eAppendix

Long-term impact of HPV vaccination on infection rates, cervical abnormalities and cancer incidence

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APPENDIX

This eAppendix gives a detailed description of the structure of the HPV transmission model and of the individual-based simulation model for cervical carcinogenesis. Further details can be found in previous publications, referenced in the main text.

HPV transmission model

HPV transmission in the heterosexual population is modeled in a deterministic fashion, by describing the flow between infection-related compartments in terms of partial differential equations (see eSupplement of this eAppendix). Model state variables are summarized in eTable 1; note that all are specific for a particular high-risk HPV type. Hence, we ignore type-specific interactions in transmission dynamics of different strains. The variables *a*, *t* denote age and time, respectively, and the subscript *k* denotes gender; $\mu_k(a)$ denotes gender-specific background mortality at age *a*, which is assumed to remain constant through time. A second subscript is used to denote the level of sexual activity, allowing for four categories: 0 denotes virgin, whereas 1, 2 and 3 denote low (less than 1 partner per year), high (between 1 to 5 partners per year), and very high (more than 5 partners per year) activity. Parameter $s_{k,0}$ is the rate of losing virginity and $f_{k,1}$, $f_{k,2}$ are the probabilities of starting sexual activity in the low- or high-activity categories. Once sexually experienced, persons may adjust their level of activity. Persons may switch between adjacent sexual-activity categories: rates $s_{k,12}$ and $s_{k,21}$ relate to switching from low to high activity and vice versa, respectively; rates $s_{k,23}$ and $s_{k,32}$ relate to switching from high to very high activity and vice versa, respectively.

The initial stage of the infectious compartment I corresponds to CIN0 (no cervical intraepithelial neoplasia). The superscript p in the infectious stage denotes persistent infection, hence I^p corresponds to CIN1 (cervical intraepithelial neoplasia grade 1). Viral clearance at CIN0 and progression to CIN1 are assumed to be two competing processes following incident infection, operating at respective rates γ and η. For men, the latter process will be neglected, i.e. we set male η to zero. Removal from CIN is determined by naturally occurring viral clearance (operating at a rate χ) and by treatment of precursor lesions (operating at a rate π) from grade 2 or 3 (CIN2/3) following detection of cellular abnormalities. The superscript d in the infectious stage denotes presence of cellular abnormalities that may be detected by means of cytologic screening and prompt treatment whenever detected, i.e. I^{pd} corresponds to CIN2/3. Progression from CIN1 to CIN2/3 occurs at a rate v and removal from this stage is a function of age such that: (*i*) before age 30, it is primarily determined by naturally occurring viral clearance at a constant rate χ; (*ii*) from age 30 onward, population-based screening provides additional removal at a rate $\pi(a)$ that depends on the type of screening program (regarding interval, compliance, diagnostic accuracy) and the overall effectiveness of treatment.

Vaccination of pre-adolescent girls occurs at a rate $\sigma_f(a, t)$ and is assumed to be effective only in those who are susceptible to the corresponding high-risk HPV type at the time of vaccination. We do not consider male vaccination, i.e. σ_m is set to zero. Vaccinated women are protected against infection as long as the protective immunity derived from vaccination is not lost. Waning of vaccine-derived immunity occurs at a rate $\psi(a)$ and vaccinated women

return to the susceptible state once the protective immunity is lost. Hysterectomy (operating at a rate *o*) results in women being no longer susceptible to high-risk HPV infection or – if already infected – in clearance of infection without ever becoming susceptible to reinfection, even though they may remain sexually active. Women having undergone hysterectomy are thus placed outside the chain of transmission; hence, they constitute a separate compartment termed *O*.

Force of infection

The force of infection is calculated under the assumption that transmission from males to females and vice versa is independent of sexual-activity category and of the stage of infection

$$\lambda_{k,i}(a,t) = \beta \sum_{j=1}^{3} \left[\int_0^{\infty} c_{k,i,j}(a,a') \rho_{k,i,j}(a,a') \frac{I_{k',j}(a',t) + I_{k',j}^{p}(a',t) + I_{k',j}^{pd}(a',t)}{N_{k',j}(a',t)} \mathrm{d}a' \right]$$

with

$$N_{k,i}(a,t) = S_{k,i}(a,t) + I_{k,i}(a,t) + I_{k,i}^{p}(a,t) + I_{k,i}^{pd}(a,t) + R_{k,i}(a,t) + V_{k,i}(a,t) + O_{k,i}(a,t)$$

Following Anderson and May,[1] the notation a' is used to denote the age of persons of the opposite gender k'. At demographic equilibrium, $N_{k,i}(a, t) \equiv N_{k,i}(a)$ and the dependence of population size on time is henceforth ignored. Acquisition rates of new sexual partners $c_{k,i}$ by gender *k* and sexual-activity category *i* are adjusted, such that there is a balance in

relationships formed between age groups within the population at a specific time.[2] The partnership balance requires

$$N_{k,i}(a)c_{k,i}(a)\rho_{k,i,j}(a,a') = N_{k',j}(a')c_{k',j}(a')\rho_{k',j,i}(a',a) \quad \forall \quad a,a',i,j$$

As this will generally not be satisfied, we have to adjust either one or both acquisition rates. Let θ_k denote the degree to which gender k will adjust their behavior, with 1 denoting complete adjustment and 0 no adjustment at all. With the restriction $\theta_k + \theta_{k'} = 1$, balance is obtained when

$$c_{k,i,j}(a,a') = c_{k,i}(a)\left\{\frac{N_{k',j}(a')c_{k',j}(a')\rho_{k',j,i}(a',a)}{N_{k,i}(a)c_{k,i}(a)\rho_{k,i,j}(a,a')}\right\}^{\theta_k}$$

