TECHNICAL APPENDIX
HPV-ADVISE US

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1 MODEL STRUCTURE

The model structure is identical to HPV-Advise Canada.[1-3] HPV- Advise is programmed in C++ compatible with the 2020 ISO standard (C++2020).

1.1 Demography

The population modeled represents the heterosexual population of the United States (US). We assume an open stable population. Ten-year-old individuals enter the population (with a 1:1 male to female ratio) at a rate η chosen to balance US age-specific death rates $\mu_g(a)$, where g and a represent gender and age, respectively. The equilibrium age distribution of the population is found by running the demographic model (i.e. model without HPV infection) for 1,000 years. Individuals younger than 10 years old are not included in the model because they have a very low prevalence of sexually acquired HPV infection. See details on demographic parameters in Section 2.2.1.

1.2 Sexual behavior and HPV Transmission

1.2.1 Sexual activity levels

Upon entry in the simulated population, 10-year-olds are assigned a level of sexual activity from low ($l = 0$) to high ($l = 3$). See Section 2.2.2 for the prior and posterior distributions of the fractions of individuals Φ_l assigned to each level. 10-year-old girls are assumed to begin sexual activity at a rate $\phi_l(a)$ that depends on their age and level of sexual activity. A specific partner acquisition rate $\theta_{g,l}(a)$ (i.e., number of new partner acquisitions per year) is then attributed to each sexual activity level by age (see Section 2.2.2 for details and parameter values).

1.2.2 Partnership formation and separation process

The model is based on a stochastic pair formation and separation process, which represents the underlying structure of the sexual contact pattern. We model sequential monogamous stable and casual partnerships. Concurrent partnerships are not simulated. The partnership formation and separation process is driven by females as illustrated in Figure A1. Each woman has an associated age and level of sexual activity specific rate of either forming a new partnership if they are single $\zeta_l(a)$, or separating $\sigma_l(a)$ if they are currently involved in a stable partnership. When a new partnership is formed, the male partner is selected according to a mixing matrix $\boldsymbol{\Omega} = [\Omega_{a,l,a',l'}]$, which reflects the

preferences of an individual of age a and level of sexual activity l for individuals of age a' and level of sexual activity l' (see next section for details on the mixing matrices). If no male partner is available in the selected category, no partnership is formed. All newly formed partnerships have an age and level of sexual activity specific probability of being stable $\psi_l(a)$ (see details and parameter values in Section 2.2.2).

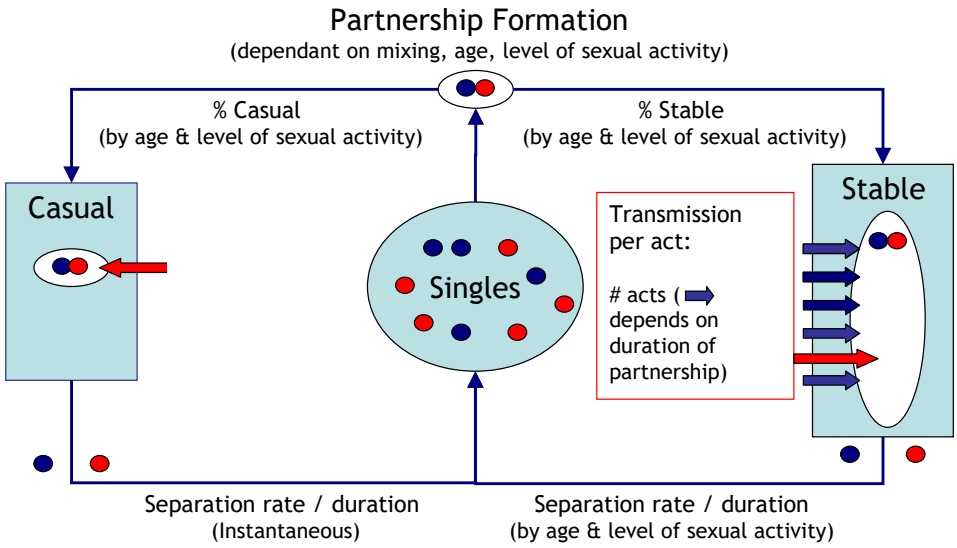


Figure A1. Partnership formation and separation process. Plain red circles represent infectious individuals, and red arrows represent HPV transmission. Casual partnerships occur instantaneously, whereas stable partnerships have a duration dependent on age and level of sexual activity.

The partnership formation rates of single females $\zeta_l(a)$ is derived from the partner acquisition rates $\theta_{g,l}(a)$ and the age and level of sexual activity specific proportions of stable partnerships $\Psi_l(a)$ taking into account the proportions of individuals not available for partnership formation as follows:

$$\zeta_l(a) = \frac{\theta_{g,l}(a)}{(1-\Psi_l(a))}\ , \qquad (1.1)$$

where g, a and l represent gender, age and sexual activity level, respectively (refer to Table A27 for the list of all symbols).

1.2.3 Contact/Network structure

Mixing by sexual activity level

The sexual activity mixing matrix, $\mathbf{\Gamma} = [\Gamma_{l,l',g}]$, defines the probability that an individual of gender g and level of sexual activity l forms a partnership with someone of the opposite gender in level of sexual activity l'. The matrix is computed as follows [4]:

$$\Gamma_{l,l',g} = \frac{W_{l,l',g} \sum_{a'} \{N_{l',g'}(a') \cdot \theta_{g',l'}(a')\}}{\sum_{l'} \left\{ W_{l,l',g} \sum_{a'} [N_{l',g'}(a') \cdot \theta_{g',l'}(a')] \right\}}, \quad (1.2)$$

where $N_{l,g}(a)$ is the number of individuals of gender g, sexual activity level l and age group a, $\theta_{g,l}(a)$ is the mean rate of sexual partner acquisition for gender g, sexual activity level l and age group a, and $W_{l,l',g}$ defines a set of weights corresponding to the preference of an individual of gender g and sexual activity level l for someone of the opposite gender with sexual activity level l' (preference matrix).

Detailed data on each element of the mixing matrix by degree is rarely available and therefore, the preference matrix is often summarized by the assortative degree parameter κ (See Section 2.2.2). The preference matrix is defined as follows [4]:

$$W_{l,l',g} = \begin{cases} \kappa, \text{ if } l = l' \\ 1, \text{ if } l \neq l' \end{cases} \quad (1.3)$$

Where $\kappa > 1$ represents assortative mixing; $\kappa = 1$ is proportionate mixing and $\kappa < 1$ disassortative mixing.

Mixing by age

Similarly, the age mixing matrix, $\mathbf{\Lambda} = [\Lambda_{a,a',l,g}]$, defines the probability that an individual of gender g in age group a and sexual activity level l forms a partnership with someone of the opposite gender in age group a'. This age mixing matrix is thus level of sexual activity-specific and was derived from observed data as explained in Section 2.2.2.

Global mixing matrix

The global mixing matrix, $\mathbf{\Omega} = [\Omega_{al,a'l'}]$, is the product of the mixing matrix by age and by sexual activity level:

$$\Omega_{al,a'l'} = \Gamma_{l,l',g=1} \cdot \Lambda_{a,a',l,g=1} \quad (1.4)$$

Because the partnership formation and dissolution process is driven by females, we computed only female matrices, $g = 1$.

1.3 Natural History of HPV-related diseases

1.3.1 Squamous cell carcinoma

HPV-ADVISE US models the following 18 HPV genotypes individually and independently: 16, 18, 6, 11, 31, 33, 45, 52, 58, 35, 39, 51, 56, 59, 66, 68, 73, and 82. That is, we assume that infection with a given genotype does not protect against infection or alter disease progression with the other genotypes (i.e. no partial or mutual exclusion). Our model reproduces progression/clearance through different clinical cytological classifications (e.g., CIN1 to CIN3), and the course of underlying HPV infection progression/clearance to CIN3 based on duration of infection and HPV-type. The infection status (susceptible, infected, and immune) of each individual is type-specific and, therefore, an individual can be infected with multiple genotypes at the same time. This assumption is particularly important as co-infections occur frequently[5-10]. Infected women can either clear the infection and return to immune/susceptible status or remain infected (Infected 1-4) and progress in the model to more severe stages of cervical intraepithelial lesions of grade 1 (CIN1), 2 (CIN2) or 3 (CIN3), and invasive squamous cervical cancer (SCC) of stage 1 (localized), stage 2 (regional) or stage 3 (distant). Women with CIN may also regress to a less severe stage or clear the infection and directly return to susceptible/immune status. For transmission probabilities and clearance, progression and regression rates see Section 2.2.3.

1.3.2 Anogenital warts

In HPV-ADVISE US, individuals have a joint probability of developing and being diagnosed with anogenital warts (AGW) or clearing their infection. Individuals can experience multiple episodes of AGW through recurrence of a persistent infection, re-infection with a previously cleared HPV-type or infection with a new HPV-type.

1.3.3 Other HPV-related diseases

In HPV-ADVISE US, infected individuals have a gender- and type-specific probability of progressing towards cervical adenocarcinoma, and cancers of the anus, oropharynx, vulva, vagina, and penis. The time of progression from persistent infection to cancer is also gender- and type-specific.

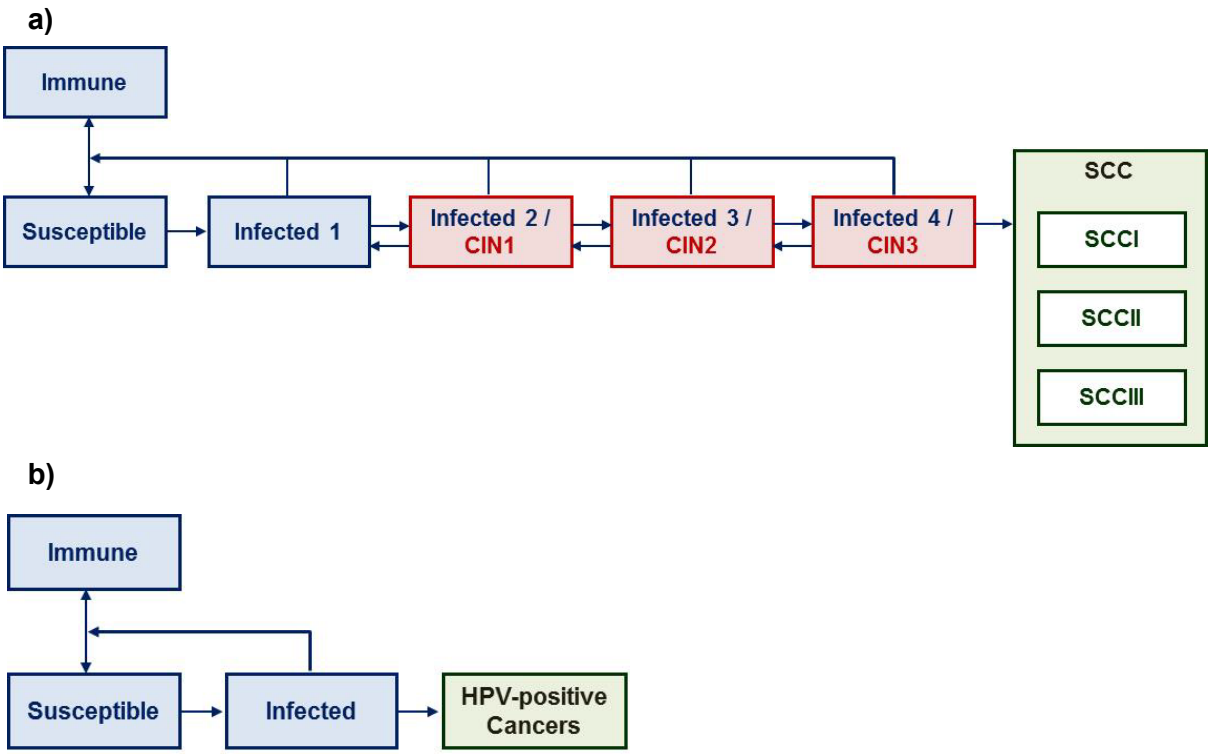


Figure A2. Flow diagram of a) the natural history of HPV infection and squamous cell carcinoma in the absence of screening, and b) other HPV-related cancers (cervical adenocarcinoma, and cancers of the anus, oropharynx, vulva, vagina, and penis). The mutually exclusive compartments represent the different HPV epidemiological states. Arrows represent the possible HPV-type specific transitions between these states for each individual. Arrows represent the possible HPV-type, age, and gender specific transitions between these states for each individual.

1.4 Screening and treatments

1.4.1 Screening behavior levels

Upon entry in the simulated population, 10-year-old females are assigned a level of screening behavior based on the interval between two routine screening tests. The levels of screening behavior range from a short interval between two routine screening tests ($S = 0$) to never being screened ($S = 4$). Please see Section 2.2.4 for the distribution of women assigned to each level of screening behavior.

In HPV-ADVISE US, women are assumed to begin cervical cancer screening at an age-specific rate. A specific screening rate (i.e. Pap or HPV test per year) is then attributed to each screening behavior level (see Section 2.1.4 for details and parameters values).

1.4.2 Screening performance for the detection of cervical lesions

Depending on their true health state (Figure A2), women tested using cytology or colposcopy are given probabilities of being diagnosed with different results. For example, a woman with CIN1 has probabilities of 37.0%, 14.5%, 40.5% and 8.0% of having a normal, ASCUS, LSIL, or HSIL cytology result, respectively. See Section 2.2.4 for the health state-specific probabilities and references for parameter values. In addition to the probability of being detected by screening, women with SCC also have a probability of developing symptoms and being diagnosed outside of the screening program. See Table A18 of Section 2.2.3 for details, parameters values and references.

1.4.3 Screening performance for HPV testing

Depending on the true infection status (infected or uninfected), women tested using a HPV DNA test are given a probability of being diagnosed either positive or negative for infection with a HR-HPV type. See Section 2.2.4 for the infection state-specific probabilities.

1.4.4 Management of women with abnormal cytology or HPV+

In the United States, cervical cancer screening has traditionally been based on Pap tests. However, recently screening guidelines have been changed[11]. In 2012, recommendations from American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), American Society for Clinical Pathology (ASCP), US Preventive Services Task Force (USPSTF), and the American College of Obstetricians and Gynecologists (ACOG) changed their guidelines to the following: 1) 21-29 year-olds should have a cytology test every 3 years, 2) 30-65 year-olds have the choice between cytology every 3 years or cytology with HPV co-testing every 5 years. Algorithms for the management of women with abnormal cytology and/or HPV+ and histology results are presented below and are based on the 2012 updated consensus for the management of abnormal cervical cancer screening test and cancer precursors[12]. These algorithms are independent of age and are a function of cytology, histology and/or HPV test results.

Cytology - Management of women with ASC-US and LSIL. Women with a cytology result of atypical squamous cells of undetermined significance (ASC-US) or low–grade squamous intraepithelial lesions (LSIL) are followed-up with repeat cervical cytological testing at 6-month intervals until 2 consecutive negative tests are obtained. Given that some guidelines also recommend a colposcopic examination for women with LSIL, we

assumed that a small proportion of these women would be referred directly for colposcopy/biopsy. Women with ASC-US or more severe cytologic abnormality on a repeat cytology test are referred to colposcopy/biospy for histological diagnosis. Depending on the colposcopy/biospy results, women can either return to routine screening (normal result), be monitored with repeat cervical cytology testing every 6 months for 2 years (CIN1) and return to routine screening after 2 consecutive normal results or be treated (CIN1 persistent for 2 years, CIN2+). The treatment of CIN can fail and have no impact on the natural history of the disease or be successful. If the treatment is successful, the lesion might clear but the woman remains infected, or both the lesion and the infection might clear. The treatment of SCC can also fail and lead to death (see 5-year survival rates in Section 2.2.3). Finally, although loss to follow-up can occur at every step of the algorithm, to simplify the model and because detailed data on lost to follow-up at every step were not available, we used a lesion-specific global estimate of the proportion of women lost throughout the follow-up.

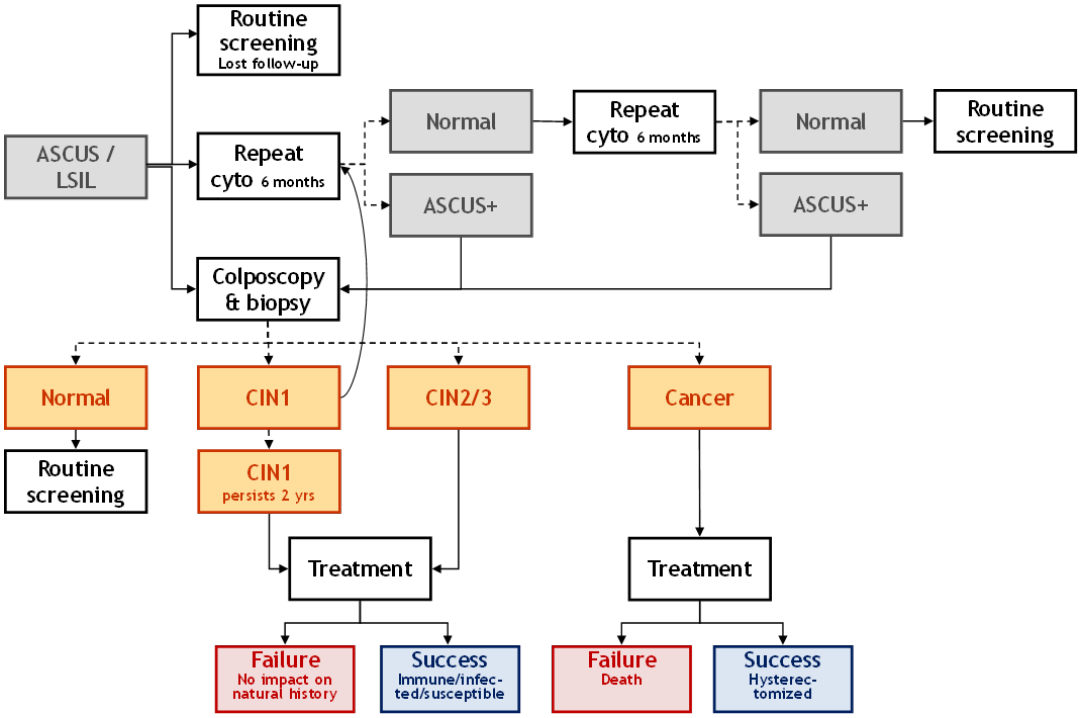


Figure A3. Management of women with ASC-US and LSIL. Gray boxes represent cytological results, white boxes represent screening, diagnosis and treatment procedures, orange boxes represent the colposcopy results and red and blue boxes represent treatment failure and success, respectively. Solid lines represent model parameters whereas dashed lines represent model outputs based on the natural history of disease.

Cytology - Management of women with HSIL, ASC-H and SCC. Women with high-grade squamous intraepithelial lesions (HSIL), atypical squamous cells-cannot exclude HSIL (ASC-H) and squamous cell carcinomas (SCC) are directly referred to colposcopy/biopsy for histological diagnosis. Women who obtain a normal or a CIN1 result at the colposcopic exam are monitored using repeat colposcopy every 6 months for 1 year. After two consecutive normal results, women are returned to routine screening. However, if CIN1 persists for 1 year or if lesions ≥ CIN2 are diagnosed, women are treated. Outcomes of treatment are similar to those previously described.

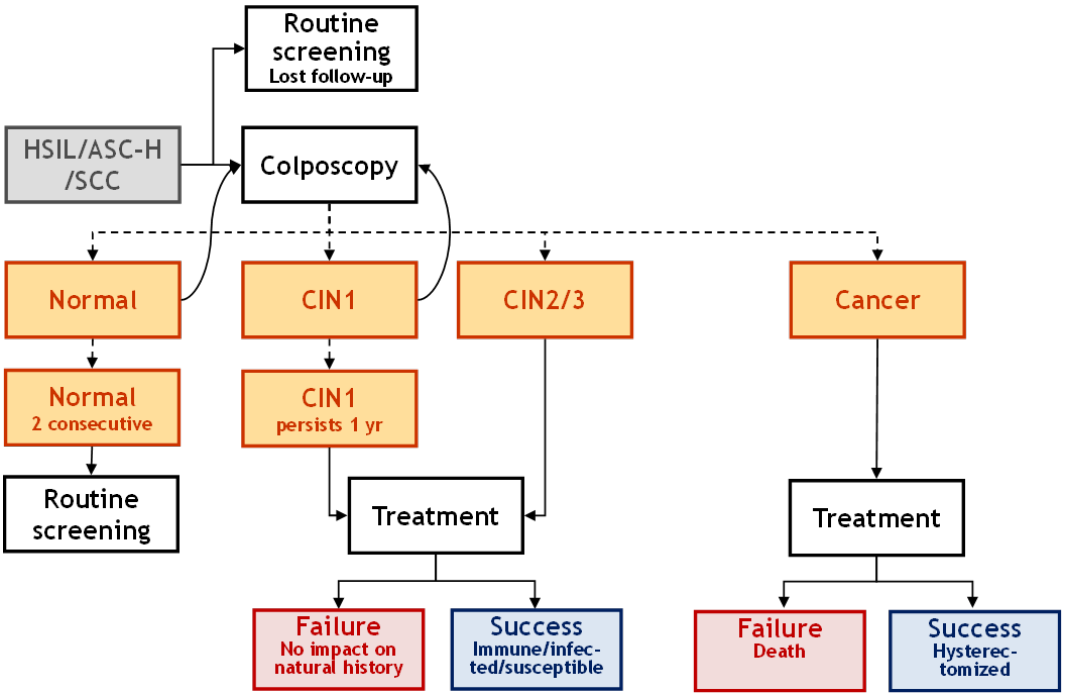


Figure A4. Management of women with HSIL and ASC-H. Gray boxes represent cytological results, white boxes represent screening, diagnosis and treatment procedures, orange boxes represent the colposcopy results and red and blue boxes represent treatment failure and success, respectively. Solid lines represent model parameters whereas dashed lines represent model outputs based on the natural history of disease.

HPV co-testing – Management of women with negative or positive HPV-test

Figure A5 illustrates the management of women with cytology and HPV DNA co-test results. Women with a negative HPV-test result and normal cytology continue to be followed-up in routine screening (co-testing every 5 years). Women with a negative HPV-test result and cytology result of ASC-US and LSIL are followed-up with repeated co-testing every 1 and 3 years, respectively. Women with a negative HPV-test and HSIL,

ASC-H or SCC are directly referred to colposcopy/biopsy for histological diagnosis, and managed similarly to those with cytology-only screening (Figure A4).

Women with a positive HPV-test result and normal cytology are followed-up with repeated co-testing every year. Women with a positive HPV-test result and abnormal cytology result (ASC-US, LSIL HSIL, ASC-H or SCC) are directly referred to colposcopy/biopsy for histological diagnosis. See Figure A4 for management following a colposcopy/biopsy result.

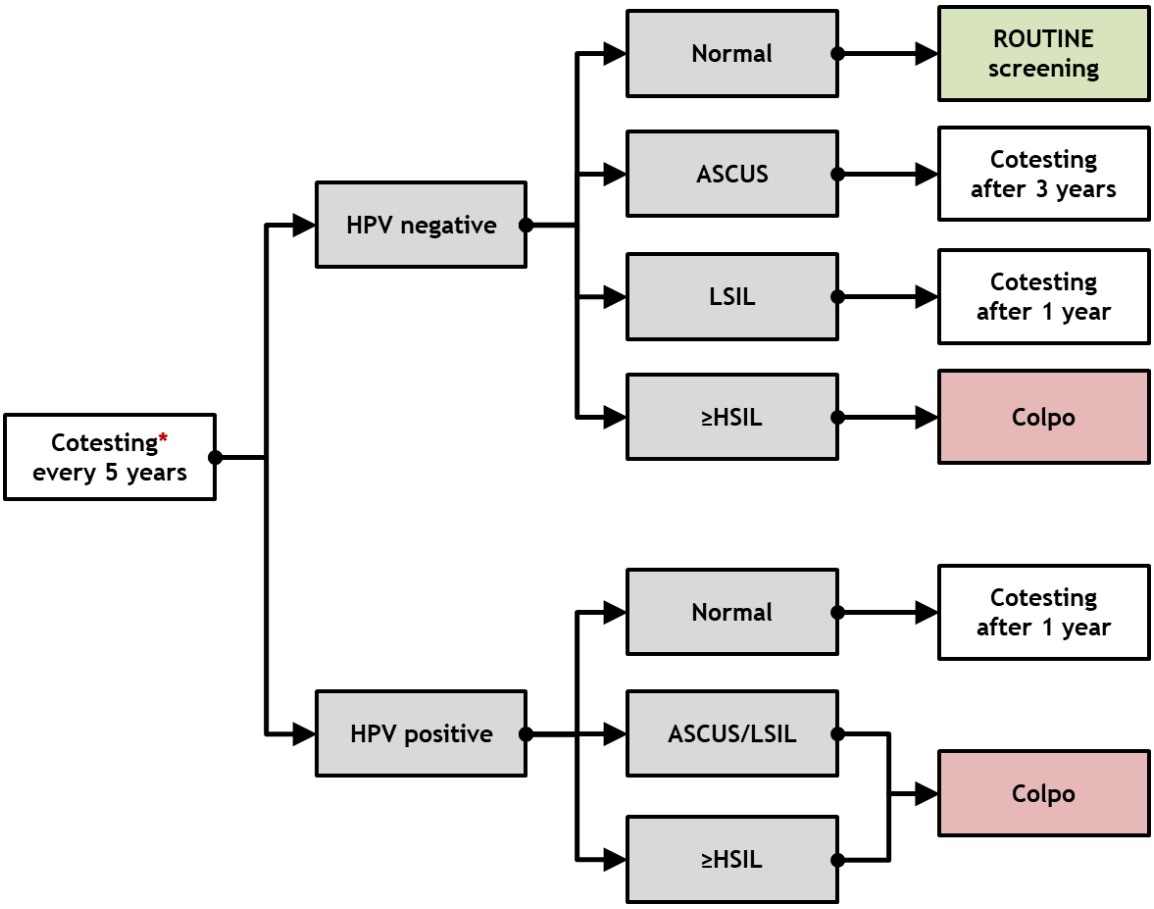


Figure A5. Management of 30-65 year old women with an HPV negative or HPV positive test.

