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Adaptive Markov chain Monte Carlo forward projection for statistical analysis in epidemic modelling of human papillomavirus

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A Bayesian statistical model and estimation methodology based on forward projection adaptive Markov chain Monte Carlo is developed in order to perform the calibration of a high-dimensional nonlinear system of ordinary differential equations representing an epidemic model for human papillomavirus types 6 and 11 (HPV-6, HPV-11). The model is compartmental and involves stratification by age, gender and sexual-activity group. Developing this model and a means to calibrate it efficiently is relevant because HPV is a very multi-typed and common sexually transmitted infection with more than 100 types currently known. The two types studied in this paper, types 6 and 11, are causing about 90% of anogenital warts.

We extend the development of a sexual mixing matrix on the basis of a formulation first suggested by Garnett and Anderson, frequently used to model sexually transmitted infections. In particular, we consider a stochastic mixing matrix framework that allows us to jointly estimate unknown attributes and parameters of the mixing matrix along with the parameters involved in the calibration of the HPV epidemic model. This matrix describes the sexual interactions between members of the population under study and relies on several quantities that are *a priori* unknown. The Bayesian model developed allows one to estimate jointly the HPV-6 and HPV-11 epidemic model parameters as well as unknown sexual mixing matrix parameters related to assortativity.

Finally, we explore the ability of an extension to the class of adaptive Markov chain Monte Carlo algorithms to incorporate a forward projection strategy for the ordinary differential equation state trajectories. Efficient exploration of the Bayesian posterior distribution developed for the ordinary differential equation parameters provides a challenge for any Markov chain sampling methodology, hence the interest in adaptive Markov chain methods. We conclude with simulation studies on synthetic and recent actual data. **Copyright © 2012 John Wiley & Sons, Ltd.**

Keywords: human papillomavirus (HPV); genital warts; forward projection; adaptive Markov chain Monte Carlo; calibration; sexual mixing matrix

1. Background on modelling human papillomavirus and relevance to community health

The human papillomaviruses (HPV) are a family of small DNA viruses that preferentially infect differentiating epithelial cells of the skin and mucosae. More than 100 HPV genotypes have thus far been identified, classified according to their tissue tropism (mucosal or cutaneous) and oncogenic potential (high or low). About 40 HPV types are known to infect the mucosae, including those of the anogenital and oral tracts, and 13–18 of these are considered to be oncogenic (high-risk) on the basis of their association with malignancies. Low-risk HPV types are associated with benign lesions such as genital warts and low-grade intraepithelial neoplasias of the cervix [1, 2]. Sexual contact is the primary mode

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of transmission [3], and HPV is the most common sexually transmitted infection in the world. HPV is known to be the causal factor in the vast majority of cervical cancer cases and is also implicated in a proportion of other anogenital cancers and cancers of the head and neck. The overall burden of disease attributed to HPV, both cancers (as much as 5.2% of incident cancers worldwide) and benign lesions such as genital warts, is considerable [4].

Two vaccines have been developed and shown through clinical trials to be highly effective in the prevention of precancerous lesions and persistent infection due to an important subset of HPV types [5, 6]. The quadrivalent vaccine (Gardasil) protects against high-risk HPV types 16 and 18, which are associated with 70–75% of cervical cancers, and against low-risk HPV types 6 and 11, which cause more than 90% of genital warts. The bivalent vaccine (Cervarix) provides protection against HPV types 16 and 18 only. Both vaccines have been licensed in more than 100 countries, and publicly funded national immunisation programmes have commenced in some of these including Australia (Gardasil) [7].

National immunisation programmes are costly, and decisions regarding their implementation are generally made on the basis of health–economic evaluations. In regard to HPV, these decisions are complicated by two related factors: (1) HPV is a sexually transmitted infection; and (2) only a small proportion of infections do not resolve and can lead to cancer many years or decades subsequent to acquisition. Both of these factors have generally been addressed by using models to estimate the long-term impact of vaccination on the incidence of HPV-related disease so that the costs and benefits can be calculated. However, it is the former of these factors that is of particular relevance in the context of this study. Because HPV is an infectious disease, the rate of transmission in a population, commonly referred to as the 'force of infection', is a function of the prevalence of the infection in the population at any given time [8]. Furthermore, the benefit of vaccination that confers immunity to infection (immunisation) is not confined only to those directly immunised—'unvaccinated individuals' (who remain susceptible to infection) enjoy a degree of indirect protection because their risk of exposure is reduced through a diminishment in circulating virus. This indirect benefit of vaccination is referred to as 'herd immunity' [9]. In order to model the impact of vaccination on the course of the HPV epidemic over time in a manner that captures the herd immunity effect, we must use dynamic transmission models [10, 11]. Failure to do so can result in an underestimation of the potential benefit of vaccination.

Dynamic mathematical transmission models have been used extensively to estimate the potential impact of HPV vaccination in a wide variety of settings (e.g. [12–16], not comprehensive) and as a component of cost-effectiveness evaluations that have informed decisions on the funding of vaccination programmes (e.g. [17–22], not comprehensive). Transmission models have traditionally been formulated in a deterministic framework as systems of differential equations (ordinary or partial) [8, 23, 24]. With the increasing power of personal desktop computers and access to high-performance computing facilities, the use of agent-based stochastic modelling approaches has become more prominent (examples for HPV include [25, 26]). The latter approach is particularly useful for low-prevalence infections where there is a possibility of extinction and/or where it is necessary to capture events that occur at the level of the individual (e.g. tracing and treating sexual partners of infected individuals). However, for their computational efficiency, analytical tractability and ability to provide mechanistic insights to epidemic dynamics, deterministic ordinary differential equation (ODE) models are often preferred, particularly for endemic infections such as HPV [16].

In this study, we develop a Bayesian statistical model and estimation methodology to perform the calibration of a high-dimensional nonlinear system of ODEs representing an epidemic model for HPV types 6 and 11. A previously published modelling study on the potential impact of vaccination on HPV prevalence in the Australian population [16] used a model of the same Susceptible–Infected–Recovered–Susceptible (SIRS) type and was focused on HPV-16. Whereas the health and economic consequences of HPV-16 are more serious than for types 6 and 11, we chose a model for HPV-6 and HPV-11 for this study because genital warts caused by the two types are a significant public health problem. For example, an extensive study conducted in several Nordic countries [27] found that close to 11% of women had genital warts at some point in their lives, whereas a similar study in Australia estimated a prevalence of 4% [28]. An individual with genital warts usually suffers from both clinical symptoms and psychosocial problems (such as anxiety) [29], which potentially further increases the costs of his or her treatment. We were also motivated by current availability of Australian genital warts incidence [30] and seroprevalence [31] data that could be used for calibration.

Despite extensive study, there remains considerable uncertainty regarding aspects of the natural history of HPV and the patterns of sexual behaviour that underpin transmission [32, 33]. Furthermore, many studies have not been designed with transmission models in mind, so the processes and phenomena

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they measure cannot always be applied directly and/or their interpretation in the context of transmission is not clear. Areas of uncertainty that present particular challenges for modelling include interpretation of vaccine efficacy from clinical trials in the context of transmission, the duration of infectiousness (as opposed to the duration of detectability using currently available tests), the duration and nature of naturally acquired immunity, the relationship between seropositivity and immunity, and the probability of transmission on sexual contact. Some of these are difficult to measure at a population level for practical and/or ethical reasons. We demonstrate a Bayesian statistical methodology that will address these uncertainties in the estimation and calibration of the ODE epidemic model we have developed. This methodology allows us to statistically quantify the extent of the uncertainty in model outcomes that are derived from uncertainty in the inputs, and the contribution of uncertainty in individual parameters to the uncertainty in the outcomes [34, 35]. Ultimately, we can use it to predict the impact of vaccination on a population.

