cancer incidence and mortality in the Netherlands. Efficient strategies to further improve health gains are to increase vaccination uptake among girls, or to extend the target group to routine boys vaccination with increased vaccination uptake. As vaccination will not prevent all cervical cancer deaths, screening does not become obsolete and participation should continue to be encouraged in the post-vaccination era.

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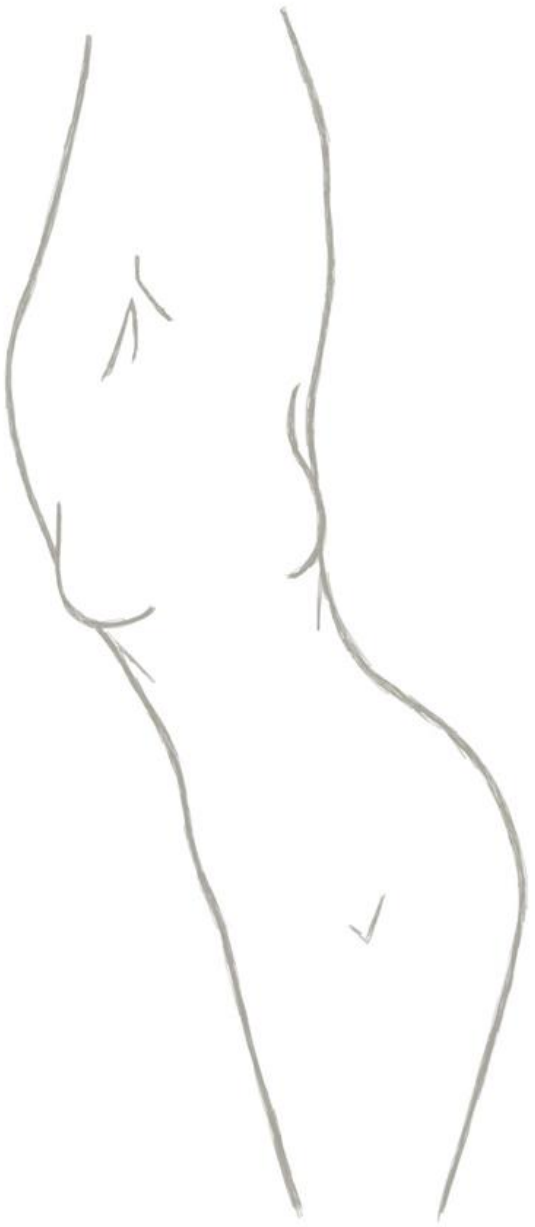
# 7

## Supplements



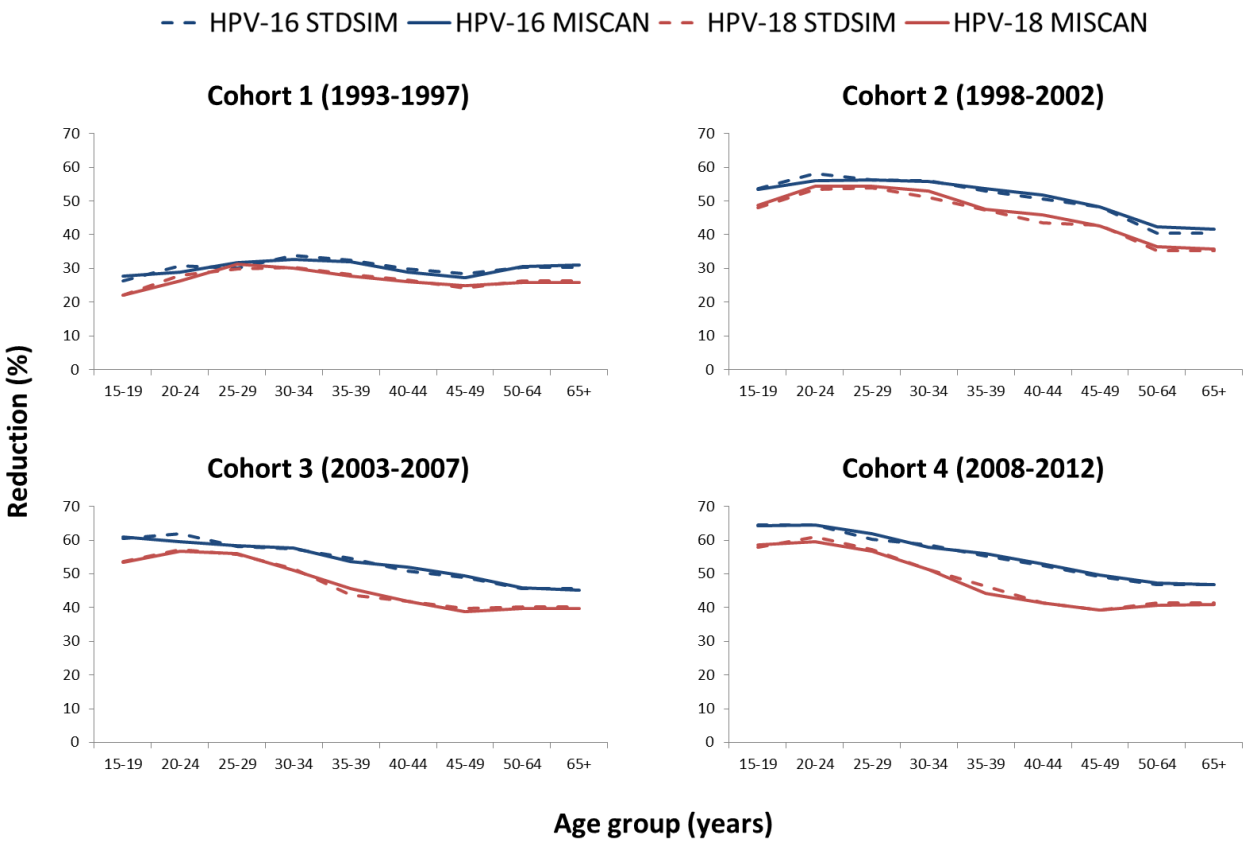
**Supplementary table S7.1. The observed and estimated proportions of HPV-16 and HPV-18 in HPV infections without cytological abnormalities, and in CIN 1, CIN 2, CIN 3, and invasive cervical cancer in the population prior to vaccination in MISCAN-Cervix.** The observed proportions are based on the studies of Coupé *et al.,* who reported age-specific HPV prevalence in women aged 18-65 years, and Guan *et al.* who determined the distribution of HPV types in CIN and cervical cancer (large meta-analysis of studies with different age ranges).[34,39]

| | | HPV infections without cytological abnormalities | CIN 1 | CIN 2 | CIN 3 | Cervical cancer |
|---|---|---|---|---|---|---|
| HPV-16 | Observed proportion | 25.4% | 15.4% | 37.6% | 47.2% | 62.5% |
| | Estimated proportion | 25.5% | 16.5% | 28.1% | 46.5% | 62.7% |
| HPV-18 | Observed proportion | 8.2% | 7.8% | 7.4% | 4.7% | 17.2% |
| | Estimated proportion | 8.3% | 9.3% | 6.9% | 7.0% | 17.5% |

*HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia.*

**Supplementary table S7.2. Attendance in the cervical cancer screening program and self-sampling kit in the base case and sensitivity analyses, based on the observed screening attendance in 2013.[45]** In the model, we assumed that 10% of women never attend screening at the general practitioner, and 90% are potential attenders.[24] Of the non-attending women, 3% opt-in to receive a self-sampling kit.

| Age (years) | Base case | | Higher attendance | | Lower attendance | |
|---|---|---|---|---|---|---|
| | Attendance office-based HPV test | Self-sampling HPV test | Attendance office-based HPV test | Self-sampling HPV test | Attendance office-based HPV test | Self-sampling HPV test |
| 30 | 58.9% | 7.3% | 70.7% | 10.2% | 47.1% | 5.7% |
| 35 | 64.4% | 8.4% | 77.3% | 13.2% | 51.6% | 6.2% |
| 40 | 71.1% | 10.4% | 85.3% | 20.5% | 56.9% | 7.0% |
| 45 | 75.6% | 12.3% | 90.7% | 32.1% | 60.4% | 7.6% |
| 50 | 77.8% | 13.5% | 93.3% | 45.0% | 62.2% | 7.9% |
| 55 | 76.7% | 12.9% | 92.0% | 37.5% | 61.3% | 7.8% |
| 60 | 75.6% | 12.3% | 90.7% | 32.1% | 60.4% | 7.6% |
| 65 | 75.6% | 12.3% | 90.7% | 32.1% | 60.4% | 7.6% |




**Supplementary figure S7.1. Relative reductions in HPV-16 and HPV-18 incidence for the first four successive 5-year birth cohorts (vaccinated and unvaccinated women) that underwent the current girls-only vaccination program estimated by STDSIM, applied to the progressive pathway (infections leading to invasive cancer) in MISCAN-Cervix.** Cohort 1 is born between 1993-1997; cohort 2 between 1998-2002; cohort 3 between 2003-2007; and cohort 4 between 2008-2012.

# 8

# General discussion

The aim of this thesis was to study the transmission dynamics of HPV-16 and HPV-18 in the Netherlands, and to estimate the impact of vaccination on the HPV-16 and HPV-18 epidemic, and cervical disease burden after the renewal of the cervical cancer screening program. The research questions stated in **Chapter 1** will now be answered, based on the results described in this thesis, as well as other recent scientific insights. In addition, exploratory analyses on HPV transmission dynamics in a low income setting with high HIV prevalence are presented. Finally, conclusions and recommendations are formulated.

## 8.1 Answering the research questions

**What is the role of naturally acquired immunity following an infection in HPV transmission?**
*Acquired immunity presumably plays a major role in HPV epidemiology, with a larger natural immune response towards HPV-18 compared to HPV-16.*

In **Chapter 2,** we concluded that it is necessary to assume that natural immunity is acquired after clearing an infection in order to reproduce the observed HPV-16 and HPV-18 prevalence in the Netherlands. In the model, we explored two mechanisms of naturally acquired immunity: 1) full immunity for a certain duration; and 2) susceptibility to re-infection is decreased with a proportion that accumulates after clearing a new infection. The estimated duration of full immunity shows large heterogeneity between individuals. We estimated that after clearing an HPV-16 infection, half of the people are immune for a period of less than 1 year, while as many as 20% have an immunity exceeding 30 years. Interestingly, more than half of the people are estimated to stay immune for more than 30 years after clearing an HPV-18 infection. When considering the second immunity mechanism, our results suggest that women need to clear about two subsequent HPV-16 infections in order to arrive at a similar level of acquired immunity that results from clearing one HPV-18 infection. As the estimated transmission probabilities per sexual contact are similar for HPV-16 and HPV-18, it is likely that the lower population prevalence of HPV-18 compared to HPV-16 is explained by a relatively larger natural immune response towards HPV-18.

Our-model derived conclusion of large individual heterogeneity is consistent with Mikolajczyk *et al.*, who concluded that the observed distribution of antibody titers reflects large individual differences in immune response.[1] For those developing naturally occurring antibodies, the amount of protection may be lower for HPV-16 than HPV-18.[2] The observed association between re-infections and sexual activity, likely due to rapidly waning immunity,[3] also supports our findings that some people only develop immunity for a short period of time.