With $\rho_{k,i,j}(a, a')$ we denote the age- and sexual-activity category-related partner preference, i.e. preference of someone aged a in activity category i towards someone aged a' in activity category j. Mixing between sexual-activity categories is included by weighing for the partner acquisition rates of each category, and by allowing for a degree of assortativeness between partners from the same activity category. The latter is commonly represented by a mixing coefficient ε that takes the value 1 when mixing between sexual-activity categories is random, and 0 when fully assortative[2]

$$\rho_{k,i,j}(a,a') = \rho_k(a,a')\left[(1-\varepsilon)\delta(i,j) + \varepsilon\frac{N_{k',j}(a')c_{k',j}(a')}{\sum_{l=1}^{3} N_{k',l}(a')c_{k',l}(a')}\right]$$

Here, $\delta(i, j)$ is the Kronecker delta, that is: 1 if $i = j$ and 0 otherwise. The age-related partner preference $\rho_k(a, a')$ is modeled conditional on the age of the index and follows a mixture distribution. We assume that partner preference is either strictly assortative with respect to age or conforms to a skew-normal probability distribution

$$\rho_k(a, a' = A) = \varphi(a)\delta(\lfloor a \rfloor, \lfloor A \rfloor) + (1-\varphi(a))[\xi_k(a) + \omega_k(a)Q]$$

Again, δ is the Kronecker delta operating on integer ages (that is, the largest integers not greater than a and A). The age-specific parameter φ denotes the probability that partner acquisition is strictly assortative. The parameters ξ and ω are gender- and age-specific location and scale parameters, respectively, for the skew-normally distributed random variable Q with density function[3]

$$\phi(q;\alpha_k(a)) = 2\phi(q)\Phi(\alpha_k(a)q)$$

Here, Φ is the standard normal distribution function. The parameter α regulates the skewness and is defined on $(-\infty, \infty)$. At $\alpha = 0$, the distribution reduces to the normal density. Positive values of α relate to right-skewed distributions and $\alpha = \infty$ corresponds to the half-normal density with left-concentrated mass. The age-specific parameter estimates were summarized

by linear regression functions that were extrapolated to older age, except for the probability that partner acquisition is strictly assortative with respect to age: $\varphi = 0$ above the age of 24.

Lifetime risk of infection

Let $F(x)$ denote the lifetime infection risk as the probability that a woman born in year x will ever become infected with a specific high-risk HPV type. This quantity is calculated as

$$F(x) = \int_0^\infty \lambda(a, x+a) \exp\{-\Lambda(a,x) - \mathrm{M}(a)\} \int_0^a s_0(\tau) \exp\{\Lambda(\tau, x) - \Sigma(\tau)\} \mathrm{d}\tau \, \mathrm{d}a$$

$$\text{with } \Lambda(a,x) = \int_0^a \lambda(u, x+u) \mathrm{d}u \,,\ \mathrm{M}(a) = \int_0^a \mu(u) \mathrm{d}u \text{ and } \Sigma(a) = \int_0^a s_0(u) \mathrm{d}u$$

Here, $s_0(a)$ denotes the rate of starting sexual activity at age a and $\Sigma(a)$ is the cumulative hazard of losing virginity before age a. In addition, M(a) denotes the cumulative background mortality at age a and $\Lambda(a, x)$ denotes the cumulative force of infection that a woman born in year x has experienced at age a. The latter is obtained by weighing according to the age-specific frequency of women in each of the three non-virgin categories of sexual activity, as follows

$$\lambda(a, x+a) = \sum_{i=1}^{3} p_i(a) \lambda_{k=f,i}(a, x+a)$$

In modeling HPV transmission, we ignore the demographic impact of HPV vaccination and assume a stable sexual contact network. Hence, the frequency of women in each of the three non-virgin categories is taken to be the same for the various birth cohorts, as

$$p_i(a) = \frac{N_{k=f,i}(a)}{\sum_{i=1}^{3} N_{k=f,i}(a)}$$

Individual-based model

The individual-based model simulates health trajectories of a specific birth cohort of girls, from the age of 10 until they are deceased. Simulations were performed with discrete time steps of half a year. The pre-invasive part of the model consists of 14 parallel Markov chains, corresponding to an infection with HPV type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. The 6-month cumulative probabilities of type-specific HPV infection were calculated from the instantaneous forces of infection in the type-specific HPV transmission model, stratified by birth cohort, age and sexual activity. We considered the same categorization in sexual-activity categories as in the HPV transmission model, i.e. a virgin category and low, high, and very high activity. Likewise, switching between sexual-activity categories was incorporated along the same lines as in the HPV transmission model.

The structure of the individual-based model with regard to the natural history of type-specific high-risk HPV infection conforms that of the HPV transmission model, up to CIN2/3 for each high-risk HPV type. A major distinction of the individual-based model lies in the notion that a woman is characterized by multiple type-specific states at a certain time point. For example, she may be susceptible to HPV-51 infection while being resistant to HPV-31 reinfection due to previously acquired immunity against this type. At the same time, she may have a HPV-18-positive CIN1 and a HPV-16-positive CIN3. As multiple HPV infections

may progress or clear at different type-specific rates, each high-risk HPV type conjures a different risk of high-grade cervical lesions. To complement the HPV transmission model, the individual-based model specifies the development from CIN2/3 to cervical cancer via additional precancerous CIN3 stages that are characterized by decreasing probabilities of viral clearance and increasing rates of lesion progression with time elapsed since its occurrence (that do not depend on the high-risk HPV type that caused the precancerous lesion). These intermediate stages were used to accurately calibrate the model to detection of high-grade lesions in current screening practice and to historical data from the Dutch cancer registry. Cervical cancer itself is composed of two stages (FIGO1, FIGO2+), differing in death rate and (symptomatic) detection probability. Stage-specific survival of cervical cancer was based on registry data.