1.1. Introduction to adaptive Markov chain Monte Carlo

Markov chain Monte Carlo (MCMC) sampling has gained a wide recognition in all areas of modelling and statistical estimation as an essential tool for performing inference in Bayesian models (see reviews and discussions in [36] and [37]). In this paper, we consider the recently developed class of algorithms known as adaptive Markov chain Monte Carlo (AdMCMC) (see a review in [38]) and demonstrate how it may be extended to solve statistically challenging estimation and prediction problems of direct relevance to the interpretation and analysis of the calibration and vaccine response dynamics for HPV epidemic models. We illustrate this on a model we develop for HPV-6 and HPV-11.

Standard MCMC algorithms that do not incorporate adaptation often require a degree of 'tuning' of the parameters controlling the algorithms' performance. This is typically performed by off-line simulations to assess performance of the mixing of the resulting Markov chain followed by numerical investigation of the convergence rates to stationarity of the chain for different algorithmic settings of the proposal distribution. For example, the widely used variant of the Metropolis–Hastings algorithm, the random walk Metropolis algorithm, has mixing performance that is controlled through specification of the Markov chain proposal distributions covariance matrix. Tuning this matrix for optimal performance can be computationally expensive and inefficient (see detailed discussions in [36, 37, 39]). Optimal performance of an MCMC algorithm is typically either specified by the convergence rate of the Markov chain to stationarity or through the related quantity, the acceptance probability of the rejection step in the MCMC algorithm. In this regard, theoretically optimal results have been derived for several classes of statistical models, which now act as guides for more complicated sampling problems (see discussions in [40]).

In this paper, we construct an ODE HPV epidemic model on a high-dimensional space both in the parameters of the model and also in the latent ODE state trajectories solved for at each discrete time point in the 'forward projection' ODE solver. This high dimensionality in the posterior parameter space provides a significant challenge for standard MCMC algorithms with respect to the design of an efficient proposal mechanism for the Markov chain. In particular, in the model considered in this paper, the fact that we incorporate a forward projection stage for the ODE solver adds additional complications in the design of the proposal. Therefore, it is desirable to automate this proposal construction for the MCMC sampler, avoiding computationally expensive tuning processes. Hence, we develop an adaptive version of the random walk Metropolis algorithm, coupled with forward projection. The incorporation of an adaptive proposal mechanism in a MCMC algorithm has been demonstrated to improve the performance of the sampling algorithm relative to standard MCMC approaches (see reviews of several examples of this improvement in [38]). The improvement is achieved by learning the structure of the Markov chain proposal distribution on-line in an automated fashion, avoiding tuning of the MCMC proposal mechanism.

There are several classes of AdMCMC algorithms, and each class has several adaptation strategies [41, 42]. These approaches can be classified as either internal adaptation mechanisms, including controlled MCMC methods, or external adaptation strategies (see discussion in [41]). The distinguishing feature of AdMCMC algorithms, when compared with standard MCMC, is that the Markov chain is generated via a sequence of transition kernels. Adaptive algorithms get their name from the fact that they utilise a combination of time or state inhomogeneous proposal kernels. Each proposal in the sequence is allowed to depend on the history of the Markov chain generated, resulting in many possible variants. When using inhomogeneous Markov kernels, it is particularly important to ensure that the generated

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Markov chain is ergodic, with the appropriate stationary distribution. Several recent papers proposing theoretical conditions that must be satisfied to ensure ergodicity of adaptive algorithms include [41] and [43]. The paper [44] proves ergodicity of AdMCMC under conditions known as *Diminishing Adaptation* and *Bounded Convergence*. Designing an adaptation strategy that satisfies these conditions guarantees asymptotic convergence of the law of the Markov chain samples to the target posterior and ensures that the Weak Law of Large Numbers holds for bounded test functions of the parameter space (an interested reader is referred to [44] for details). In this paper, we work with a transition kernel that is well known to satisfy these conditions, has been used successfully in several applications [38] and is based on the adaptive Metropolis algorithm.

1.2. Contributions

This paper formulates a model for HPV types 6 and 11, which is minimalistic yet adequate for covering all aspects of the disease transmission and incorporates seropositivity as a state associated with an individual's natural immunity after recovery.

Using a deterministic ODE model, three key tasks are considered: construction of a robust statistical modelling framework under a Bayesian paradigm to perform calibration of this coupled ODE transmission model with extensions to a stochastic population mixing matrix formulation; development of an automated statistical estimation methodology based on a modification to AdMCMC to incorporate forward projection for the ODE, which will provide a robust means of performing calibration and statistical analysis of the calibration performance; and a statistical methodology to study vaccination responses on the basis of the posterior predictive distribution that is estimated via AdMCMC.

Detailed studies are undertaken on synthetic data to assess the properties of the model and AdMCMC forward projection methodology. In addition, to investigate model specification and design assumptions, several sensitivity studies are undertaken to assess appropriateness of the proposed model as a model of the sexually active Australian population. This is followed by assessment of the calibration performance on real data collected from Australian sources (genital warts incidence [30] and HPV-6 and HPV-11 seroprevalence [31]).

2. Human papillomavirus transmission model

In developing a model for HPV transmission dynamics, one could consider one of two widely accepted modelling approaches that are adopted in the epidemiological literature for addressing epidemic modelling in a population. Fundamentally, these involve consideration of the dynamics of the spread of the disease through the population either specified according to a deterministic dynamical system of coupled ODEs or, as a possible alternative, via a system of coupled stochastic differential equations (SDE) based on individuals in the population, which combine to specify the 'state' of the system at a given time.

Typically, the approach adopted will depend on both the expected epidemiological outcomes as well as the model specification, which will be based on the state of knowledge of the system and the available survey data for calibration. In addition, practical modelling features such as the temporal resolution and the dimension of the 'state vector' in the system model will often be of significance in such decisions regarding the use of deterministic equations versus their stochastic alternative frameworks.

As discussed in [45, 46], what differentiate models developed for epidemics in a deterministic framework versus a stochastic individual based model are three primary considerations: (1) the size of the population under consideration; (2) the proportion of the population that is involved in the epidemic over time [47]; and (3) relevance of individual level effects to the research goals (see book length discussions in [48]). Hence, we note that the development of ODE models is justified typically under the assumptions that one is considering large populations in which the mean equilibrium dynamics become of interest to the epidemic modellers. This is a reasonable assumption to make when modelling the sexually active Australian population, and it has the added advantage that it also lets us avoid the need to perform stochastic simulations of SDE models over time in thousands of dimensions.

Therefore, we develop a dynamic compartmental transmission model for HPV types 6 and 11 (Figure 1) of SIRS type. The entire modelled population is viewed as being distributed between a set of non-overlapping groups ('compartments') representing the stages of disease progression. The model is intended to describe how the number of people in each compartment changes over time. For example, members of the susceptible population 'move' from S to I as they become infected, and members of the recovered seropositive population 'move' from P to S as they lose their immunity.