In order to derive at these estimates, we assumed that the duration of immunity is randomly drawn from a Weibull distribution. This duration might be dependent on individual characteristics,

such as age or history of HPV infections, and could therefore actually be a combination of the two mechanisms we explored in Chapter 2, i.e. full immunity for a certain duration that extends after each new infection. A longitudinal study, ideally with HPV discordant couples, that measures whether the level of natural antibodies increases after multiple infections could provide more insight into the immunity mechanisms of HPV.

New data recently showed that the HPV prevalence in the Netherlands might be twice as high as previously thought based on the POBASCAM study.[4-6] To reproduce a higher overall HPV prevalence, while assuming the same shape parameter of the Weibull distribution, the average duration of immunity would need to decrease from 112 years to 18 years for HPV-16, and from 43 years to 10 years for HPV-18. This corresponds to 65% of people developing acquired immunity for less than 1 year after clearing an HPV-16 infection, and 8% for more than 30 years. For HPV-18, these proportions are 9% and 6%, respectively. However, it could also be that the higher prevalence is caused by a higher transmission probability per sexual contact, or simply a higher tendency to practice sexual risk behavior than currently assumed in the model. Further research should explore the impact of these parameters on the estimated HPV prevalence.

In the model, we assumed that both HPV-types act independently. In other words, individuals can still acquire an infection of HPV-16 or HPV-18 while being immune for the other type at the same time. However, trials show that the bivalent and quadrivalent vaccines also have a protective effect against high-risk types other than HPV-16 and HPV-18 (i.e. cross-protection), in particular against HPV-31, HPV-45, HPV-33.[7] This suggests, on the one hand, that naturally acquired immunity for one type may also convey protection against other types, which would mean that the proportion of people developing long-term naturally acquired immunity in our model could be overestimated. On the other hand, vaccine cross-protection seems to wane over time,[7] suggesting that if cross-protection of naturally acquired immunity really occurs, it probably does not have a large impact on HPV epidemiology.

**What is the impact of vaccination on HPV epidemiology in the Netherlands?**

*HPV vaccination under the current program guidelines leads to substantial reductions in HPV incidence. Significant incremental benefits can be achieved by also including boys and adults.*

In **Chapter 3**, we showed that girls-only vaccination is expected to reduce HPV-16 and HPV-18 incidence by 64-75% and 58-73%, respectively. We also explored alternative vaccination strategies, i.e. increased coverage among girls, and including routine vaccination of boys in addition to girls. According to our model, coverage among girls needs to exceed 80% to outweigh the inclusion of boys with 60% coverage. The estimated vaccination effectiveness varies under different assumptions on naturally acquired immunity, yet these differences do not have an effect on policy decisions to further

reduce HPV incidence. In **Chapter 4**, we found that expanding routine vaccination to adult women has a modest impact compared to girls-only vaccination, with an incremental reduction of about 20% for HPV-16 and HPV-18 incidence. Including also male vaccination leads to larger reductions in HPV incidence. Especially offering vaccination to women at their first cervical cancer screening visit and to both men (including routine vaccination of boys) and women at STI clinics is expected to lead to substantial incremental incidence reductions, i.e. 63% for HPV-16 and 84% for HPV-18, compared to the current girls-only vaccination program. Even with modest adult vaccination uptake and low vaccine efficacy, reductions in HPV incidence are larger and achieved quicker than the reductions under the current vaccination program.

These extensions of the current vaccination program to boys and adults are not only efficient, but likely they are cost-effective as well, especially when considering the reduction in other HPV-related cancers in both men and women, lower doses recommendation, and the expected further reduced vaccine prices in the nearby future. Also, the use of existing public health facilities would limit the need for large up-front investments, and might encourage vaccine acceptability due to the familiarity of the settings.

Prior to any policy changes in the current vaccination program, efforts could be made to improve coverage in girls. One of the important determinants in the decision to vaccinate against HPV is the risk of (presumed serious) side effects.[8,9] Also, some of the parents felt inadequately informed and reported to lack sufficient information about HPV before the introduction of HPV vaccination in the Netherlands.[10] They felt insecure about the safety and effectiveness of the vaccine, and had an ambivalent attitude towards HPV vaccination. These factors likely made parents more susceptible towards negative and often unfounded claims. The National Institute for Public Health and the Environment (RIVM) points towards online myths concerning the vaccine as one of the causes of the low coverage at the start of HPV vaccination.[11] RIVM, as well as European Medicines Agency (EMA) and Centers for Disease Control (CDC) all consider the HPV vaccines safe based on the outcomes of clinical trials and evaluations in several countries that have implemented HPV vaccination programs. In the trials, vaccine-related serious adverse events occurred in about 0.1% of women in both the control and intervention group of the bivalent vaccine (6 and 11 out of 9300 women, respectively), and in only 0.03% of women for the quadrivalent and nonavalent vaccines (2 out of 7000 women).[12,13] None of the reported deaths during the trials were related to the vaccines. In the Netherlands, the reporting rate of long-lasting (two months or more) adverse events following immunization with the bivalent vaccine has been constant at around 5 per 10,000 vaccinated girls.[14] The most frequently reported event was fatigue. However, before the implementation of HPV vaccination, chronic fatigue and other chronic complaints were already well known symptoms in adolescents, and a causal relation could not be established. Furthermore, a recent Dutch report mentions that the use of aluminum in the placebo of the trials might have diluted the relative difference in side-effects between the intervention and placebo group, as aluminum can cause side-

effects as well.[15] The report emphasizes that, while severe side-effects have not been demonstrated in the clinical trials and post marketing studies, they cannot be ruled out yet for the long term.[14,15] Continuous close monitoring of vaccinated girls for potential side-effects later in life remains therefore essential. Transparency and clear communication about the outcomes of this monitoring and on the health benefits of HPV vaccination will be crucial in influencing coverage rates among girls.

Another development besides the implementation of HPV vaccination is the renewal of the cervical cancer screening program from 2017. Primary HPV screening with reflex cytology and cytology triage after 6 months will be offered to women aged 30, 35, 40, 50, and 60. Additional HPV testing is offered at age 45 and 55 for women who had a positive HPV test or did not attend screening at ages 40 and 50, respectively. Furthermore, women who test positive at age 60 will be additionally invited at age 65. Also, a self-sampling kit is offered to women who do not attend screening at the general practitioner.

As the switch from cytology to primary HPV screening will take place before the first vaccinated women will enter the screening program, we assessed the potential harms of primary HPV screening for women who are over-screened (i.e. from a younger age and with a shorter time interval than recommended) while considering only unvaccinated cohorts. **Chapter 5** shows that while deaths will be prevented, the harms due to the lower test specificity of HPV screening compared to cytology can be quite substantial if a large part of the population is over-screened. For women who are screened annually, the increase in positive tests and subsequent follow-up procedures even results in a net loss in health, due to losses in quality of life associated with screening and treatment. Over-screening should therefore be minimized after the implementation of primary HPV screening, by emphasizing adherence to screening guidelines, and monitoring closely. In populations with relatively small numbers of over-screened women, i.e. with little opportunistic screening such as in the Netherlands, switching to HPV screening may very well be cost-effective.[16]

**What is the impact of HPV vaccination on cervical disease burden and its control in the Netherlands?**

*Cervical cancer incidence and mortality are estimated to reduce substantially when the first (partly) vaccinated women will reach the starting age for screening. However, even perfect coverage of vaccination will not make screening obsolete, though a less intensive screening program may become more cost-effective.*

We show that primary HPV screening with 8 lifetime screens starting at age 30 was most cost-effective for a pre-vaccination cohort (**Chapter 6**). For a vaccinated cohort, the optimal screening

strategy consisted of 3 life-time screens starting at age 35. Assuming a willingness-to-pay threshold of €50,000 per QALY gained, unvaccinated women can be screened according to less intensive strategies optimized for vaccinated women from a herd immunity level of 50%. In (partly) vaccinated women to whom the new screening program will be offered, vaccination is estimated to reduce cervical cancer incidence and mortality by about 35%, compared to no vaccination (**Chapter 7**). Efficient strategies to improve cervical cancer control are to increase vaccination coverage among girls to at least 80%, and to include routine vaccination of boys if a coverage of at least 80% can be achieved. If full coverage can be achieved among girls and boys, cervical cancer incidence and mortality is predicted to decrease by over 60%. Even complete vaccination coverage cannot avert all cervical cancer cases and deaths, and screening participation should therefore still be encouraged.

The new screening program of 2017, with extended screening intervals from age 40, was based on cost-effectiveness calculations with unvaccinated women. As shown in Chapter 6, the reduced risk in vaccinated women may warrant fewer life-time screens compared to unvaccinated women, indicating that a less intensive screening schedule as the one commencing in 2017 may be more cost-effective in a partly vaccinated population. Therefore, the new screening program should be reassessed when vaccinated girls reach the starting age of screening. This reassessment could point towards two ways of modifying the screening program: (1) a likely less intensive uniform screening schedule (i.e. later starting age and/or longer screening intervals); or (2) tailored screening based on vaccination status, in which vaccinated women will have fewer lifetime screens than unvaccinated women. There are ethical and practical issues to consider with the latter strategy though. As vaccinated women are likely more inclined to participate in screening than unvaccinated women,[17] they might consider it unsafe and unfair to be screened less frequently compared to unvaccinated women. Also, an integrative vaccine registration and screening invitational system needs to be set in place, which may be costly. Future health economic analyses should determine whether tailored screening or the use of a uniform screening program is more cost-effective, and how exactly the program should be designed regarding starting age and screening interval.

In conclusion, uniform primary HPV screening fewer lifetime screens is likely cost-effective for unvaccinated women from a herd immunity level of 50%. Cervical cancer incidence and mortality are estimated to substantially reduce when the first birth cohorts to whom vaccination was offered are invited for the new cervical cancer screening program. For these women, prevention can be even further improved by increasing vaccination uptake and by extending the target group to boys. It is crucial to note that even perfect coverage of the vaccine will not make screening obsolete, and reassessment of the screening program may become necessary.

### 8.2 The association between HPV and HIV

Cervical cancer and genital warts are not the only consequences of HPV. Over the past years, several studies indicated that HPV infection doubles the risk of HIV acquisition, even after controlling for demographic, behavioral, environmental, and socio-economic factors associated with HIV acquisition.[18-22] A plausible biological mechanism underlying this causal relationship is that HPV infection disrupts the local and systemic immune systems and makes an individual more susceptible to HIV infection.[19] This could occur through recruitment of cells targeted by HIV, facilitating its acquisition, or by the stimulation of cytokine, increasing HIV replication. Another possibility is that HIV acquisition may be facilitated by genital lesions caused by HPV.