1.5 Economic component

The model attributes, over time, direct medical costs and Quality-Adjusted Life-Year (QALY) weights to model outcomes (e.g., Pap tests, HPV tests, diagnosed lesions, AGW, cancer, mortality) to estimate the cost-effectiveness of HPV vaccination and cervical cancer screening. See Section 2.2.6 for parameter values and references.

2 MODEL PARAMETERIZATION

A calibration procedure is used to identify multiple parameter sets that simultaneously fit highly-stratified sexual behavior, natural history, and screening data. It should be noted that the calibration process only uses Pap test-based screening algorithms as the epidemiological and screening behavior data used for calibration relate to the period prior to changes in screening recommendations (i.e., before 2012). Table A1 in Section 2.1 presents the data sources used for calibration and Table A2 in Section 2.2 lists all the model parameters that have been derived through calibration. Section 2.2 describes in detail the prior ranges and the posterior parameter sets for each parameter.

2.1 Calibration procedure

The calibration approach has been described extensively in prior publications[1,13,14]: 1) prior distributions are defined for each of the 88 calibrated model parameters (Table A2) (min.–max. values for each parameter are derived from the literature); 2) thousands of different combinations of parameter values are drawn from the prior distributions using Latin Hypercube sampling; 3) parameter sets are qualified as producing a "good fit", and included in the posterior parameter sets, if the associated model predictions fall simultaneously within at least 90% of pre-specified targets (ranges) of the observed sexual behavior, natural history, and screening data described in Table A1; 4) posterior parameter sets are cross-validated by comparing model predictions with observed epidemiological data not used during the fitting procedure.

We purposely used uniform distributions because the data and evidence used for our priors were scarce. It was therefore very difficult to define informed prior distributions other than a uniform between a maximum and minimum found in the literature. Given that we are fitting to data, using another distribution (that would span the same range) instead of a uniform distribution would make little difference on the values of the parameter sets that fit the data. Obviously, having more information to inform the prior distributions would have facilitated our search for suitable parameter sets fitting the data, as our search would have been more efficient and less computer intensive.

We performed the calibration procedure in multiple steps given 1) the large number of model parameters and target points and, 2) fitting the incidence of squamous cell

carcinoma requires a larger population (to reduce stochasticity) than infection or sexual behavior. Hence, we performed the calibration in four steps:

1) *Sexual behavior, Screening debut, prevalence of HPV-16, HPV-18, all High oncogenic risk (HR) HPV-types, HR cross-protective types (HRC-HPV), HR non cross-protective types (HRNC-HPV), and incidence of LSIL/ASCUS and HSIL:* The goal of the first step was to estimate the values for the sexual behavior parameters, screening debut and the parameters influencing the transmission and clearance of high oncogenic risk HPV-types (HR-HPV) (57 parameters). To do so, we sampled 132,000 parameter sets using Latin Hypercube. Of note: We oversampled the number of simulations in which the natural immunity of men was set at 0%. Simulations were performed using a population of 55,600, the number of runs per simulation was 2, and the duration of a run was 100 years. A total of 176 parameter sets fell within the 372 pre-specified target points for sexual behavior (e.g., Percent that ever had sexual intercourse, Number of partners in past 12 months), screening debut (e.g., Proportion of women ever screened), prevalence of HPV-16, HPV-18, HPV-16/18, *HRC-HPV*, *HRNC-HPV* and *all HR-HPV*, and incidence of *LSIL* and of *HSIL* (Table A1). Incidence of LSIL and HSIL were included at this stage because they have an impact on HPV prevalence.
2) Positivity of HPV types in CIN2/3 and SCC: The objective of step 2 was to parameterize the progression and regression rates of the natural history of SCC from infection to CIN3 (25 parameters). We calibrated all natural history parameters in one stage as they are closely correlated with one another. To do so, we repeated a forward selection process for each of the parameter sets identified in step 1. The number of individuals in the population was 111,200, the number of runs per simulation was 10, and the duration of one run was 100 years. It is important to note that at each step of our forward selection process, the selected sets needed to fall within all previous target points in addition to the ones being evaluated. This is important as the natural history parameters related to progression and regression can have an impact on the prevalence of infection. A total of 255 parameter sets were found to fit the 392 pre-specified target points for steps 1-2. Among these parameter sets, we selected those that best fit HPV positivity among CIN2/3 and SCC cases using weighted least square methods, thus retaining 48 parameter sets (20% best fitting parameter sets).
3) Incidence of SCC: We calibrated the progression from CIN3 to SCC using the forward selection process described in step 2. For the 48 parameter sets identified in steps 1-

2, we sampled multiple gamma distributions (2 parameters) representing the cumulative probability over time of progressing from CIN3 to SCC. The number of individuals in the population was 187,900, the number of runs per simulation was 10, and the duration of one run was 100 years. A total of 335 parameter sets fell simultaneously within at least 90% of the 406 pre-specified targets. Among these parameter sets, we selected the 50 best fits to age-specific SCC incidence, using weighted least squares.

4) *HPV-6 and HPV-11 prevalence*: The objective of step 4 was to find parameter values for HPV-6 and HPV-11 transmission probabilities and clearance rates (4 parameters). HPV-6 and HPV-11 prevalence being largely independent of the other outcomes, we performed this step at the end of the calibration procedure. For each of the 50 parameter sets identified in step 1-3, we re-sampled 40 new combinations by varying only the 4 parameters related to HPV-6 and HPV-11 prevalence. The number of individuals in the population was 55,600, the number of runs per simulation was 2, and the duration of one run was 100 years. A total of 214 parameter sets fell within the 432 pre-specified target points for step 1-4. Using weighted least square on HPV-6 and HPV-11 prevalence, we selected the best fitting parameter set for each the 50 sets selected in steps 1-3. We thus obtained 50 “good fitting parameter sets” that produced predictions falling within at least 90% of 432 pre-specified targets.

We calibrated the age- and gender-specific proportion of HPV-6/11 leading to an AGW consultation separately because these parameters have no influence on the other natural history targets. For each of the 50 parameter sets currently from steps 1-4, we identified the AGW parameter values that best fit US data[15,16].

We also calibrated the age-, gender- and type-specific incidence of adenocarcinoma, and cancers of the vulva, vagina, anus, penis, and oropharynx separately. For each of the 50 parameter sets identified in steps 1-4, we estimated the parameter values that best fit 320 target points estimated from US incidence data[17,18] and HPV-type distribution [19-23], using least squares.

In summary, of 175,000 different combinations of parameters sampled (corresponds to 580,000 runs) from the prior parameter distributions, we have currently identified 50 parameter sets that produced model results that fall simultaneously within at least 90% of the 776 pre-specified target points. We refer to these 50 parameter sets as the “posterior

parameter sets". Table A1 presents the data sources used for calibration and Table A2 lists all model parameters that have been derived through calibration. Section 2.2 describes in details the prior ranges and the posterior parameter sets found for each parameter.

Section 2.3 shows examples of model fit to behavior, screening and epidemiological data using the 50 posterior parameter sets. Section 2.4 compares model results obtained using the 50 posterior parameter sets to observed data not used in the calibration procedure (model validation). Finally, Section 2.5 explains how targets were defined.

Table A1. Description of calibration data

	Stratification	Ref	Targets Points
Sexual Behavior			
Percent that ever had sexual intercourse	Age (15, … 24, [25-29], …, [40-44]yrs); Gender ($g \in \{1, 2\}$)	[24-26]	56
Number of partners in past 12 months	Age ([15-19], …, [30-34], [35-44]yrs); Gender ($g \in \{1, 2\}$); ¥ Number of partners (0, 1, 2, 3, ≥4)	[24,26]	98
Average number of partners in past 12 months	Age ([15-19], …, [30-34], [35-44]yrs); Gender ($g \in \{1, 2\}$)¥; Sexual Activity Level ($l \in \{0, 1, 2, 3\}$)	[24,26]	78
Natural history			
Prevalence of HPV-16¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	[25]	12
Prevalence of HPV-18¶	Age ([20-24] & [25-29]yrs); Sexual Activity Level ($l = 2$)	[25]	2
Prevalence of HPV-16/18¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	[25]	12
Prevalence of HPV-6¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	[25]	12
Prevalence of HPV-11¶	Age ([20-24] & [25-29]yrs); Sexual Activity Level ($l = 2$)	[25]	2
Prevalence of HPV-6/11¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	[25]	12
Prevalence of HPV-HR¶	Age ([15-19], …, [45-49]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	[25,27]	42
Prevalence of HPV-HRC¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	[25]	12
Prevalence of HPV-HRNC¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0, 1, 2\}, l \neq 3$)	[25]	12
Rate of genital warts consultations	Age ([15-19], …[65+]yrs); Gender ($g \in \{1, 2\}$)	[15]	24

	Stratification	Ref	Targets Points
Positivity of HPV types in CIN2/3	HPV-16,18,6,11,HRC¥,HRNC§	28,29	12
Positivity of HPV types in SCC	HPV-16,18,HRC¥,HRNC§	19,30-32	8
Incidence of SCC	Age ([20-24], …, [50-54]yrs)	17	14
Proportion of cervical adenocarcinoma	Age ([20-24], [25-29],…, [60-64]yrs) HPV-16, 18, 31, 33, 45 ,52, 58	18	63
Incidence of anal cancer	Age ([25-29], [30-34],…, [60-64]yrs) Gender ($g \in \{1,2\}$) HPV-16, 18, 31, 33	17	64
Incidence of oropharyngeal cancer	Age ([20-24], [25-29], …, [60-64]yrs) Gender ($g \in \{1,2\}$) HPV-16, 18, 33	17	54
Incidence of vulvar cancer	Age ([20-24], [25-29],…, [60-64]yrs) HPV-16, 18, 31, 33, 45	17	45
Incidence of vaginal cancer	Age ([30-34], [35-39],…, [60-64]yrs) HPV-16, 18, 31, 33, 45, 52, 58	17	49
Incidence of penile cancer	Age ([20-24], [25-29],…, [60-64]yrs) HPV-16, 18, 31, 33, 45	17	45
Screening			
Proportion of women ever screened	Age ([15-19], [20-24], [25-29], [30-34]yrs)	33	8
Incidence of ASC-US/LSIL	Age ([20-24], ..., [60-64], [65+]yrs)	34	20
Incidence of HSIL	Age ([20-24], ..., [60-64], [65+]yrs)	34	20
Total number of data points			776

¶ Among sexually active individuals; HR=High oncogenic risk types; HRC=HR cross-protective types: 31, 33, 45, 52, 58; HRNC= HR non cross-protective types: 35, 39, 51, 56, 59, 66, 68, 73, 82. Prevalence estimates were adjusted to take into account misclassification in number of lifetime partners and false positives due to test specificity. ¥. We were unable to fit the % of boys with less than 1 partner in the last year in the 15-19 age group (mainly because of age-specific mixing where females are more likely to choose male partners older than them).

2.2 Parameters

Table A2. List of model parameters

Parameters	Stratification	Parameter values
Demography (Section 2.2.1)		
Sex ratio at birth	none	
Mortality rates* (per person-year)	Age (a = [10-14], …, [84-89], [90+]yrs); Gender ($g \in \{1, 2\}$)	Table A3
Hysterectomy rates unrelated to cervical cancer (per person-year)	Age (a = [10-14], [15-24], [25-29], …, [40-44], [45-54], [55+]yrs)	Table A4
Sexual Behavior (section 2.2.2)		
Proportion of individuals in sexual activity levels	Sexual Activity Levels ($l \in \{0, 1, 2, 3\}$); Gender ($g \in \{1, 2\}$)	Table A5/ Figure A6
Partner acquisition rates (per person-year)	Age (10,… 19, [20-24], …, [45-49], [50-59], [60-69], [70+]yrs); Sexual Activity Levels ($l \in \{0, 1, 2, 3\}$)	Table A6-7/ Figure A7-8
Separation rates for stable partnerships (per partnership-year)	Age ([10-14], …, [45-49], [50-59], [60-69], [70+]yrs); Sexual Activity Levels ($l \in \{0, 1, 2, 3\}$)	Table A8/ Figure A9
Proportion of individuals in stable partnerships	Age (10, …, 24, [25-29], [30-39], [40+]yrs); Sexual Activity Levels ($l \in \{0, 1, 2, 3\}$)	Table A9/ Figure A10
Proportion of partnerships that lead to stable partnerships	Age ([10-14], [15+]yrs); Sexual Activity Levels ($l \in \{0, 1, 2, 3\}$)	Table A10/ Figure A11
Contact rates in stable partnerships (per week)	None	Figure A12
Number of contacts per casual partnership	None	Figure A13

Parameters	Stratification	Parameter values
Onset of sexual activity	Age (10, …, 19yrs, [20-24]); Sexual Activity Levels ($l \in \{0, 1, 2, 3\}$)	Table A11/ Figure A14
Assortative degree for sexual activity matrix	none	Figure A15
Age matrix, probabilities of one age group to form a partnership with any other age group	Age ([10-14], …, [65+]yrs); Sexual Activity Levels ($l \in \{0, 1, 2, 3\}$); Gender ($g \in \{1, 2\}$)	Table A12-14 Figure A16
Natural history (Section 2.2.3)		
Transmission probability for HPV-16 (per act)	Gender ($g \in \{1, 2\}$)	Table A15/ Figure A17
Relative rate of transmission (vs HPV-16)	HPV-18,6,11,HRC[¥],HRNC[§]	Table A15/ Figure A17
Clearance rate of infection with HPV-16 (per person-year)	Age ([15-65]yrs[‡]); Gender ($g \in \{1, 2\}$)	Table A16/ Figure A18
Relative rate of clearance from infection (vs HPV-16)	HPV-18,6,11,HRC[¥],HRNC[§]	Table A16/ Figure A19
Probability of developing lifelong natural immunity	Gender ($g \in \{1, 2\}$)	Figure A20
Progression rates from infection with HPV-16 to CIN1 (per person-year)	None	Table A17/ Figure A22
Relative rate of progression from infection to CIN1 (vs HPV-16)	HPV-18,6/11[*],HRC[¥],HRNC[§]	Table A17/ Figure A22
Progression rates from CIN1 with HPV-16 to CIN2 (per person-year)	None	Table A17/ Figure A24

Parameters	Stratification	Parameter values
Relative rate of progression from CIN1 to CIN2 (vs HPV-16)	HPV-18,HRC[¥],HRNC[§]	Table A17/ Figure A24
Progression rates from CIN2 with HPV-16 to CIN3 (per person-year)	None	Table A17/ Figure A27
Relative rate of progression from CIN2 to CIN3 (vs HPV-16)	HPV-18,HRC[¥],HRNC[§]	Table A17/ Figure A27
Progression rate CIN3 to SCC (per person-year)	None	Table A17/ Figure A29-30
Regression rate from CIN1 with HPV-16 (per person-year)	None	Table A17/ Figure A23
Relative rate of regression from CIN1 (vs HPV-16)	HPV-18,6/11[*],HR[#]	Table A17/ Figure A23
Proportion of regressing CIN1 that clears the infection	None	Table A17/ Figure A21
Regression rate from CIN2 with HPV-16 to CIN1 (per person-year)	None	Table A17/ Figure A25
Relative rate of regression from CIN2 to CIN1 (vs HPV-16)	HPV-18,HR[#]	Table A17/ Figure A25
Regression rate from CIN3 to CIN2 (per person-year)	None	Table A17/ Figure A28
Clearance rates from CIN2 with HPV-16 (per person-year)	None	Table A17/ Figure A26

	Parameters	Stratification	Parameter values
	Relative clearance rate from CIN2 (vs HPV-16)	HPV-18,HR[#]	Table A17/ Figure A26
	Progression rate from SCCI to SCCII (per person-year)	None	Table A18
	Progression rate from SCCII to SCCIII (per person-year)	None	Table A18
	Probability of developing symptoms	Stage of SCC	Table A18
	Mortality rates from SCC (per person-year)	Stage of SCC	Table A18
	Proportion of HPV-6/11 leading to AGW consultation	Age ([<35], [35+]yrs); Gender ($g \in \{1, 2\}$)	
	Progression from infection to other HPV related cancers (cervical adenocarcinoma, cancer of the anus, oropharynx, vulva, vagina and penis)	HPV-16,18,31,33,45,52,58 Gender ($g \in \{1, 2\}$)	Table A19/ Figure A31
Screening (Section 2.2.4)			
	Proportion of individuals in screening behavior levels	Screening Behavior Levels ($S \in \{0, 1, 2, 3, 4\}$)	Table A20
	Age distribution of first screening test	Age (a = [18], …, [38], [39+]yrs)	Figure A32
	Screening rates (per person-year)	Age ([10-14], …,[45-49], [50-59], [60-69], [70+]yrs); Screening behavior levels ($S \in \{0, 1, 2, 3, 4\}$); Previous screening results	Table A21
	Probability of detecting cervical lesions by cytology	Severity of lesion (Normal, CIN1, CIN2/3, SCC)	Table A22

Parameters	Stratification	Parameter values
Sensitivity and specificity of detecting HR[#] HPV infection by HPV-testing	Neoplastic state (no lesion, with lesions)	Section 2.2.4
Probability of diagnosing cervical lesions by colposcopy/biopsy	Severity of lesion (Normal, CIN1, CIN2, CIN3, SCC)	Table A23
Proportion of individuals followed-up with colposcopy/biopsy after an abnormal cytology	Cytology result (ASC-US, LSIL, HSIL, SCC)	Table A24
Proportion of individuals lost to follow-up after an abnormal cytology	Cytology result (ASC-US, LSIL, HSIL, SCC)	Table A24
Probability of CIN treatment success	None	Section 2.2.4
Probability of clearing the infection after CIN treatment success	None	Section 2.2.4

¶ Stationary population; ¥ HRC=HR cross-protective : 31, 33, 45, 52, 58; § HRNC=HR non cross-protective : 35, 39, 51, 56, 59, 66, 68, 73, 82; ǂ Linear trend based on values sampled at 15 and 65 years old; *HPV-6 and 11 are modeled separately but have the same value for this parameter; # HR=All high oncogenic risk types

2.2.1 Demographic parameters

Table A3. Mortality rates (per 100,000 person-years) – parameter values

Age group	Female	Male
10-14	13	18
15-19	32	74
20-24	46	127
25-29	57	131
30-34	74	145
35-39	105	181
40-44	166	264
45-49	260	410
50-54	385	641
55-59	537	926
60-64	809	1306
65-69	1252	1945
70-74	1962	2905
75-79	3155	4548
80-84	5248	7301
85-89	12224	14741
90+	12224	14741

Source: NCHS US Life tables[35]

Table A4. Hysterectomies unrelated to cervical cancer (per 1000 woman-years) – parameter values

Age group	
15-24	0.2
25-29	2.6
30-34	5.3
35-39	8.9
40-44	11.7
45-54	9.9
≥55	3.6

Source: NSFG [24]

2.2.2 Sexual Behavior Parameters

Prior ranges for the sexual behavior parameters are primarily based on data from the NSFG 2006-2010 (National Survey of Family Growth)[24,26], and, when US-specific data were not available, data from PISCES (Psychosocial Impact of cervical Screening and Condylomas: an Epidemiological Study[36,37] were adapted to the US context. The NSFG is a population-based national survey of more than 20,000 men and women between 15-44 years of age, and living in households in the US. The NSFG is conducted by the National Center for Health Statistics, an agency of the US Department of Health, in collaboration with other federal agencies. PISCES is a Canadian prospective multicentre clinical study which includes two cohorts: 1) men and women seeking medical care for genital warts and 2) women receiving a normal or an abnormal Pap test result. Recruitment occurred between 2006 and 2008 across Canada. Patients were recruited by general practitioners

and gynecologists during the course of routine clinical practice (42 and 59 physicians recruited for the genital warts and Pap test cohorts, respectively). A total of 127 men with genital warts, 145 women with genital warts, 460 women with a normal Pap test results and 492 women with an abnormal Pap test result were recruited in the study[36].

Proportion of individuals in sexual activity levels Φ_l . The prior ranges for the proportion of individuals in the different sexual activity levels in Table A5 were calculated from the NSFG 2006-2010 data. We assumed that individuals in sexual activity levels $l \in \{0, 1, 2, 3\}$ have 0-1, 2-10, 11-39 and 40+ lifetime partners, respectively. The range of proportions of individuals in each sexual activity level was determined by using the minimum and maximum values of all age-specific proportions between 25 and 44 years old. To be as inclusive as possible, the prior ranges for the proportion of individuals in the sexual activity levels were calculated by multiplying the minimum (maximum) values estimated from the NSFG by 80% (120%). Finally, we assume that men have the same priors for the proportion of individuals in the sexual activity levels as women. However, as described later, for a same level of sexual activity men have a higher rate of partner acquisition.

Table A5. Proportion of individuals in the sexual activity levels (Φ_l) - Prior ranges

	$l = 0$		$l = 1$		$l = 2$		$l = 3$	
	MIN	**MAX**	**MIN**	**MAX**	**MIN**	**MAX**	**MIN**	**MAX**
Female	0.11	0.30	0.33	0.72	0.13	0.41	0.01	0.11
Male	0.11	0.30	0.33	0.72	0.13	0.41	0.01	0.11

Based on the prior ranges from Table A5, the sampling algorithm proceeds as follows: 1) for each sexual activity level we sample a pseudo-random number (RAND) and compute a proportion of individuals ($\mathrm{MIN} + \mathrm{RAND} \times [\mathrm{MAX} - \mathrm{MIN}]$), and 2) we rescale the 4 proportions to ensure they sum to 1. Figure A6 represents the posterior parameter sets for the proportion of individuals in the sexual activity levels.

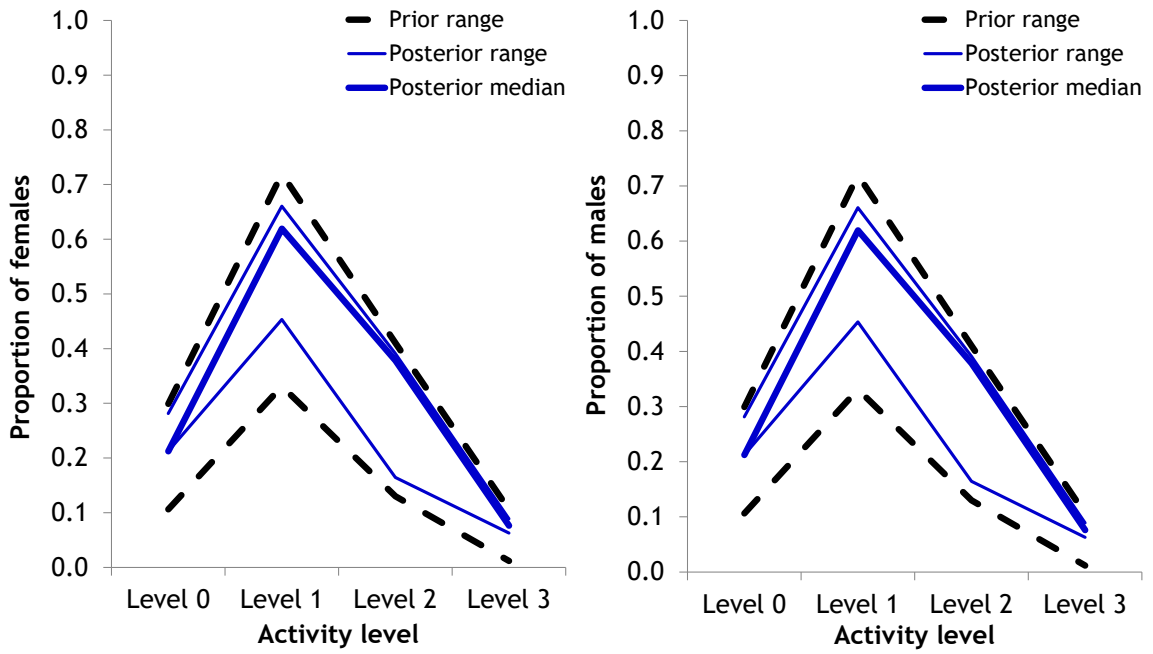


Figure A6. Sexual activity level distribution in a) females and b) males - Posterior distributions. Dashed black lines represent the minimum and maximum values of the prior ranges. Blue lines represent the medians, minimums and maximums of the posterior parameter sets.