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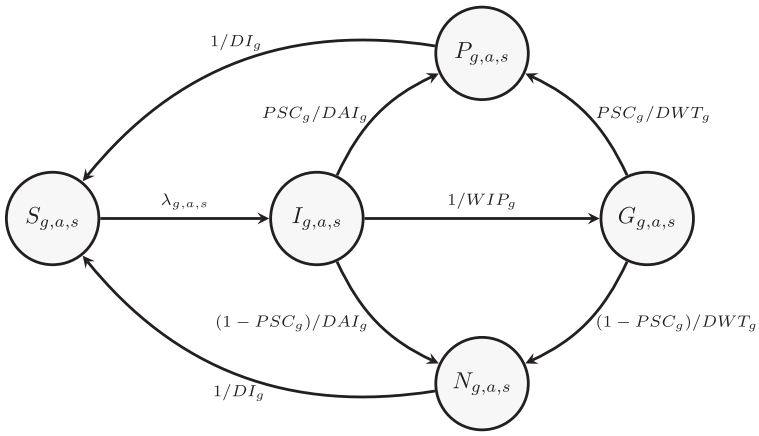

Figure 1. A compartmental HPV-6 or HPV-11 transmission model. We divide the studied population into the following non-overlapping compartments: S denotes individuals who are at risk of HPV infection; I denotes infected individuals; G denotes infected individuals who developed genital warts; P denotes those who recovered and are seropositive and immune; and N denotes individuals who are recovered and immune but seronegative. The indices g, a and s indicate that every compartment is stratified by gender, age and level of sexual activity. Movements between compartments are occurring at per capita rates specified by the following parameters: λ is the force of infection dependent on the proportion of individuals in I; *PSC* is the probability of becoming seropositive; *WIP* is the genital warts incubation period; *DAI* is the duration of asymptomatic (i.e. without genital warts) HPV infection; *DWT* is the duration of treatment for genital warts; and *DI* is the duration of immunity. Subscripts denote stratification of parameters: for example, DWT_g means that in our model this parameter is gender-dependent.

Underlying epidemic model assumptions

We present the key assumptions upon which the model is based. We note that the effect of these assumptions on the sensitivity of the calibration of the developed HPV models are studied and summarised in the discussion and technical Appendices A through to E.

Population

(a) The modelled population consists of people aged 15–59 years who are divided into nine separate 5-year age groups (Table VI). Limiting the population to this particular age range is motivated by a presumed low level of sexual activity in people younger than 15 years and people over 59 years, although any extensions to these ranges is not precluded by our methodology; 5-year age groups are commonly used for reporting results of surveys and trials including the one providing the sexual behaviour data for our model (for example, [30, 31, 49]); (b) the modelled population is constant over time; consequently, immigrants and temporary visitors are not accounted for, which may be an important simplification for Australia whose population has been steadily growing because of immigration; furthermore, Australia is a popular destination for young travellers who often maintain a high level of sexual activity; (c) mortality, although formally implemented, is not caused by HPV infection but rather serves as a convenient way of removing individuals who do not contribute to the HPV transmission because of advanced age signified by a cessation of sexual activity; (d) the number of men in the whole population and every sexual-activity or age group is equal to the number of women; (e) no transition between genders is allowed (i.e. men cannot become women and vice versa);

Sexual behaviour

(a) The modelled population is heterosexual with all people belonging to one of four sexual-activity (risk) groups (group 1 being the least active and group 4 the most active); the proportions of the population in each of risk groups 1–4 are 0.6, 0.27, 0.11 and 0.02, respectively, as determined in [16] using the Australian Study of Health and Relationships (ASHR) data [50] (Table A.1); it has to be noted that the assumption that these proportions are constant and have not changed since ASHR was conducted is reasonable because we do not want to complicate our model by utilising time-dependent proportions not supported by any data describing their dynamics; ASHR is the only comparatively reliable data

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source we currently have, and we are not aware of any indications of recent substantial changes in sexual behaviour of the Australian population; (b) people are 'born' into a particular risk group and can never leave this group, but their activity level is a function of their age; this restriction implies, for example, that even when someone from the most active group gets older, his or her activity level declines but does not drop to the level of representatives of a less active group of the same age; (c) the annual sexual partner change rate for an individual is fully specified by his or her age group and risk group; the manner in which an individual of a given age group, gender group and risk group 'chooses' partners of the opposite gender and of a given age group and risk group is described by means of a sexual mixing matrix (discussed in section 2.1);

Human papillomavirus transmission and seropositivity

(a) We assume that people seek treatment immediately upon becoming aware that they have genital warts; (b) we associate seropositivity exclusively with the recovered state such that only those in the recovered (immune) state can be seropositive. Seropositive status is lost upon removal from the recovered state to the susceptible state (i.e. loss of immunity). In the context of our model, the recovered/seropositive state corresponds to those people who have developed detectable antibodies to HPV-6/-11 through an immunogenic response. Conversely, the recovered/seronegative state corresponds to those who have recovered and are immune to reinfection but have not developed detectable antibodies. In general, seropositivity can serve as a long-lasting marker of ongoing or prior infection, although not a particularly reliable one in the case of HPV as only a proportion of those exposed to infection develop detectable antibodies [31]. Furthermore, there is some evidence suggesting that seropositivity may be simply a marker of previous infection and an individual who is seropositive may not necessarily be immune [51]. Such a perspective would lead to a more complicated model structure, and we therefore do not focus on it in this paper. However, the methodology we develop can be extended to this context.

Comments on assumptions and sensitivity studies

The development of these assumptions is a combination of informed decisions regarding expert medical opinion on the proposed model and the population under study, combined with considerations of the quality and properties of the data under study. They take into account the complexity and intricacies of the system under investigation and allow modellers to address parsimonious model specifications that capture some of the most relevant features of the HPV transmission dynamics in the population. Because the focus of the study revolves around Australian sexual behaviour data, we also consider such assumptions in light of the target population and the data source provided by the ASHR study.

In addition, we note that the implications of these assumptions are that we can provide a tractable model to address the public health implications arising from direct modelling of HPV-6 or HPV-11 required to analyse the impact of vaccination programmes (recall that we have in mind Gardasil vaccine against HPV-6, HPV-11, HVP-16 or HPV-18 currently used in Australia) on the genital warts incidence in the Australian population.

We specifically mention the following points regarding the modelled age groups and the consideration of heterosexual populations. With regard to age group stratification, we note that it has been reported [52,53] that the median age of sexual debut is 16 years in Australia. This therefore may suggest that there are sexually active individuals younger than 16 years old. However, the challenge here is that we do not have any representative data that could help us quantify the level of their activity. The ASHR study, which we use as the primary source of sexual behaviour information, only included people 16 years and older for ethical reasons. We therefore consider this group's influence in the model via a sensitivity study summarised in Appendix B. This was performed by calibration of the model to the available ASHR data under different assumptions regarding the level of sexual activity in the under-15 years age group.