On the other hand, HIV has an impact on the natural history of HPV as well. HIV-infected individuals are more susceptible to an HPV infection, likely due to suppression of their immune system, with an estimated relative risk of 2.3 (95% CI: 1.08-4.9).[23] Furthermore, HPV infections are more likely to persist in HIV positive compared to HIV negative individuals, and consequently HIV is associated with a higher risk for cervical lesions.[23] Studies show inconsistent results with regard to the effect of ART on HPV.[24-26]

Given that HPV and HIV are potentially important drivers in each other's epidemic, it does not come as a surprise that these viruses usually go hand in hand in the same, mostly low and middle income, settings. In South Africa, there are over 5,700 new cervical cancer cases per year, with an age-standardized incidence rate of 26.6 per 100,000 women. KwaZulu-Natal is a rural province in South Africa where HPV prevalence is estimated to be twice as high compared to the rest of the world, i.e. 21%. KwaZulu-Natal is also the province that is most heavily affected by HIV, with a prevalence rate of 24% in 2011 for the adult population.[27,28] Especially in low and middle income countries, where resources are scarce, it is essential to find public health interventions that are cost-effective. Existing interventions against HIV could however be more cost-effective than previously assumed if they also protect against HPV, and vice versa.[18,28]

Mathematical modeling can be used to reproduce the spread of HPV in an HIV endemic area and study the interaction of both dynamics. STDSIM is especially suitable to study the impact of STIs on each other, as STIs are modeled simultaneously in a dynamic sexual network. This model was previously used to study HIV and the impact of HIV interventions in the Hlabisa-district of the Umkhanyakunde District in KwaZulu-Natal.[29] The impact of STIs known to facilitate HIV acquisition, i.e. HSV-2, syphilis, gonorrhea, and chlamydia, have previously been taking into account by assigning so-called 'cofactors' in the model. As HPV was not included in this list of cofactors, the real-life facilitating effect of HPV on HIV acquisition probably has to some extent been incorporated in the estimated cofactor effects of the other STIs. Assigning an explicit cofactor to HPV (and decreasing the cofactor effect of the other STIs) could potentially influence the previously estimated impact of ART, as a lower HIV prevalence would lead to a lower HPV prevalence, which in turn

could lead to less HIV acquisition. This would also mean that interventions targeted at HPV, i.e. HPV vaccination, could influence the HIV epidemic as well.

*Modeling HPV in KwaZulu-Natal*

In an exploratory analysis, we included (one aggregated) high-risk (hr)HPV in the model using data published by Mbulawa *et al.*[30] In this South African study, a hrHPV infection was present in 53% (95% CI: 47-60%) of the HIV positive and 26% (95% CI: 19-33%) of HIV negative women aged 18-45 years. The observed average duration of an HPV infection was 9.4 months for HIV negative men and 12.5 months for HIV positive men.[23] For women, these durations were 9.1 months and 18.2 months, respectively. Based on the Dutch HPV transmission model, we assumed a Weibull shape of 0.50 for the duration of infection (see Chapter 2 of this thesis).[31]

We then ran the model for thousands of random sets of quantifications for 4 parameters: (1) transmission probability of HPV per sexual contact (assumed equal for male-to-female and female-to-male transmission); (2) average duration of naturally acquired immunity; (3) the corresponding Weibull shape; and (4) the cofactor of HIV on HPV acquisition (all assumed equal between men and women). From these sets, only those were selected that lead to a good fit of the observed relative risk of HIV on HPV acquisition (i.e. RR of 2.3 (95% CI: 1.08-4.9)),[23] and the observed HPV proportions in HIV positive and HIV negative women aged 20-44 years.[30] For each selected model quantification we then fitted the cofactor of HPV on HIV acquisition, while simultaneously decreasing the currently modeled cofactors of HSV-2, syphilis, gonorrhea, and chlamydia with a single multiplication factor, to arrive at the same HIV prevalence and reproduce the observed doubled risk of HPV on HIV acquisition, i.e. OR of 2.4 (95% CI: 1.5-4.0), adjusted for HSV-2, syphilis, gonorrhea, and chlamydia.[18]

With STDSIM now including HPV, we explored the impact of interventions on the prevalence of HPV and HIV. First, from 2017 onwards, we changed the eligibility for HIV treatment according to the most recent WHO treatment recommendations, i.e. from ART at CD4+ cell counts of ≤350 cells/μl to ART at any CD4+ cell count ('ART for all HIV-infected people'). Second, we predicted the impact of starting HPV vaccination in 2017 for 9-year-old girls (60% vaccination coverage) with a vaccine efficacy of 90%. Third, we modeled both interventions simultaneously.

*Results and conclusions*

Out of 24 thousand sets of random parameter combinations, we could select 5 model quantifications which showed a good fit to the observed relative risk of HIV on HPV acquisition, and observed HPV proportions in HIV negative and HIV positive women.[23,30] In the five model fits (labeled here as models A to E), the estimated cofactor parameter of HIV on HPV ranges from 4.8 to 56.8 (Table 8.1). The corresponding transmission probability for a high-risk HPV infection ranges from 8.2-14.3% per sexual contact. After clearing an HPV infection, over 85% of women are full immune against HPV

for less than half a year, while up to 5% of women are fully immune for longer than 1 year. The estimated cofactor of HPV on HIV acquisition ranges from 1.2 to 3.5, after fitting to the observed HIV prevalence and doubled risk of HPV on HIV acquisition.[18] This cofactor effect is of the same order of magnitude as the cofactors of gonorrhea and chlamydia on HIV. The cofactors of the other STIs on HIV acquisition need to be multiplied with a relatively modest factor, ranging from 0.86 to 0.99, to compensate for the facilitating effect of HPV on HIV acquisition.

The estimated HIV prevalence also fits well to the observed age-specific HIV prevalence after the inclusion of the facilitating effect of HPV on HIV acquisition (Figure 8.1A). The corresponding estimated hrHPV prevalence is comparable to the HIV prevalence, and has a peak of 40-45% in women aged 25-29 years (Figure 8.1B). The fit of our models to the observed increased risk of HIV on HPV acquisition, and vice versa, and to the observed percentages of HIV positive and negative women with a high-risk HPV infection is shown in Figures 8.1C and 8.1D.

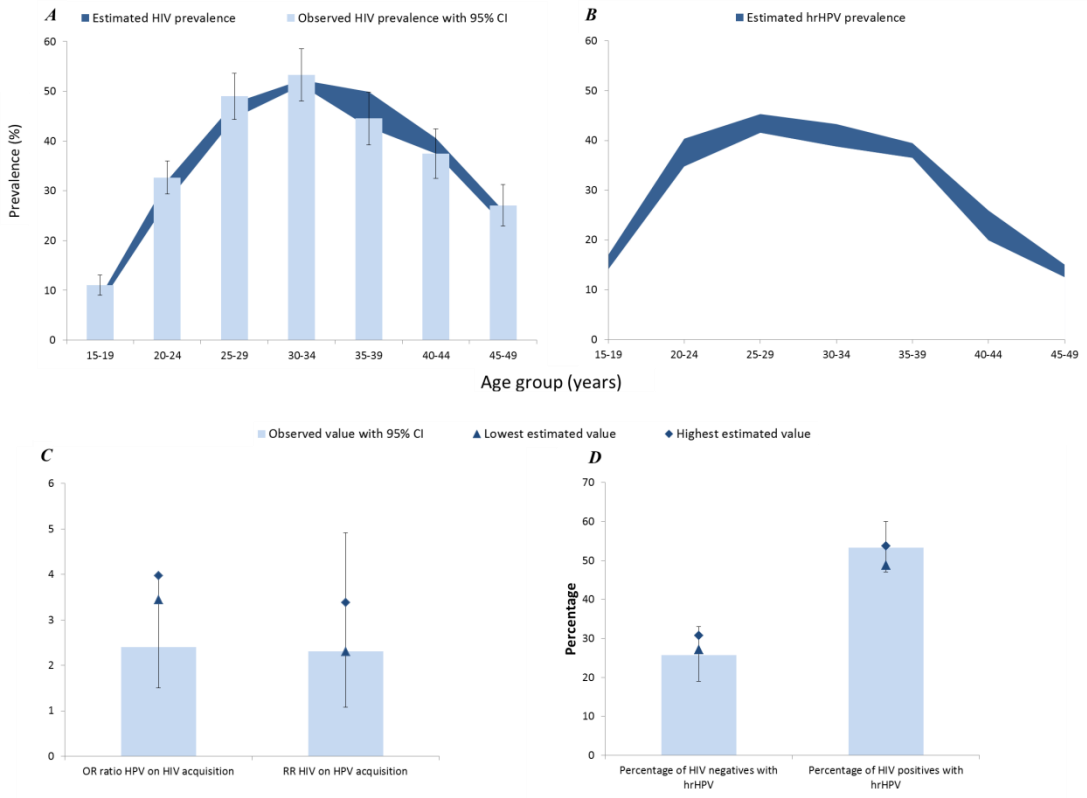



**Figure 8.1. HIV prevalence (A), high-risk HPV (hrHPV) prevalence (B), increased risk of HIV on HPV acquisition and vice versa (C), and percentages of HIV negative and positive women with a hrHPV infection (D), estimated by the five selected good fitting model parametrizations (see Table 8.1), and compared to observed data.** The error bars reflect the 95% confidence intervals in the observed data.[18,23,30] *Abbreviations: OR = odds ratio, RR = relative risk.*

**Table 8.1. Estimated parameter values and distribution of naturally acquired immunity against HPV in the selected five model fits (labeled here as models A to E).**

| Model | Estimated cofactor effect of HIV on HPV acquisition | Estimated transmission probability of HPV per sexual contact (%) | Estimated average immunity duration in years (Weibull distributed) | Estimated shape parameter of the immunity duration | Corresponding immunity duration distribution of HPV in years (%) | | | Estimated cofactor effect of HPV on HIV acquisition | Estimated multiplication factor for other STIs* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | < 0.5 | 0.5-1 | >1 | | |
| A | 42.2 | 14.3 | 0.31 | 1.757 | 84.6 | 15.2 | 0.2 | 3.5 | 0.91 |
| B | 7.9 | 8.3 | 55.12 | 0.098 | 94.6 | 1.0 | 4.4 | 2.4 | 0.88 |
| C | 54.8 | 10.7 | 24.52 | 0.111 | 93.2 | 1.3 | 5.4 | 1.6 | 0.89 |
| D | 4.8 | 8.8 | 65.69 | 0.097 | 94.4 | 1.0 | 4.5 | 1.3 | 0.86 |
| E | 56.8 | 8.2 | 27.97 | 0.105 | 94.3 | 1.1 | 4.6 | 1.2 | 0.99 |

** This multiplication factor is applied simultaneously to the cofactors of HSV-2, gonorrhea, chlamydia, and syphilis on HIV acquisition.*

Figure 8.2 shows that adding a facilitating effect of HPV on HIV acquisition does not markedly affect the estimated impact of changing ART treatment eligibility from ART at CD4+ cell counts of ≤350 cells/µl to ART for all HIV-infected people on HIV prevalence over time. This is because there is only an indirect effect of ART on HPV through HIV, and the cofactor of HPV on HIV is relatively small.