In the model, cervical screening is implemented according the current Dutch guidelines. That is, women between 30 and 60 years of age are invited to cytologic screening once every five years. Compliance per screening round is 80% and it is assumed that 10% of women never attend the screening program.[4,5] The referral policy is to send a woman to the gynecologist for colposcopy and a biopsy if the test result is moderate dyskaryosis or worse (comparable to ≥Pap3a2)[6] or if an otherwise abnormal smear is followed by a second one at 6 or 18 months. We used a 0.015 positive smear rate in CIN0, 0.40 in CIN1, and 0.50-0.75 in CIN2/3.[7] For simplicity, we assumed that high-grade CIN is always detected by colposcopically guided biopsy (possibly after multiple visits to the gynecologist) and that, if a woman is treated after detection of high-grade lesions, she is cleared of all concomitant high-risk HPV infections.

The age-specific probabilities of cervical cancer for each birth cohort were obtained by simulating 100 times the health trajectories of 100 000 girls, roughly to the size of female birth cohorts in the Netherlands since 1975.

Model parameterization

Parameters of the HPV transmission model are summarized in eTable 2. The force of infection is not listed, because it is a composite parameter, i.e. it is calculated from state variables and other parameters in the model. We used stable background mortality rates, taken from Dutch survival tables as of 2007 obtained from Statistics Netherlands (www.cbs.nl). Hysterectomy rates were taken from a publication of the Erasmus University in 1993.[8] The parameters for the sexual contact network were obtained from two large-scale surveys on sexual health and behavior in the Netherlands.[9,10] For some parameters we could not obtain reference values, hence we had to assume particular values. The probabilities to start sexual activity in the low- or high-activity category were chosen in such a manner that the age-specific proportions in each category were in line with survey outcomes. We assumed equal adjustment in the rates of partnership formation reported by men and women to achieve partnership balance, as well as random mixing between sexual-activity categories. We also assumed a similar duration of the acute infection period in men and women.

In the absence of Dutch data, we took the duration of HPV infection in men to be similar to that observed in a cohort study among 290 US males.[11] Type-specific parameters for viral

transmissibility, natural immunity and the course of high-risk HPV infection in women up to CIN2/3 were estimated from a prospective population-based randomized controlled trial among close to 45,000 women for the implementation of high-risk HPV testing in cervical screening in the Netherlands (POBASCAM), which has been described in detail elsewhere.[7] This was done by fitting the transmission model for each high-risk HPV type to the prevalence of type-specific DNA in cervical smears, as observed in the baseline round of POBASCAM.[12] Longitudinal observations from the same trial were added to the estimation framework to inform those parameters related to viral clearance and clinical progression.

Combining all type-specific parameters (those that best fitted the prevalence of each high-risk HPV type separately) in the individual-based model also yielded a satisfactory fit to the overall prevalence of high-risk HPV infection in normal smears (eFig 1A). Parameters related to progression from CIN2/3 via additional CIN3 states to cervical cancer were quantified by calibrating the individual-based model to detection of high-grade lesions in current screening practice and to the incidence of cervical cancer. Former figures were obtained from POBASCAM, whereas latter figures were obtained from Dutch registry data (www.ikcnet.nl). Model predictions for the current situation of five-yearly screening of women between 30 and 60 years of age agree well with observations in the POBASCAM study as regards the proportion of screened women with detected high-grade lesions (eFig 1B). The age-specific hazard of cervical cancer as predicted by our model fits the cancer registry data rather well up to 65 years of age, although the observed patterns tend to be somewhat flatter than the modeled cervical cancer hazard (eFig 1C). Our model severely underestimates the hazard of cervical cancer among 65+ year-old women in data up to 2008.

This may be due to suboptimal screening histories of women born before 1940, as organized screening in its current form was introduced in the Netherlands in 1992. The absolute incidence of cervical cancer in the Netherlands over the period 2000-2008 clearly shows a different age profile as compared to the incidence over the period 1990-1999 (eFig 1D). We deliberately did not incorporate cohort effects arising from the introduction of organized cervical cancer screening, to keep the focus of the analysis on the temporal impact of the introduction of HPV vaccination.

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eSupplement. HPV transmission model equations

$$\frac{\partial S_{k,0}(a,t)}{\partial a}+\frac{\partial S_{k,0}(a,t)}{\partial t}=-(s_{k,0}(a)+o_k(a)+\mu_k(a)+\sigma_k(a,t))S_{k,0}(a,t)+\psi(a)V_{k,0}(a,t)$$

$$\begin{aligned}\frac{\partial S_{k,1}(a,t)}{\partial a}+\frac{\partial S_{k,1}(a,t)}{\partial t}=&\ f_{k,1}s_{k,0}(a)S_{k,0}(a,t)+s_{k,21}(a)S_{k,2}(a,t)\\&-(s_{k,12}(a)+o_k(a)+\mu_k(a)+\sigma_k(a,t)+\lambda_{k,1}(a,t))S_{k,1}(a,t)\\&+\kappa R_{k,1}(a,t)+\psi(a)V_{k,1}(a,t)\end{aligned}$$

$$\begin{aligned}\frac{\partial S_{k,2}(a,t)}{\partial a}+\frac{\partial S_{k,2}(a,t)}{\partial t}=&\ f_{k,2}s_{k,0}(a)S_{k,0}(a,t)+s_{k,12}(a)S_{k,1}(a,t)+s_{k,32}(a)S_{k,3}(a,t)\\&-(s_{k,21}(a)+s_{k,23}(a)+o_k(a)+\mu_k(a)+\sigma_k(a,t)+\lambda_{k,2}(a,t))S_{k,2}(a,t)\\&+\kappa R_{k,2}(a,t)+\psi(a)V_{k,2}(a,t)\end{aligned}$$