Partner acquisition rates $\Theta_{g,l}(a)$. The rate of partner acquisition is the rate of new sexual partner acquisition amongst individuals who are sexually active (i.e. number of new partners per year). The prior ranges for the partner acquisition rates for women and men by sexual activity level and age were calculated using the Seattle Sex Survey[38]. Because the partners acquisition rates were not available for each sexual activity level from the Seattle Sex Survey, we used data from PISCES (previously used in HPV ADVISE Canada) to estimate the proportion of the overall rate contributed by each sexual activity levels and used these proportions (i.e. weights) to distribute the overall US rates across the four sexual activity levels. See Table A6 for the prior ranges of the female and males partner acquisition rates.

Table A6. Partner acquisition rates for females (per person-year)[§] ($\Theta_{g=1,l}(a)$) – Prior ranges

Age groups	$l=0$		$l=1$		$l=2$		$l=3$	
(years)	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
10-17	0.25	1.03	0.42	1.75	1.09	4.53	2.21	9.53
18-19	0.32	0.89	0.54	1.51	1.39	3.90	2.81	9.52
20-24	0.07	0.53	0.27	1.15	0.69	3.12	1.56	10.08
25-29	0.03	0.31	0.18	0.73	0.45	1.97	0.82	5.20
30-34	0.01	0.25	0.13	0.60	0.30	1.57	0.42	2.89
35-39	0.01	0.27	0.10	0.67	0.21	1.64	0.21	1.95
40-44	0.00	0.21	0.07	0.52	0.14	1.12	0.12	1.30
45-49	0.00	0.12	0.04	0.31	0.07	0.53	0.05	0.58
50-59	0.00	0.06	0.02	0.15	0.02	0.16	0.01	0.17
60-69	0.00	0.03	0.01	0.07	0.01	0.08	0.01	0.09
70+	0.00	0.01	0.00	0.04	0.00	0.04	0.00	0.04

§ Rate among sexually active only.

Table A7. Partner acquisition rates for males (per person-year)[§] ($\Theta_{g=2,l}(a)$) - Prior ranges.

Age groups	$l=0$		$l=1$		$l=2$		$l=3$	
(years)	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
10-17	0.33	1.03	0.55	1.75	1.41	4.53	2.85	14.41
18-19	0.48	0.89	0.81	1.50	2.07	3.90	4.21	14.41
20-24	0.10	0.54	0.37	1.15	0.95	3.12	2.14	11.75
25-29	0.04	0.31	0.26	0.73	0.64	1.97	1.16	7.23
30-34	0.02	0.25	0.21	0.60	0.50	1.58	0.70	4.30
35-39	0.02	0.27	0.26	0.66	0.54	1.63	0.57	2.43
40-44	0.01	0.21	0.20	0.52	0.38	1.12	0.33	1.20
45-49	0.00	0.12	0.12	0.31	0.19	0.53	0.14	0.44
50-59	0.00	0.06	0.05	0.15	0.06	0.16	0.04	0.22
60-69	0.00	0.03	0.02	0.07	0.03	0.08	0.02	0.11
70+	0.00	0.01	0.01	0.04	0.01	0.04	0.01	0.06

§ Rate among sexually active only

From the priors of Table A6 and Table A7, the program samples different partner acquisition rates for each prior parameter set. To allow for realistic trends over age meanwhile keeping the number of varying model parameters to a minimum, the sampling algorithm proceeds as follows. First, because observed data only provides one estimate of partner acquisition for age range 10 to 17 years old, whereas we can expect this rate to vary significantly over this period and early partner acquisition rates (just after the onset

of sexual activity) are likely to have an important impact on vaccination strategies, the sampling algorithm allows the partner acquisition rates (among those sexually active) to follow an increasing linear trend from 10 to 17 years of age. This is done by sampling one rate for 10-year-olds (start) and one rate for 17-year-olds. Because we assume the rates are increasing, the start rates are sampled between 0 and the upper limits of the prior ranges defined in Table A6 and Table A7, and the 17-year-old rates are sampled between the start rates and the upper limits of the prior ranges. Second, to minimize the number of dimensions of the Latin Hypercube, we sample one random number per sexual activity level that we call relative rate (RR_l), and compute the rates over age with the formula:

$$\theta_{g,l}(a) = \underset{g,l}{\mathrm{MIN}}(a) + RR_l \cdot \left[\underset{g,l}{\mathrm{MAX}}(a) - \underset{g,l}{\mathrm{MIN}}(a)\right] \quad (2.1)$$

Where a is the age group, and MIN and MAX are the minimum and maximum of the age and sexual activity level specific prior ranges, respectively. Figure A7 and A8 represent the posterior parameters sets for the female and male rates of partner acquisition, respectively.

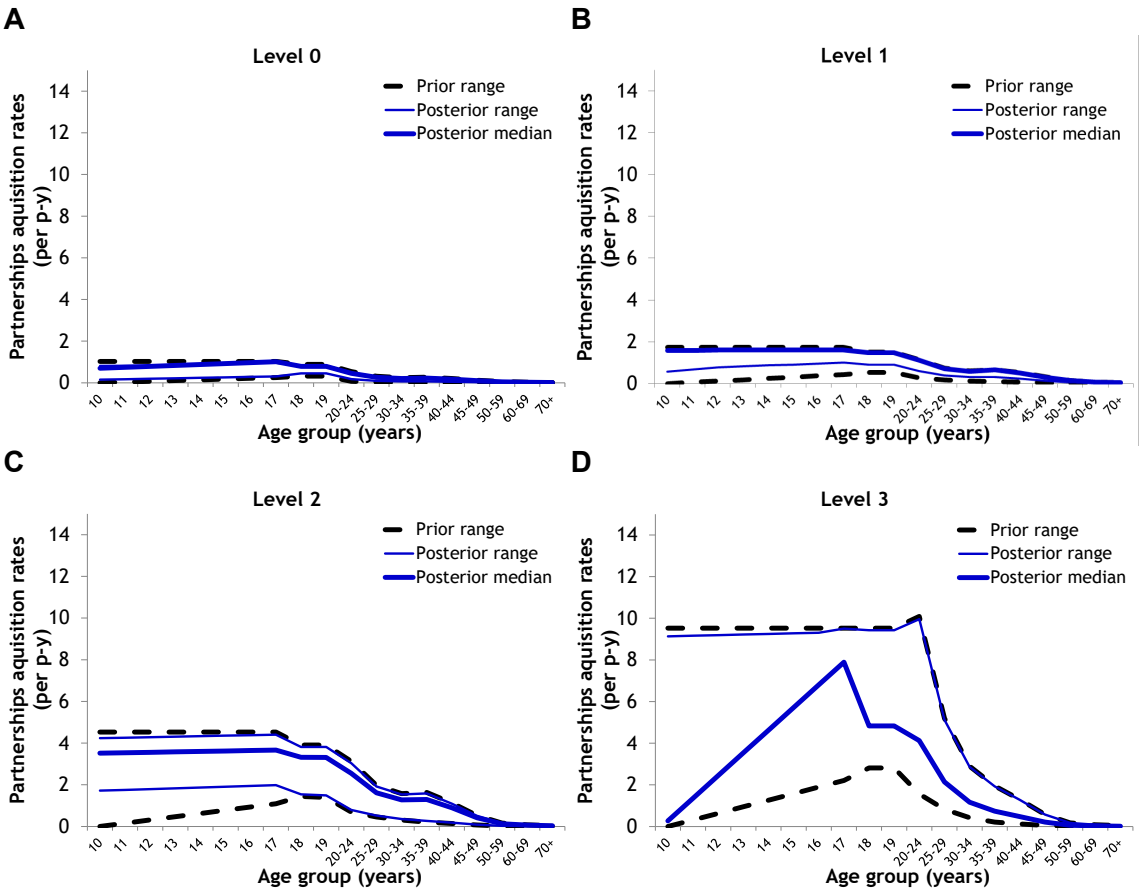


Figure A7. Partner acquisition rates of sexually active females in sexual activity level a) $l = 0$, b) $l = 1$, c) $l = 2$ and d) $l = 3$ **- Posterior distributions.** Dashed black lines represent the minimums and maximums of the prior ranges over age. Blue lines represent the medians**,** minimums and maximums of the posterior parameter sets.

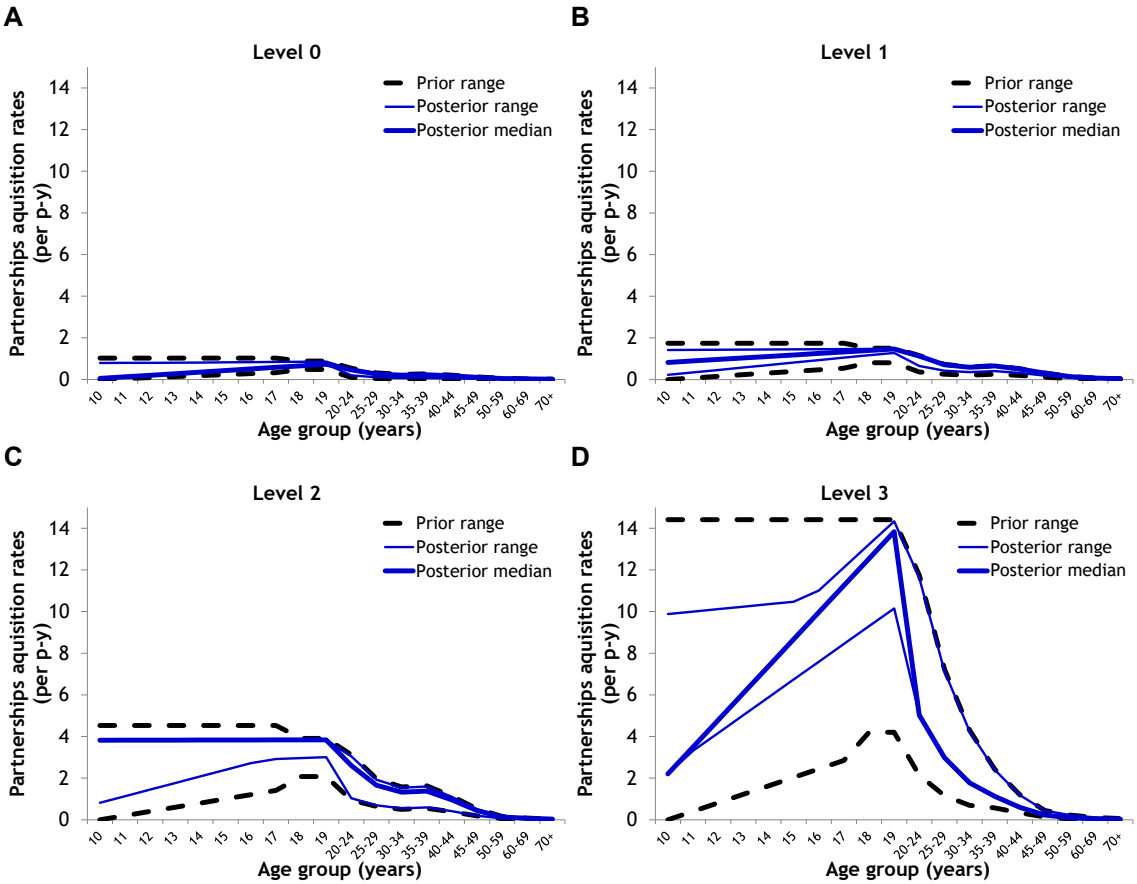


Figure A8. Partner acquisition rates of sexually active males in sexual activity level a) $l = 0$, b) $l = 1$, c) $l = 2$ and d) $l = 3$ - Posterior distributions. Dashed black lines represent the minimums and maximums of the prior ranges over age. Blue lines represent the medians, minimums and maximums of the posterior parameter sets.

Stable partnership separation rates $\sigma_l(a)$. The rate of separation amongst stable partnerships $\sigma_l(a)$ was estimated from two sources. The maximum scenario for stable partnership separation rates were calculated from PISCES data (all female cohorts were included in the analyses). We assumed that the rate of separation, stratified by age and level of sexual activity, was equal to 1/average duration of partnerships $d_l(a)$. Since the average duration of a partnership in PISCES is right censored, we most likely overestimate the rate of separation. The minimum rates of separation were derived from US divorce rates[24,36,39]. Given the uncertainty around our estimates of separation rates due to limited data, the prior ranges were calculated by multiplying the maximum estimated values by 120% (see Table A8 for priors). The program used Equation (2.1) to sample the separation rates from prior ranges (see Figure A9 for the posterior separation rates). Partnership separation can also occur following the death of one of the stable partners.

Table A8. Stable partnership separation rates (per partnership-year) $\sigma_l(a)$ – Prior ranges

Age (yrs)	$l = 0$		$l = 1$		$l = 2$		$l = 3$	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
10-14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15-19	0.05	0.64	0.06	1.05	0.07	1.25	0.17	2.07
20-24	0.02	0.30	0.04	0.74	0.06	1.02	0.14	1.72
25-29	0.01	0.18	0.02	0.41	0.03	0.52	0.07	0.88
30-34	0.01	0.11	0.01	0.24	0.02	0.32	0.05	0.59
35-39	0.01	0.06	0.01	0.15	0.03	0.52	0.08	1.03
40-44	0.00	0.06	0.01	0.11	0.01	0.16	0.02	0.21
45-49	0.00	0.04	0.01	0.11	0.01	0.12	0.01	0.09
50-59	0.00	0.03	0.01	0.09	0.00	0.08	0.01	0.09
60-69	0.00	0.02	0.00	0.04	0.00	0.04	0.00	0.09
70+	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.09

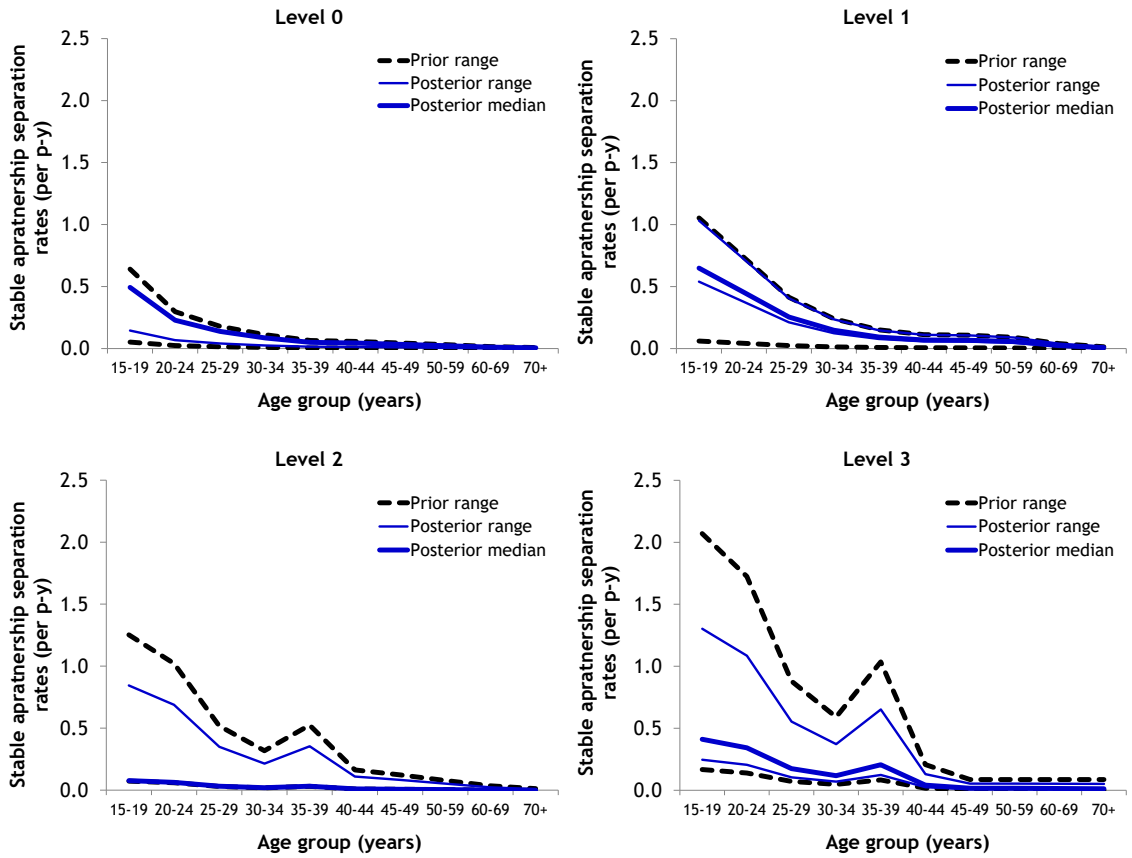


Figure A9. Stable partnership separation rates by level of sexual activity - Posterior distributions. Dashed black lines represent the minimums and maximums of the prior ranges over age. Blue lines represent the medians, minimums and maximums of the posterior parameter sets.

Proportion of women in a stable partnership $\Psi_l(a)$. The prior ranges for the proportion of women in a stable relationship by age and level of sexual activity $\Psi_l(a)$ were calculated from NSFG[24], PISCES[36] and the Canadian Community Health Survey (CCHS), Cycle 3.1[40]. Using NSFG data we estimated the overall minimum and maximum proportion of women in stable partnership in the US by age. Given that these numbers were not available by level of sexual activity, they were weighted using the Canadian proportion of women in stable partnership by age and sexual activity level to reproduce the US overall value from the NSFG data. We used PISCES to estimate the proportion of sexually active women in stable relationships. To estimate the age and level of sexual activity specific proportion of women in a stable relationship $\Psi_l(a)$ we multiplied the proportion of sexually active women in a stable relationship by the proportion of women sexually active. The proportion of women that are sexually active by age and level of sexual activity were estimated from the CCHS. The prior ranges were calculated by multiplying the minimum

(maximum) values by 80% (120%) (see Table A9 for priors). The program used Equation (2.1) to sample the proportions of women in stable partnerships from prior ranges. Figure A10 shows the posterior proportions of women in stable partnerships.

Table A9. Proportions of women in stable partnerships§ ($\Psi_l(a)$) - Prior ranges

Age groups	$l = 0$		$l = 1$		$l = 2$		$l = 3$	
(years)	Min	Max	Min	Max	Min	Max	Min	Max
15	0%	0%	2%	3%	6%	10%	6%	9%
16	0%	0%	6%	9%	14%	21%	14%	21%
17	2%	3%	13%	21%	22%	33%	21%	33%
18	4%	6%	24%	38%	31%	47%	30%	47%
19	7%	11%	31%	50%	36%	55%	35%	54%
20	15%	24%	48%	78%	51%	80%	49%	80%
21	20%	33%	52%	85%	54%	83%	51%	83%
22	25%	41%	54%	89%	55%	85%	53%	85%
23	30%	48%	57%	93%	56%	86%	53%	86%
24	33%	54%	58%	95%	56%	86%	53%	86%
25-29	78%	100%	71%	100%	66%	100%	59%	94%
30-39	78%	100%	73%	100%	67%	100%	55%	87%
40-49	78%	100%	77%	100%	64%	100%	57%	91%
50-59	78%	100%	77%	100%	64%	100%	57%	91%
60-69	78%	100%	77%	100%	64%	100%	57%	91%
70+	78%	100%	77%	100%	64%	100%	57%	91%

§ Women 60+ years old were given the same priors as those aged 50-59 years.

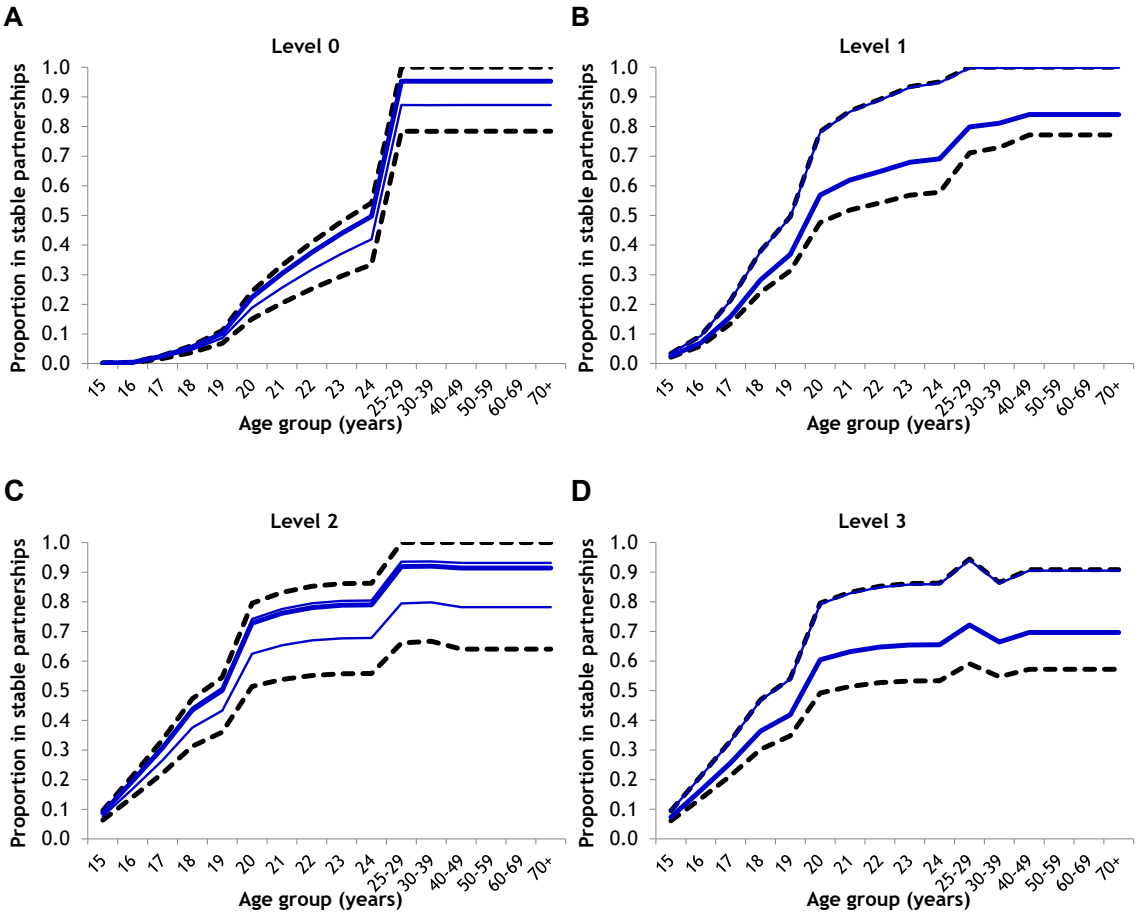


Figure A10. Proportions of women in stable partnerships by age and level of sexual activity - Posterior distributions. Dashed black lines represent the minimums and maximums of the prior ranges over age. Blue lines represent the medians, minimums and maximums of the posterior parameter sets.

Proportion of new partnerships that lead to stable partnerships $\psi_l(a)$. The prior ranges for the proportion of new partnerships that lead to stable partnerships by sexual activity levels and age were calculated using the following formula:

$$\psi_l(a) = \begin{pmatrix} \text{\% new} \\ \text{partnerships} \\ \text{that lead to a} \\ \text{stable} \\ \text{partnership} \end{pmatrix} = \frac{\begin{pmatrix} \text{\% in stable} \\ \text{relationship} \end{pmatrix} \times \begin{pmatrix} \text{Rate of} \\ \text{separation} \end{pmatrix}}{\left(1 - \begin{pmatrix} \text{\% in stable} \\ \text{relationship} \end{pmatrix}\right) \times \begin{pmatrix} \text{Rate of partner} \\ \text{acquisition singles} \end{pmatrix}}$$

or:

$$\psi_l(a) = \frac{\Psi_l(a) \cdot \sigma_l(a)}{\left[1 - \Psi_l(a)\right] \cdot \varsigma_l(a)}. \qquad (2.2)$$

For women aged 15+ and in levels of sexual activity $l \in \{0, 1, 2, 3\}$, the estimated proportions of partnerships that lead to stable partnerships varied between 0.63-1.00, 0.25-0.65, 0.09-0.51 and 0.08-0.17, respectively. We assumed that all relationships involving 10-14 year olds are casual (i.e., do not lead to stable relationships). See Table A10 for prior ranges. From the Latin Hypercube, 4 random numbers are attributed to each prior parameter set and the sampling algorithm computes the level of sexual activity specific proportions of new partnerships that lead to stable partnership using Equation (2.1). Figure A11 shows the posterior distributions for the proportions of new partnerships that lead to stable partnership.