The older portion of the population of ages 60 years and older was not incorporated into our model. This was motivated by the results of the ASHR study, which demonstrated that the annual sexual partner change rate in this cohort was both very low and approximately the same for people 45–59 years old. We had no reason to think that the 60 years and older individuals are more active than the younger 45–59 year-old group. Taking into account the absence of any reliable Australian data describing sexual behaviour in the 60 years and older cohort, it was assumed that ignoring this cohort in the model to ensure an associated reduction in dimensionality was justified.

Regarding the decision to study only the heterosexual population in the ASHR survey, we note that it has been estimated that there are approximately 158 000 men who identify themselves as heterosexual

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but have some history of sexual contacts with other men and 148 000 who identify themselves as gay or bisexual ([54] on the basis of ASHR) in Australia. They are commonly referred to as men who have sex with men (MSM). Whereas it may be reasonable to model the strictly homosexual population separately (because they mix sexually only with other members of this group and not with those who identify as strictly heterosexual), the rest of MSMs would ideally be incorporated into our model. Unfortunately, there is a challenge associated with this as there are currently very limited data on their sexual behaviour patterns, making their inclusion the subject of future research and survey design.

To further provide insight into our model in light of these assumptions, we provide three technical appendices undertaking the following sensitivity studies relating to model assumptions and Bayesian prior specifications:

Sensitivity study 1—Adolescents <15 years and their influence on calibration (Appendix B)

This study presents the effect of the assumption that there are sexually active individuals younger than 15 years on model calibration to age-specific seroprevalence and genital warts incidence for each gender.

Sensitivity study 2—Sensitivity of calibration to prior specifications on duration of immunity (Appendix C)

This study presents the sensitivity of the class of developed models to the prior specifications and assumptions discussed relating to the duration of immunity. In particular, we again focus on the calibration to seroprevalence and new diagnoses in each age bracket per gender. Sensitivity studies incorporating prior specifications allowing for a range of durations of immunity in the population, involving relatively short durations specified in the priors for 10–15 years, medium-range durations of 20–25 years and long-range durations of immunity of 40–45 years were assessed.

Sensitivity study 3—Sensitivity to birth and death process assumptions (Appendix D)

This study presents the sensitivity of developed models to the prior specifications and assumptions relating to the population growth characteristics. Considering that the studied population and sexual behaviour survey data utilised is Australian, we consider the application of Australian Bureau of Statistics (ABS) population census data for age-specific birth rates (ABS 3021.0 population by age and sex) and death rates (ABS 3302.0 population by age and sex). These rates are averaged over the defined age strata and applied to the dynamics in the ageing structure in the model. Again, the focus involves the calibration to seroprevalence and new diagnoses in each age bracket per gender.

Sensitivity study 4—Sensitivity to prior elicitation from previous population study characteristics (Appendix E)

We consider specification of the priors under two scenarios. The first involves utilising the data from medical studies given in Table II, currently available on the model parameters (*WIPm*, *WIPf*, *DWTm*, *DWTf*, *DAIm*, *DAIf*) stratified by gender. Note that these data were obtained for young US university students. Then we compare this with alternative prior specifications based on less informed prior choices, presented in Table III.

We performed these studies for strains HPV-6, HPV-11, and HPV-6 and HPV-11 separately, focusing on the incorporation in the technical appendices of the joint calibration to both strains.

Formulation of the model as a system of ordinary differential equations

We formulate our model as the following system of ODEs:

$$\dot{S}_{g,s,a} = -\lambda_{g,s,a}(t)S_{g,s,a} + (P_{g,s,a} + N_{g,s,a})/DI_g + \frac{1}{5}S_{g,s,(a-1)} - \frac{1}{5}S_{g,s,a}$$

$$+ \frac{1}{40}\sum_{g,s}(S_{g,s,9} + I_{g,s,9} + G_{g,s,9} + P_{g,s,9} + N_{g,s,9}) \quad (1)$$

$$\times \delta_1(a)(0.6\delta_1(s) + 0.27\delta_2(s) + 0.11\delta_3(s) + 0.02\delta_4(s)), \quad (2)$$

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$$\dot{I}_{g,s,a} = \lambda_{g,s,a}(t)S_{g,s,a} - (1/WIP_g + 1/DAI_g)I_{g,s,a} + \frac{1}{5}I_{g,s,(a-1)} - \frac{1}{5}I_{g,s,a}, \quad (3)$$

$$\dot{G}_{g,s,a} = I_{g,s,a}/WIP_g - G_{g,s,a}/DWT_g + \frac{1}{5}G_{g,s,(a-1)} - \frac{1}{5}G_{g,s,a}, \quad (4)$$

$$\dot{P}_{g,s,a} = PSC_g(I_{g,s,a}/DAI_g + G_{g,s,a}/DWT_g) - P_{g,s,a}/DI_g + \frac{1}{5}P_{g,s,(a-1)} - \frac{1}{5}P_{g,s,a}, \quad (5)$$

$$\dot{N}_{g,s,a} = (1 - PSC_g)(I_{g,s,a}/DAI_g + G_{g,s,a}/DWT_g) - N_{g,s,a}/DI_g + \frac{1}{5}N_{g,s,(a-1)} - \frac{1}{5}N_{g,s,a}. \quad (6)$$

Here the capital letters denote the number of people in a compartment, and the subscripts denote gender (g; for men $g = 1$, for women $g = 2$), one of the four sexual-activity groups mentioned previously ($s \in \{1, \ldots, 4\}$) and an age group ($a \in \{1, \ldots, 9\}$); the dot denotes a derivative with respect to time; $\delta_i(a)$, $i = 1, 2, 3, 4$ is the Kronecker delta function, equal to 1 if $a = i$ or 0 otherwise, and the system coefficients are as in Figure 1. We should emphasise that all coefficients in the model formulation are gender specific, that is, they can take different values for men and women. System (2)–(6) contains a number of terms describing the process of ageing. Each age group in our model comprises a 5-year band with the same number of people of every age included in the band. Hence, members of the population age (i.e. move to the next age group) at a yearly rate of $1/5$. To maintain a constant population size, we assume that there is an inflow of people into the susceptible compartment of the youngest age group (group 1) as defined by the following:

$$\frac{1}{40}\sum_{g,s}(S_{g,s,9} + I_{g,s,9} + G_{g,s,9} + P_{g,s,9} + N_{g,s,9})\delta_1(a)(0.6\delta_{s,1} + 0.27\delta_2(s) + 0.11\delta_3(s) + 0.02\delta_4(s)).$$

We obtain this term by dividing the total number of individuals leaving the oldest age group (group 9) each year on reaching age 60 years, $(S_{g,s,9} + I_{g,s,9} + G_{g,s,9} + P_{g,s,9} + N_{g,s,9})/5$, evenly between two genders and four sexual-activity groups. We add $S_{g,s,1}$ to every g and s according to the previously defined distribution of the population across risk groups (Table A.1). The implementation of ageing is a mechanism for people to enter and leave the sexually active population continuously and is necessary to propagate the effect of vaccination: we must ensure that vaccination of individuals in a particular age group will later contribute to the number of vaccinated individuals in older age groups.