$$\begin{aligned}\frac{\partial S_{k,3}(a,t)}{\partial a}+\frac{\partial S_{k,3}(a,t)}{\partial t}=&\ (1-f_{k,1}-f_{k,2})s_{k,0}(a)S_{k,0}(a,t)+s_{k,23}(a)S_{k,2}(a,t)\\&-(s_{k,32}(a)+o_k(a)+\mu_k(a)+\sigma_k(a,t)+\lambda_{k,3}(a,t))S_{k,3}(a,t)\\&+\kappa R_{k,3}(a,t)+\psi(a)V_{k,3}(a,t)\end{aligned}$$

$$\begin{aligned}\frac{\partial I_{k,1}(a,t)}{\partial a}+\frac{\partial I_{k,1}(a,t)}{\partial t}=&\ \lambda_{k,1}(a,t)S_{k,1}(a,t)+s_{k,21}(a)I_{k,2}(a,t)\\&-(s_{k,12}(a)+o_k(a)+\mu_k(a)+\gamma_k+\eta_k)I_{k,1}(a,t)\end{aligned}$$

$$\begin{aligned}\frac{\partial I_{k,2}(a,t)}{\partial a}+\frac{\partial I_{k,2}(a,t)}{\partial t}=&\ \lambda_{k,2}(a,t)S_{k,2}(a,t)+s_{k,12}(a)I_{k,1}(a,t)+s_{k,32}(a)I_{k,3}(a,t)\\&-(s_{k,21}(a)+s_{k,23}(a)+o_k(a)+\mu_k(a)+\gamma_k+\eta_k)I_{k,2}(a,t)\end{aligned}$$

$$\begin{aligned}\frac{\partial I_{k,3}(a,t)}{\partial a}+\frac{\partial I_{k,3}(a,t)}{\partial t}=&\ \lambda_{k,3}(a,t)S_{k,3}(a,t)+s_{k,23}(a)I_{k,2}(a,t)\\&-(s_{k,32}(a)+o_k(a)+\mu_k(a)+\gamma_k+\eta_k)I_{k,3}(a,t)\end{aligned}$$

$$\begin{aligned}\frac{\partial I^p_{k,1}(a,t)}{\partial a}+\frac{\partial I^p_{k,1}(a,t)}{\partial t}=&\ \eta_k I_{k,1}(a,t)+s_{k,21}(a)I^p_{k,2}(a,t)\\&-(s_{k,12}(a)+o_k(a)+\mu_k(a)+\nu+\chi)I^p_{k,1}(a,t)\end{aligned}$$

$$\begin{aligned}\frac{\partial I^p_{k,2}(a,t)}{\partial a}+\frac{\partial I^p_{k,2}(a,t)}{\partial t}=&\ \eta_k I_{k,2}(a,t)+s_{k,12}(a)I^p_{k,1}(a,t)+s_{k,32}(a)I^p_{k,3}(a,t)\\&-(s_{k,21}(a)+s_{k,23}(a)+o_k(a)+\mu_k(a)+\nu+\chi)I^p_{k,2}(a,t)\end{aligned}$$

$$\begin{aligned}\frac{\partial I^p_{k,3}(a,t)}{\partial a}+\frac{\partial I^p_{k,3}(a,t)}{\partial t}=&\ \eta_k I_{k,2}(a,t)+s_{k,23}(a)I^p_{k,2}(a,t)\\&-(s_{k,32}(a)+o_k(a)+\mu_k(a)+\nu+\chi)I^p_{k,3}(a,t)\end{aligned}$$

$$\frac{\partial I_{k,1}^{pd}(a,t)}{\partial a}+\frac{\partial I_{k,1}^{pd}(a,t)}{\partial t}=\nu\, I_{k,1}^{p}(a,t)+s_{k,21}(a)I_{k,2}^{pd}(a,t)$$
$$-(s_{k,12}(a)+o_k(a)+\mu_k(a)+\chi+\pi(a))I_{k,1}^{pd}(a,t)$$

$$\frac{\partial I_{k,2}^{pd}(a,t)}{\partial a}+\frac{\partial I_{k,2}^{pd}(a,t)}{\partial t}=\nu\, I_{k,2}^{p}(a,t)+s_{k,12}(a)I_{k,1}^{pd}(a,t)+s_{k,32}(a)I_{k,3}^{pd}(a,t)$$
$$-(s_{k,21}(a)+s_{k,23}(a)+o_k(a)+\mu_k(a)+\chi+\pi(a))I_{k,2}^{pd}(a,t)$$

$$\frac{\partial I_{k,3}^{pd}(a,t)}{\partial a}+\frac{\partial I_{k,3}^{pd}(a,t)}{\partial t}=\nu\, I_{k,2}^{p}(a,t)+s_{k,23}(a)I_{k,2}^{pd}(a,t)$$
$$-(s_{k,32}(a)+o_k(a)+\mu_k(a)+\chi+\pi(a))I_{k,3}^{pd}(a,t)$$

$$\frac{\partial R_{k,1}(a,t)}{\partial a}+\frac{\partial R_{k,1}(a,t)}{\partial t}=\gamma_k I_{k,1}(a,t)+\chi\, I_{k,1}^{p}(a,t)+(\chi+\pi(a))I_{k,1}^{pd}(a,t)+s_{k,21}(a)R_{k,2}(a,t)$$
$$-(s_{k,12}(a)+o_k(a)+\mu_k(a)+\kappa)R_{k,1}(a,t)$$