Table A10. Proportion of new partnerships that lead to a stable partnership $\Psi_l(a)$ – Prior ranges

	$l = 0$		$l = 1$		$l = 2$		$l = 3$	
	MIN	**MAX**	**MIN**	**MAX**	**MIN**	**MAX**	**MIN**	**MAX**
10-14 YRS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15+ YRS	0.63	1.00	0.25	0.65	0.09	0.51	0.08	0.17

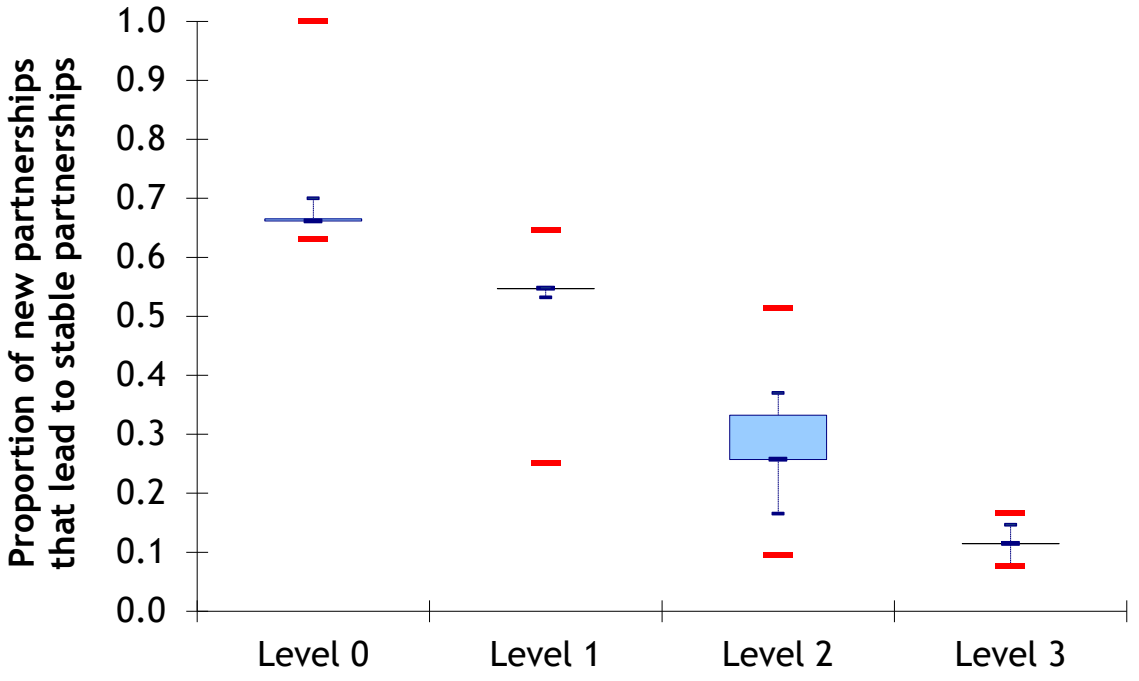


Figure A11. Proportions of new partnerships that lead to a stable partnership - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

Frequency of sex acts in stable partnerships ω. During the course of a stable partnership, the average frequency of sex acts is assumed to vary between 1.5 and 4 acts per week[41-43]. The frequency of sex acts during a stable partnership ω is assumed to be independent of the age and level of sexual activity of the partners, and the duration of the partnership. However, the duration of a partnership is dependent on the age and level of sexual activity of the partners (see Stable partnership separation rates). From the Latin Hypercube, 1 random number is attributed to each prior parameter set by the sampling algorithm and the weekly frequency of sex acts in a stable relationship is computed using Equation (2.1). Figure A12 represents the posterior distribution for the weekly frequency of sex acts in a stable relationship.

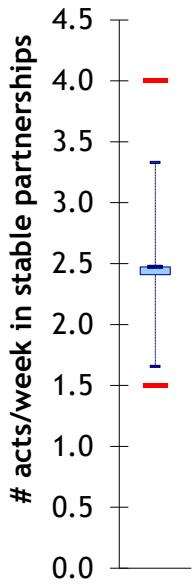


Figure A12. Number of acts per week in stable partnerships - Posterior distributions. Box plot represents the median, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior range.

Number of sex acts per casual partnership C. We set the prior range for the average number of sex acts per casual partnership C to between 1.5 and 4.0. Casual partnerships are assumed to be instantaneous (see Figure A1, Section 1.2.2). It should be noted that the number of sex acts during a casual partnership is independent of the age and level of sexual activity of the partners. From the Latin Hypercube, 1 random number is attributed to each prior parameter set by the sampling algorithm and the number of sex acts per casual partnership is computed using Equation (2.1). Figure A13 represents the posterior distribution for the number of sex acts per casual partnership.

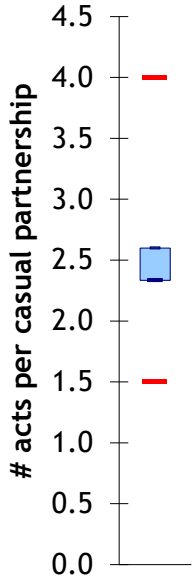


Figure A13. Number of acts per casual partnership - Posterior distributions. Box plot represents the median, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior range.

Onset of sexual activity in females $\phi_l(a)$. In the model, it was impossible to fit the onset of sexual activity in girls using the age-specific rates of partner acquisition (amongst sexually active women) because the age-specific rate towards the first sexual partnership is different from subsequent partnerships. To define the prior ranges for the rates of onset of sexual activity, we first computed the exact rates required to fit the data on the percentage of girls who ever had sex (stratified by age and level of sexual activity[24], then we allowed for a 20% variation above and under these estimates. The sampling algorithm provides each prior parameter set with rates of onset of sexual activity computed using Equation (2.1) and 4 random numbers from the Latin Hypercube (1 per level of sexual activity). Refer to Table A11 for prior ranges and to Figure A14 for the posterior distributions of the rates of onset of sexual activity in girls/women.

Table A11. Rates of onset of sexual activity for girls $\phi_l(a)$ – Prior ranges

Age	$l = 0$		$l = 1$		$l = 2$		$l = 3$	
(years)	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
11	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01
12	0.00	0.00	0.01	0.01	0.05	0.07	0.05	0.07
13	0.00	0.00	0.03	0.04	0.07	0.11	0.07	0.11
14	0.00	0.00	0.07	0.10	0.19	0.28	0.19	0.28
15	0.02	0.03	0.16	0.24	0.26	0.38	0.26	0.38
16	0.03	0.05	0.31	0.47	0.43	0.64	0.43	0.64
17	0.05	0.08	0.32	0.48	0.43	0.64	0.43	0.64
18	0.09	0.13	0.42	0.62	0.60	0.90	0.60	0.90
19	0.09	0.13	0.42	0.64	0.60	0.90	0.60	0.90
20-24	0.09	0.13	0.43	0.65	0.84	1.26	0.84	1.26
25+	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

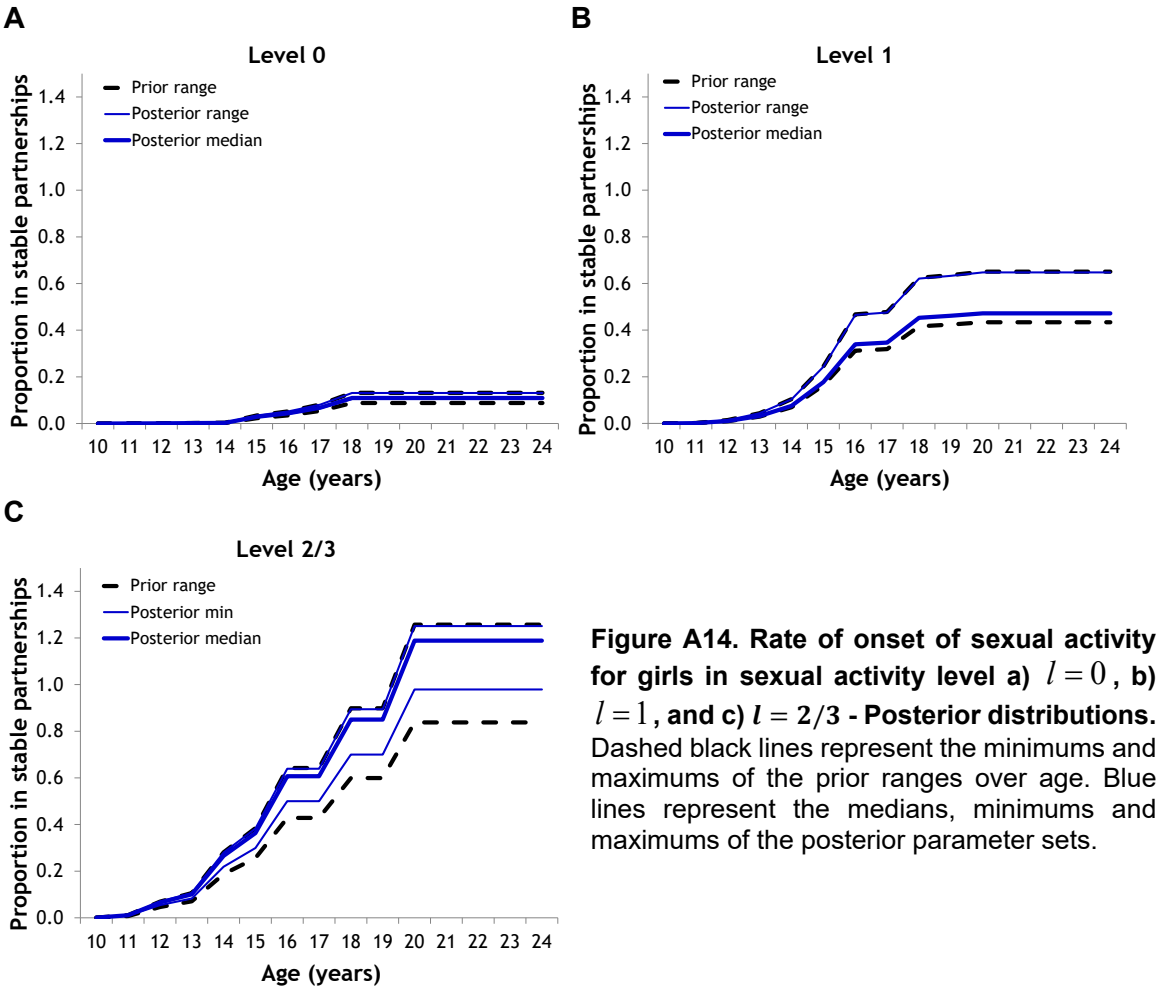


Figure A14. Rate of onset of sexual activity for girls in sexual activity level a) $l = 0$, b) $l = 1$, and c) $l = 2/3$ - Posterior distributions. Dashed black lines represent the minimums and maximums of the prior ranges over age. Blue lines represent the medians, minimums and maximums of the posterior parameter sets.

Assortative degree of mixing by level of sexual activity κ. Refer to Section 1.2.3 for the definition of the mixing matrices. In particular, Equation (1.2) and (1.3) define the mixing by level of sexual activity $\mathbf{\Gamma} = [\Gamma_{l,l',g}]$ and the assortative degree κ, respectively. For each prior parameter set, 1 assortative degree is sampled from 50 to 150 using a uniform distribution. See Figure A15 for the posterior distribution of the assortative degree.

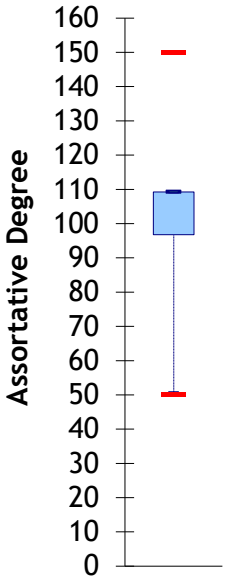
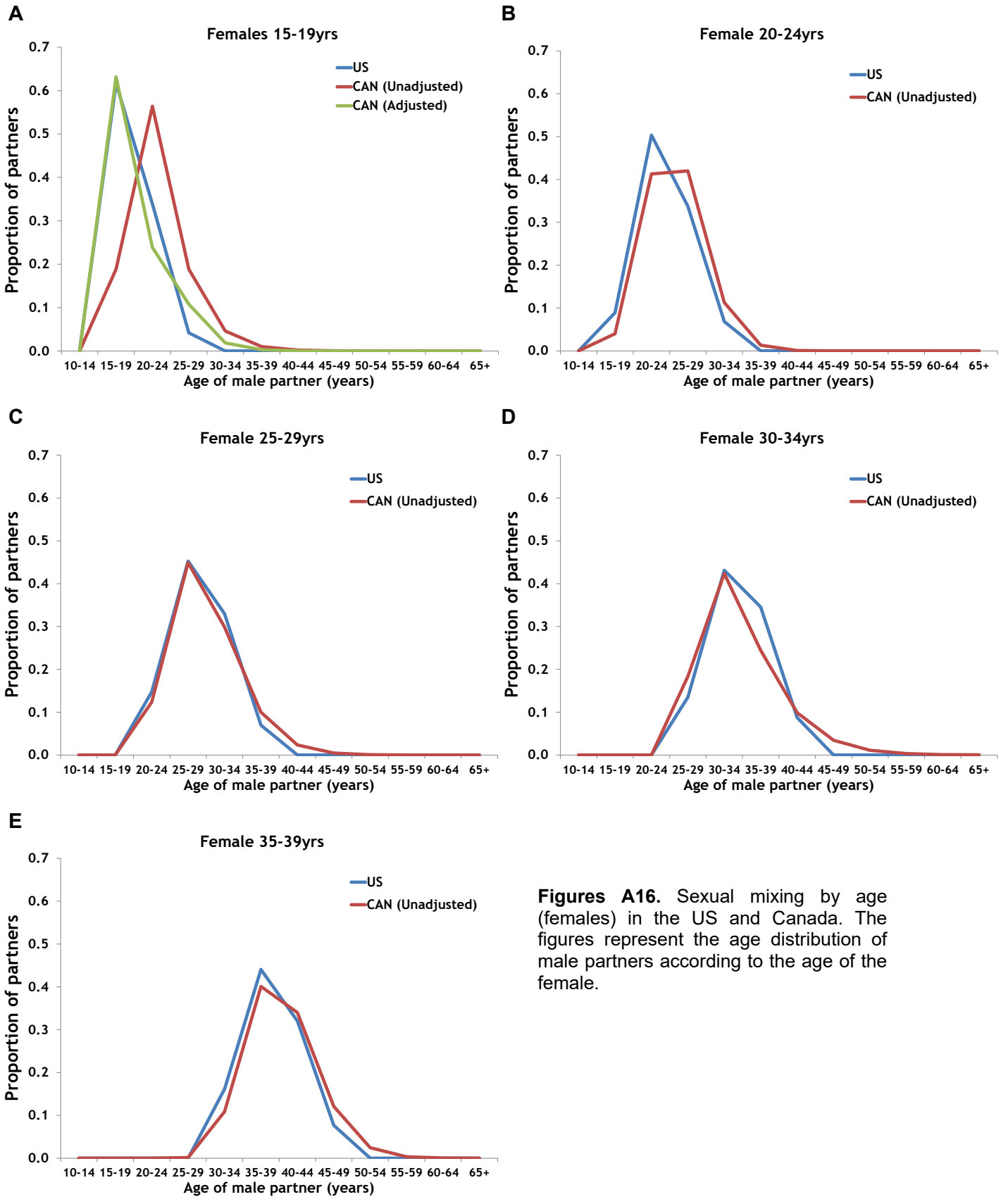


Figure A15. The assortative degree of the mixing by level of sexual activity - Posterior distributions. Box plot represents the median, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior range.

Age mixing matrix $\mathbf{\Lambda} = [\mathbf{\Lambda}_{a,a',l,g}]$. The age mixing matrix was estimated using data from the National Survey of Family Growth (NSFG)[44] and PISCES[36] (data source used for HPV-ADVISE Canada). The NSFG contains information on the age difference between females aged 15-44 years old and their partners. However, data stratified by level of sexual activity were not available from the US. We thus compared the overall age-specific mixing patterns between the US and Canada, to verify whether we could use sexual mixing data from Canada. Since mixing patterns were strikingly similar between Canada and the US, except for 15-19 years old, we used the Canadian mixing matrices by level of sexual activity (see Figure A16). For females aged 15-19 years, we adjusted the Canadian mixing matrices by level of sexual activity in order to fit the US mixing data (see Figure A16).



Figures A16. Sexual mixing by age (females) in the US and Canada. The figures represent the age distribution of male partners according to the age of the female.

Table A12. Age mixing matrix $\Lambda = [\Lambda_{a,a',l=0,g}]$ - Level of sexual activity $l = 0$

Men\Women Age (years)	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
10-14	67%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
15-19	27%	74%	5%	0%	0%	0%	0%	0%	0%	0%	0%	0%
20-24	5%	22%	62%	14%	0%	0%	0%	0%	0%	0%	0%	0%
25-29	1%	4%	27%	49%	13%	0%	0%	0%	0%	0%	0%	0%
30-34	0%	0%	5%	29%	41%	11%	0%	0%	0%	0%	0%	0%
35-39	0%	0%	1%	7%	29%	40%	11%	0%	0%	0%	0%	0%
40-44	0%	0%	0%	1%	12%	34%	40%	10%	0%	0%	0%	0%
45-49	0%	0%	0%	0%	4%	12%	34%	46%	10%	0%	0%	0%
50-54	0%	0%	0%	0%	1%	3%	12%	37%	46%	11%	0%	0%
55-59	0%	0%	0%	0%	0%	0%	3%	7%	37%	52%	11%	0%
60-64	0%	0%	0%	0%	0%	0%	0%	0%	7%	30%	53%	11%
65+	0%	0%	0%	0%	0%	0%	0%	0%	0%	7%	36%	89%

Table A13. Age mixing matrix $\Lambda = [\Lambda_{a,a',l=1,g}]$ - Level of sexual activity $l = 1$

Men\Women Age (years)	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
10-14	36%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
15-19	49%	60%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
20-24	13%	35%	36%	14%	0%	0%	0%	0%	0%	0%	0%	0%
25-29	2%	5%	49%	47%	16%	0%	0%	0%	0%	0%	0%	0%
30-34	0%	0%	12%	28%	38%	8%	0%	0%	0%	0%	0%	0%
35-39	0%	0%	2%	9%	30%	36%	18%	0%	0%	0%	0%	0%
40-44	0%	0%	1%	2%	12%	34%	45%	24%	0%	0%	0%	0%
45-49	0%	0%	0%	0%	3%	16%	24%	55%	24%	0%	0%	0%
50-54	0%	0%	0%	0%	1%	5%	9%	17%	55%	14%	0%	0%
55-59	0%	0%	0%	0%	0%	1%	3%	3%	17%	43%	14%	0%
60-64	0%	0%	0%	0%	0%	0%	1%	1%	3%	26%	43%	14%
65+	0%	0%	0%	0%	0%	0%	0%	0%	1%	17%	43%	86%

Table A14. Age mixing matrix $\Lambda = \left[\Lambda_{a,a',l=\{2,3\},g}\right]$ - Level of sexual activity $l = 2,\ 3$

Men\Women Age (years)	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
10-14	37%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
15-19	50%	62%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
20-24	11%	32%	37%	14%	0%	0%	0%	0%	0%	0%	0%	0%
25-29	2%	6%	50%	47%	28%	0%	0%	0%	0%	0%	0%	0%
30-34	0%	0%	11%	28%	45%	20%	0%	0%	0%	0%	0%	0%
35-39	0%	0%	2%	9%	18%	39%	20%	0%	0%	0%	0%	0%
40-44	0%	0%	0%	2%	6%	22%	39%	20%	0%	0%	0%	0%
45-49	0%	0%	0%	0%	2%	10%	22%	39%	20%	0%	0%	0%
50-54	0%	0%	0%	0%	1%	5%	10%	22%	39%	20%	0%	0%
55-59	0%	0%	0%	0%	0%	2%	5%	10%	22%	39%	20%	0%
60-64	0%	0%	0%	0%	0%	1%	2%	5%	10%	22%	39%	20%
65+	0%	0%	0%	0%	0%	1%	2%	4%	9%	19%	41%	80%

2.2.3 Biological Parameters

Per-act transmission probability $\boldsymbol{\beta_g^\tau}$. The transmission probability of HPV infection per act or per partnership has yet to be empirically estimated. The transmission probabilities used in previous modeling studies were mainly per partnership and varied significantly from one study to another[43,45-47]. Empirical estimates of per-act transmission probability range between 5–100%[43]. We use this range for our uniform prior distribution of the per-act transmission probability. Given the important differences in the prevalence of the different HPV types (and similarities in clearance rates[48]), it is likely that the transmission probability is type-specific. Therefore, in our model, we allocated different per-act transmission probabilities to types HPV-16, 18, 6, 11, cross-protective and non cross-protective high-risk types (HR Cross: 31, 33, 45, 52, 58; HR Not Cross: 35, 39, 51, 56, 59, 66, 68, 73, 82). Furthermore, we allow male-to-female and female-to-male transmission probabilities to be different. Transmission probabilities are sampled as follows:

- A female-to-male ($\mathrm{F} \rightarrow M$) transmission probability $\beta_{g=2}^{\tau}$ is sampled from the uniform distribution 5-100% and is attributed to HPV-16. The remaining transmission probabilities are relative to the base HPV-16 value.

- An HPV-16 male-to-female ($\mathrm{F} \rightarrow M$) transmission probability $\beta_{g=1}^{\tau}$ is computed by multiplying the female-to-male value with a relative probability, $RP_{\mathrm{M}\rightarrow\mathrm{F}}^{\mathrm{HPV}-16}$, sampled from a uniform prior distribution of 0.4-2.00:

$$\beta_{g=1}^{\text{HPV-16}} = \min\left\{\beta_{g=2}^{\text{HPV-16}} \cdot RP_{\mathrm{M}\rightarrow\mathrm{F}}^{\text{HPV-16}},\ 1\right\} \quad (2.3)$$

- Finally, we sample relative probabilities (vs. HPV-16) for HPV-18, HPV-6, 11, HR Cross and HR Not Cross types from the prior ranges defined in Table A15. The female-to-male and male-to-female transmission probabilities are then computed by multiplying the respective HPV-16 transmission probabilities ($\mathrm{F} \rightarrow M$ & $\mathrm{M} \rightarrow F$) by these relative probabilities RP^{τ}:

$$\beta_{g}^{\tau} = \min\left\{\beta_{g}^{\text{HPV-16}} \cdot RP^{\tau},\ 1\right\} \quad (2.4)$$

Figure A17 shows the posterior per-act transmission probabilities.

Table A15. Transmission probabilities per-act β_g^{τ} – Prior ranges

	MIN	MAX
Per-act probability of HPV-16 transmission (female-to-male) $\beta_{g=2}^{\text{HPV-16}}$	0.05	1.00
Relative Probability HPV-16 male-to-female (vs. $\beta_{g=2}^{\text{HPV-16}}$) $RP_{\mathrm{M}\rightarrow\mathrm{F}}^{\text{HPV-16}}$	0.40	2.00
Relative Probabilities (vs. $\beta_g^{\text{HPV-16}}$)		
$RP^{\text{HPV-18}}$	0.11	1.00
$RP^{\text{HPV-6}}$	0.20	1.00
$RP^{\text{HPV-11}}$	0.13	0.50
RP^{Cross}¶	0.02	0.72
RP^{NotCross}¶	0.02	0.72

¶ Cross: high-risk cross-protective types 31, 33, 45, 52, 58; Not Cross: high-risk non cross-protective types 35, 39, 51, 56, 59, 66, 68, 73, 82. Although the cross-protective and non cross-protective types have the same priors, they`ll take different values in all parameter sets.

Given that there is no evidence on the relative transmission probabilities of one HPV-type versus others, assumptions were made to estimate the priors. Relative transmission probabilities of types versus HPV-16 were estimated to be equal to the relative prevalence of these types. For each type, the prior ranges are the minimum and maximum relative prevalence (versus HPV-16) estimated from the Biomarkers of Cervical Cancer Risk Study (BCCR)[49], the McGill/Concordia Cohort (McGill)[50] and the Canadian Cervical Cancer Screening Trial (CCCaST)[51]. Our priors encompass the values from Choi et al., which

estimate that the relative transmission probability of HPV-18, HPV-6 and HPV-OHR versus HPV-16 are 0.38-0.50, 0.25-0.92 and 0.19-0.38[46].