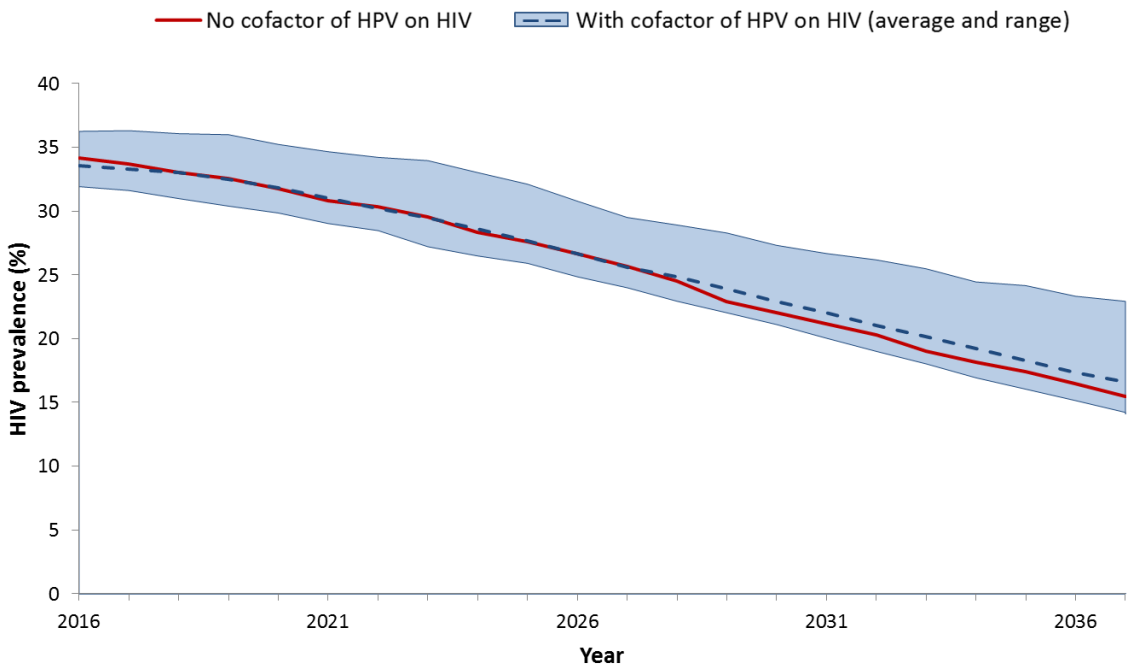



**Figure 8.2. Predicted HIV prevalence over time in women aged 15-49 years, using STDSIM with and without the facilitating effect of HPV on HIV acquisition.** In all predictions, the ART treatment eligibility changes in 2017 from ART at CD4+ cell counts of ≤350 cells/µl to ART for all HIV-infected people. The range is the result of the five selected model fits (see Table 8.1).

HPV vaccination does have an effect on the HIV epidemic though, by reducing the HIV prevalence 10 years after the start of vaccination by almost 2%, and 6% after 20 years, compared to only offering ART for CD4+ cell counts of ≤350 cells/µl (Figure 8.3). However, this reduction due to HPV vaccination is overshadowed when offering ART to all HIV-infected people. Either with or without HPV vaccination, changing the ART treatment eligibility to ART for all HIV-infected people is estimated to decrease HIV prevalence with over 8% after 10 years and almost 25% after 20 years. HPV vaccination also has a limited impact on HPV prevalence itself: there are no clear reductions in prevalence 10 years after the start of vaccination, and HPV prevalence is expected to reduce by only 3% after 20 years. These small reductions are due to the fact that the first vaccinated girls are only 29 years old in 2037, so that only a limited reduction is visible in HPV prevalence in women aged 15-49 years. The small reductions are also caused by the facilitating effect of HIV on HPV, as excluding this

facilitation leads to a larger impact of vaccination on HPV prevalence (not shown here). The facilitating effect of HIV on HPV is also clearly visible in the effect of changing ART treatment eligibility to ART for all HIV-infected people on HPV prevalence. Again, changing ART treatment eligibility diminishes the possible effect of HPV vaccination, and is expected to reduce HPV prevalence by about 12% after 20 years, either with or without vaccination.

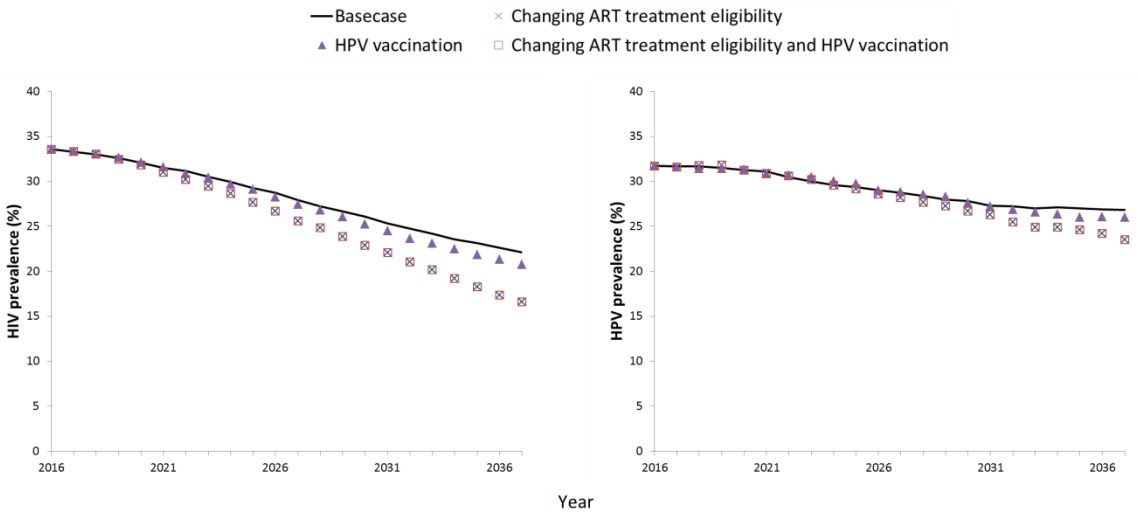



**Figure 8.3. The estimated average impact of changing ART treatment eligibility from ART at CD4+ cell counts of ≤350 cells/µl to ART for all HIV-infected people, offering HPV vaccination, or both interventions from 2017 onwards on HIV and HPV prevalence in women aged 15-49 years.**

The estimated transmission probability of HPV resulting from these exploratory analyses for South Africa are similar to the estimated transmission probabilities of HPV-16 (about 7% per sexual contact) and HPV-18 (7-9%) in the Netherlands.[31] However, the estimated distribution of naturally acquired immunity is very different. While our model now shows a best fit for almost all people being fully immune for only a very short duration after clearing HPV, we estimated that about 20% are fully immune for more than 30 years after clearing an HPV-16 infection, and about 40-50% after an HPV-18 infection in the Netherlands (Chapter 2 of this thesis). The age pattern of HPV prevalence in South Africa is also quite different compared to that observed in the Netherlands, as HPV prevalence is still relatively high in women aged 35-39 years due to the short duration of immunity after clearing an HPV infection.

Important considerations in interpreting these results are the simplifying assumptions that we made regarding naturally acquired immunity and the cofactor of HIV on HPV acquisition. We assumed that the duration of acquired immunity after clearing an HPV infection is independent of HIV status. However, it could be that HIV positive individuals have a fully developed immunity for a much shorter time or no immunity at all against a new HPV infection, due to their compromised immune system, especially when they are not on ART. By not stratifying the average duration of immunity according to HIV status, we possibly underestimated this duration for HIV negative individuals. This might also explain the surprisingly short durations of acquired immunity found here compared to the Dutch model, as a large part of the population is immunosuppressed in KwaZulu-Natal. Also, we assumed an equal risk for HPV acquisition in people infected with HIV, while it could be that the risk level increases with decreasing CD4+ cell count. The impact of these assumptions should be examined more closely in future research. Furthermore, we only looked at the short-term impact of the interventions in these analyses, so that the full benefits of HPV vaccination have not been established yet. As the proportion of vaccinated women in the population will increase over time, the HPV prevalence will decline further in the future, and the spillover effects of HPV vaccination on HIV acquisition may also become more prominent. Finally, we only have 5 model fits in these exploratory analyses. Detailed analyses with more model fits are necessary to determine a more accurate range of the intervention impact estimates on HIV and HPV prevalence.

In conclusion, we did a first attempt to reproduce the observed HIV prevalence, the proportion of HIV positive and negative women with HPV, as well as the association between HPV and HIV, by including HPV in STDSIM quantified for KwaZulu-Natal. Our model suggests that interventions targeting HIV also impact HPV and thus the cervical cancer epidemic. The impact of HPV vaccination on HIV is limited. Future research should explore different intervention combinations over a longer time span to optimize HPV and HIV prevention in high endemic settings.

## 8.3 Conclusions and recommendations

*Conclusions*

1. Naturally acquired immunity after clearing an infection likely plays a major role in HPV epidemiology.
2. HPV vaccination is expected to lead to a substantial decrease in HPV prevalence, precancerous lesions, and the incidence and mortality of cervical cancer in the Netherlands.
3. Improving vaccine uptake among girls and extending vaccination to boys are efficient strategies to further improve HPV transmission control and prevent more cervical cancer deaths.

*Recommendations*

1. Additional model-based health economic analyses should be performed to determine whether cervical cancer screening tailored to vaccination status, instead of a uniform screening program, is more cost-effective once (partly) vaccinated cohorts reach the screening start age.
2. Further longitudinal research on the association between HPV and HIV is needed, as well as on the potential spillover benefits of HIV prevention strategies on HPV and cervical cancer, and vice versa.

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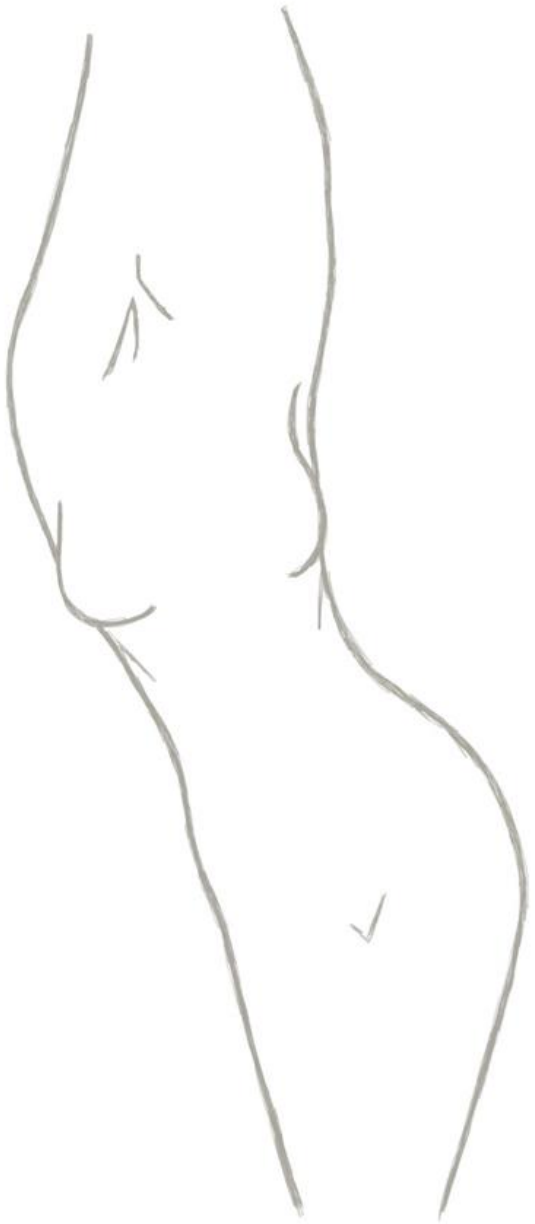
Summary



The overall aim of this thesis was to study the transmission dynamics of HPV-16 and HPV-18 in the Netherlands, and to estimate the impact of vaccination on HPV-16, HPV-18, and cervical cancer after the renewal of the cervical cancer screening program.