Each of Equations (2)–(6) describes the change in the number of individuals that occurs during a small time period as the sum of the number of individuals entering this compartment from other compartments and those leaving the compartment. Discussions on construction of compartmental disease transmission models are presented in [23] and [24]. Consider, for example, compartment G (Figure 1): we can calculate the change in the number of individuals in this compartment during a small interval of time by adding up the individuals entering the compartment during this time interval (the infected who developed genital warts, $I_{g,s,a}/WIP_g$, and the ageing members of G from age group $a - 1$, $G_{g,s,a}/5$) and subtracting the number that leave the compartment (recovered who go either to P or N, $G_{g,s,a}/DWT_g$, and the ageing members of G moving to age group $a + 1$, $G_{g,s,a}/5$). In so doing, we will obtain $I_{g,s,a}/WIP_g + G_{g,s,(a-1)}/5 - G_{g,s,a}/DWT_g - G_{g,s,a}/5$, which is the right-hand side of Equation (4).

It is necessary to point out the crucial role of the force of infection (7) in our model. This is the only non-constant coefficient we have to deal with, which introduces nonlinearity into the system (2)–(6). Its specification utilises a matrix usually known as a 'sexual mixing' matrix [8], which describes age-specific and risk group-specific patterns of sexual behaviour in a population.

In the following subsection, we provide a concise description of the construction of the sexual mixing matrix. For complete details, we refer the reader to Appendix A and an associated research paper [55].

2.1. *Sexual mixing matrix*

In this section, we present the construction and extensions developed for statistical modelling of the sexual interaction of members of the population, as defined by the sexual mixing matrix. We consider a Sexually Transmitted Infection (STI) transmission model that has many features in common with other STI models, for example, the models for gonorrhoea in [56] or those developed for HIV in [55] and [57],

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which describe patterns of mixing between age and sexual-activity groups with respect to HIV in heterosexual communities. Like these other models, our approach relies on certain assumptions about the way individuals form their sexual partnerships. This partnership formation process is commonly referred to as 'sexual mixing'. We can describe a simplified model for sexual mixing via a sexual mixing matrix as described in [8], for which examples can be found in [55, 58–60].

It is common practice in the medical literature to assume the parameters of this mixing matrix to be known throughout the calibration of the resulting ODE epidemic model [58]. This is because these parameters are normally derived from the data obtained from an extensive sexual behaviour survey, which often serves as the only comparatively reliable source of information on the subject. Therefore, if the number of participants in a particular survey is significantly larger than in other surveys, this survey will likely be considered as the most trustworthy source of information on sexual mixing, *often irrespective of the experimental design and population studied*. However, because of the personal nature of such surveys, it is understood that their results are to be taken cautiously. In our model, we will assume that two of the parameters specifying the sexual mixing matrix are unknown and should be jointly estimated with the ODE model parameters.

In our heterosexual model formulation, the mixing matrix is a $(2 \times 4 \times 4 \times 9 \times 9)$ dimensional matrix comprising the terms $c^*_{g,s,s',a,a'}$, which are the mean per capita annual rates at which an individual of gender g from a risk or activity group s and age group a acquires new sexual partners of the opposite gender g' from a risk group s' and age group a'; $\rho_{g,s,s',a,a'}$ is the conditional probability that an individual of gender g from sexual-activity group s and age group a acquires a sexual partner of the opposite gender g' from sexual-activity group s' and age group a'. It is clear that estimation of all of these parameters is an almost insurmountable statistical challenge, which is one of the reasons why these parameters are often taken as fixed in any given calibration study of STI transmission models. There are two broad approaches one could pursue. Given that we are working in a Bayesian modelling framework, the first approach would involve prior elicitation for these population parameters on the basis of expert opinions of annual interaction rates that would be reasonably understood by medical practitioners in sexual health clinics, sexual health workers and social workers in regions in which respondents were recorded. The other alternative involves re-parameterising aspects of this matrix, simplifying it significantly, allowing one to account for the uncertainty associated with specification of this matrix in an appropriate simplified stochastic model. This would involve finding suitable factors common to aspects of this matrix that could instead be taken as stochastic and estimated in the model calibration, which in turn allow one to derive each element of the sexual mixing matrix. Most importantly, the framework we develop and present for the estimation and calibration of the transmission model is general enough to be used for either of these approaches and any degree of unknown parameters in the sexual mixing matrix and any parameterisation deemed suitable for a given population study.

In this paper, we then utilise this matrix to specify the force of infection (see Equations (2) and (3)) for any individual from any subgroup (g, s, a). This term is effectively a yearly rate at which an individual becomes infected, and it is defined as

$$\lambda_{g,s,a} = \beta_g \sum_{s',a'} \left\{ c^*_{g,s,s',a,a'} \frac{I_{g',s',a'}}{S_{g',s',a'} + I_{g',s',a'} + G_{g',s',a'} + P_{g',s',a'} + N_{g',s',a'}} \right\}, \tag{7}$$

where β_g is the transmission probability per partnership, that is, the probability that a susceptible person of gender g will become infected from his or her infectious partner of gender g'; $c^*_{g,s,s',a,a'}$ is the mean per capita rate per year at which an individual from g, s, a acquires new sexual partners from g', s', a', and $I_{g',s',a'} / \left(S_{g',s',a'} + I_{g',s',a'} + G_{g',s',a'} + P_{g',s',a'} + N_{g',s',a'}\right)$ is a proportion of infected individuals in g, s, a, which defines the probability that a new sexual partner from g, s, a is infected.

As discussed in [55], we can easily incorporate into the specification of (7) several parameters allowing us to control to what extent the matrix should reflect assortative partnership formation patterns, that is, how likely individuals are to find sexual partners among 'similar' individuals, thereby altering the properties of the matrix, making it more or less dense. For example, we can vary the extent to which older men prefer to have younger female sexual partners, or, possibly, a tendency of older women to choose younger male sexual partners. It is also necessary to be able to account for the readiness of each gender to compromise with the wishes of the opposite gender. This last point becomes significant whenever the supply of individuals of one gender does not meet the demand for sexual partners from the individuals of the opposite gender.

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In this paper, we treat the degrees of assortativity by age and sexual-activity groups, observed to have a noticeable effect on the model calibration, as uncertain, whereas the rest of the sexual mixing matrix parameters are fixed. We do not assume that all of the parameters specifying this matrix are unknown because we want to keep the total number of parameters in our model as low as possible.

Although a matrix with these features cannot encompass all the complexities of human sexual mixing, it certainly enables us to explore various relatively plausible mixing scenarios. In addition, it is a manageable model formulation, and this framework has been widely used by STI modellers (for examples of its use in HPV models, see [12, 16, 61, 62]).

3. Bayesian framework for nonlinear ordinary differential equation human papillomavirus epidemic model

In constructing a statistical model for the HPV epidemic model, we treat the parameters of the nonlinear system of ODE equations describing the epidemic as unknown random variables. In addition, we treat some of the parameters of the sexual mixing matrix associated with assortativity as unknown random variables to be estimated jointly with the ODE epidemic model parameters. We formulate a Bayesian model for this system with the prior specifications given in Table I. Furthermore, we treat the ODE system as purely deterministic, conditional on a set of system parameters. In other words, the trajectories of the latent states in the ODE system over time are conditionally deterministically specified by the system of ODEs. Therefore, we do not derive a system of SDE as has been done in the Pharmaco-Kinetic/Pharmaco-dynamics literature (see [63] or [64]). Instead, our focus lies purely in the 'calibration' of this ODE epidemic model to an observed set of data based on observations that are formed by a transformation of the state of the ODE system and observed in noise. We detail the process of forward projection we utilise to obtain the state of the nonlinear ODE system at any given time point, conditional on the model parameters defined in Section 3.1.