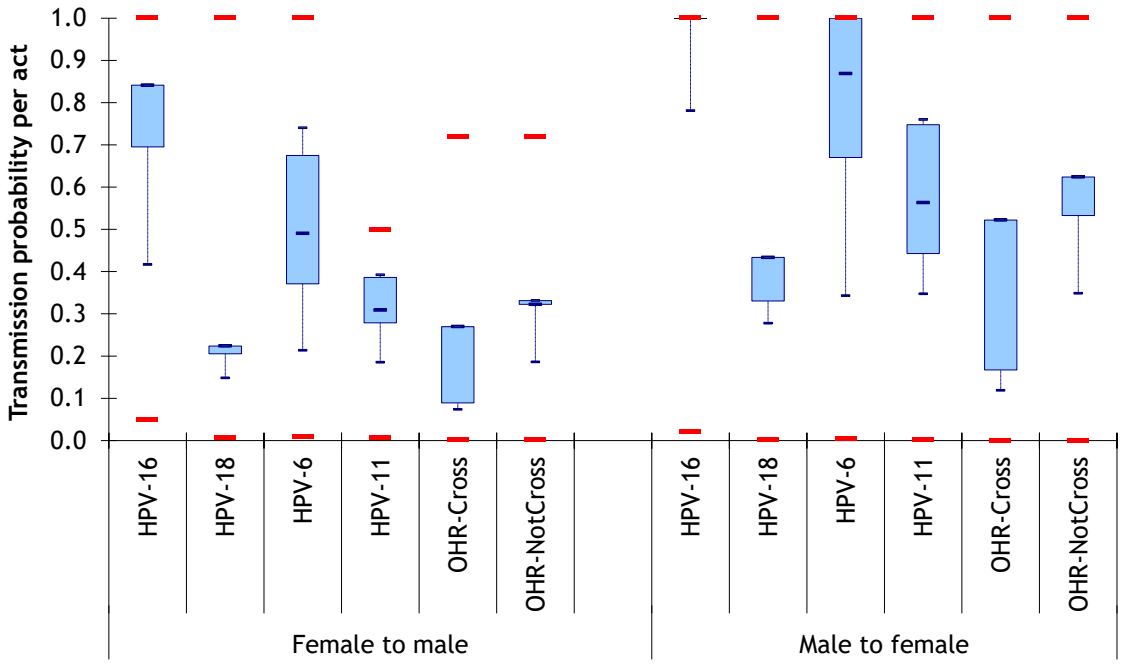


Figure A17. Per-act transmission probabilities - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

Clearance rates $\gamma_g^{\tau}(a)$. Type-specific clearance rates were extracted from Insinga et al.[52], Kulmala et al.[53] and Trottier et al.[48] (see Table A16). It is unknown whether clearance rates are age dependent. To allow clearance to be age dependent whilst keeping the number of parameters to a minimum, we modeled age-specific clearance rates using a linear trend. For female and male clearance rates, we sample two points from the uniform distribution of HPV-16 clearance (Table A16). These values are attributed to the first and last age groups, and clearance rates for the intermediate age groups are inferred from the linear trend joining the two values. The HPV-16 clearance rates serve as reference rates. Relative rates for HPV-18, 6, 11, HR cross-protective and non cross-protective types are sampled from the uniform distributions presented in Table A16. Clearance rates for HPV-18, 6, 11, cross-protective and non cross-protective high-risk types are obtained by multiplying the HPV-16 rates with the sampled relative rates:

$$\gamma_g^{\tau}(a) = \gamma_g^{\text{HPV-16}}(a) \cdot RR^{\tau} \qquad (2.5)$$

We assumed the same parameter priors for HPV-16 clearance rates for men and women based on results published by Giuliano et al.[54]. Of note, the posterior parameter values for the clearance rates are allowed to be different for females and males.

Of note, even though the high risk types labeled as cross-protective have the same clearance rates, it is important to understand that they are modeled individually and not as a group of types. Figure A18 shows the posterior HPV-16 clearance rates for females and males, and Figure A19 shows the posterior distribution of the relative clearance rates compared to HPV-16.

Table A16. HPV clearance rates $\gamma_g^{\tau}(a)$ – Prior ranges

	MIN	MAX
Clearance rate HPV-16 women (per-year)¶ $\gamma_{g=1}^{\text{HPV-16}}(a)$	0.58	1.70
Relative Rate (vs $\gamma_g^{\text{HPV-16}}(a)$)¥		
$RR^{\text{HPV-18}}$	0.93	1.12
$RR^{\text{HPV-6}}$	1.27	1.96
$RR^{\text{HPV-11}}$	1.27	2.17
$RR^{\text{Cross‡}}$	0.79	1.57
$RR^{\text{NotCross‡}}$	0.79	1.57
Clearance rate HPV-16 men (per-year)§	0.58	1.70

¶. Minimum and maximum value taken from the minimum and maximum bound of the confidence intervals from [52,53]. ¥. Minimum and Maximum are the minimum and maximum Relative Rates from [48-52]. §. We assumed same range as for women. ‡ Cross: high-risk cross-protective types 31, 33, 45, 52, 58; Not Cross: high-risk non cross-protective types 35, 39, 51, 56, 59, 66, 68, 73, 82.

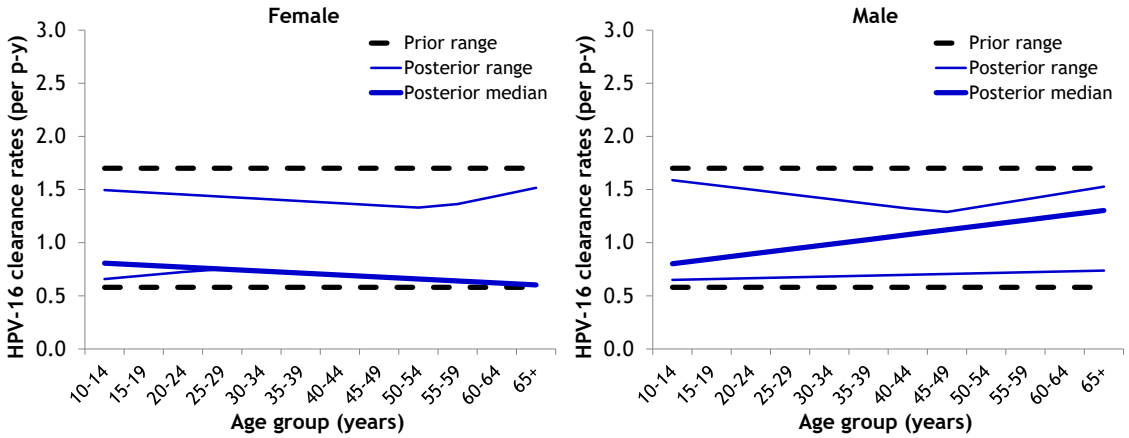


Figure A18. HPV-16 clearance rates for females and males - Posterior distributions. Dashed black lines represent the minimum and maximum of the prior ranges. Blue lines represent the medians, minimums and maximums of the posterior parameter sets.

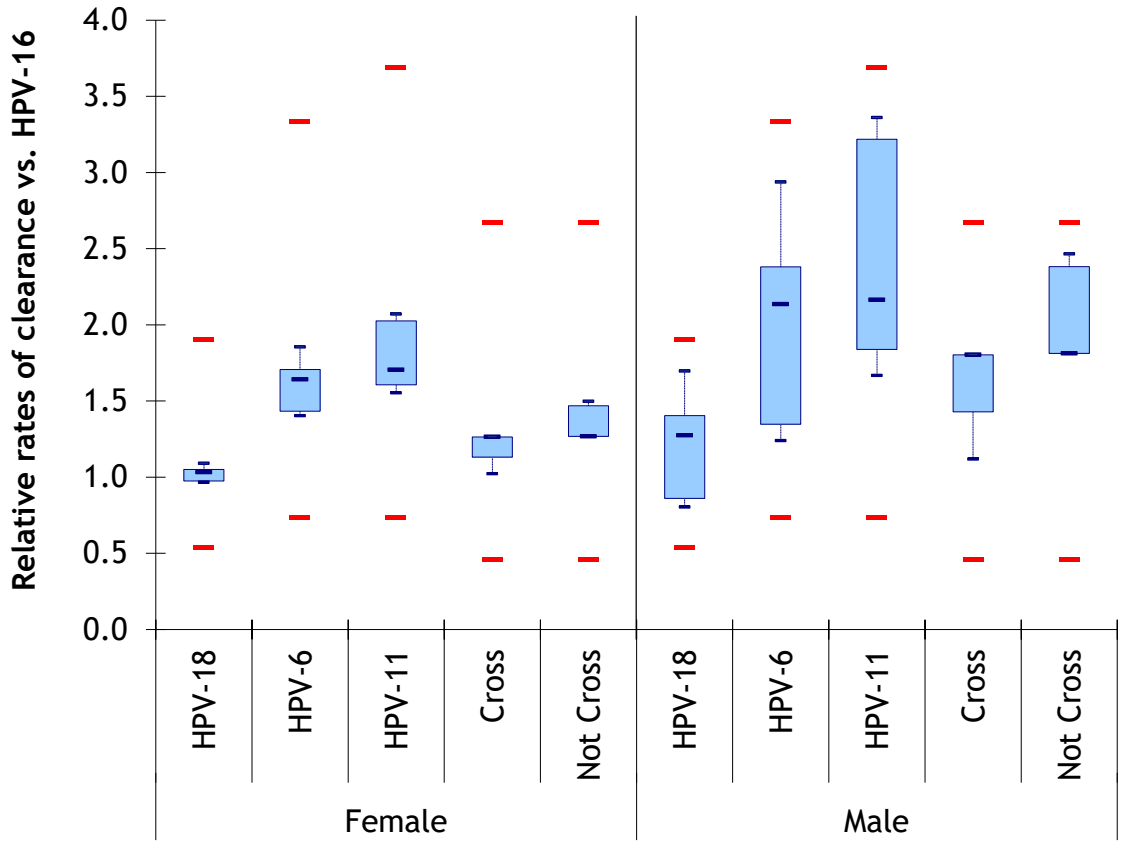


Figure A19. Relative clearance rates compared to HPV-16 - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges. Cross: high-risk cross-protective types 31, 33, 45, 52, 58; Not Cross: high-risk non cross-protective types 35, 39, 51, 56, 59, 66, 68, 73, 82.

Probability of developing lifelong natural immunity M_g . We use an uninformed prior for the male and female probabilities of developing lifelong natural immunity following clearance of infection (0-100%) given the lack of empirical data in the literature. See Figure A20 for posterior distributions.

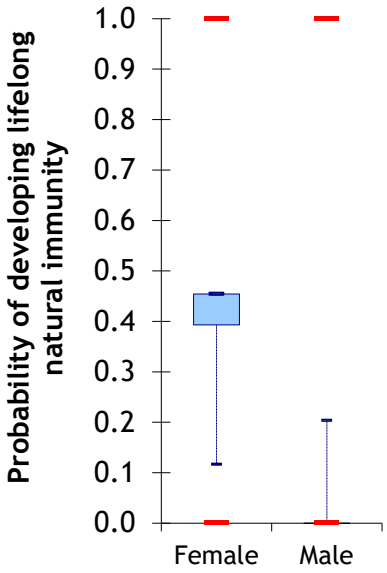


Figure A20. Probabilities of developing lifelong natural immunity following clearance of infection - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

Progression, regression and clearance rates for cervical intraepithelial lesions. Although several epidemiological studies have estimated the probability of developing CIN lesions following an HPV infection, it is very difficult to directly estimate progression and regression rates between the different grades of CIN from these studies. The different study designs, follow-up intervals, performance of screening for the detection of cervical lesions and protocols for the management of abnormal results lead to values that differ widely between studies.

To overcome this difficulty, we developed a simple Markov model to estimate progression, regression and clearance rates that reproduced type-specific (HPV-16, 18, 6, 11) cumulative incidence of HPV persistent infection, CIN1, 2 and 3 at 12, 24 and 36 months available in Insinga et al. 2007[55]. The model includes 4 health states: HPV infection (without CIN), CIN1, CIN2 and CIN3 and women can clear the infection, progress or regress between the different grades of lesions. We simulated a cohort of women over time with a 1-month time step and we used the least square method to obtain the sets of

parameters that minimized the difference between the observed and modeled cumulative incidence of CIN1, CIN2 and CIN3. To take into account the uncertainty surrounding the natural history parameters for each vaccine HPV-type (16, 18, 6, 11), we estimated parameter sets for 5 different scenarios. We estimated the parameter fit to the point estimates reported in Insinga et al. 2007[55] (scenario 1), and the upper and lower bounds of the 95% confidence interval (scenario 2 and 3). We then varied the proportion of women censored after a CIN1+ diagnosis (scenario 4) and the proportion of lesions detected by screening (scenario 5). Our initial prior range for each natural history parameter was obtained by selecting the minimum and maximum values over the 5 different scenarios. These ranges were compared to those published by Jit et al[56]. To be as inclusive as possible, we chose the Jit et al. parameter value as our minimum or maximum prior value if it was lower or higher than our estimated prior range. We assumed uninformative prior ranges for the natural history of cross-protective and not cross-protective types, given the scarcity of data to inform these parameters.

Data on the progression from CIN3 to SCC are scarce due to ethical reasons. Our prior range for the time interval between CIN3 and SCC (25 to 40 years) was based on data from Gustafsson 1997 et al.[57], which reported the age-specific incidence of cervical cancer prior to screening. In our model, each woman with CIN3 is given a time to SCC based on a Gamma distribution $\Gamma\left(\alpha = \sqrt{\mu \cdot \sigma},\ \beta = \sqrt{\mu/\sigma}\right)$, where μ is the sampled average time interval between CIN3 and SCC and σ is a sampled parameter affecting the shape of the distribution.

Table A17 summarizes the prior ranges for the natural history parameters and Figures A21-30 represent the posterior parameter sets.

Table A17. Progression, regression and clearance rates for cervical intraepithelial lesions and squamous cervical cancer– Prior ranges

	HPV 16		HPV 18		HPV 6/11		HPV HR†		HPV Cross		HPV Not Cross	
	Rate (per w-y)		Relative rate (vs HPV 16)		Relative rate (vs HPV 16)		Relative rate (vs HPV 16)		Relative rate (vs HPV 16)		Relative rate (vs HPV 16)	
	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
Progressions												
Infected to CIN1	0.25	1.33	0.40	0.79	0.79	3.02			0.50	1.50	0.25	1.00
CIN1 to CIN2	0.07	3.84	0.81	1.61	0.00	0.00			0.50	1.50	0.25	1.00
CIN2 to CIN3	0.43	4.27	0.37	0.60	0.00	0.00			0.50	1.50	0.25	1.00
CIN3 to CC1	0.02	0.04										
Regressions												
Regression from CIN1	0.00	3.62	0.00	5.05	3.43	15.26	0.50	2.00				
% CIN1 regress to cleared	0.70	0.90										
CIN2 to CIN1	0.00	2.48	0.80	1.20	0.00	0.00	1.00	2.00				
CIN2 to cleared	0.00	1.89	0.79	1.19	0.00	0.00	1.00	2.00				
CIN3 to CIN2	0.00	0.00										

†. HPV HR represents the cross-protective and not cross-protective types together. If there is a value in this category, it means that the cross-protective and non cross-protective types take exactly the same parameter for this health transition.

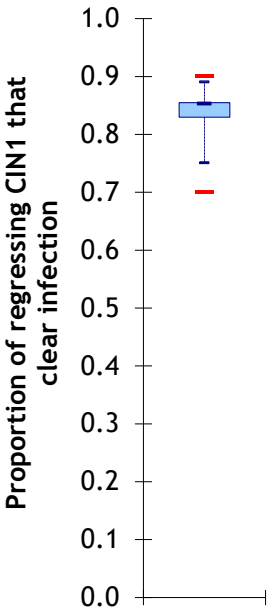


Figure A21. Proportion of regressing CIN1 that clear HPV infection – Posterior distribution. Box plot represents the median, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges. Women regressing from CIN1 can either return to the infected or susceptible state.

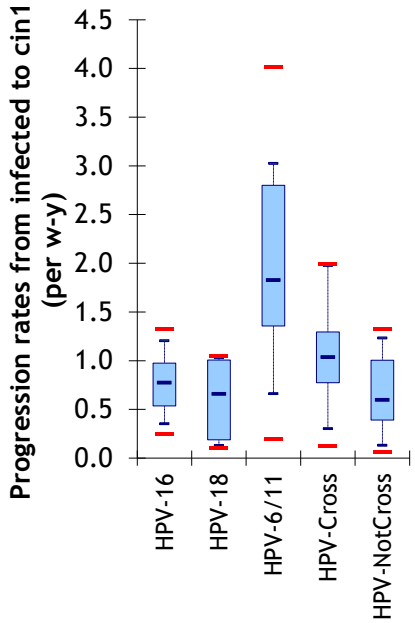


Figure A22. Progression rates from infected to CIN1 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

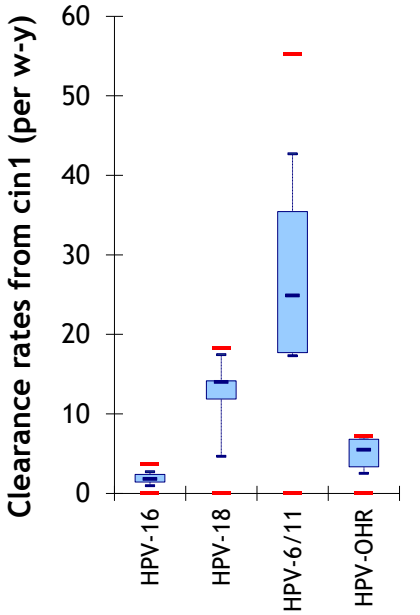


Figure A23. Clearance rates from CIN1 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

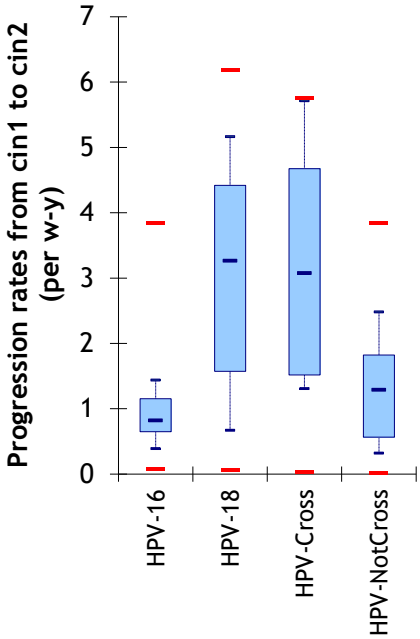


Figure A24. Progression rates from CIN1 to CIN2 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

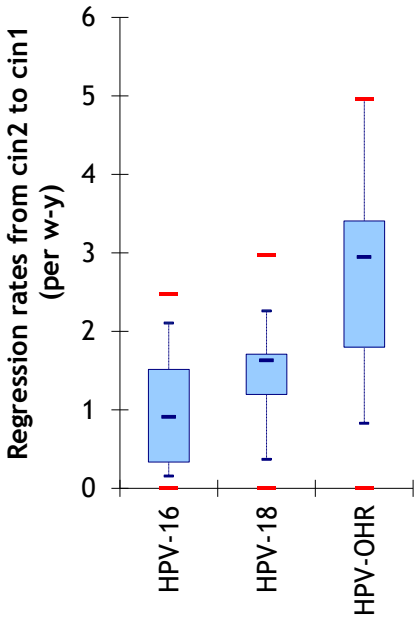


Figure A25. Regression rates from CIN2 to CIN1 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

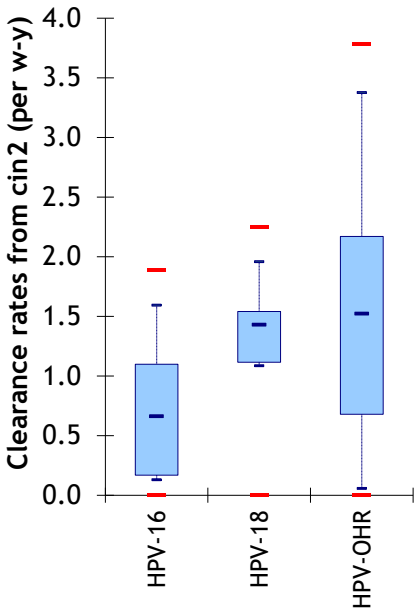


Figure A26. Clearance rates from CIN2 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

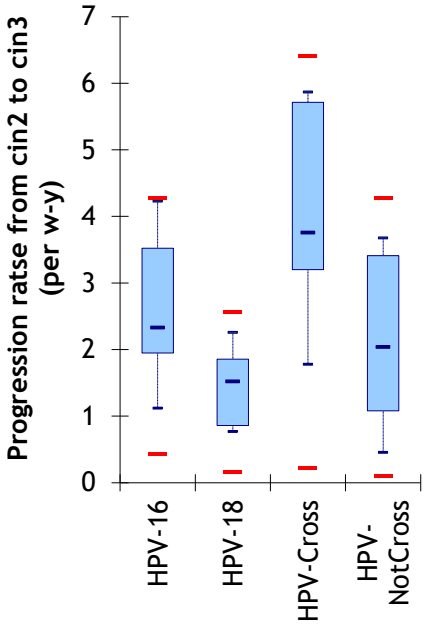


Figure A27. Progression rates from CIN2 to CIN3 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

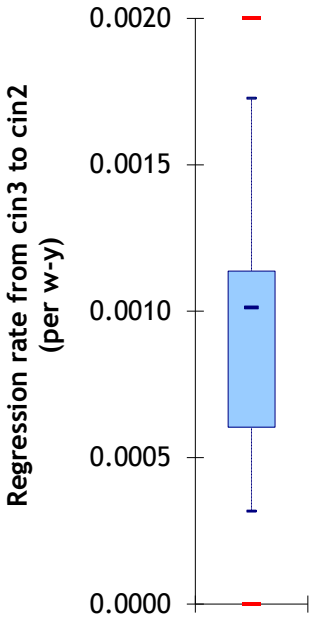


Figure A28. Regression rates from CIN3 to CIN2 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

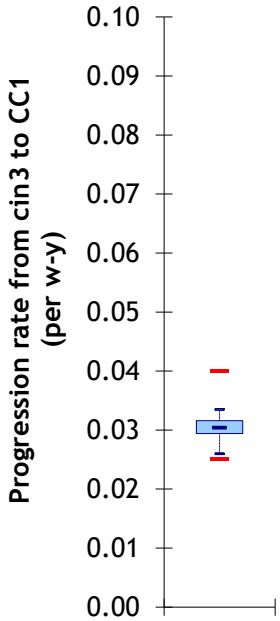


Figure A29. Progression rates from CIN3 to CC1 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum of the prior ranges.

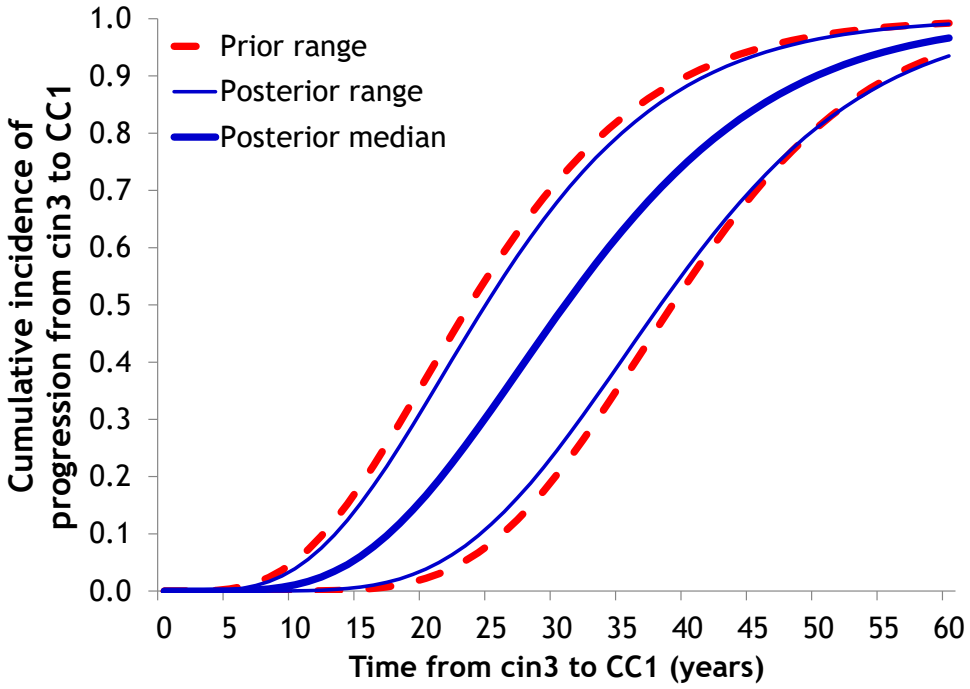


Figure A30. Cumulative incidence of progression from CIN3 to CC1 in absence of screening and mortality – Posterior range. Probability is modeled as a gamma distribution. Dashed red lines represent the minimum and maximum of the prior ranges. Blue lines represent the median, minimum and maximum of the posterior parameter sets.

Progression, symptoms and mortality in cancer stages. Because virtually no data exist on the rate of progression from localized SCC through distant stage, we used the

mean age at diagnosis of each cancer stage (available in the SEER database[17]) to approximate the delay between two consecutive cancer stages and then obtain the progression rates. We also used SEER data to obtain the stage-specific mortality rates. Finally, we used previously published estimates of the probability of developing symptoms from Myers et al[58].

Table A18. Progression, symptoms and mortality in cancer stages - Parameters

	SCC I Local	SCC II Regional	SCC III Distant
Progression rates to next cancer stage (per women-year)	0.15	0.31	NA
Probability of developing symptoms	15.0%	40.0%	90.0%
Mortality rates (per women-year)	0.018	0.110	0.354

Anogenital warts (AGW) parameters. The proportion of HPV-6/11 leading to an AGW consultation was assumed to be dependent on age and gender. The median posterior parameter values of the proportion of HPV-6/11 infections leading to AGW and an AGW consultation for women (men) aged < 35 and 35+ years was 8% (6%) and 70% (33%), respectively.