**Chapter 1** gives an introduction into cervical cancer, HPV, and the microsimulation models that were used in this thesis. Cervical cancer is the fourth most common cancer among women worldwide, with an estimated 528,000 new cases and 266,000 deaths in 2012. In the Netherlands, about 700 new cervical cancer cases and 200 cervical cancer deaths occur annually. An infection with a high-risk HPV-type is considered the necessary cause for developing cervical cancer, and about 80% of all cervical cancers can be attributed to two high-risk types: HPV-16 and HPV-18. Fortunately, highly effective prophylactic vaccines against these types of HPV have been developed. The bivalent vaccine, which protects against HPV-16 and HPV-18, has been used in the Netherlands since 2009 as part of the national immunization program, with 12-year-old girls being eligible for vaccination. Also, as of January 2017, the cervical cancer screening program in Netherlands uses primary HPV testing rather than primary cytology. The implementation of HPV vaccination and the renewal of the screening program are expected to change the epidemiology of HPV and cervical cancer. To study this change and the consequences for control, we used the established STDSIM and MISCAN microsimulation models, and addressed the following research questions:

1) *What is the role of naturally acquired immunity following an infection in HPV transmission?*
2) *What is the impact of vaccination on HPV epidemiology in the Netherlands?*
3) *What is the impact of vaccination on cervical disease burden and its control in the Netherlands?*

In **Chapter 2**, we explored the transmission dynamics of HPV-16 and HPV-18 in the Netherlands, using STDSIM. We showed that it is necessary to assume that natural immunity is acquired after clearing an infection in order to reproduce the observed HPV-16 and HPV-18 prevalence in the Netherlands. We explored two mechanisms of naturally acquired immunity in our model: (1) full immunity for a certain duration; and (2) a decreased susceptibility to reinfection with a proportion that accumulates after clearing a new infection. The estimated duration of full immunity shows large heterogeneity between individuals. For HPV-16, half of the people are only immune for a short period of time (i.e. less than 1 year), while one in five will still be immune 30 years after clearing the infection. In contrast to HPV-16, we estimated that only up to 12% of the individuals are immune for less than 1 year after clearing an HPV-18 infection, while half of the people are immune for more than 30 years. When considering the second immunity mechanism, susceptibility to reinfection is estimated to be reduced by 58% after each infection for HPV-16 and 80% for HPV-18. These results suggest that women need to clear about two subsequent HPV-16 infections in order to arrive at a

similar level of acquired immunity (83%) after clearing one HPV-18 infection. As the estimated transmission probability per sexual contact is similar for HPV-16 and HPV-18, it is likely that the lower population prevalence of HPV-18 compared to HPV-16 is explained by this relatively larger natural immune response towards HPV-18.

The estimated impact of the current girls-only vaccination program in the Netherlands on HPV-16 and HPV-18 incidence, as well as the incremental health benefits of increased uptake among girls and the inclusion of boys are described in **Chapter 3**. Both acquired immunity mechanisms described in Chapter 2 were considered in STDSIM, so that we could determine the importance of different model assumptions regarding acquired immunity on the predicted effectiveness of vaccination. We found that the current girls-only vaccination has a substantial effect on HPV in the Netherlands. The incidences of HPV-16 and HPV-18 are expected to reduce by 64-75% and 58-73%, respectively. According to our model, vaccine coverage among girls needs to exceed 80% to outweigh the inclusion of boys with 60% coverage in addition to the current vaccination program. The effectiveness estimates differ between the two acquired immunity mechanisms, yet these differences should not have an effect on policy decisions to further improve cervical cancer prevention.

The public health benefits of including routine adult HPV vaccination into the Dutch vaccination program are described in **Chapter 4**. We implemented adult vaccination in our model through existing public health settings (sexual health clinics and the organized cervical cancer screening program), and through a one-time mass campaign. In our scenarios, vaccination was offered to either women only, or women and men (including routine vaccination for boys). Offering vaccination to only adult women leads to modest incremental benefits (i.e. HPV-16 and HPV-18 incidence decrease by about 20%). However, using a combined strategy of offering vaccination to women at their first cervical cancer screening visit and to both men and women at sexual health clinics leads to substantial incremental incidence reductions compared to the current girls-only vaccination program (i.e. reductions of 63% for HPV-16 and 84% for HPV-18 incidence). This strategy would be an efficient policy option to improve HPV prevention and subsequently avert cervical and possibly male HPV-related cancers.

In **Chapter 5**, we studied the impact of switching from primary cytology to primary HPV screening for unvaccinated women who are considered over-screened (i.e. from a younger age and with a shorter time interval than recommended), using the MISCAN-Cervix microsimulation model. Results show that while deaths will be prevented, the harms (i.e. unnecessary anxiety and treatments) due to the lower test specificity of HPV screening compared to cytology can be quite substantial if a large part of the population is over-screened. For women who are screened annually, the increase in positive tests and subsequent follow-up procedures even resulted in a net loss in health, due to losses in quality of life associated with screening and treatment. As over-screening is unavoidable, the level of over-screening should be monitored carefully after the implementation of primary HPV screening.

In populations with relatively small numbers of over-screened women, i.e. with little opportunistic screening such as in the Netherlands, switching to HPV screening may very well be cost-effective.

Using MISCAN-Cervix, we studied at what level of herd immunity it is cost-effective to reduce screening intensity in unvaccinated women (**Chapter 6)**. We first determined the optimal screening strategy for unvaccinated women, and subsequently for a vaccinated cohort. We then applied both optimal screening schedules to unvaccinated women, assuming different levels of herd immunity. For a pre-vaccination cohort, 6-yearly primary HPV screening for women aged 30-72 years was most cost-effective (i.e. 8 life-time screens). For the vaccinated cohort of women, 12-yearly primary HPV screening for women aged 35-59 years is most cost-effective (i.e. 3 life-time screens). Assuming a willingness-to-pay threshold of €50,000 per QALY (quality-adjusted life year) gained, we found that the screening strategy based on the pre-vaccination risk level for cervical cancer becomes cost-ineffective for unvaccinated women from a herd immunity level of 50%. At this level of herd immunity, screening intensity can be reduced, and unvaccinated women can be screened according to strategies optimized for vaccinated women.

In **Chapter 7**, we calculated cervical disease burden among the first vaccinated cohorts given the primary HPV cervical cancer screening program that will be offered to them, by linking the STDSIM and MISCAN-Cervix models. Both the direct and herd immunity effects of the current girls-only vaccination program and alternative strategies are taken into account. The alternative vaccination strategies are: increased vaccine uptake among girls; the addition of routine vaccination for boys; and the addition of adult vaccination at sexual health clinics. Our results show that the current vaccination program leads to substantial reductions in cervical cancer incidence and mortality, i.e. reductions of about 35% for both incidence and mortality. Most efficient strategies to improve cervical cancer prevention are to improve vaccine coverage among girls, and to include routine vaccination for boys if a coverage of 80% can be achieved. As even full vaccine coverage cannot avert all cervical cancer cases and deaths, screening participation should still be encouraged.

Finally, the research questions are answered and further discussed in **Chapter 8**, and results from exploratory analyses on the association between HPV and HIV are shown. Using STDSIM, we were able to reproduce the observed HIV prevalence, the proportion of HIV positive and negative women with HPV, and the association between HPV and HIV in KwaZulu-Natal, South Africa. Our model suggests that interventions targeting HIV also impact HPV and thus the cervical cancer epidemic. The impact of HPV vaccination on HIV is limited. We end the general discussion with the following conclusions and recommendations:

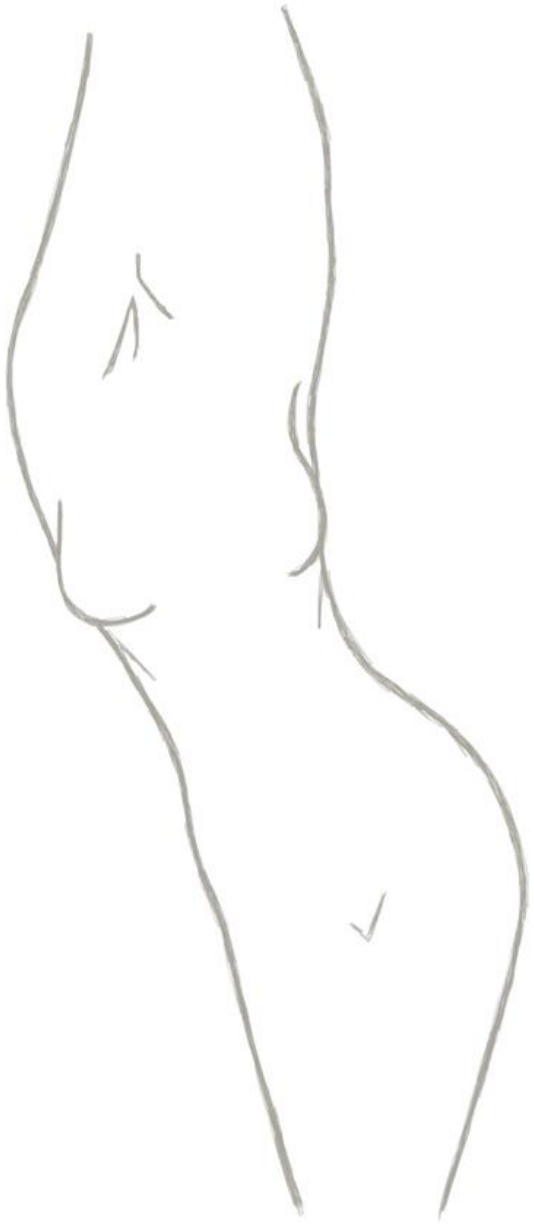
*Conclusions*

1. Naturally acquired immunity after clearing an infection likely plays a major role in HPV epidemiology.
2. HPV vaccination is expected to lead to a substantial decrease in HPV prevalence, precancerous lesions, and the incidence and mortality of cervical cancer in the Netherlands.
3. Improving vaccine uptake among girls and extending vaccination to boys are efficient strategies to further improve HPV transmission control and prevent more cervical cancer deaths.

*Recommendations*

1. Additional model-based health economic analyses should be performed to determine whether cervical cancer screening tailored to vaccination status, instead of a uniform screening program, is more cost-effective once (partly) vaccinated cohorts reach the screening start age.
2. Further longitudinal research on the association between HPV and HIV is needed, as well as on the potential spillover benefits of HIV prevention strategies on HPV and cervical cancer, and vice versa.