$$\frac{\partial R_{k,2}(a,t)}{\partial a}+\frac{\partial R_{k,2}(a,t)}{\partial t}=\gamma_k I_{k,2}(a,t)+\chi\, I_{k,2}^{p}(a,t)+(\chi+\pi(a))I_{k,2}^{pd}(a,t)+s_{k,12}(a)R_{k,1}(a,t)+s_{k,32}(a)R_{k,3}(a,t)$$
$$-(s_{k,21}(a)+s_{k,23}(a)+o_k(a)+\mu_k(a)+\kappa)R_{k,2}(a,t)$$

$$\frac{\partial R_{k,3}(a,t)}{\partial a}+\frac{\partial R_{k,3}(a,t)}{\partial t}=\gamma_k I_{k,3}(a,t)+\chi\, I_{k,3}^{p}(a,t)+(\chi+\pi(a))I_{k,3}^{pd}(a,t)+s_{k,23}(a)R_{k,2}(a,t)$$
$$-(s_{k,32}(a)+o_k(a)+\mu_k(a)+\kappa)R_{k,3}(a,t)$$

$$\frac{\partial V_{k,0}(a,t)}{\partial a}+\frac{\partial V_{k,0}(a,t)}{\partial t}=\sigma_k(a,t)S_{k,0}(a,t)-(s_{k,0}(a)+o_k(a)+\mu_k(a)+\psi(a))V_{k,0}(a,t)$$

$$\frac{\partial V_{k,1}(a,t)}{\partial a}+\frac{\partial V_{k,1}(a,t)}{\partial t}=\sigma_k(a,t)S_{k,1}(a,t)+f_{k,1}s_{k,0}(a)V_{k,0}(a,t)+s_{k,21}(a)V_{k,2}(a,t)$$
$$-(s_{k,12}(a)+o_k(a)+\mu_k(a)+\psi(a))V_{k,1}(a,t)$$

$$\frac{\partial V_{k,2}(a,t)}{\partial a}+\frac{\partial V_{k,2}(a,t)}{\partial t}=\sigma_k(a,t)S_{k,2}(a,t)+f_{k,2}s_{k,0}(a)V_{k,0}(a,t)+s_{k,12}(a)V_{k,1}(a,t)+s_{k,32}(a)V_{k,3}(a,t)$$
$$-(s_{k,21}(a)+s_{k,23}(a)+o_k(a)+\mu_k(a)+\psi(a))V_{k,2}(a,t)$$

$$\frac{\partial V_{k,3}(a,t)}{\partial a}+\frac{\partial V_{k,3}(a,t)}{\partial t}=\sigma_k(a,t)S_{k,3}(a,t)+(1-f_{k,1}-f_{k,2})s_{k,0}(a)V_{k,0}(a,t)+s_{k,23}(a)V_{k,2}(a,t)$$
$$-(s_{k,32}(a)+o_k(a)+\mu_k(a)+\psi(a))V_{k,3}(a,t)$$

$$\frac{\partial O_{k,0}(a,t)}{\partial a}+\frac{\partial O_{k,0}(a,t)}{\partial t}=o_k(a)(S_{k,0}(a,t)+V_{k,0}(a,t))-(s_{k,0}(a)+\mu_k(a))O_{k,0}(a,t)$$

$$\frac{\partial O_{k,1}(a,t)}{\partial a}+\frac{\partial O_{k,1}(a,t)}{\partial t}=o_k(a)(S_{k,1}(a,t)+I_{k,1}(a,t)+I_{k,1}^{p}(a,t)+I_{k,1}^{pd}(a,t)+R_{k,1}(a,t)+V_{k,1}(a,t))$$
$$+f_{k,1}s_{k,0}(a)O_{k,0}(a,t)+s_{k,21}(a)O_{k,2}(a,t)-(s_{k,12}(a)+\mu_k(a))O_{k,1}(a,t)$$

$$\frac{\partial O_{k,2}(a,t)}{\partial a}+\frac{\partial O_{k,2}(a,t)}{\partial t}=o_k(a)(S_{k,2}(a,t)+I_{k,2}(a,t)+I_{k,2}^{p}(a,t)+I_{k,2}^{pd}(a,t)+R_{k,2}(a,t)+V_{k,2}(a,t))$$
$$+f_{k,2}s_{k,0}(a)O_{k,0}(a,t)+s_{k,12}(a)O_{k,1}(a,t)+s_{k,32}(a)O_{k,3}(a,t)$$
$$-(s_{k,21}(a)+s_{k,23}(a)+\mu_k(a))O_{k,2}(a,t)$$
$$\frac{\partial O_{k,3}(a,t)}{\partial a}+\frac{\partial O_{k,3}(a,t)}{\partial t}=o_k(a)(S_{k,3}(a,t)+I_{k,3}(a,t)+I_{k,3}^{p}(a,t)+I_{k,3}^{pd}(a,t)+R_{k,3}(a,t)+V_{k,3}(a,t))$$
$$+(1-f_{k,1}-f_{k,2})s_{k,0}(a)O_{k,0}(a,t)+s_{k,23}(a)O_{k,2}(a,t)-(s_{k,32}(a)+\mu_k(a))O_{k,3}(a,t)$$

eTable 1. Description of state variables in the HPV transmission model

$S_{k,0}(a,t)$	Virgins (gender *k*, age *a*) at time *t*
$S_{k,i}(a,t)$	Persons (gender *k*, age *a*, sexual activity *i*) susceptible to HPV type at time *t*
$I_{k,i}(a,t)$	Persons (gender *k*, age *a*, sexual activity *i*) infected with HPV type at time *t*
$I_{f,i}^{p}(a,t)$	Women (age *a*, sexual activity *i*) with low-grade lesions linked to HPV type at time *t*
$I_{f,i}^{pd}(a,t)$	Women (age *a*, sexual activity *i*) with high-grade lesions linked to HPV type at time *t*
$R_{k,i}(a,t)$	Persons (gender *k*, age *a*, sexual activity *i*) resistant to HPV type at time *t*
$V_{f,0}(a,t)$	Female virgins (age *a*) vaccine-protected against HPV type at time *t*
$V_{f,i}(a,t)$	Women (age *a*, sexual activity *i*) vaccine-protected against HPV type at time *t*
$O_{f,0}(a,t)$	Female virgins (age *a*) with a history of hysterectomy at time *t*
$O_{f,i}(a,t)$	Women (age *a*, sexual activity *i*) with a history of hysterectomy at time *t*