Other HPV-attributable cancer parameters. In our model, each infected individual is given a probability of progressing towards cancer (type and gender-specific) and a time to cancer based on a normal distribution $N(\mu, \sigma)$, where μ is the sampled average time interval between persistent infection and cancer. A different probability distribution is estimated for cervical adenocarcinomas, and cancers of the anus, oropharynx, vulva, vagina, and penis, and for each HPV-type. Table A19 summarizes the posterior parameter sets.

Table A19. Model parameters for other-HPV related cancers*

	Proportion of infections progressing toward cancer† (%)		Probability distribution of cancer‡ over time since infection $N(\mu, \sigma)$			
			Mean μ (years)		Standard deviation σ (years)	
	Med	80% Range	Med	80% Range	Med	80% Range
FEMALE						
Cervical Adenocarcinoma						
HPV-16	0.050	(0.033;0.057)	25.6	(23.9;25.9)	9.1	(8.6;9.2)
HPV-18	0.181	(0.076;0.259)	25.8	(23.7;25.9)	8.9	(8.4;9.2)
HPV-31	0.004	(0.003;0.007)	23.9	(23.9;24.7)	8.2	(8.2;8.7)
HPV-33	0.004	(0.003;0.007)	23.9	(23.9;26.3)	8.2	(8.2;8.8)
HPV-45	0.022	(0.018;0.044)	26.1	(22.9;26.2)	8.9	(7.9;9.0)
HPV-52	0.004	(0.003;0.007)	23.8	(23.8;26.1)	8.2	(8.2;8.7)
HPV-58	0.004	(0.003;0.007)	23.9	(23.9;26.1)	8.2	(8.2;8.7)
Vulvar Cancer						
HPV-16	0.058	(0.041;0.066)	44.8	(43.6;45.2)	15.1	(15.0;15.5)
HPV-18	0.007	(0.003;0.010)	44.4	(44.4;44.4)	15.1	(15.1;15.1)
HPV-31	0.004	(0.003;0.009)	44.4	(44.4;44.4)	15.1	(15.1;15.1)
HPV-33	0.043	(0.035;0.094)	44.5	(43.7;44.6)	14.7	(14.5;15.8)
HPV-45	0.009	(0.007;0.020)	44.4	(44.4;44.4)	15.1	(15.1;15.1)
Vaginal Cancer						
HPV-16	0.025	(0.018;0.028)	57.8	(56.8;57.8)	17.7	(17.4;18.2)
HPV-18	0.003	(0.001;0.005)	67.1	(66.9;67.1)	21.6	(21.5;21.8)
HPV-31	0.005	(0.004;0.012)	56.9	(56.2;57.9)	17.4	(17.0;18.2)
HPV-33	0.005	(0.004;0.012)	55.4	(55.1;56.2)	16.8	(16.4;17.6)
HPV-45	0.005	(0.004;0.012)	54.9	(54.6;55.6)	16.6	(16.2;17.3)
HPV-52	0.005	(0.004;0.012)	55.6	(55.2;56.4)	16.8	(16.5;17.5)
HPV-58	0.005	(0.004;0.012)	55.9	(55.4;56.7)	17.0	(16.6;17.8)
Anal Cancer						
HPV-16	0.088	(0.059;0.100)	41.5	(39.9;41.8)	9.9	(9.7;9.9)
HPV-18	0.032	(0.013;0.046)	41.5	(39.5;41.7)	9.9	(9.5;9.9)
HPV-31	0.007	(0.005;0.015)	40.8	(39.7;41.2)	9.2	(8.8;9.8)
HPV-33	0.009	(0.007;0.020)	40.7	(39.9;41.3)	9.4	(9.0;9.9)
Oropharyngeal Cancer						
HPV-16	0.069	(0.047;0.077)	47.4	(45.8;47.6)	11.9	(11.6;12.0)
HPV-18	0.010	(0.004;0.015)	47.6	(47.6;47.6)	12.1	(12.1;12.1)
HPV-33	0.015	(0.012;0.033)	47.1	(46.8;47.4)	12.0	(11.6;12.6)

	Proportion of infections progressing toward cancer† (%)		Probability distribution of cancer‡ over time since infection $N(\mu, \sigma)$			
			Mean μ (years)		Standard deviation σ (years)	
	Med	**80% Range**	**Med**	**80% Range**	**Med**	**80% Range**
MALE						
Anal Cancer						
HPV-16	0.006	(0.003;0.008)	37.9	(37.4;38.4)	11.8	(11.5;12.0)
HPV-18	0.040	(0.015;0.077)	39.2	(38.6;40.1)	11.7	(11.4;12.9)
HPV-31	0.013	(0.008;0.020)	42.2	(41.6;42.8)	13.5	(12.7;14.0)
HPV-33	0.017	(0.010;0.026)	41.6	(38.5;42.7)	13.2	(10.2;13.9)
Oropharyngeal Cancer						
HPV-16	0.170	(0.082;0.197)	40.8	(39.7;41.3)	7.6	(7.3;7.8)
HPV-18	0.029	(0.010;0.055)	42.0	(41.5;42.5)	7.6	(7.3;7.8)
HPV-33	0.057	(0.036;0.094)	42.4	(41.9;44.6)	7.8	(7.7;8.0)
Penile Cancer						
HPV-16	0.038	(0.020;0.044)	74.9	(74.8;84.7)	20.8	(20.4;23.3)
HPV-18	0.017	(0.006;0.029)	75.0	(75.0;75.0)	20.0	(20.0;20.0)
HPV-31	0.018	(0.012;0.024)	75.0	(75.0;75.0)	20.0	(20.0;20.0)
HPV-33	0.006	(0.004;0.008)	75.0	(75.0;75.0)	20.0	(20.0;20.0)
HPV-45	0.012	(0.008;0.016)	75.0	(75.0;75.0)	20.0	(20.0;20.0)

Med: Median value of simulations; 80% Range: 10th and 90th percentiles of simulations.

*. The values shown in this table should not directly be interpreted as biological processes. In the absence of epidemiological data on natural history, these parameters were estimated in order for the model to reproduce the observed incidence of HPV-related cancers given age-specific type specific HPV incidence of infection. †. In our model, not all infections "progressing toward cancer" will result in cancer due to competing risks of natural mortality. ‡. Without competing risks such as natural mortality or mortality related to other HPV cancers.

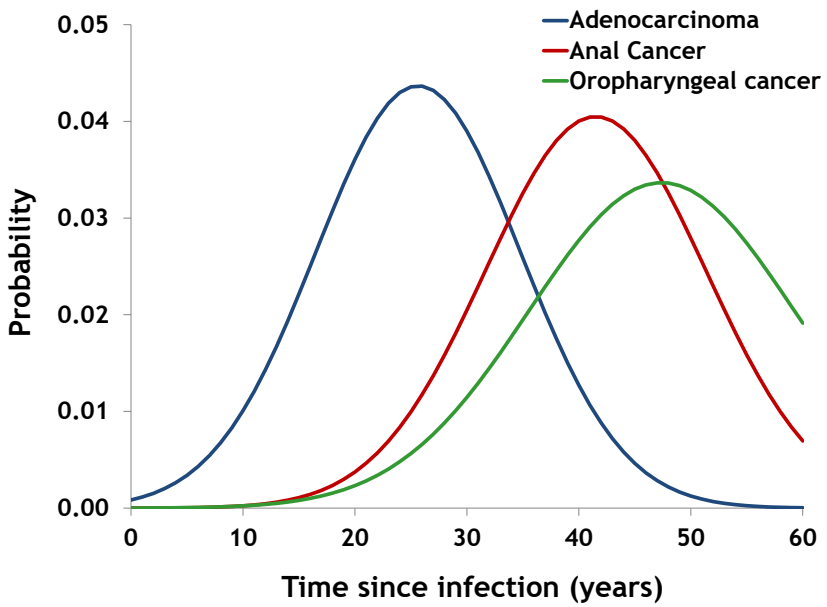


Figure A31. Examples of probability distributions of HPV-16 related cervical adenocarcinoma, and anal and oropharyngeal cancer over time since infection. Of note: In the model, these distributions are truncated due to natural mortality.

2.2.4 Screening Parameters

Screening parameters are based on data from the US National Breast and Cervical Cancer Early Detection Program (NBCCEDP)[59], and US Behavioral Risk Factor Surveillance System (BRFSS)[33,60].

Proportion of women in screening behavior levels. The parameters for the proportion of women in the different screening behavior levels in Table A20 were calculated from the National Breast and Cervical Cancer Early Detection Program (NBCCEDP). For routine cytological screening scenarios, we assumed that women in screening behavior levels 0, 1, 2, and 3 have time intervals between two routine screening tests (i.e., the time between a normal cytology result and the previous one) of 1 year, 2 years, 3-5 years, and ≥ 5 years. Level 4 represents women who will never be screened in their lifetime. The proportion of women in each level of screening behavior was calculated using data from the NBCCEDP (2005-2010). For the cytology with DNA HPV co-testing scenarios, we assumed that women in screening behavior levels 0, 1, and 2 have perfect adherence to guidelines: 1) 21-29 year-olds have a cytology test every 3 years, and 2) 30-65 year-olds have cytology and HPV DNA co-testing every 5 years. Women in screening behavior level 3 have a test ≥ 5 years and those in level 4 will never be screened either through cytology or co-testing.

Table A20. Proportion of women in the screening behavior levels - Parameters

Interval	*S* = 0 Short (1 yr)	*S* = 1 Medium (2 yrs)	*S* = 2 Long (3-5 yrs)	*S* = 3 Very long (≥ 5 yrs)	*S* = 4 Never
	0.10	0.52	0.26	0.06	0.06

Onset of cervical cancer screening. The parameters for the onset of cervical screening were obtained from the Behavioral Risk Factor Surveillance System (BRFSS)[33]. We estimated the age at first Pap using the proportions of women who reported never having received a Pap test at a given age. Based on this distribution, each woman in the model is attributed a first screening appointment. We assume that the age at start of cervical screening was independent of the screening behavior level.

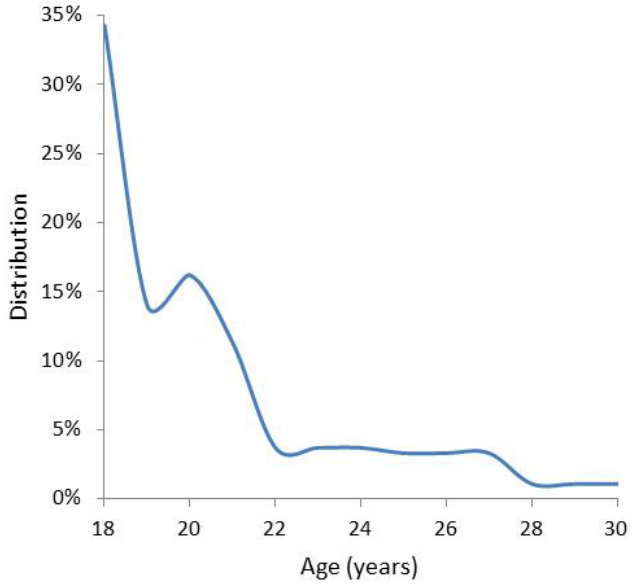


Figure A32. Age distribution of onset of cervical screening - Parameters.

Screening rate. The screening rate represents the rate of routine screening tests (i.e. excludes screening tests performed for the follow-up of abnormal results). The parameters for the screening rate were calculated from the NBCCEDP data. They are dependent on the level of screening behavior of women but are independent of age. Screening rates are obtained by the reciprocal of the mean delay between two consecutive routine screening tests.

Table A21. Cytology-only screening rates (per person-year) – Parameters

	S = 0 Short (1 yr)	*S* = 1 Medium (2 yrs)	*S* = 2 Long (3-5 yrs)	*S* = 3 Very long (≥ 5 yrs)	*S* = 4 Never
Mean delay between 2 routine screening	1 yr	2 yrs	4 yrs	8 yrs	NA
Screening rate	1.00	0.50	0.25	0.125	0.00

Screening performance for the detection of infection and cervical lesions. Parameters for the probabilities of detecting women in each neoplastic state by cervical cytology were estimated using the data of two systematic reviews on psychometric performance of cervical cancer screening with cytology[61,62]. More specifically, in Nanda et al.[61], we used data collected in low HPV prevalence settings and corrected for verification bias whereas in Arbyn et al.[62] we used data presented for conventional cytology. We complemented these data with information from two studies presenting the specific

cytological result obtained by women diagnosed with an invasive cancer [63,64]. Given uncertainty around the estimates of sensitivity and specificity, we used the 95% confidence intervals provided in the papers to obtain a range of probabilities. When confidence intervals were unavailable, we varied the point estimate by ±10%. Base-case values were identified through preliminary sensitivity analyses within the estimated range of probabilities.

Table A22. Probabilities of detecting a neoplastic state by cytology – Parameters

	Cytological results					
Health States	**Normal %**	**ASCUS %**	**LSIL %**	**HSIL/ASC-H+ %**	**Cancer %**	**Total %**
Normal	97.0 (95.0-98.0)	1.5 (1.0-2.0)	1.0 (0.5-1.5)	0.45 (0.0-1.0)	0.05 (0.0-0.5)	100.0
CIN1	41.0 (37.0-45.0)	12.0 (10.5-14.5)	29.0 (26.5-40.5)	18.0 (8.0-18.0)	0.0 (0.0-0.0)	100.0
CIN2/3	20.0 (18.0-22.0)	5.0 (3.0-7.0)	20.0 (18.0-22.0)	53.0 (48.0-54.0)	2.0 (1.0-3.0)	100.0
Cancer	0.0 (0.0-2.0)	6.0 (2.0-9.0)	9.0 (3.0-12.0)	54.0 (50.0-60.0)	31.0 (27.0-35.0)	100.0

Parameters for the probabilities of confirming the neoplastic state by colposcopy / biopsy were estimated using the data from several articles assessing the success of colposcopy at diagnosing CIN or the inter- intra-observer agreement in CIN diagnosis[65-69]. Given that sensitivity estimates of colposcopy/biopsy to diagnose CIN highly depends on the number and location of biopsies taken[65], we considered a wide range of probabilities to account for different biopsy practices. The probability of detecting an HPV infection was assumed to be 80% for women infected without a lesion (state Infected 1) and 95% for women with CIN1-3 (state Infected 2-4 and SCC1-3).

Table A23. Probabilities of diagnosing a neoplastic state by colposcopy/biopsy – Parameters

	Colposcopy/biopsy results					
Health States	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Normal	88.0% (65-100)	7.0% (0-28)	3.0% (0-5)	2.0% (0-2)	0.0% (0-0)	100.0%
CIN1	22.0% (10-38)	62.0% (57-90)	15.0% (0-3)	1.0% (0-2)	0.0% (0-0)	100.0%
CIN2	10.0% (5-19)	10.0% (5-13)	47.0% (52-85)	35.0% (0-16)	0.0% (0-0)	100.0%
CIN3	10.0% (1-19)	10.0% (3-13)	16.0% (6-16)	56.0% (42-81)	10.0% (0-10)	100.0%
Cancer	0% (0-0.5)	0.0% (0-2)	0.0% (0-2.5)	5.0% (0-5)	95.0% (90-100)	100.0%

Management of women with abnormal results. Based on a Cochrane systematic review on the efficacy of seven alternative surgical treatments for CIN[70], we assumed that treatment fails for 5% of women (the health state of these women remains unchanged after treatment). Using data from Kreimer et al[71], we assumed that 80% of women clear both the lesion and the infection after treatment and 15% clear the lesion but remain HPV infected.

Table A24. Parameters for the management of women with a first or repeated abnormal cytology result, according to the severity of the result - Parameters.

	First abnormal result				Repeat abnormal result			
Follow-up	ASCUS	LSIL	HSIL/ ASC-H	SCC	ASCUS	LSIL	HSIL/ ASC-H	SCC
Lost to follow-up	12.7%	8.9%	4.5%	0.0%	0.0%	0.0%	0.0%	0.0%
Repeat cytology	84.3%	85.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Colposcopy/biopsy	3.0%	6.1%	95.5%	100.0%	100.0%	100.0%	100.0%	100.0%

2.2.5 HPV type-specific positivity in cervical and non-cervical cancers

HPV type distributions in cervical and non-cervical cancers were mainly based on data provided by Dr. Markowitz[19]. We used additional data from 3 meta-analyses containing worldwide data on HPV prevalence in non-cervical cancers (Backes et al.[21], De Vuyst et al.[20] and Kreimer et al.[22]). We calculated North-American HPV prevalences using country-

specific data available in the Appendix of these articles. Finally, we also obtained North-American estimates of HPV prevalence in cervical cancer stratified by histological type from Dr. Gary Clifford (International Agency for Research in Cancer)[31]. Table A25 presents US HPV type distributions in HPV-related cancers used to estimate the long-term impact of HPV vaccination on other HPV-related cancers (see Section 2.2.5).

Table A25. HPV type-specific positivity in cervical and non-cervical cancers

Cancers	**Cervical (ALL)**	**SCC**	**Adeno**	**Vulvar**	**Vagina**	**Anal Male**	**Anal Female**	**Penile**	**Oropharynx Male**	**Oropharynx Female**
References	Clifford[31] Saraiya[19]	Saraiya[19]	Clifford[31]	Saraiya[19]	Saraiya[19]	Saraiya[19]	Saraiya[19]	Saraiya[19]	Saraiya[19]	Saraiya[19]
	%	%	%	%	%	%	%	%	%	%
Any HPV	100	100	100	69	75	89	92	63	72	63
HPV 16	61	56	47	70	73	85	85	72	85	77
HPV 18	21	19	47	2	2	9	1	8	3	4
HR cross	16	20	10	33	22	6	12	22	9	20
HR not cross	7	9	2	7	7	9	1	4	5	6
HPV 6	0	0	0	1	0	9	2	4	0	0
HPV 11	0	1	0	0	0	11	0	0	0	0

2.2.6 Economic parameters

Table A26. Healthcare resource use, QALY-weights and Case-fatality

	Base-case*	Sensitivity analysis		References
		Minimum	Maximum	
Case-fatality†				
Cervical cancer (stage 1; 2-3; 4)	9%; 42%; 82%			
Vulvar/vaginal	33%	31%	39%	[72]
Anal	31%	30%	32%	[72]
Oropharyngeal	39%	39%	40%	[72]
Penile	32%	29%	35%	[72]
% AGW attributed to HPV-6/11‡	90%	66%	100%	[73-76]
AGW consultations per episode				
Women	1.15	1.12	1.23	[77]
Men	1.21	1.15	1.33	[77]
QALYs-lost				
QALYs-lost per episode				
AGW	0.02	0.01	0.04	[37,78]
CIN1 or LSIL	0.006	0.006	0.008	[36]
CIN2/3 or HSIL	0.01	0.009	0.012	[36]
Disutility				
Cervical cancer (stage 1; 2-3; 4)	28%;39%;45%	19%;29%;29%	51%;58%;64%	[14,79,80]
Vulvar/vaginal	32%			
Anal	51%			
Oropharyngeal	25%			
Penile	29%			

Abbreviations: AGW: Anogenital warts; CIN: Cervical intraepithelial neoplasia; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; QALY: Quality-adjusted life-years; * Base-case values are the median from the literature †. (Case fatality) = 100% − (5-year survival [%]); ‡. Proportion of HPV-6 and 11 among HPV positive anogenital warts.

Utility parameters are shown in Table A26. Most parameter values are US specific and were provided by Dr. Harrell Chesson (CDC). When values were unavailable for the US, we used UK and Canadian data sources (e.g., QALYs-lost per episode of CIN or SIL).

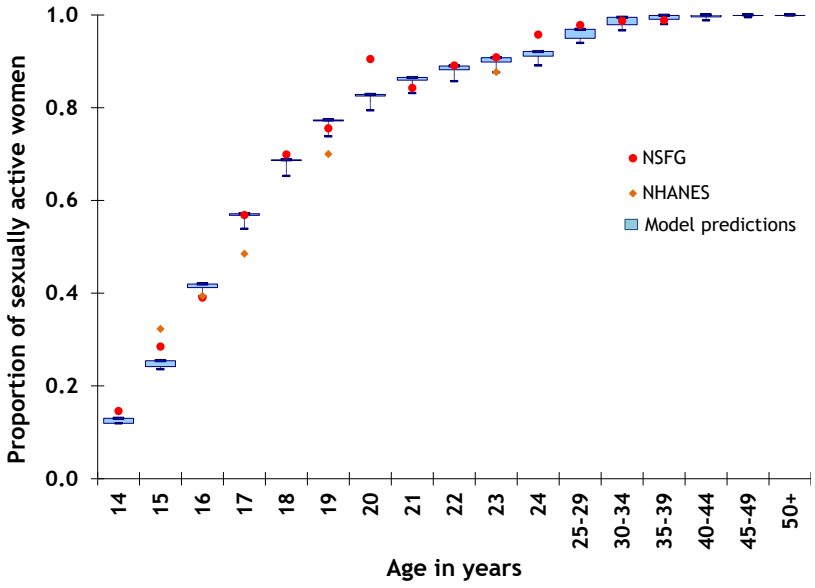
2.3 Model fit

Please see Table A1 for details on the data used to fit the model (stratifications, references and number of data points), and Section 2.5 for target definitions. Figures A33-34, A35-39, A40-41, A42-43, A44, and A45 illustrate the model fit to sexual behavior, HPV prevalence, screening and

cervical cancer, HPV type-specific positivity in CIN and SCC samples, anogenital warts consultations, and other HPV-related cancers data, respectively.

2.3.1 Examples of fit to sexual behavior data

A



B

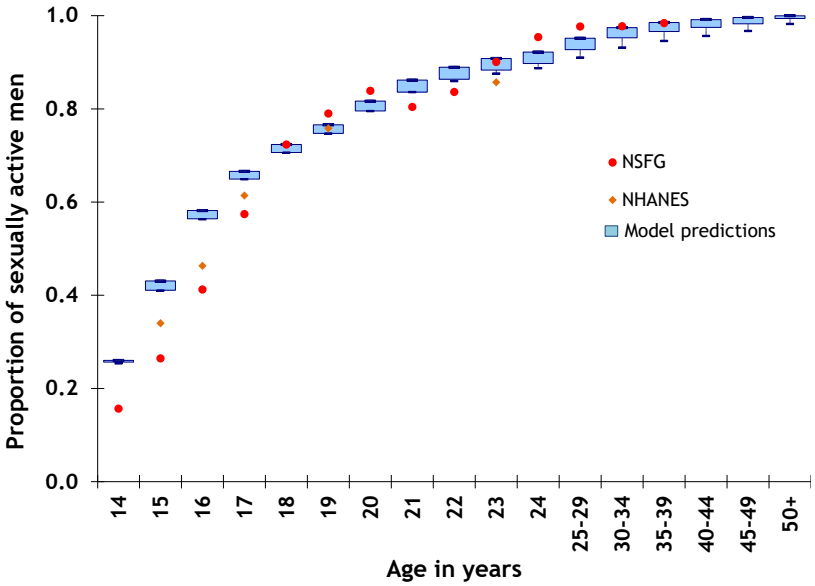


Figure A33. Proportion of sexually active A) women and B) men. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Diamonds and dots represent observed data[24-26].