# Samenvatting



Het doel van het onderzoek, zoals beschreven in dit proefschrift, was om de transmissiedynamiek van HPV-16 en HPV-18 in Nederland te bestuderen en om de impact van vaccinatie op HPV-16, HPV-18 en baarmoederhalskanker te voorspellen na de vernieuwing van het bevolkingsonderzoek baarmoederhalskanker.

**Hoofdstuk 1** geeft een introductie over baarmoederhalskanker, HPV en de microsimulatiemodellen die gebruikt zijn in dit proefschrift. Baarmoederhalskanker is de vierde meest voorkomende kanker bij vrouwen wereldwijd, met ongeveer 528.000 nieuwe gevallen en 266.000 sterftegevallen in 2012. Elk jaar zijn er in Nederland ongeveer 700 nieuwe gevallen van baarmoederhalskanker en 200 sterfgevallen door deze kanker. Een infectie met een hoog-risico HPV-type wordt beschouwd als de noodzakelijke oorzaak voor de ontwikkeling van baarmoederhalskanker. Ongeveer 80% van de kankers kunnen worden toegeschreven aan twee hoog-risico typen: HPV-16 en HPV-18. Gelukkig zijn profylactische vaccins tegen deze HPV-typen ontwikkeld. Het bivalente vaccin, dat bescherming biedt tegen HPV-16 en HPV-18 infecties, wordt in Nederland sinds 2009 aangeboden aan 12-jarige meisjes. Daarnaast is Nederland sinds januari 2017 overgestapt van primaire cytologie screening naar primaire HPV-screening in het bevolkingsonderzoek baarmoederhalskanker. Men verwacht dat de implementatie van HPV-vaccinatie en de vernieuwing van het bevolkingsonderzoek zal leiden tot veranderingen in de epidemiologie van HPV en baarmoederhalskanker. Om een schatting te maken van deze verwachte veranderingen gebruikten wij de STDSIM en MISCAN-Cervix microsimulatiemodellen waarmee wij de volgende onderzoeksvragen beantwoorden:

1. *Wat is de rol van natuurlijk verworven immuniteit na het opschonen van een infectie in HPV-transmissie?*
2. *Wat is het effect van vaccinatie op de HPV-epidemiologie in Nederland?*
3. *Wat is het effect van vaccinatie op de ziektelast van de baarmoederhals en de controle hiervan in Nederland?*

In **Hoofdstuk 2** hebben we met behulp van STDSIM de transmissiedynamiek van HPV-16 en HPV-18 in Nederland onderzocht. Om de geobserveerde HPV-16 en HPV-18 prevalentie in Nederland te kunnen reproduceren met ons model is het noodzakelijk om te veronderstellen dat natuurlijke immuniteit wordt verworven na het opschonen van een infectie. We onderzochten twee verschillende mechanismen van natuurlijk verworven immuniteit in ons model: (1) volledige immuniteit voor een bepaalde duur; en (2) de vatbaarheid voor een nieuwe infectie wordt verminderd met een proportie die accumuleert na iedere infectie. Bij het eerste mechanisme toont de geschatte duur van volledige immuniteit grote heterogeniteit tussen individuen. Na een HPV-16 infectie is de helft van de mensen slechts immuun voor een korte periode (minder dan 1 jaar), terwijl 1 op de 5 mensen 30 jaar na het opschonen van een infectie nog steeds immuun is. In tegenstelling tot HPV-16 voorspelden we dat

maximaal 12% van de individuen immuun is voor korter dan 1 jaar na het opschonen van een HPV-18 infectie, terwijl de helft van de mensen langer dan 30 jaar immuun is. Bij het tweede immuniteitsmechanisme is de geschatte vermindering van de vatbaarheid voor een nieuwe infectie 58% na elke infectie voor HPV-16 en 80% voor HPV-18. Deze resultaten suggereren dat vrouwen twee opeenvolgende HPV-16 infecties moeten opschonen om tot een vergelijkbaar niveau van verworven immuniteit (83%) te komen na het opheffen van een HPV-18 infectie. Omdat de geschatte transmissiekans per seksueel contact vergelijkbaar is voor beide HPV-typen wordt de lagere HPV-18 prevalentie in de populatie in vergelijking tot HPV-16 waarschijnlijk verklaard door een relatief sterkere natuurlijke immuunrespons tegen HPV-18.

**Hoofdstuk 3** beschrijft de geschatte impact van het huidige Nederlandse vaccinatieprogramma voor meisjes op de incidentie van HPV-16 en HPV-18, evenals de incrementele gezondheidswinst van een hogere dekkingsgraad van het vaccin bij meisjes en het includeren van jongens in het programma. Beide mechanismen van natuurlijk verworven immuniteit werden in het model meegenomen zodat we het effect van verschillende modelaannames ten aanzien van natuurlijke immuniteit op onze gezondheidsschattingen van HPV-vaccinatie konden bepalen. We concludeerden dat het huidige vaccinatieprogramma een aanzienlijke impact heeft op HPV in Nederland. De geschatte incidentie van HPV-16 en HPV-18 zal naar verwachting verminderen met respectievelijk 64-75% en 58-73%. Volgens ons model zal de vaccinatiegraad bij meisjes hoger dan 80% moeten zijn om de geschatte gezondheidswinst door de inclusie van jongens met 60% dekking in aanvulling op het huidige vaccinatieprogramma te overtreffen. De impactschattingen verschillen tussen de twee natuurlijk verworven immuniteitsmechanismen, maar deze verschillen hebben geen invloed op beleidsbeslissingen voor een verdere verbetering van de preventie van HPV en baarmoederhalskanker.

In **Hoofdstuk 4** is gekeken naar de gezondheidswinst door het aanbieden van vaccinatie aan volwassenen in aanvulling op het reguliere vaccinatieprogramma. In ons model boden we deze vaccinatie voor volwassenen aan via bestaande gezondheidsinstellingen (soa-klinieken en het bevolkingsonderzoek baarmoederhalskanker) en door middel van een eenmalige massacampagne. In onze scenario's wordt vaccinatie aangeboden aan alleen vrouwen of zowel vrouwen als mannen (inclusief routine vaccinatie voor jongens). We concludeerden dat er slechts een bescheiden incrementele gezondheidswinst is wanneer vaccinatie alleen aan volwassen vrouwen wordt aangeboden (dat wil zeggen: HPV-16 en HPV-18 incidentie verminderen met ongeveer 20%). Een gecombineerde strategie van het aanbieden van vaccinatie aan vrouwen bij hun eerste deelname aan het bevolkingsonderzoek baarmoederhalskanker en aan zowel mannen als vrouwen bij soa-klinieken leidt echter tot substantiële incidentiereducties vergeleken met het huidige vaccinatieprogramma voor meisjes (reducties van 63% voor HPV-16 en 84% voor HPV-18 incidentie). Deze strategie zal een efficiënte beleidsoptie zijn om HPV preventie te verbeteren en vervolgens baarmoederhalskanker en mogelijk andere HPV-gerelateerde kankers bij mannen te voorkomen.

In **Hoofdstuk 5** bestudeerden we de impact van de overgang van primaire cytologie naar primaire HPV-screening voor ongevaccineerde vrouwen met overmatige screening (dat wil zeggen: vanaf een jongere leeftijd en met een korter tijdsinterval dan aanbevolen) met het MISCAN-Cervix microsimulatiemodel. De resultaten tonen aan dat hoewel sterfgevallen worden voorkomen, de nadelen (zoals onnodige stress en behandelingen) door de lagere specificiteit van de HPV-test ten opzichte van cytologie aanzienlijk kunnen zijn indien een groot deel van de bevolking overmatig wordt gescreend. Voor vrouwen die jaarlijks worden gescreend kan de toename in positieve testen en vervolgonderzoeken zelfs leiden tot een netto verlies in gezondheid als gevolg van een verminderde kwaliteit van leven door screening en behandelingen. Als overmatige screening onvermijdelijk is, moet het niveau van overmatige screening zorgvuldig worden gecontroleerd na de implementatie van primaire HPV-screening. In populaties met relatief weinig overmatige screening, dat wil zeggen met weinig opportunistische screening zoals in Nederland, zal de overschakeling van cytologie naar HPV-screening waarschijnlijk kosteneffectief zijn.

Met behulp van MISCAN-Cervix onderzochten we in **Hoofdstuk 6** bij welk niveau van kudde-immuniteit het kosteneffectief is om de intensiteit van screening te verminderen in ongevaccineerde vrouwen. We optimaliseerden het screeningsschema allereerst naar het risiconiveau van voor de invoer van HPV-vaccinatie, en daarna naar het risiconiveau in gevaccineerde vrouwen. Vervolgens pasten wij deze optimale screeningsschema's toe op ongevaccineerde vrouwen, uitgaande van verschillende niveaus van kudde-immuniteit. Voor ongevaccineerde vrouwen is 6-jaarlijkse primaire HPV-screening voor vrouwen van 30-72 jaar (dat wil zeggen: 8 uitstrijkjes in totaal per vrouw) het meest kosteneffectief. Voor gevaccineerde vrouwen is 12-jaarlijkse primaire HPV-screening voor vrouwen in de leeftijd van 35-59 jaar het meest kosteneffectief (3 uitstrijkjes in totaal). Uitgaande van een drempelwaarde voor kosteneffectiviteit van € 50.000 per QALY (*quality-adjusted life year*; levensjaren gecorrigeerd voor de kwaliteit van die levensjaren) vonden we dat de screeningsintensiteit op basis van het pre-vaccinatie risiconiveau niet meer kosteneffectief is voor ongevaccineerde vrouwen wanneer kudde-immuniteit in de populatie een niveau van 50% behaalt. Op dit niveau van kudde-immuniteit zouden ongevaccineerde vrouwen gescreend kunnen worden volgens strategieën die geoptimaliseerd zijn op basis van gevaccineerde vrouwen.

In **Hoofdstuk 7** berekenden we de ziektelast van de baarmoederhals bij de eerste gevaccineerde cohorten na de vernieuwing van het bevolkingsonderzoek baarmoederhalskanker in Nederland door STDSIM en MISCAN-Cervix te integreren. Zowel directe als indirecte (door kudde-immuniteit) effecten van HPV-vaccinatie vanuit verschillende vaccinatiescenario's zijn meegenomen in deze berekeningen. De verschillende vaccinatiescenario's zijn: het huidige programma voor meisjes met de geobserveerde dekkingsgraad; hogere dekkingsgraad onder meisjes; de toevoeging van routine vaccinatie voor jongens aan het huidige vaccinatieprogramma; en de toevoeging van de vaccinatie voor volwassenen in soa-klinieken. Onze resultaten tonen aan dat vaccinatie leidt tot een aanzienlijke vermindering van baarmoederhalskankerincidentie en sterfte voor de eerste gevaccineerde cohorten,

namelijk een reductie van ongeveer 35% voor zowel de incidentie als de sterfte. De meest efficiënte strategieën om de preventie van baarmoederhalskanker te verbeteren zijn het verhogen van de dekkingsgraad onder meisjes en het includeren van vaccinatie bij jongens indien een dekkingsgraad van 80% kan worden bereikt. Aangezien zelfs een perfecte dekkingsgraad niet alle gevallen van baarmoederhalskanker en sterfgevallen kan voorkomen, moet deelname aan screening nog steeds worden aangemoedigd.