3.1. Forward projection of the nonlinear ordinary differential equation model

The states of the system at time points $t \in \{1, \ldots, T\}$ are denoted by vectors $\boldsymbol{X}_{g,a,s}(1:T) = [\boldsymbol{X}_{g,a,s}(1), \ldots, \boldsymbol{X}_{g,a,s}(T)]$, which generically represent the dynamic evolution of the ODE system,

Table I. Prior specification for nonlinear ODE models for HPV-6 or HPV-11.

Parameter	Interpretation	Prior
Nonlinear ODE model parameter priors		
Transmission probability (men)	TRm	$U[Ba, Bb]$
Transmission probability (women)	TRf	$U[Ba, Bb]$
Average genital warts incubation period (men)	WIPm	$Ga(k_{WIPm}, \theta_{WIPm})$
Average genital warts incubation period (women)	WIPf	$Ga(k_{WIPf}, \theta_{WIPf})$
Average duration of genital warts treatment (men)	DWTm	$Ga(k_{DWTm}, \theta_{DWTm})$
Average duration of genital warts treatment (women)	DWTf	$Ga(k_{DWTf}, \theta_{DWTf})$
Average duration of asymptomatic HPV infection (men)	DAIm	$Ga(k_{DAIm}, \theta_{DAIm})$
Average duration of asymptomatic HPV infection (women)	DAIf	$Ga(k_{DAIf}, \theta_{DAIf})$
Average duration of immunity (men)	DIm	$U(k_{DIm}, \theta_{DIm})$
Average duration of immunity (women)	DIf	$U(k_{DIf}, \theta_{DIf})$
Probability of becoming seropositive (men)	PSCm	$Be(\alpha_{PSCm}, \beta_{PSCm})$
Probability of becoming seropositive (women)	PSCf	$Be(\alpha_{PSCf}, \beta_{PSCf})$
Observation error parameters priors		
Diagonal element of the observation error covariance matrix for incidence $\Sigma = \mathrm{diag}(\sigma)$	σ	$invGa(k_\sigma, \theta_\sigma)$
Observation error scale for seroprevalence	A_Y	$Ga\left(k_{A_Y}, \theta_{A_Y}\right)$
Mixing matrix parameter priors		
Degree of assortativeness by age group	EPSa	$Be\left(\alpha_{\epsilon_a}, \beta_{\epsilon_a}\right)$
Degree of assortativeness by risk group	EPSr	$Be\left(\alpha_{\epsilon_r}, \beta_{\epsilon_r}\right)$

Note that the nonlinear ODE model parameter priors can all be assumed non-informative.

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where for a given gender, age and sexual-activity group at time t the state encompasses the following components $\boldsymbol{X}_{g,a,s}(t) = [S_{g,a,s}(t), I_{g,a,s}(t), G_{g,a,s}(t), P_{g,a,s}(t), N_{g,a,s}(t)]$. Therefore, conditional on a set of parameters in the ODE system, we can iterate the ODE system forward in time using an ODE solver to obtain the states for each population group at time t. Note that the times t, for which the system is solved, will generally be of a much finer granularity than those at which observations are collected in a population study. This set of times should include at least the observation times.

In our estimation procedure, we considered several different solvers and noticed that the choice of solver can have a significant effect on the accuracy and on the efficiency of the computations undertaken in the statistical estimation. In particular, depending on parameterisation and development of the relationships between states or compartments of the model and parameterisation of the mixing matrix, one can obtain non-stiff or stiff systems of equations. In this context, the concept often referred to as stiffness involves the fact that solving numerically a large system of coupled ODEs can be numerically unstable unless the step size is taken to be extremely small. Given the dimensions of the problems we consider and under an AdMCMC procedure, such small step sizes make repeated application of generic solvers computationally inefficient (see discussions in [65]).

Hence, to overcome these complications, the software implementation of the framework described in the paper was written in Fortran 90/95/2003 and utilised a universal solver `dodesol`, which is a part of the Intel® Ordinary Differential Equation Solver Library.[‡] This solver is, in fact, a collection of five different solvers designed to solve numerically initial value problems of the form

$$\dot{\boldsymbol{x}} = \boldsymbol{g}(\boldsymbol{x}, t), \ \boldsymbol{x}(t_0) = \boldsymbol{x}_0, \ t > t_0, \tag{8}$$

where t is an independent variable, $\boldsymbol{x}$ is a vector of state variables to be solved for and $g(\boldsymbol{x}, t)$ is a function of t and $\boldsymbol{x}$.

An important distinction between these solvers is that each of them being of explicit, implicit or hybrid type is particularly efficient for a given degree of stiffness of the system. The universal solver first estimates how stiff the system is and then uses an appropriate solver to handle it. It is pertinent to note that in the case where (8) can be solved explicitly, a modification of the fourth-order Merson's method combined with a first-order multi-stage method will be applied. Should (8) be treated implicitly, an L-stable fourth-order $(5, 2)$-method with an option to fix the Jacobian will be used.

We chose the `dodesol` solver not only because of its convenient FORTRAN interface, for which the remainder of the model and code was developed, but also because of its efficient performance, which we compared with that of the two standard MATLAB solvers `ode45` and `ode15s`. The solver `dodesol` was especially superior to those provided by MATLAB solvers `ode45` and `ode15s` when the stiffness of our ODE system increased. However, it should be pointed out that `dodesol` speed can be considerably affected by the selection of its minimal time step and relative error threshold. To obtain the simulation results discussed in this paper, we use the minimal step size 1×10^{-10}, the initial step size 1×10^{-6} and the relative error tolerance 1×10^{-3}. Also, we do not make use of the option to pre-specify the Jacobian provided by the solver.

3.2. Prior choices for parameters of nonlinear ordinary differential equations and the sexual mixing matrix

In developing the prior specifications for the model, one has options of hierarchical prior specifications versus assumptions of independence. In the case of the model parameters proposed, shown in Table I, we summarise the state of medical literature and the limited knowledge of such model parameters in Table II. However, medical opinion in the referred to papers and associated literature indicate that an assumption of *a priori* independence is reasonable. As more sexual survey data become available, we can further test these assumptions for the Australian population.
We consider two cases for the prior specification:

Case 1 Specification of hyper-parameters in the priors for (*WIPm*, *WIPf*, *DWTm*, *DWTf*, *DAIm*, *DAIf*) stratified by gender, to information provided in Table II based on US studies. Detailed prior specification based on moment matching and elemental percentile methods, and calibration processes are provided in Appendix E.

[‡] *http://software.intel.com*

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Table II. Data from medical literature, which aid in specification of prior hyper-parameter values for the HPV-6 or HPV-11 model.

	Men			Women		
Duration of (years)	Value	95%CI	Source	Value	95%CI	Source
Genital warts incubation period, median	0.916	0–1.341	[66]	0.241	0–0.475	[67]
Treatment for genital warts, mean	0.281	0.213–0.349	[68]	0.232	0.185–0.280	[68]
Treatment for genital warts, median	N/A	N/A	N/A	0.491	0.325–0.666	[68]
Untreated infection, median	0.45	0.425–0.475	[49]	0.5	0.475–0.575	[51]
Untreated infection, mean	N/A	N/A	N/A	0.7916	0.575–1.0	[51]

Table III. Selected prior distributions actually used in our simulations.