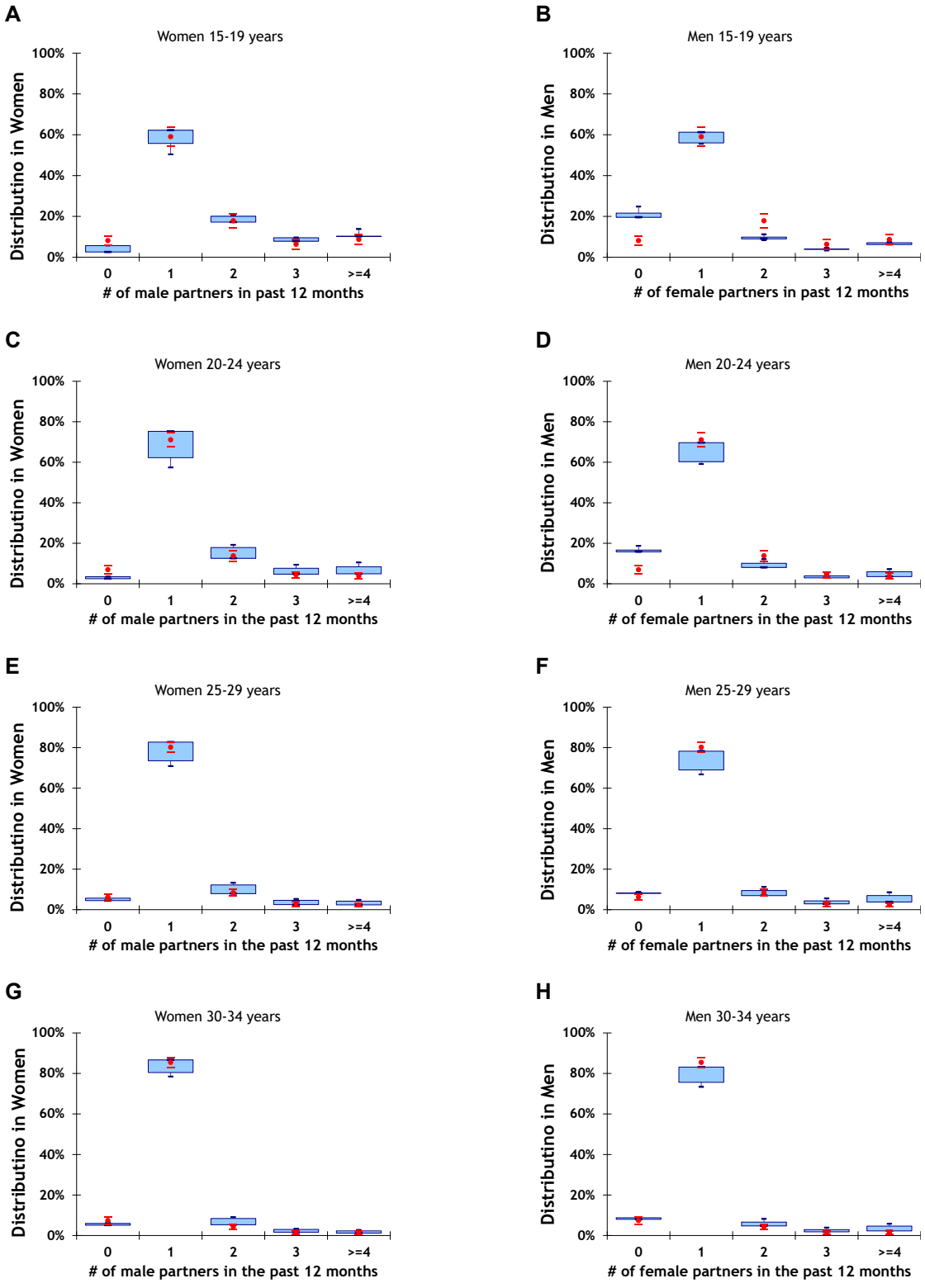


Figure A34. Number of partners in the last 12 months in sexually active women and men aged a-b) 15-19yrs, c-d) 20-24yrs, e-f) 25-29yrs, and g-h) 30-34yrs. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red dots and lines represent observed data with 95% confidence intervals[24,26].

2.3.2 Examples of fit to HPV prevalence data

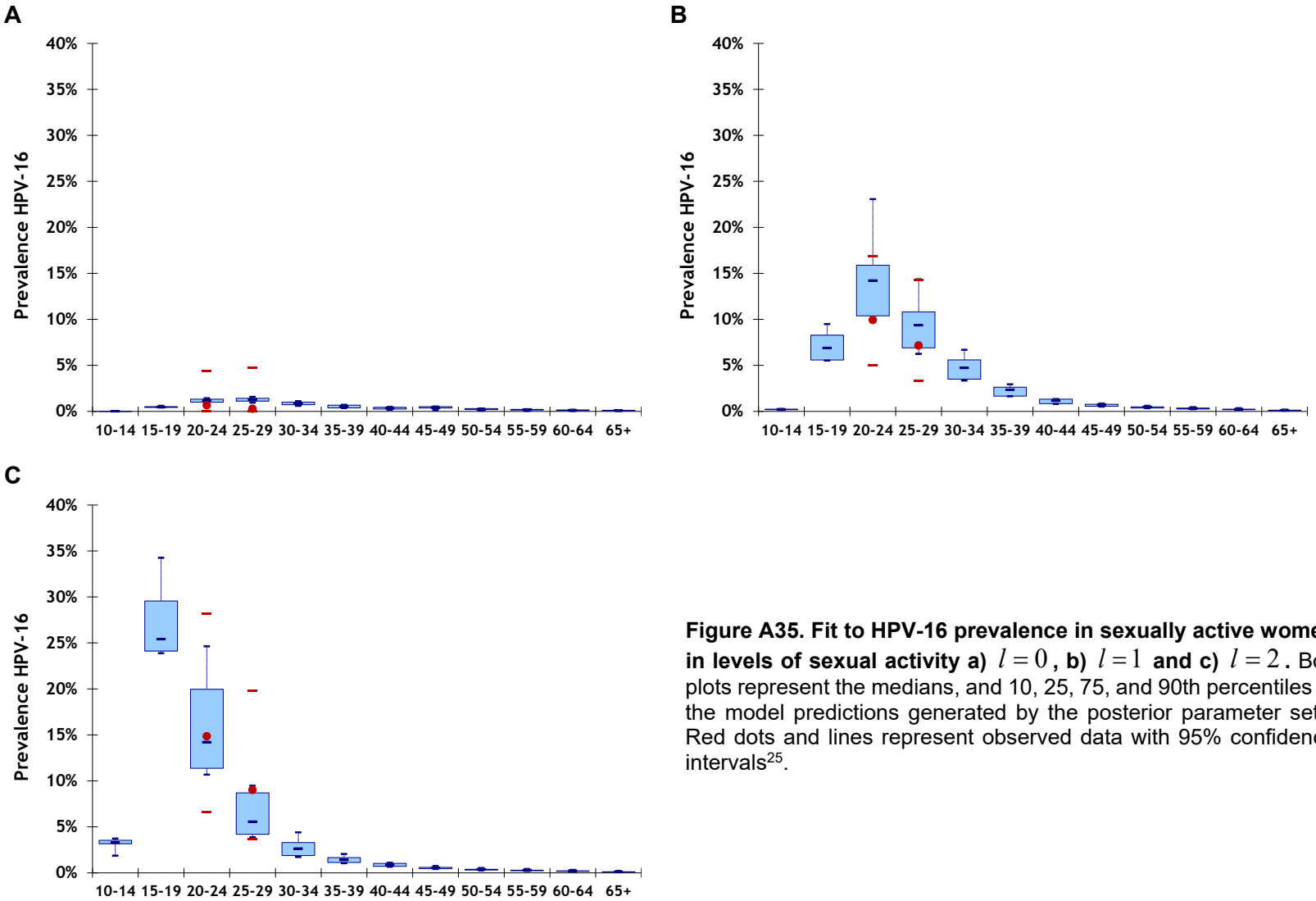


Figure A35. Fit to HPV-16 prevalence in sexually active women in levels of sexual activity a) $l = 0$**, b)** $l = 1$ **and c)** $l = 2$**.** Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red dots and lines represent observed data with 95% confidence intervals[25].

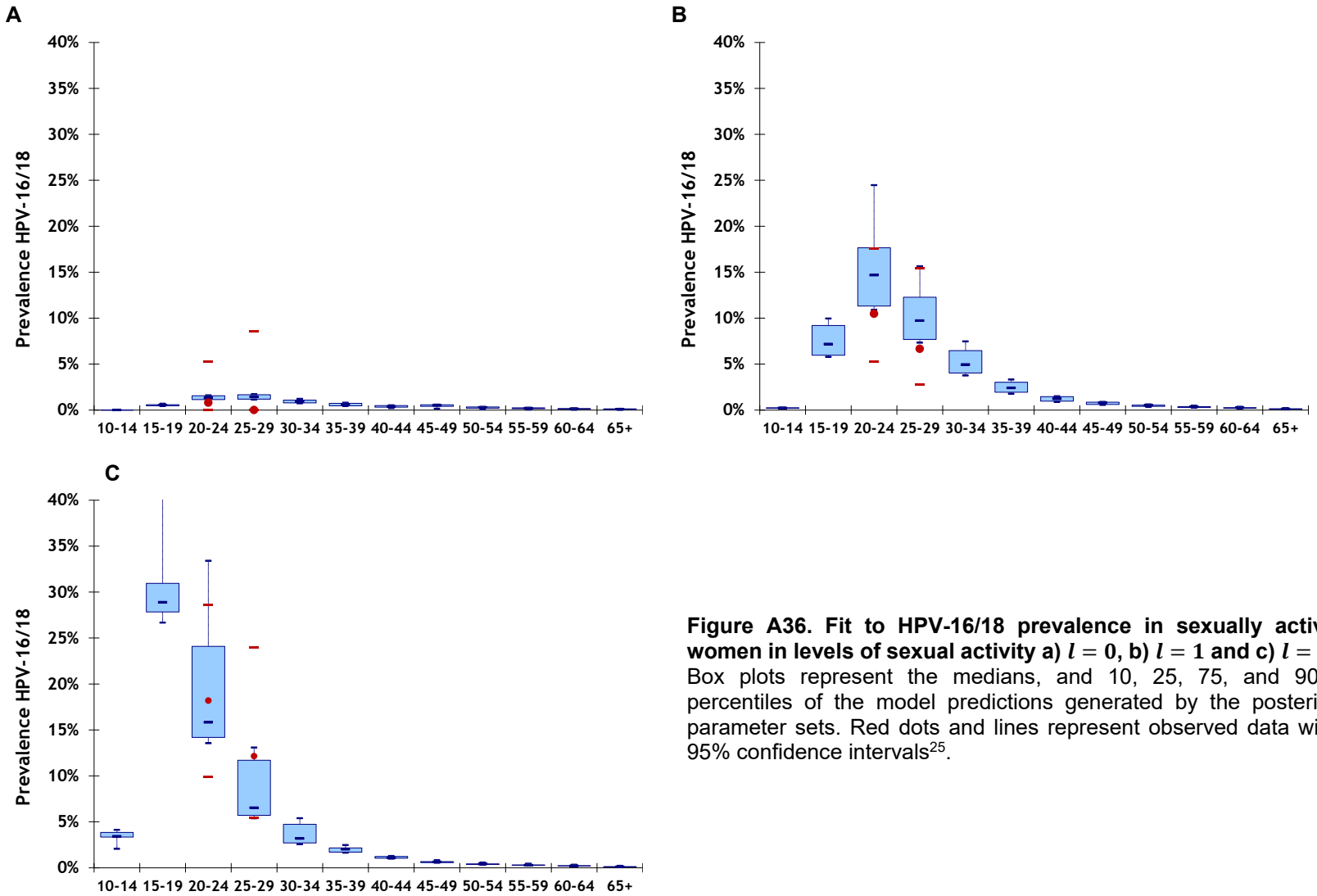


Figure A36. Fit to HPV-16/18 prevalence in sexually active women in levels of sexual activity a) $l = 0$, b) $l = 1$ and c) $l = 2$. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red dots and lines represent observed data with 95% confidence intervals[25].

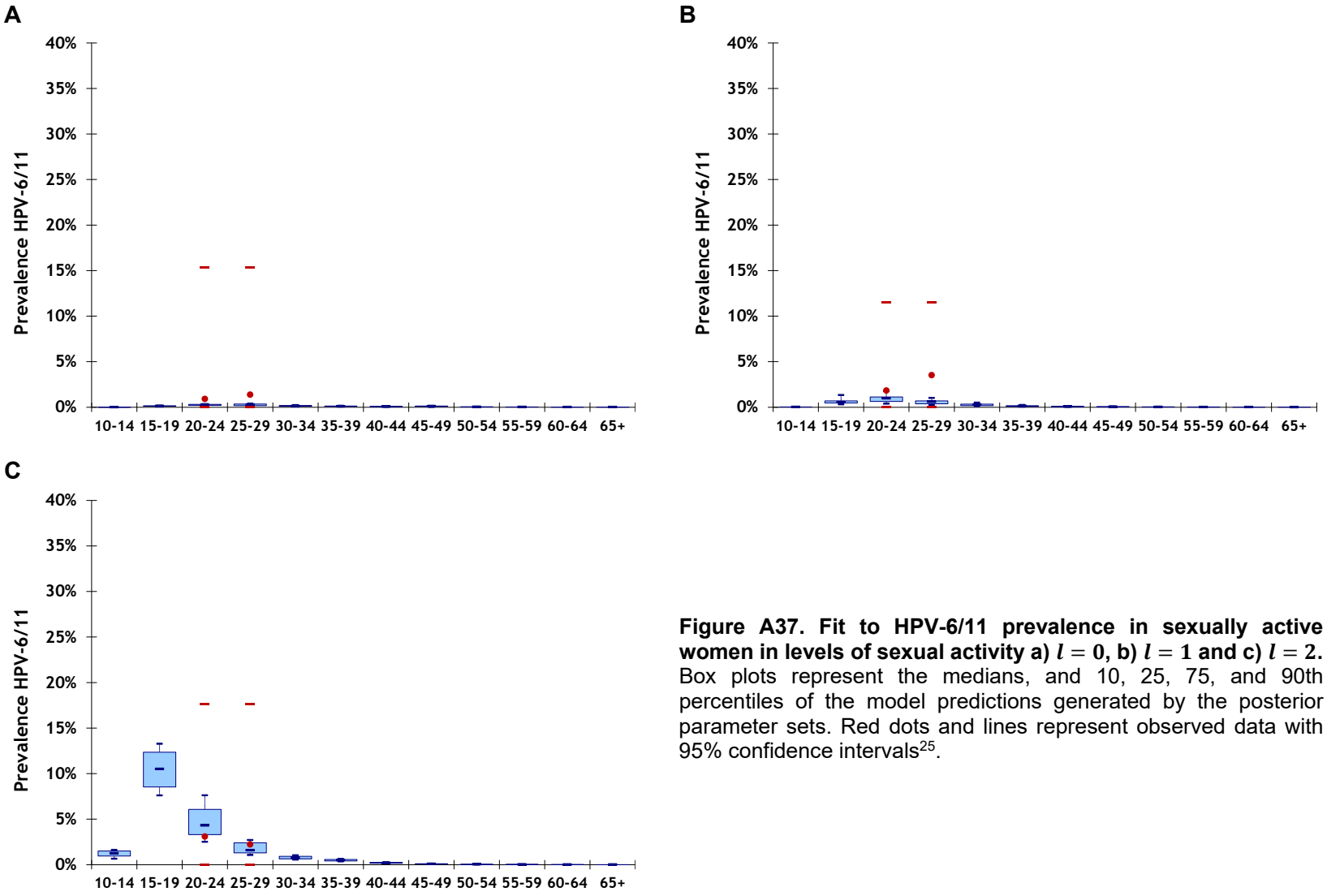


Figure A37. Fit to HPV-6/11 prevalence in sexually active women in levels of sexual activity a) $l = 0$, b) $l = 1$ and c) $l = 2$. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red dots and lines represent observed data with 95% confidence intervals[25].

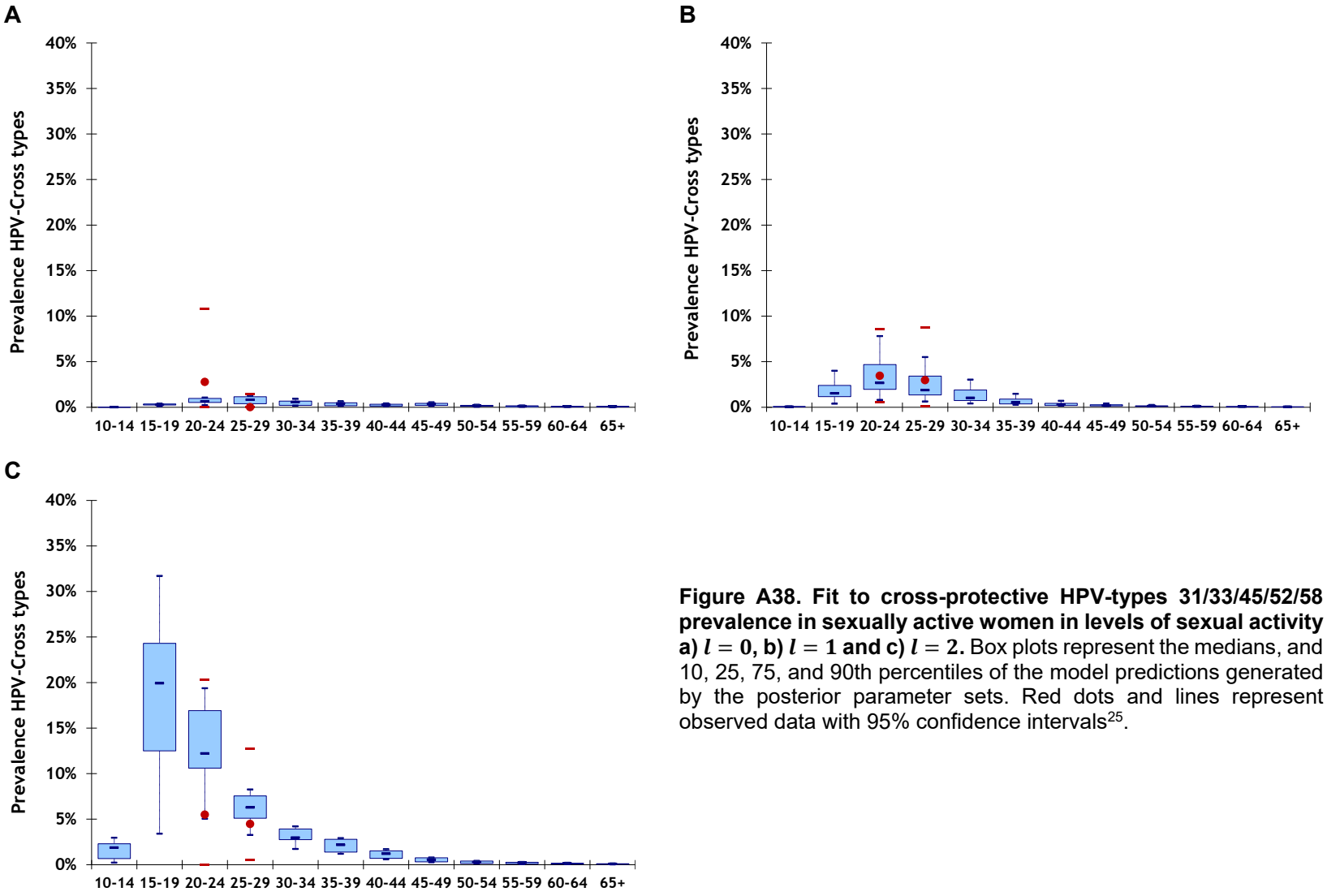


Figure A38. Fit to cross-protective HPV-types 31/33/45/52/58 prevalence in sexually active women in levels of sexual activity a) $l = 0$, b) $l = 1$ and c) $l = 2$. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red dots and lines represent observed data with 95% confidence intervals[25].

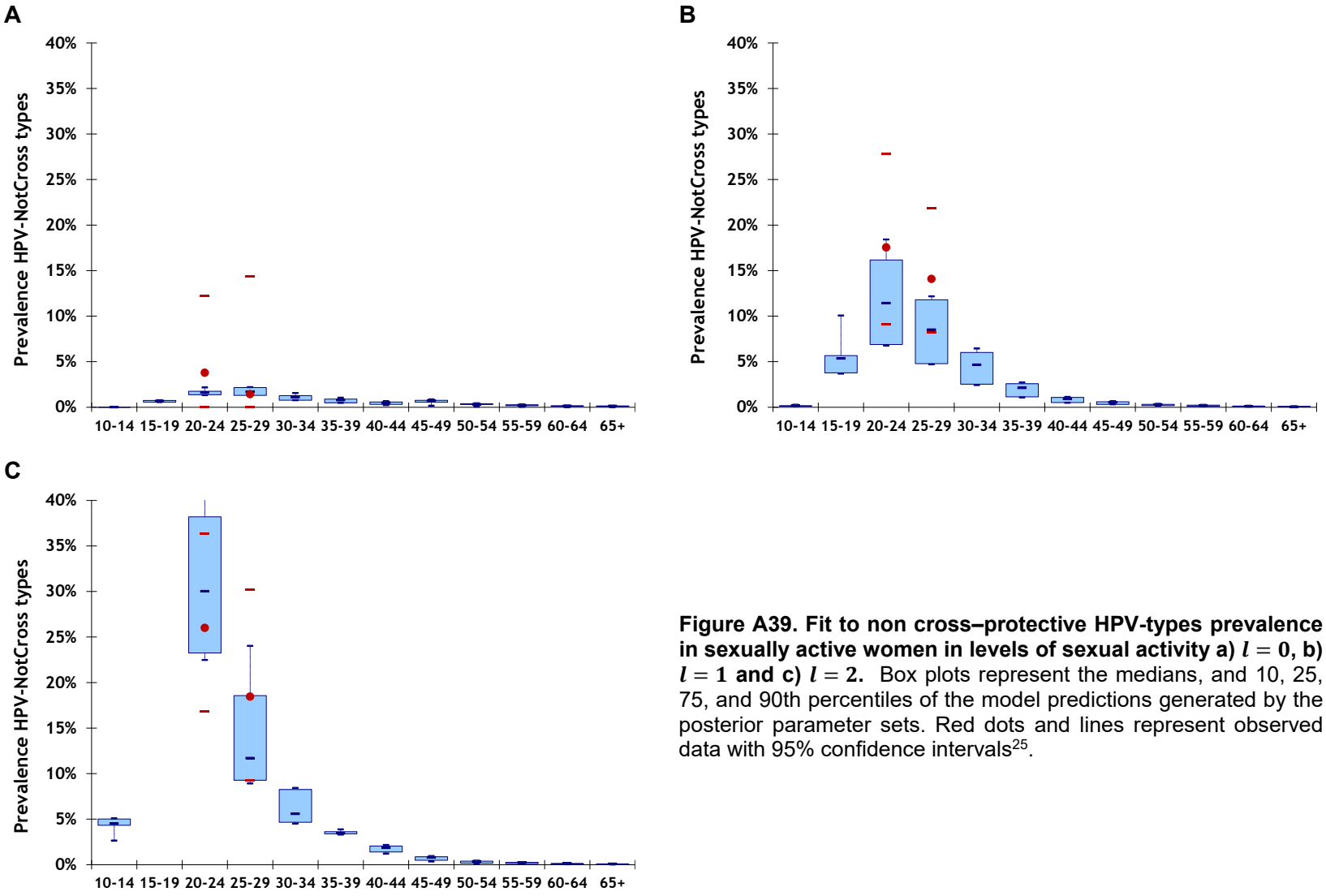


Figure A39. Fit to non cross–protective HPV-types prevalence in sexually active women in levels of sexual activity a) $l = 0$, b) $l = 1$ and c) $l = 2$. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red dots and lines represent observed data with 95% confidence intervals[25].

The model also fits the prevalence of HPV-6 and overall HR HPV by age and level of sexual activity[25] (data not shown).

2.3.3 Examples of fit to screening data

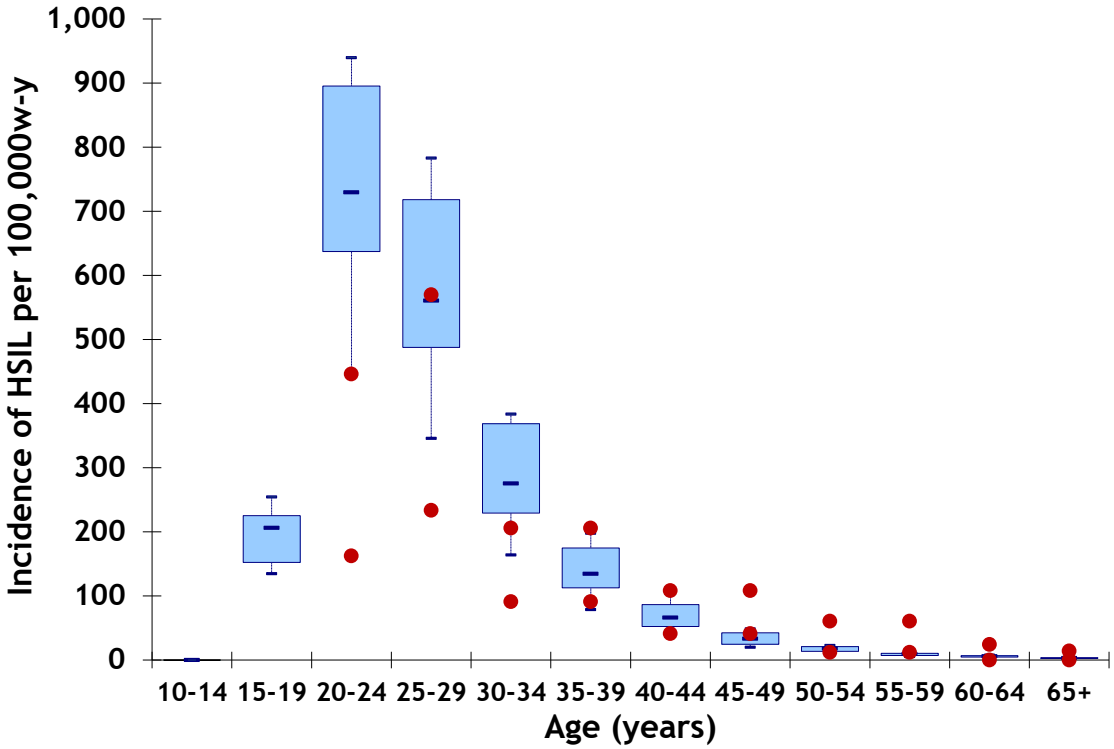


Figure A40. Incidence of HSIL over age. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Dots represent the minimum and maximum value of the observed data[34].