Ten slotte hebben we de onderzoeksvragen beantwoord en verder besproken in **Hoofdstuk 8**, en resultaten van de verkennende analyses over de associatie tussen HPV en HIV getoond. We waren in staat om de geobserveerde HIV prevalentie, de proporties HIV positieve en negatieve vrouwen met HPV en de associatie tussen HPV en HIV in KwaZulu-Natal, Zuid Afrika, te reproduceren met STDSIM. Ons model toont aan dat interventies die gericht zijn op HIV ook een impact hebben op HPV en daarmee dus ook op baarmoederhalskanker. De impact van HPV vaccinatie op HIV is beperkt. We eindigden de algemene discussie met de volgende conclusies en aanbevelingen:

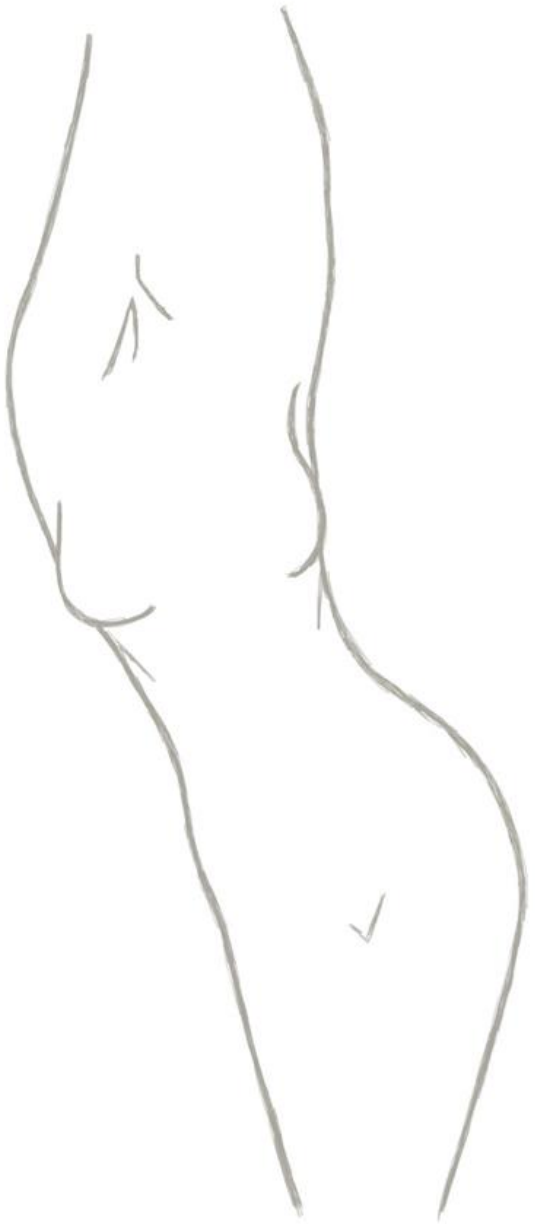
*Conclusies:*

1. Natuurlijk verworven immuniteit na het opschonen van een infectie speelt waarschijnlijk een belangrijke rol in de HPV-epidemiologie.
2. HPV vaccinatie zal leiden tot een aanzienlijke vermindering van de HPV-prevalentie, voorstadia van baarmoederhalskanker, en de incidentie en sterfte als gevolg van baarmoederhalskanker in Nederland.
3. Het verhogen van de dekkingsgraad van vaccinatie bij meisjes en het uitbreiden van het vaccinatieprogramma door de includering van jongens zijn efficiënte strategieën om de preventie van HPV-transmissie te verbeteren en om meer sterfte aan baarmoederhalskanker te voorkomen.

*Aanbevelingen:*

1. Aanvullende modelmatige gezondheidseconomische analyses moeten worden verricht om te bepalen of screening op baarmoederhalskanker op basis van vaccinatiestatus, in plaats van een uniform bevolkingsonderzoek, meer kosteneffectief is zodra (gedeeltelijk) gevaccineerde cohorten de startleeftijd van het bevolkingsonderzoek bereiken.
2. Meer longitudinaal onderzoek naar de associatie tussen HPV en HIV is noodzakelijk, evenals naar de mogelijke overloopeffecten van HIV preventiestrategieën op HPV en baarmoederhalskanker en vice versa.

# Acknowledgements



Nu het einde van het boekje nadert, wil ik graag iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift. Dankzij jullie heb ik de afgelopen jaren kunnen groeien op zowel persoonlijk als professioneel vlak, en heb ik de nodige ontspanning naast het werk gehad.

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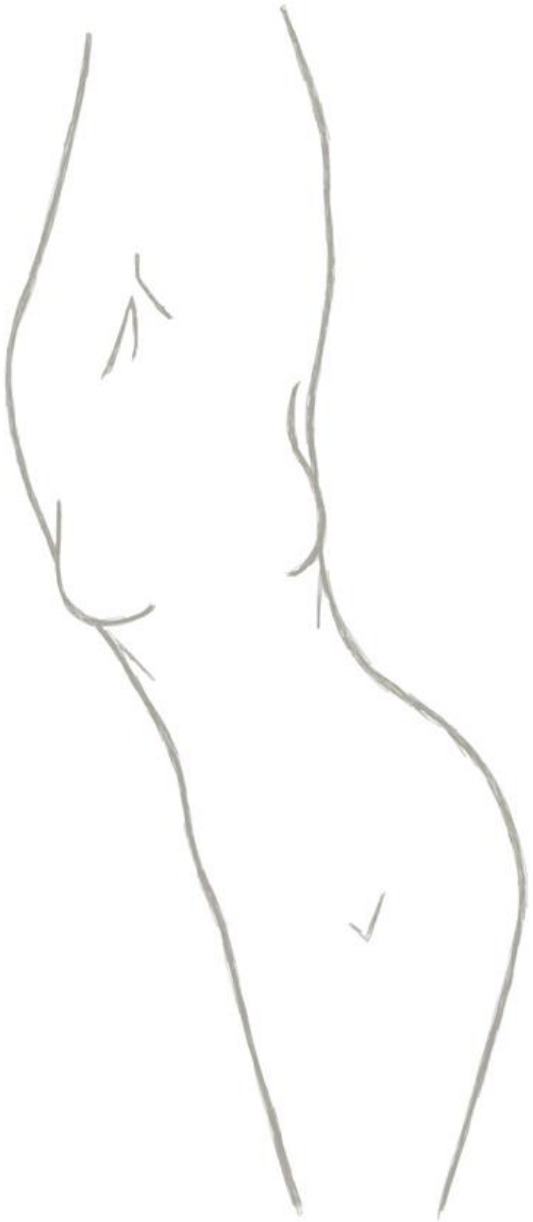
# About the author



Suzette Matthijsse was born on October 6th, 1987 in Gouda. In 2006, she passed her secondary school Gymnasium exams (*cum laude*) at the Revius Lyceum in Doorn, and started studying Psychology at Utrecht University. In addition, she completed a one-year Honours track and two-years multidisciplinary Honours Program during her bachelor. She started the two-years research master program Methodology and Statistics of Behavioral and Social Sciences in 2009 at the Graduate School of Utrecht University, and obtained her Master's degree in 2011. In August 2011, she started her PhD at the department of Public Health at Erasmus MC in Rotterdam. During the first year of her PhD, she obtained a Master's degree in Health Sciences, specialization Public Health, at the Netherlands Institute of Health Sciences (NIHES) in Rotterdam. While working at Erasmus MC, Suzette has worked for 1 month on a project on neglected tropical diseases, aimed at estimating the global health impact of meeting the WHO Roadmap targets. She has also worked 10 months on a project on HIV combination prevention in Zimbabwe, for which she spent nearly 2 months in Zimbabwe. During her stay in Zimbabwe, she also gave lectures and practicals for the course "Mathematical Modelling Training". In January 2017, Suzette received the Encouragement Award for best PhD publication of 2016 from the department of Public Health. Since May 2016, she has been part of the NCI sponsored Cancer Intervention and Surveillance Modeling Network for cervical cancer in the USA, in which she will continue as a senior scientific researcher.

# List of publications

**THIS THESIS**

1. **S.M. Matthijsse**, S.K. Naber, J.A.C. Hontelez, I.M.C.M. de Kok, K. Rozemeijer, R. Bakker, I. Lansdorp-Vogelaar, H.J. de Koning, J. van Rosmalen, S.J. de Vlas (2016). The health impact of HPV vaccination in the situation of primary HPV screening: a mathematical modeling study. (*Submitted for publication*)

2. **S.M. Matthijsse**, J.A.C. Hontelez, S.K. Naber, K. Rozemeijer, R. Bakker, M. van Ballegooijen, J. van Rosmalen, S.J. de Vlas (2016). Public health benefits of routine human papillomavirus vaccination for adults in the Netherlands: a mathematical modelling study. Journal of Infectious Diseases 214(6):854-61.

3. S.K. Naber, I.M.C.M de Kok, **S.M. Matthijsse**, M. van Ballegooijen (2016). The potential harms of primary human papillomavirus screening in over-screened women - a microsimulation study. Cancer Causes Control 27(4): 569-81.

4. S.K. Naber, **S.M. Matthijsse**, K. Rozemeijer, C. Penning, I.M.C.M. de Kok, M. van Ballegooijen (2016). Cervical cancer screening in partly HPV vaccinated cohorts - a cost-effectiveness analysis. PLoS ONE 11(1): e0145548.

5. **S.M. Matthijsse**, J.A.C. Hontelez, S.K. Naber, J. van Rosmalen, K. Rozemeijer, C. Penning, R. Bakker, M. van Ballegooijen, I.M.C.M. de Kok, S.J. de Vlas (2015). The estimated impact of natural immunity on the effectiveness of human papillomavirus vaccination. Vaccine 33(41): 5357-5364.

6. **S.M. Matthijsse**, J. van Rosmalen, J.A.C. Hontelez, R. Bakker, I.M.C.M. de Kok, M. van Ballegooijen, S.J. de Vlas (2015). The role of acquired immunity in the spread of human papillomavirus (HPV): explorations with a microsimulation model. PLoS ONE 10(2): e0116618.

**OTHER PUBLICATIONS**

7. K. Rozemeijer, C. Penning, F.J. van Kemenade, S.K. Naber, **S.M. Matthijsse**, A.G. Siebers, I.M.C.M. de Kok, M. van Ballegooijen (2016). Lower socioeconomic status is associated with an increased risk of cervical cancer regardless of screening coverage. (*Submitted for publication*)

8. K. Rozemeijer, S.K. Naber, C. Penning, L.I. Overbeek, C.W.N. Looman, I.M.C.M. de Kok, **S.M. Matthijsse**, M. Rebolj, F.J. van Kemenade, M. van Ballegooijen (2017). Cervical cancer incidence after a negative cytological sample in routine screening: comparing SurePath, ThinPrep and conventional cytology. A population-based observational study. BMJ; 356:j504.