eTable 2. Description and data sources of model parameters

Parameter	Description	Value (Source)
$\mu_k(a)$	Mortality rate (by gender *k* and age *a*)	Historic (1)
$o_f(a)$	Hysterectomy rate among women	Historic (2)
$s_{k,0}(a)$	Rate of losing virginity	Calibrated (3)
$f_{k,1}$ [a]	Probability of starting sexual activity in the low-activity category	0.66 (-)
$f_{k,2}$ [a]	Probability of starting sexual activity in the high-activity category	0.33 (-)
$s_{k,ij}(a)$	Rate of switching from sexual activity category *i* to *j*	Calibrated (3)
$c_{k,1}(a)$ [a]	Number of new partners per year for persons with low activity	0.3; 0.2 [b] (3)
$c_{m,2}(a)$	Number of new partners per year for men with high activity	1.5; 0.2 [b] (3)
$c_{f,2}(a)$	Number of new partners per year for women with high activity	1.3; 0.2 [b] (3)
$c_{m,3}(a)$	Number of new partners per year for men with very high activity	12 [c] (3)
$c_{f,3}(a)$	Number of new partners per year for women with very high activity	9 [c] (3)
θ_f	Degree to which contact rates among women are adjusted	0.5 (-)
ε	Mixing coefficient by category of sexual activity	1 (-)
$\varphi_k(a)$ [a]	Probability that partner acquisition is strictly assortative with respect to age	0.35 [d] (3)
$\xi_m(a)$	Location of skew-normal probability distribution for male preference	12–51 [e] (3)
$\xi_f(a)$	Location of skew-normal probability distribution for female preference	12–69 [e] (3)
$\omega_m(a)$	Scale of skew-normal probability distribution for male preference	2.3–15 [e] (3)

$\omega_f(a)$	Scale of skew-normal probability distribution for female preference	4.7–11 [e] (3)
$\alpha_m(a)$	Skewness of skew-normal probability distribution for male preference	3 [c] (3)
$\alpha_f(a)$	Skewness of skew-normal probability distribution for female preference	2 [c] (3)
$\pi(a)$	Treatment rate of high-grade lesions in cervical screening	0.139 yr^{-1} [f] (4)
γ_m	Clearance rate of acute infection among men	1.5 yr^{-1} (5)
η_f	Rate of developing persistent infection among women	$\gamma_m - \gamma_f$ (-)
γ_f	Clearance rate of acute infection among women	Estimated (6)
ν	Rate of developing high-grade lesions among women	Estimated (6)
χ	Clearance rate of persistent infection	Estimated (6)
κ	Rate of losing resistance to infection	Estimated (6)
β	Transmission probability per infected-susceptible partnership	Estimated (6)
$\sigma_f(a,t)$	Vaccination rate of pre-adolescent girls	Variable
$\psi(a)$	Rate of losing vaccine protection	Variable

(1) Statistics Netherlands (www.cbs.nl)

(2) van Ballegooijen et al. (1993)

(3) de Graaf et al. (2005); Bakker & Vanwesenbeeck (2006)

(4) Rebolj et al. (2006); Bulk et al. (2007)

(5) Giuliano et al. (2008)

(6) Bogaards et al. (2010)

[a] Similar value for men ($k = m$) and women ($k = f$)