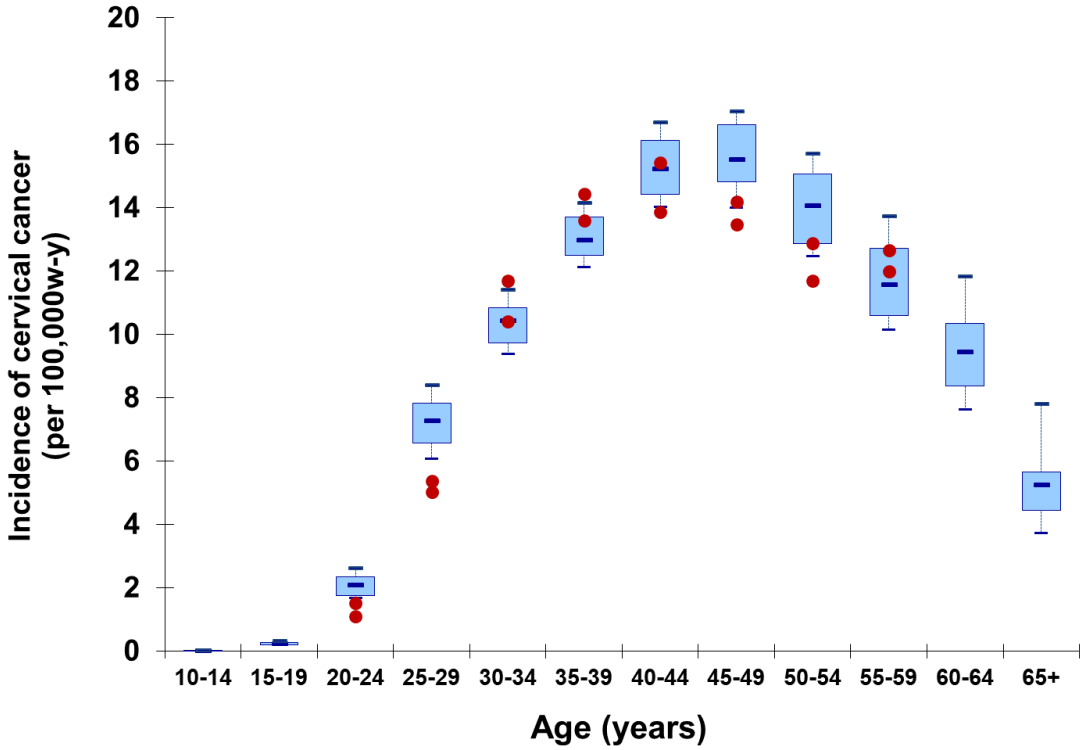


Figure A41. Cancer incidence. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Dots represent the minimum and maximum value of the observed data[17,18].

The model also fits the data on the incidence of ASCUS/LSIL by age[34] and the proportion of women ever screened by age[33] (data not shown).

2.3.4 Examples of fit to HPV type-specific positivity in CIN and SCC samples

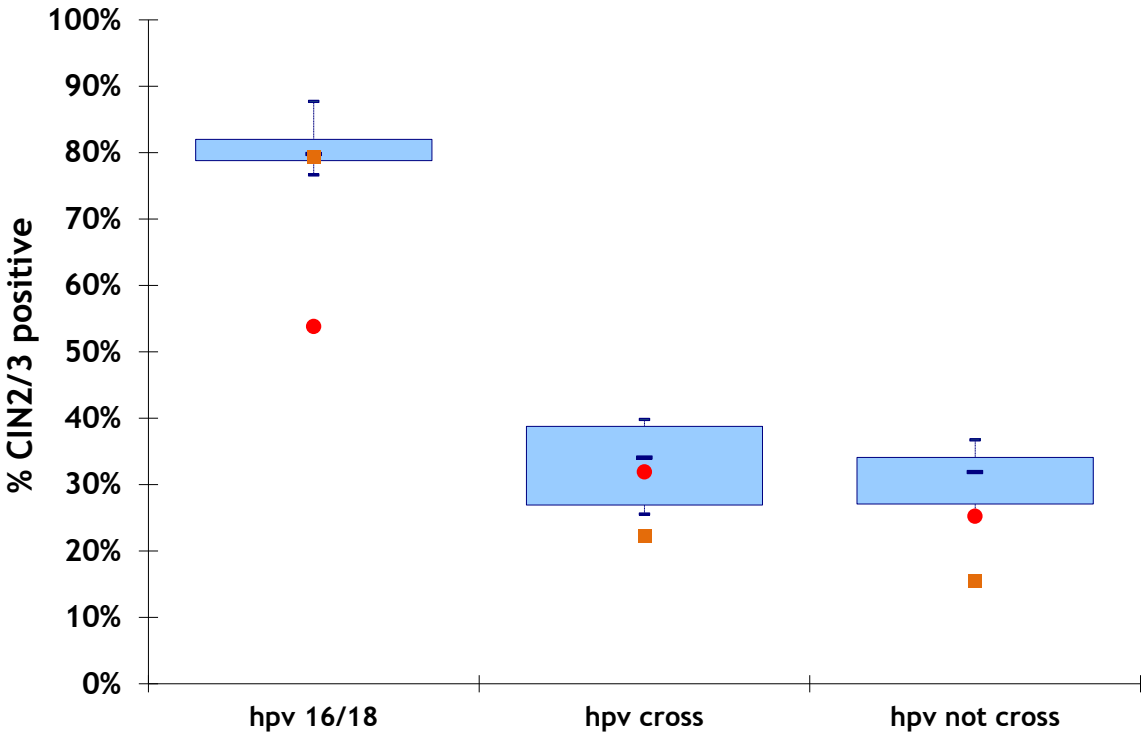


Figure A42. Proportion of diagnosed CIN2/3 with detected HPV-types 16/18, cross-protective and not cross-protective types. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red dots represent observed data in US[28] and the orange dots represent data from North America[29].

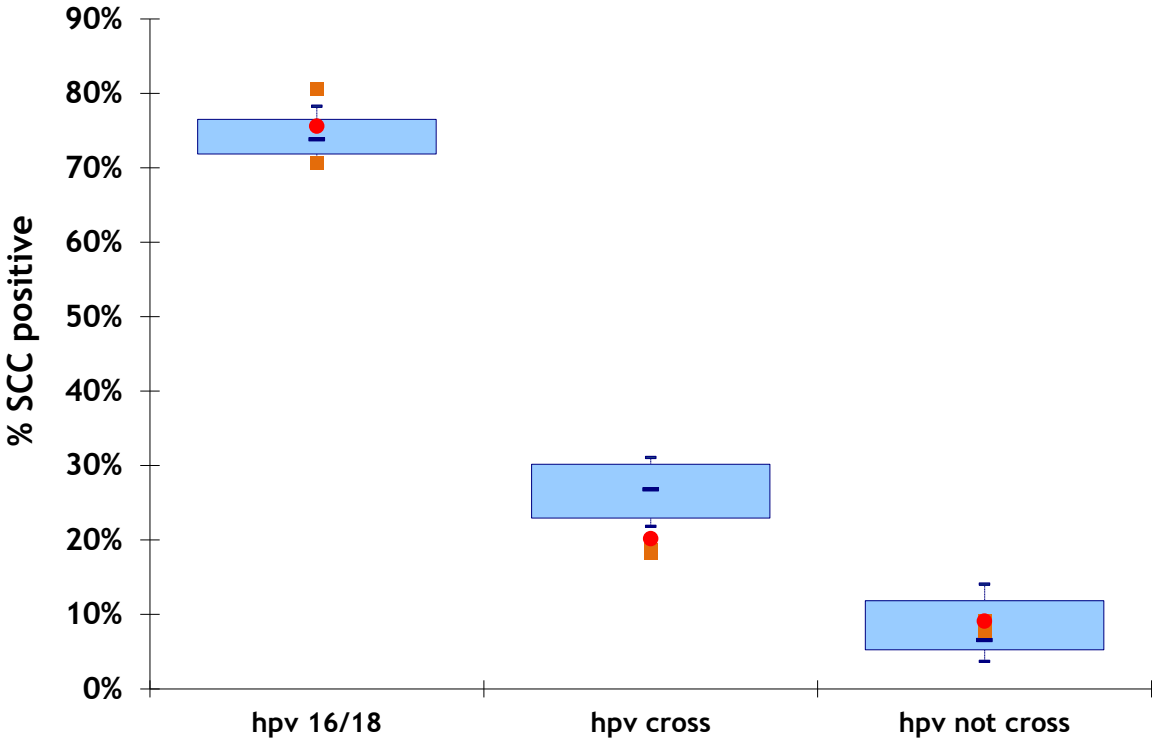


Figure A43. Proportion of diagnosed SCC with detected HPV-types 16/18, cross-protective and not cross-protective types. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red lines and dots represent the observed data from HPV Typing conducted in 7 US Cancer Registries[19] and orange dots represent maximum and minimum estimates from other studies from North America[30-32]

The model also fits the proportion of diagnosed CIN with detected HPV-6 and HPV-11[28].

2.3.5 Examples of fit to anogenital warts data

The model fits the incidence of anogenital warts (AGW) consultations in US[15]. For these fits, we assume that 90% of AGW consultations are due to HPV-6/11.

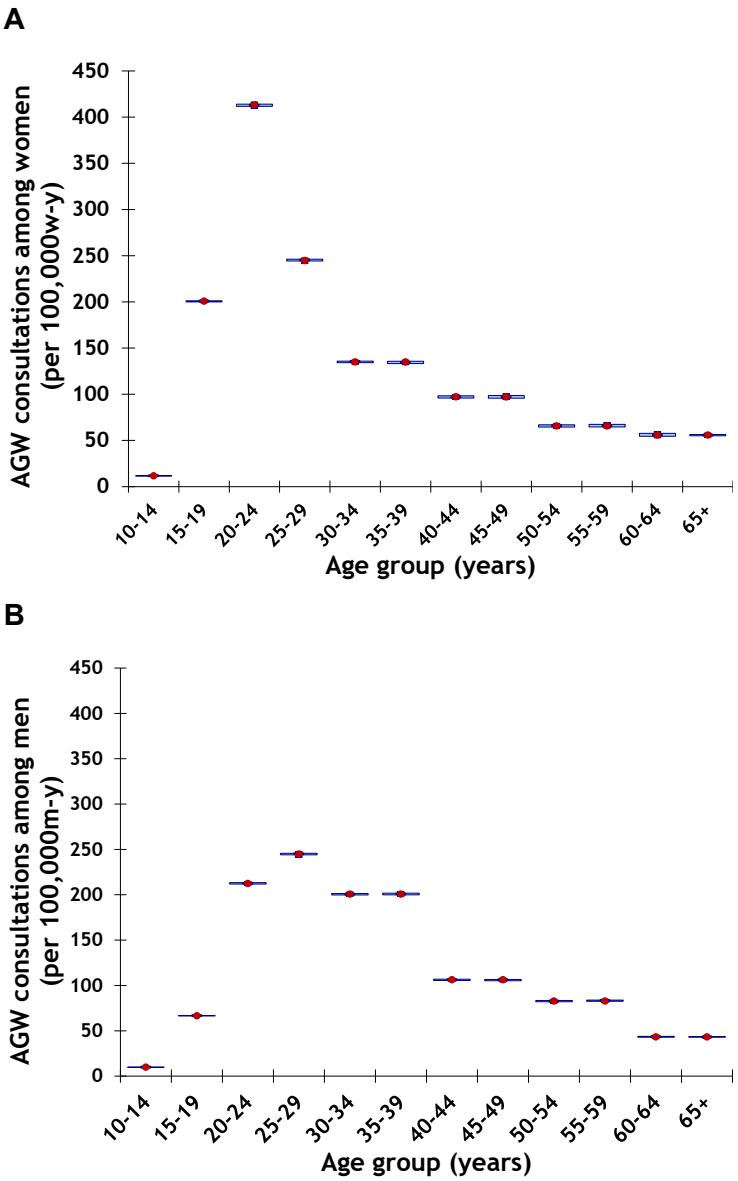


Figure A44. Anogenital warts consultation rates A) women and B) men. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[15].

2.3.6 Fit to other HPV-related cancers

The model fits the age-, gender and type-specific incidence of cancers of the vulva, vagina, anus, penis, and oropharynx in the US[17,19-22].

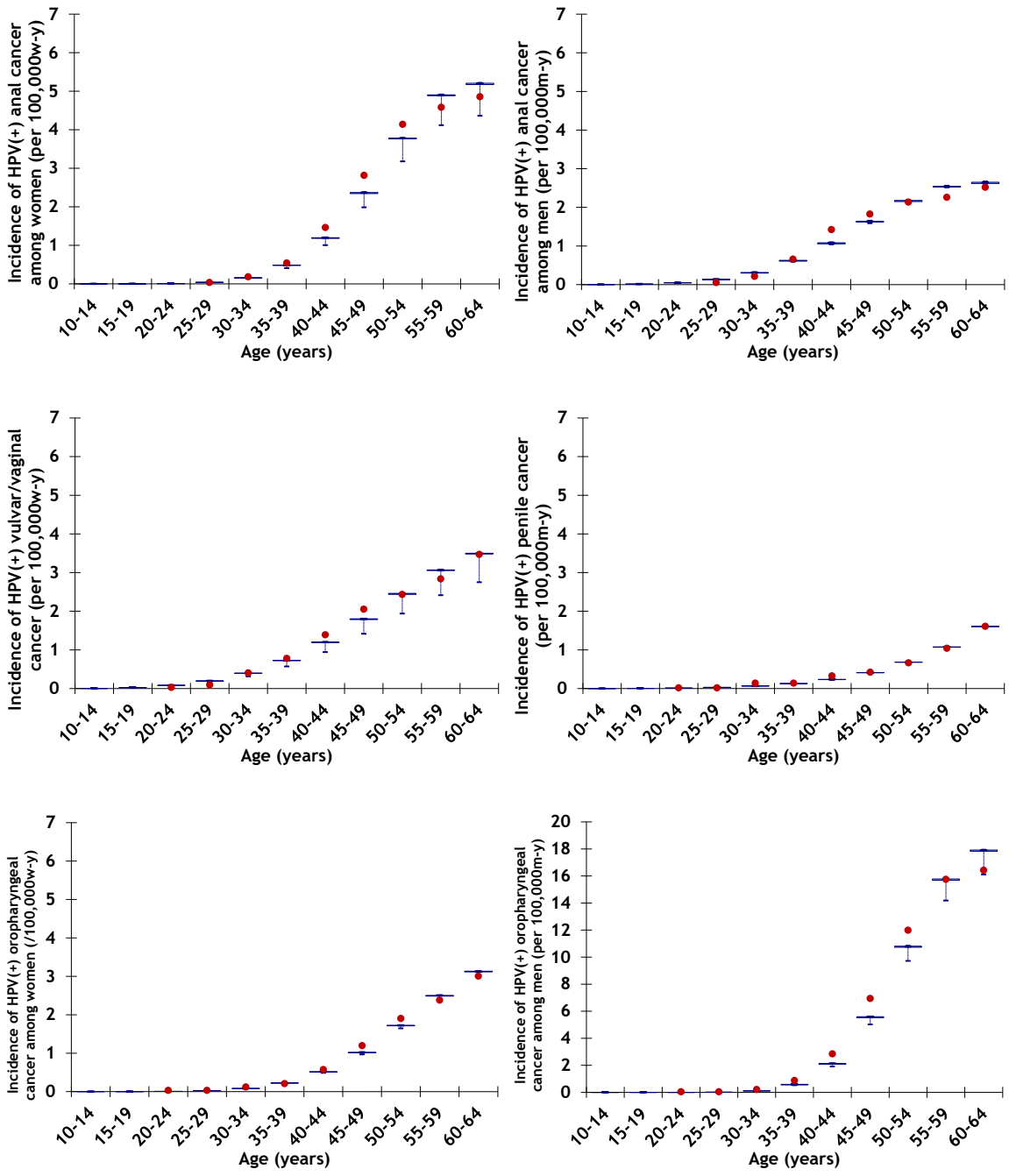


Figure A45. Rates of HPV positive cancers of the vulva/vagina, penis, anus and oropharynx. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the model predictions generated by the posterior parameter sets. Red dots represent observed data[17,19-22].

2.4 Model validation

Model fit was cross-validated by comparing model predictions using the posterior parameter sets with observed data not used during the fitting procedure.

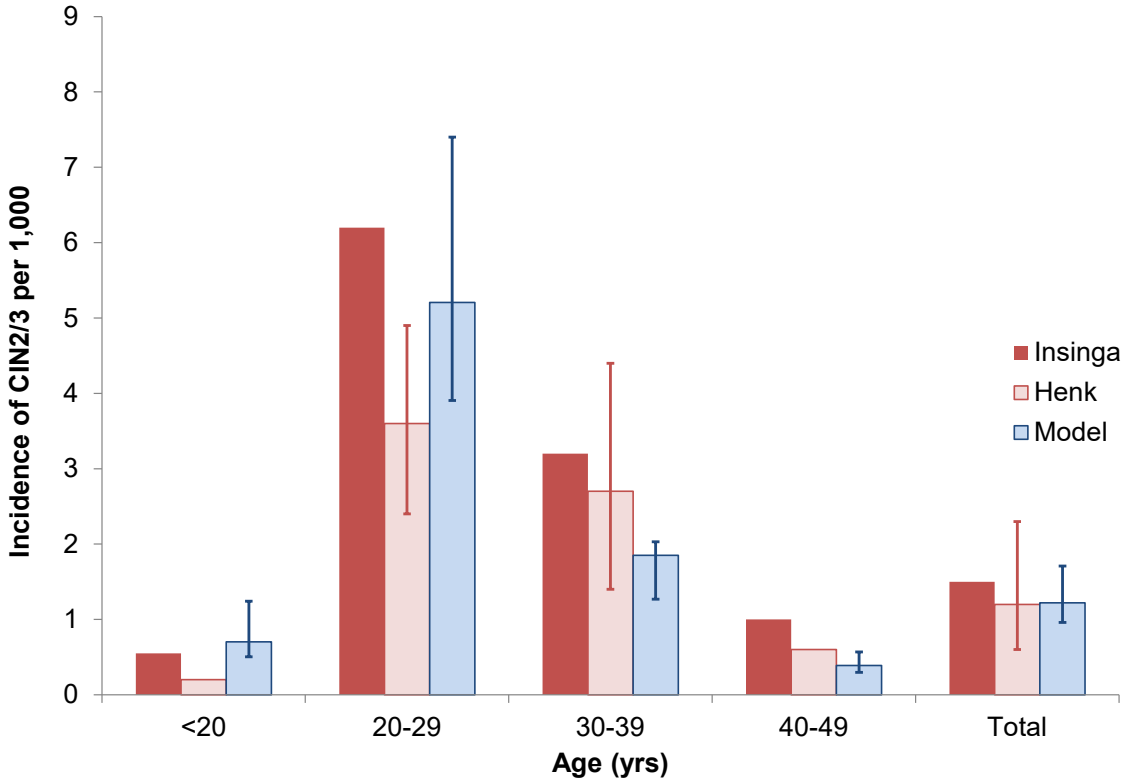


Figure A46. Incidence rate of CIN2/3 by age. Model output are the medians, and 10 and 90th percentiles of predictions generated by the posterior parameter sets. Red histograms represent the value of the observed US data[34,81] with 95% confidence intervals (Confidence intervals were not stated in Henk et al. for women aged less than 20 years and older than 40).

2.5 Target definition

A prior parameter set is qualified as producing a ‘‘good fit”, and included as a posterior parameter set, if the associated model predictions fall simultaneously within pre-specified targets (ranges) of the sexual behavior, screening and epidemiological data defined in Table A1. The lower and upper bounds of these ranges are built based on target values, ξ, as follows:

$$\text{Lower bound} = \min_j\left(O_{i,g,a,l}\right) - \xi \qquad (2.6)$$

$$\text{Upper bound} = \max_j\left(O_{i,g,a,l}\right) + \xi$$

here i represents the data source and $\min_{i}(\cdot)$ takes the minimum value of all data sources for a specific data point $O_{i,g,a,l}$.

The target values are defined as follows:

$$\xi_l = f \cdot \max_{i,a}\left(O_{i,a,l}\right) \tag{2.7}$$

Where $\max_{i,a}(\cdot)$ takes the maximum value over age of all data sources and $f = 0.5$, except for type distribution targets where $f = 0.2$.

2.6 List of symbols

Table A27. List of symbols.

Symbol	Units	Definition
Θ_i	(-)	i^{th}individual. Defined as the following individual state vector: $\Theta_i = (g, l, u, h^\tau, s, S; a)$, where $i = 1, 2, \ldots, N$
N	(#)	Number of individuals
e	(-)	The index e refers to a particular event (or change) in the state of an individual (*e.g.* death, infection, partnership formation). This index takes the following values: $e = 1, 2, \ldots, n_e$, where n_e is the total number of events and $e = 0$ refers to the null event.
a	(year)	Age
l	(-)	Level of sexual activity: $l \in \{0, 1, 2, 3\}$
g	(-)	Gender $g = 1$: female $g = 2$: male
h^τ	(-)	Health states $h = 0$: susceptible h =1: infected h =2: naturally immune h =3: vaccine immune to the particular HPV type τ
τ	(-)	HPV type $\tau \in$ $\{16, 18, 6, 11, 31, 33, 45, 52, 58, 35, 39, 51, 56, 59, 66, 68, 73, 82\}$
s	(-)	Partnership status s =0: single s =1: stable partnership s =2: casual partnership
u	(-)	Sexual debut u =0: not sexually active u =1: sexually active
S	(-)	Screening behavior levels $S \in \{0, 1, 2, 3, 4\}$)
$\mu_g(a)$	(per person-year)	Death rates with respect to age a, for a given gender g.
η	(per person-year)	Rates of entry in the population (at 10 years of age).
$\phi_l(a)$	(per woman-year)	Rates of onset of sexual activity in females with respect to age a, for a given level of sexual activity l.
Φ_l	(%)	Percentage of individuals in each sexual activity level l.

Symbol	Units	Definition
$\zeta_l(a)$	(per woman-year)	Partnership formation rates in single females with respect to age a, for a given level of sexual activity l.
$\theta_{g,l}(a)$	(per person-year)	Partner acquisition rates with respect to age a, for a given level of sexual activity l.
$\psi_l(a)$	(%)	Percentage of partnerships that lead to a stable partnership with respect to the age a and level of sexual activity l of the female partner.
$\Psi_l(a)$	(%)	Percentage of women in stable partnerships with respect to age a, for a given sexual activity level l.
$\boldsymbol{\Omega} = [\Omega_{al,a'l'}]$	(-)	Global mixing matrix. Represents the probability that a female of age a and level of sexual activity l will choose a male of age a' and level of sexual activity l'.
$\boldsymbol{\Gamma} = [\Gamma_{l,l',g}]$	(-)	Mixing by level of sexual activity. Represents the probability that an individual of sex g and level of sexual activity l forms a partnership with someone of the opposite sex in level of sexual activity l'.
$\boldsymbol{\Lambda} = [\Lambda_{a,a',l,g}]$	(-)	Mixing by age. Represents the probability that an individual of sex g in age group a and sexual activity level l forms a partnership with someone of the opposite sex in age group a'.
κ	(-)	Assortative degree
$\mathbf{W}$	(-)	Preference matrix $W_{l,l',g} = \begin{cases} \kappa, \text{ if } l = l' \\ 1, \text{ if } l \neq l' \end{cases}$
$\sigma_l(a)$	(per woman-year)	Rates of partnership separation in females with respect to age a, for a given level of sexual activity l.
ω	(# acts per week)	Frequency of sex acts per week in stable partnerships
$d_l(a)$	(year)	Duration of stable partnerships with respect to age a, for a given level of sexual activity l.
C	(# acts)	Number of sex acts in casual partnerships
β_g^τ	(-)	Per-act transmission probability, for a given HPV type τ and gender g(i.e. $g = 1$ and 2 for male-to-female and female-to-male transmission, respectively).
$\gamma_g^\tau(a)$	(per infection-year)	Clearance rates of a given HPV type τ, depending on the gender g and age a of the host.
M_g	(-)	Probability of developing lifelong natural immunity, for a given gender g.

Symbol	Units	Definition
Δt	(hours)	Time step
$\rho_{g,l,u,s,S}^{e,h^\tau}(a)$	(per person-year)	Rates of occurrence of event e for individuals in risk category $(g, l, u, s, S; h^\tau; a)$
$X_{g,l,u,s,S}^{h^\tau}(a; t_{k-1}, t_k$	(#)	Number of individuals in a given health state h^τ and risk categories $\{g, l, u, s, S, a\}$ during time interval $\Delta t_k = t_k - t_{k-1}$
$I_{g,l}^{\tau}(a; t_{k-1}, t_k)$	(#)	Number of new type-specific infections by gender g, age a and level of sexual activity l during time interval Δt_k
VA	(year)	Vaccination age
VC	(%)	Vaccine coverage
VD	(year)	Vaccine duration
VE	(%)	Vaccine efficacy (degree of protection per act)

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