9. I.M.C.M. de Kok & **S.M. Matthijsse** (2017). HPV vaccinatie. Bijblijven 33:29-40.

10. M. Brisson, É. Bénard, M. Drolet, J.A. Bogaards, I. Baussano, S. Vänskä, M. Jit, M-C Boily, M.A. Smith, J. Berkhof, K. Canfell, H.W. Chesson, E.A. Burger, Y.H. Choi, B. Freiesleben De Blasio, S.J. De Vlas, G. Guzzetta, J.A.C. Hontelez, J. Horn, M.R. Jepsen, J.J. Kim, F. Lazzarato, **S.M. Matthijsse**, R. Mikolajczyk, A. Pavelyev, M. Pillsbury, L.A. Shafer, S.P. Tully, H.C. Turner, C. Usher, C. Walsh (2016). Population-level impact, herd immunity and elimination after HPV vaccination: a systematic review and meta-analysis of predictions of 16 transmission-dynamic models. The Lancet Public Health 1(1): e8-e17.

11. E.D. de Leeuw & **S.M. Matthijsse** (2016). Professional respondents in online panels: threat or blessing? MRA Alert, http://www.marketingresearch.org/article/professional-respondents-online-panels.

12. S.J. de Vlas, W.A. Stolk, E.A. le Rutte, J.A.C. Hontelez, R. Bakker, D.J. Blok, R. Cai, T.A.J. Houweling, M.C. Kulik, E.J. Lenk, M. Luyendijk, **S.M. Matthijsse**, W.K. Redekop, I. Wagenaar, J. Jacobson, N.J.D. Nagelkerke, J.H. Richardus (2016). Concerted efforts to control or eliminate neglected tropical diseases: how much health will be gained? PLoS Negl Trop Dis 10(2): e0004386.

13. K. Rozemeijer, C. Penning, A.G. Siebers, S.K. Naber, **S.M. Matthijsse**, M. van Ballegooijen, F.J. van Kemenade, I.M.C.M. de Kok (2015). Comparing SurePath, ThinPrep, and conventional cytology as primary test method: SurePath is associated with increased CIN II+ detection rates. Cancer Causes and Control 27(1):15-25.

14. K. Rozemeijer, F.J. van Kemenade, C. Penning, **S.M. Matthijsse**, S.K. Naber, J. van Rosmalen, M. van Ballegooijen, I.M.C.M. de Kok (2015). Exploring the trend of increased cervical intraepithelial neoplasia detection rates in the Netherlands. Journal of Medical Screening, 22(3): 144-50.

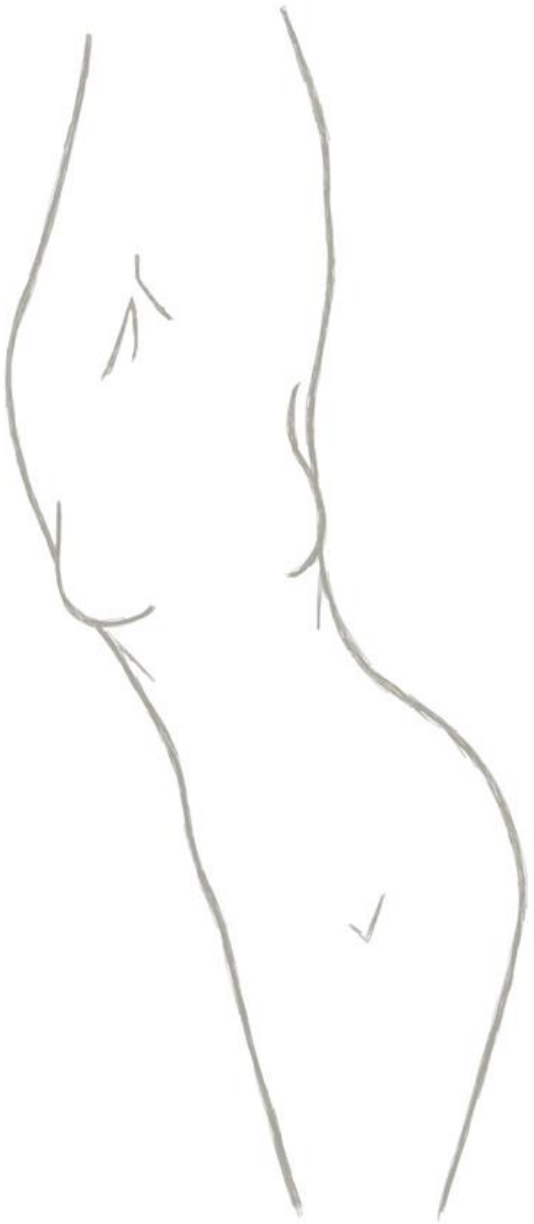
15. **S.M. Matthijsse**, E.D. de Leeuw, J.J. Hox (2015). Internet panels, professional respondents, and data quality. Methodology: European Journal of Research Methods for the Behavioral and Social Sciences, Vol 11(3), 2015, 81-88.

16. J. Hox, R. van der Schoot, **S.M. Matthijsse** (2012). How few countries will do? Comparative survey analysis from a Bayesian perspective. Survey Research Methods (2012), 6(2): 87-93.

17. **S.M. Matthijsse**, E.D. de Leeuw, J.J. Hox (2012). Professionele respondenten in online panels: een bedreiging voor de datakwaliteit? De NOPVO-data nader geanalyseerd. In: A.E. Bronner et al. (Red.) Ontwikkelingen in het Marktonderzoek, Jaarboek MOA 2012, Chapter 6.

18. E.D. de Leeuw & **S.M. Matthijsse** (2011). Uit op geld en plezier. De professionele respondent 2.0. Clou (2011), 55.

PhD portfolio



**Summary of PhD training**

| | Period | Workload |
|---|---|---|
| **MSc. in Health Sciences, specialization Public Health** | **2011-2012** | **70 ECTS** |
| **Specific courses:** | | |
| *Erasmus Summer Program* | | |
| Principles of Research in Medicine | | 0.7 ECTS |
| Methods of Clinical Research | | 0.7 ECTS |
| Methods of Public Health Research | | 0.7 ECTS |
| Clinical Trials | | 0.7 ECTS |
| Health Economics | | 0.7 ECTS |
| Introduction to Global Public Health | | 0.7 ECTS |
| Methods of Health Services Research | | 0.7 ECTS |
| Primary and Secondary Prevention Research | | 0.7 ECTS |
| Demography of Ageing | | 0.7 ECTS |
| Social Epidemiology | | 0.7 ECTS |
| Markers and Prognostic Research | | 0.7 ECTS |
| *Core curriculum* | | |
| Study Design | | 4.3 ECTS |
| Biostatistical Methods I: Basic Principles | | 5.7 ECTS |
| Biostatistical Methods II: Popular Regression Models | | 4.3 ECTS |
| Public Health Research Methods | | 5.7 ECTS |
| International Comparison of Health Care Systems | | 1.4 ECTS |
| Site visit to Municipal Health Service Rotterdam | | 0.3 ECTS |
| Integration Module | | 0.3 ECTS |
| *Advanced short courses* | | |
| Epidemiology of Infectious Diseases | | 1.4 ECTS |
| Cancer Epidemiology | | 1.4 ECTS |
| Planning and Evaluation of Screening | | 1.4 ECTS |
| Quality of Life Measurement | | 0.9 ECTS |
| From Problem to Solution in Public Health | | 1.1 ECTS |
| **Symposia and workshops** | | |
| Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen, Rotterdam | 2012 | 6 hours |
| Mini-symposium "Implementatie van HPV-testen - zaken om te overwegen", Utrecht | 2012 | 3 hours |
| Statistics Day VVS-OR, Utrecht | 2012 | 8 hours |
| Symposium "HPV Primaire Screening: belangrijke besluiten en kritische consequenties", Utrecht | 2013 | 4 hours |

| | | |
|---|---|---|
| UCID Seminar Infection Dynamics, Utrecht, 2013 | 2013 | 2 hours |
| Erasmus MC PhD-day | 2013 | 6 hours |
| Workshop Scientific Integrity, Erasmus MC, Rotterdam | 2014 | 8 hours |
| Expertmeeting kwaliteitseisen aanbestedingen vernieuwing bevolkingsonderzoek baarmoederhalskanker, Utrecht | 2014 | 6 hours |
| Symposium "Modelling the transmission dynamics of HIV and assessing the impact of public health interventions", RIVM, Bilthoven | 2015 | 6 hours |
| Symposium "Quantitative methods in medical research", Erasmus MC | 2015 | 3 hours |
| Symposium "Modelling the transmission dynamics of HIV and other STIs", RIVM, Bilthoven | 2016 | 6 hours |
| HPV research day, RIVM, Bilthoven | 2016 | 6 hours |
| BKO workshop 'Individuele begeleiding', Erasmus MC Desiderius School | 2016 | 3 hours |

## (Inter)national conferences and presentations

| | | |
|---|---|---|
| Erasmus MC (oral presentations) | 2011-2016 | |
| 27th International Papillomavirus Conference and Clinical Workshop, Berlin, Germany | 2011 | 40 hours |
| WEON, Rotterdam, the Netherlands | 2012 | 16 hours |
| 28th International Papillomavirus Conference, San Juan, Puerto Rico (poster presentation) | 2012 | 40 hours |
| Eurogin 2013, Florence, Italy (oral presentation) | 2013 | 32 hours |
| 29th International Papillomavirus Conference, Seattle, USA (poster and oral presentation) | 2014 | 40 hours |
| Eurogin 2015, Sevilla, Spain (oral poster presentation) | 2015 | 32 hours |
| ICSN 2015, Rotterdam, the Netherlands (poster presentation) | 2015 | 16 hours |
| RIVM, De Bilt, the Netherlands (invited oral presentations) | 2015-2017 | |
| 30th International Papillomavirus Conference, Lisbon, Portugal (poster presentation) | 2015 | 40 hours |
| Nationaal Congres Soa*HIV*Seks, Amsterdam | 2015 | 6 hours |
| Eurogin 2016, Salzburg, Austria (oral presentation) | 2016 | 32 hours |
| Programmacommissie Bevolkingsonderzoek naar Baarmoederhalskanker, Utrecht, Nederland (oral presentation) | 2016 | 2 hours |
| 31st International Papillomavirus Conference, Cape Town, South Africa (poster presentation) | 2017 | 40 hours |

## Teaching

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|---|---|---|
| Supervising community project for medical students, as part of | 2014 | 0.6 ECTS |

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| educational theme 3.C 'Arts en volksgezondheid' at the Erasmus MC | | |
| Practical of NIHES course "Public health in low and middle income countries (LMICs)" | 2015-2016 | 12 hours |
| 3 days lectures and practicals during the course "Mathematical Modelling Training, Module 3", Harare, Zimbabwe | 2015 | 24 hours |

**Extracurricular**

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|---|---|---|
| Peer reviews for several medical journals | 2013-2017 | 40 hours |
| Junior representative for section Infectious Disease Control | 2011-2014 | |
| Project on neglected tropical diseases | 2014 | 1 month |
| Project on modeling HIV combination prevention, Zimbabwe | 2015 | 10 months |
| CISNET comparative modeling project, USA | 2016-now | 1 year |