[b] Mean; standard deviation for age-specific values

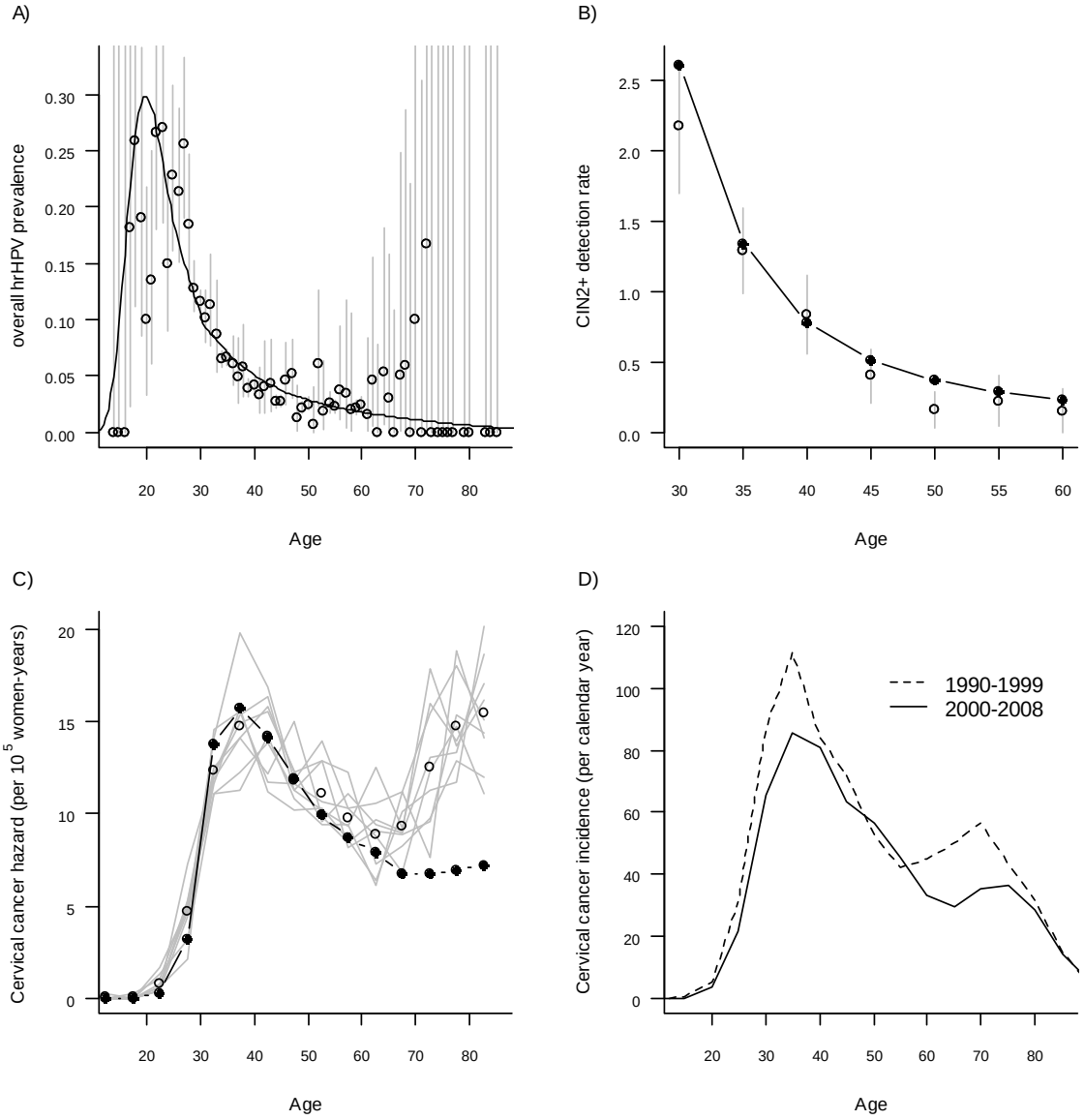
[c] Constant value across age range

[d] Constant value until age 22, linear decline to 0 at age 25

[e] Linear increase from age 12 to age 75

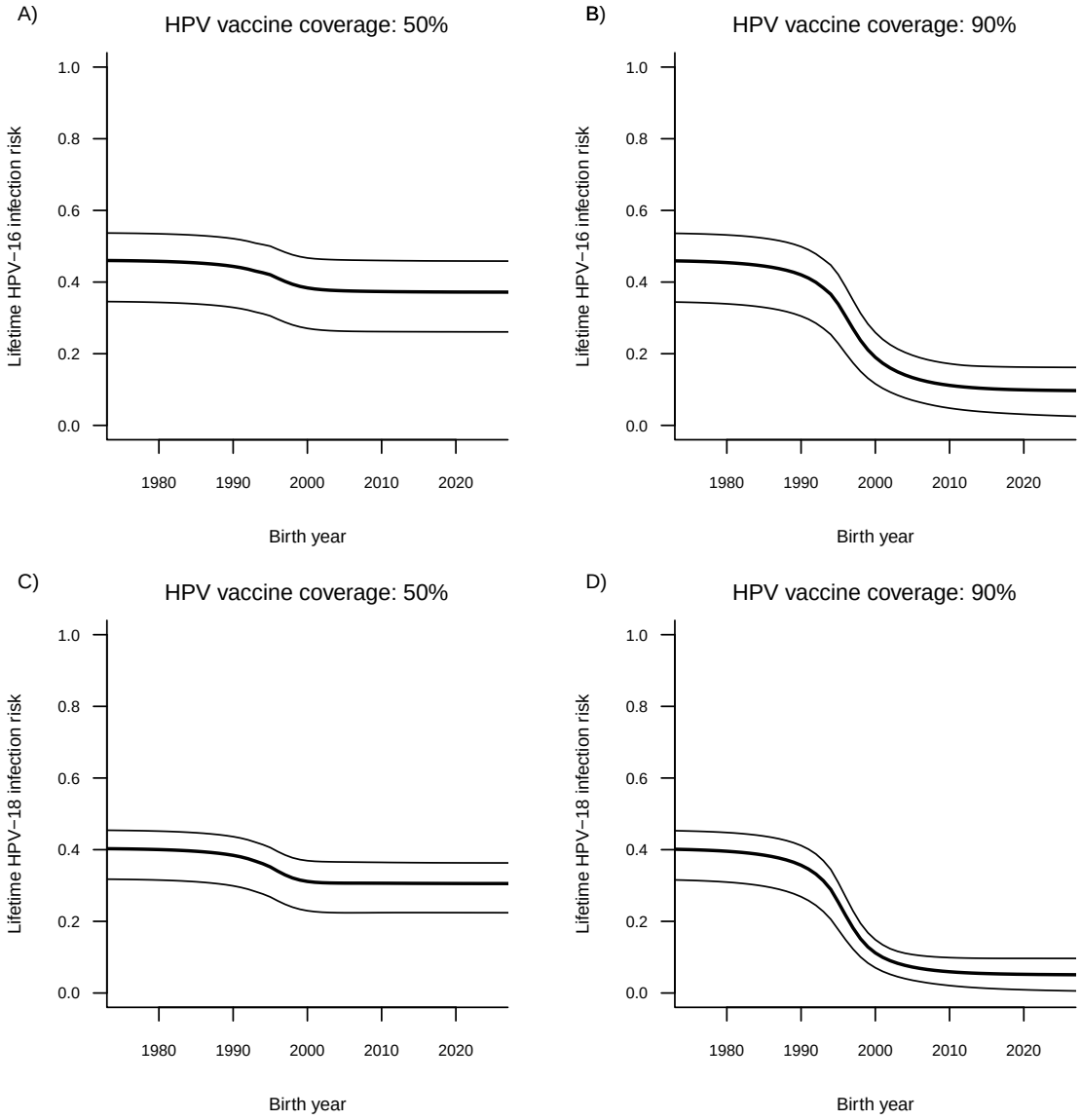
[f] Constant value from age 30 to age 65, 0 outside this age range

eFigure 1.