		WIP	*DAI*	*DWT*
6	Men	$U(0.9, 1.3)$	$U(2.2, 3.6)$	$Ga(92.00, 0.003)$
	Women	$U(0.6, 0.9)$	$U(2.2, 3.6)$	$Be(69.00, 231.00)$
11	Men	$U(0.9, 1.3)$	$U(2.0, 3.6)$	$Ga(92.00, 0.003)$
	Women	$U(0.6, 0.9)$	$U(2.0, 3.6)$	$Be(69.00, 231.00)$
6/11	Men	$U(1.0, 2.0)$	$U(3.8, 4.8)$	$Ga(92.00, 0.003)$
	Women	$U(1.0, 2.0)$	$U(3.8, 4.8)$	$Be(69.00, 231.00)$

Whereas *DWT* is in agreement with the real data, *WIP* and *DAI* were allowed to take values beyond their reported ranges (Table II).

Case 2 Prior specifications developed for Australia based on ASHR background supplementary information, provided in Table III.

The first studies the ability to accurately calibrate our model to the Australian sexual behaviour ASHR data, based on existing knowledge of suggested associated parameter values obtained from alternative empirical studies. The interest here is in the effect of sensitivity to different population studies and dynamics. This is then compared with priors developed for Australian populations.

In both prior specification cases, parameters for which there is an apparent lack of medical knowledge, (*TRm*, *TRf*, *DIm*, *DIf*, *PSCm*, *PSCf*), were specified for both men and women as uninformative. Results of the performed sensitivity studies are provided in Appendices B–E.

We summarise the distributional prior choices made for each of the model parameters (Table I) by the following basic prior structure:

$$\begin{aligned} p(&TRm, TRf, WIPm, WIPf, DWTm, DWTf, DAIm, DAIf, PSCm, PSCf, DIm, DIf, \Sigma, A_Y, EPSa, EPSr) \\ &= p(TRm)\,p(TRf)\,p(WIPm)\,p(WIPf)\,p(DWTm)\,p(DWTf)\,p(DAIm)\,p(DAIf)\,p(PSCm)\,p(PSCf) \\ &\quad \times p(DIm)\,p(DIf)\,p(\Sigma)\,p(A_Y)\,p(EPSa)\,p(EPSr). \end{aligned} \tag{9}$$

We also note that, when specifying the prior distributions and their hyper-parameters (i.e. parameters describing the shape of distributions assigned to the prior distribution parameters), we utilise data reported in the literature from previous studies of HPV transmission to inform some appropriate prior specifications (Table II). Importantly, these data are completely different from the real data sets that were studied in the present paper, on the basis of different populations, different time periods and different locations; hence, we have not used our observation data twice. As is usually the case with interpreting any reported HPV data, it is appropriate to consider the reported values of observations and calibrations as estimation with limitations and proneness to error. This means that we can safely consider values outside of the reported confidence intervals (CI) to be plausible in our study. Using the real data (Table II), we specify the priors for each of the HPV models (Table I).

The technical detail regarding the statistical moment matching and elemental percentile approach to the prior specification to existing literature is provided in Appendix E. In addition, we provide in Appendix E the relationship between the model parameters and the existing state of partial knowledge from previous US studies.

The prior parameters for seroprevalence observation errors denoted by A_Y had hyper-prior parameters given by $(k_{Am}, \theta_{Am}) = (2, 2)$, and the diagonal element σ of the incidence observation error covariance

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matrix was distributed according to $(k_\sigma, \theta_\sigma) = (2, 5)$. Finally, the priors for the sexual mixing matrix parameters associated with assortativity had hyper-priors specified according to $(\alpha_{\epsilon_a}, \beta_{\epsilon_a}) = (0.5, 0.7)$ and $(\alpha_{\epsilon_r}, \beta_{\epsilon_r}) = (0.5, 0.7)$.

3.3. Likelihood model for parameters of nonlinear ordinary differential equations and Garnett mixing matrix

Having specified the prior structure of the model, we present the observation model, likelihood and details of the actual data studied. In particular, we note that, conditional on a particular realisation of the model parameters in Table I, the latent unobserved state trajectories of the system are deterministic, non-analytic solutions to the system of ODEs in Equation (6). These solution trajectories are transformed according to age group, gender group and risk group to produce a set of results that can be directly observed in noise in the population under study. In the following section, we will describe and detail these transformations and the associated statistical assumptions made on the observation error. In doing so, we will also specify models suitable for situations of disequilibrium of the disease states within the population such as what occur after a serious outbreak, a vaccination or community education awareness programme, and so forth, and models for situations in which the disease in the population under study can be considered to be at equilibrium.

In this section, we first describe the observations that are utilised in the calibration of the ODE epidemic model and the sexual mixing matrix. Importantly, the real observations utilised in this paper, based on HPV-6 or HPV-11 data collected in Australia, are treated as taken from a population at endemic equilibrium.

Then we present the resulting likelihood model utilised, followed by the derivation of the posterior distribution. We first note that the general likelihood model will be presented, in which observations of the transformed state trajectories are known at a fixed set of discrete time points $t \in \{1, 2, \ldots, T\}$. In practice, these discrete time points may be unevenly spaced, and this would not affect the estimation procedure to be developed.

The actual observations we consider in this model are seroprevalence and genital warts incidence by age group, which make up the 'observations' considered in our model. They are specified as follows:

Seroprevalence is the proportion (or percentage, in our model) of individuals in a given group who are recovered and seropositive.

Genital warts incidence is a rate defined as the number of new cases of genital warts in the population per person (or per 1000 persons, in our model) per year.

In order to evaluate the output of our model, we intend to compare it with the real-life seroprevalence [31] and genital warts incidence [30] data. The seroprevalence data were collected in the second half of 2005 from various laboratories in New South Wales, Victoria and Queensland, where about 80% of the Australian population resides. We applied a validated sampling method for serosurveillance to test 1523 serum samples from women and 1247 samples from men aged from 0 to 69 years. For each individual, the age group, sex and date of sample collection were recorded. We derived the overall population HPV seroprevalence by weighting the results obtained from the samples to 2005 Australian midyear population estimates by age. Incidence data were estimated from the Bettering the Evaluation of Care and Health (BEACH) cross-sectional database. In particular, we analysed the annualised new case consultation rate stratified by gender and age from April 2000 to September 2006 and normalised this to the corresponding 2004 Australian population. In total, 639 consultations related to genital warts were registered, and of these roughly 35% were new cases. BEACH did not capture data on the people who attended sexual health clinics to seek treatment for genital warts. However, it was estimated that for every person visiting a GP there was 0.298 persons visiting a sexual health clinic, so the genital warts cases managed in such clinics were accounted for by multiplying the incidence rates obtained from the GP data by 1.298. We summarise the data in Tables IV and V.

Generally, in this model we can consider observations as arriving at irregularly spaced intervals and generally not at all times $t \in \{1, \ldots, T\}$. For simplicity, we will assume that a full panel of observations for all age groups, activity groups and genders is available at each observation time, although we can also relax this assumption under the model developed in this paper. We will also assume for simplicity that because we can solve for the state of the nonlinear system at any specified time point conditional on a set of model parameters, we will always have the observation time corresponding to one of the time points $t \in \{1, \ldots, T\}$.