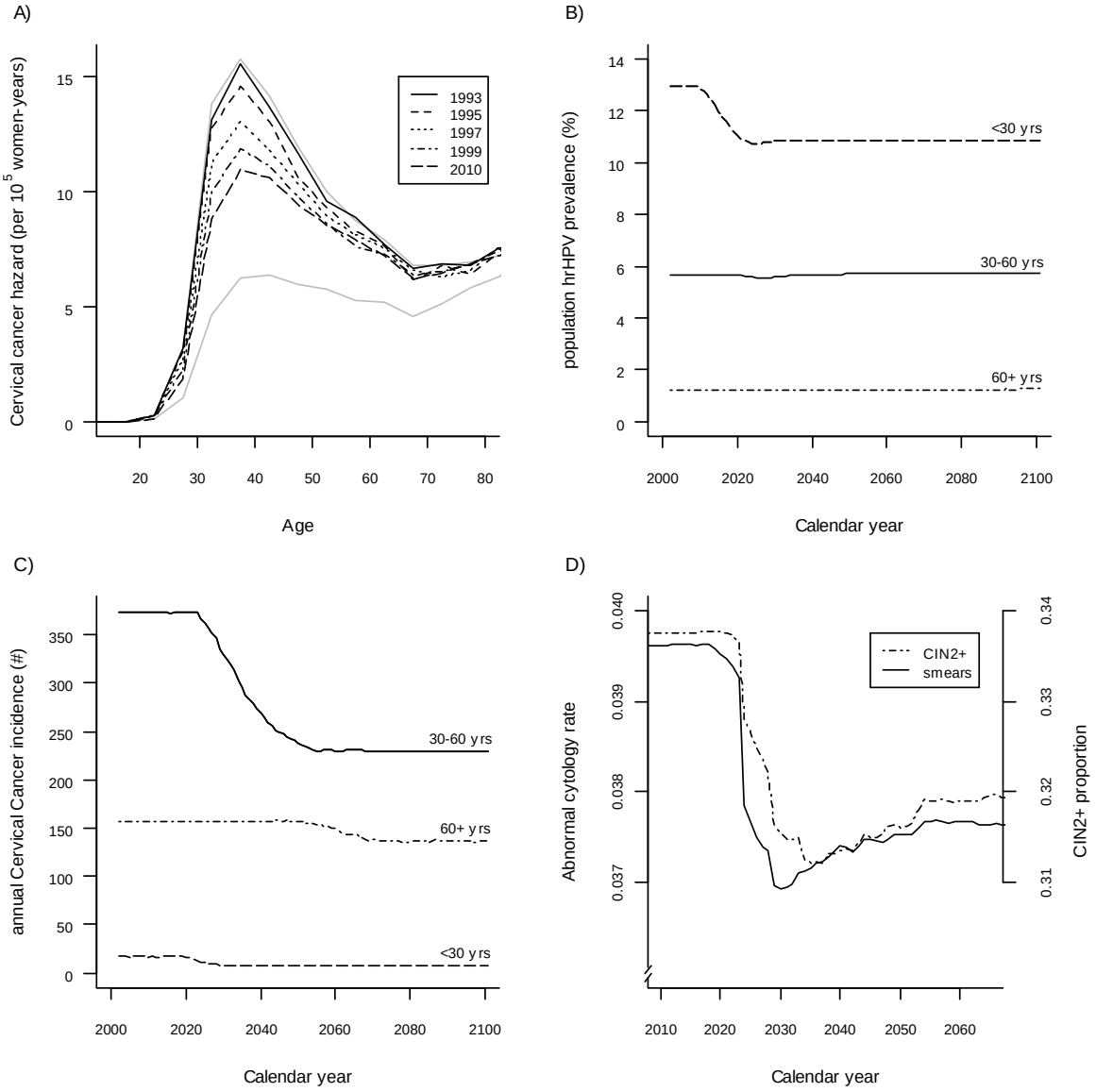
The prevalence of high-risk HPV infection (any type) in normal cytology (A), the proportion of screened women with detected CIN2/3 lesions (B), the hazard of cervical cancer (C) and the mean annual number of cancer cases as registered over two time periods (D). Model predictions in (A), (B), and (C) are represented by black curves. Open circles in (A) and (B) represent POBASCAM data, grey lines show 95% confidence intervals. Open circles in (C) represent averages from the cancer registry over the period 2000-2008, grey lines show individual year curves.

eFigure 2.



The lifetime risk of HPV-16 infection according birth year of non-vaccinated women under constant 50% (A) or 90% (B) vaccine coverage, and that of HPV-18 infection under constant 50% (C) or 90% (D) vaccine coverage. Vaccination is started in 2010 and is assumed to induce lifelong protection to HPV-16/18 infection. Thick curves show medians and thin curves denote 95% credible intervals of model-based predictions, based on the joint posterior distribution of type-specific parameters inferred from pre-vaccine data on HPV-16/18 infection.

eFigure 3.



Results of an analysis with 50% vaccine coverage and vaccine protection for a median of 15 years: (A) shows the hazard of cervical cancer for non-vaccinated women according birth cohort (see legend); (B) shows the population prevalence of high-risk HPV infection by calendar year in women aged <30 years, 30-60 years or >60 years; (C) shows the incidence of cervical cancer by calendar year in women aged <30 years, 30-60 years or >60 years; and (D) shows the projected abnormal cytology rate and the CIN2/3 proportion of abnormal smears.