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Table IV. Seroprevalence data for Australia as percentages of the whole male or female population (as reported in [31]).

	HPV-6				HPV-11				Combined HPV-6 and HPV-11			
	Men		Women		Men		Women		Men		Women	
No.	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI
1	0.6	0.0 – 3.3	7.0	3.4 – 12.6	1.2	0.1 – 4.3	1.4	0.2 – 5	1.2	0.1 – 4.3	7.7	3.9 – 13.4
2	9.6	5.9 – 14.4	12.2	7.5 – 16.9	7.2	4.1 – 11.6	4.9	2.1 – 7.7	13.4	9.1 – 18.8	18.2	13.6 – 23.6
3	9.6	5.9 – 14.4	17.7	13.0 – 22.4	7.2	4.1 – 11.6	4.0	1.2 – 6.8	13.4	9.1 – 18.8	18.2	13.6 – 23.6
4	15.1	10.1 – 21.4	22.0	17.6 – 27.1	7.6	4.1 – 12.6	6.4	3.9 – 9.7	17.4	12.1 – 24.0	23.6	19.0 – 28.7
5	15.1	10.1 – 21.4	22.0	17.6 – 27.1	7.6	4.1 – 12.6	6.4	3.9 – 9.7	17.4	12.1 – 24.0	23.6	19.0 – 28.7
6	15.4	9.9 – 22.4	18.8	14.4 – 23.7	9.1	4.9 – 15.0	11.8	8.3 – 16.1	20.3	14.0 – 27.8	24.0	19.1 – 29.3
7	15.4	9.9 – 22.4	18.8	14.4 – 23.7	9.1	4.9 – 15.0	11.8	8.3 – 16.1	20.3	14.0 – 27.8	24.0	19.1 – 29.3
8	12.9	8.0 – 19.4	17.7	12.1 – 24.6	7.5	3.8 – 13.0	4.4	1.8 – 8.9	15.6	10.2 – 22.5	19.0	13.2 – 26.0
9	12.9	8.0 – 19.4	17.7	12.1 – 24.6	7.5	3.8 – 13.0	4.4	1.8 – 8.9	15.6	10.2 – 22.5	19.0	13.2 – 26.0

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Table V. Genital warts incidence data for Australia measured as the mean number of new cases per 1000 persons per year (as reported in [30]).

Age group		Men		Women	
No.	Ages (years)	Mean	95%CI	Mean	95%CI
1	15 – 19	1.66	0.46 – 2.86	7.28	4.18 – 10.38
2	20 – 24	6.27	3.77 – 8.77	8.61	5.61 – 11.61
3	25 – 29	7.4	4.4 – 10.4	6.37	3.77 – 8.97
4	30 – 34	4.64	2.44 – 6.84	4.33	2.13 – 6.53
5	35 – 39	2.34	1.34 – 3.34	2.19	1.19 – 3.19
6	40 – 44	2.34	1.34 – 3.34	2.19	1.19 – 3.19
7	45 – 49	0.83	0.33 – 1.33	0.48	0.08 – 0.88
8	50 – 54	0.83	0.33 – 1.33	0.48	0.08 – 0.88
9	55 – 59	0.83	0.33 – 1.33	0.48	0.08 – 0.88

We model the observation vector as the result of a vector function of the nonlinear ODE system state $\boldsymbol{X}_{g,a,s,t}$ at each time t, denoted by $\boldsymbol{O}_{g,a,s}(t) = [D_{g,a,s}(t), Y_{g,a,s}(t)]$, which contains the observation $D_{g,a,s}(t)$ representing incidence at time t for a given gender, age group and sexual-activity group as well as $Y_{g,a,s}(t)$, which represents the seroprevalence in the given category.

We assume the observed numbers of new diagnoses to be observed in Gaussian noise. This assumption is reasonable as the counts obtained are very large, so it is suitable to make a continuous distributional assumption. We assume the likelihood model for the observed seroprevalence to be a beta distribution because it represents observations of proportions given the parameters. Furthermore, conditional on the parameters of the model, we assume the joint likelihood model to have the following conditional independence properties between observations conditional on information on the individuals' categories of gender, age and activity group as follows:

$$\begin{aligned}
&\mathcal{L}(\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(1), \ldots, \boldsymbol{X}_{g,a,s}(T); \boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T)) \\
&= \prod_{g\in\{1,2\}} \prod_{a\in\{1,\ldots,9\}} \prod_{s\in\{1,\ldots,4\}} \prod_{t=1}^{T} P(\boldsymbol{O}_{g,a,s}(t)|\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(t)) \\
&= \prod_{g\in\{1,2\}} \prod_{a\in\{1,\ldots,9\}} \prod_{s\in\{1,\ldots,4\}} \prod_{t=1}^{T} P(D_{g,a,s}(t)|\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(t)) \\
&\quad \times P(Y_{g,a,s}(t)|\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(t)) \\
&= \prod_{g\in\{1,2\}} \prod_{a\in\{1,\ldots,9\}} \prod_{s\in\{1,\ldots,4\}} \prod_{t=1}^{T} \mathcal{N}\left(D_{g,a,s}(t); \boldsymbol{\mu}_{D_{g,a,s}(t)}, \sigma_{D_{g,a,s}(t)}\right) Be(Y_{g,a,s}(t); A_Y, B_Y),
\end{aligned} \tag{10}$$

where we denote in bold the vectors of parameters corresponding to men and women. For example, $\boldsymbol{TR} = (TRm, TRf)$; the equilibrium mean structure for the genital warts incidence in category g, a, s is defined as

$$\begin{aligned}
\boldsymbol{\mu}_{D_{g,a,s}(t)} &= f(\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(t)) \\
&= \frac{1}{WIP_g} \times \frac{I_{g,s,a}}{S_{g,s,a} + I_{g,s,a} + G_{g,s,a} + P_{g,s,a} + N_{g,s,a}} \times 1000,
\end{aligned} \tag{11}$$

which is a function of the state vector at time t and the model parameters. The multiplier 1000 appears here because we compare the simulated incidence with the real incidence data reported per 1000 individuals [30].

In this paper, we always consider gender to be male or female coded with a 1 or 2, respectively, sexual activity to be split into four classes coded with 1, 2, 3, 4, and ages as decomposed in Table VI coded by the indices 1 through 9. We have to stress that (11) is valid only under the assumption that our model is at endemic equilibrium. Otherwise, the incidence would be time dependent: for any two time points, t_0 and t_1 such that $t_1 = t_0 + 1$ (they are 1 year apart) would be given by the following:

$$\boldsymbol{\mu}_{D_{g,a,s}(t_1)} = \frac{1}{WIP_g} \times \frac{I_{g,s,a}(t_0)}{S_{g,s,a}(t_0) + I_{g,s,a}(t_0) + G_{g,s,a}(t_0) + P_{g,s,a}(t_0) + N_{g,s,a}(t_0)} \times 1000. \tag{12}$$

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Table VI. Relative new sexual partner acquisition rates by age group.

	Age group								
No.	1	2	3	4	5	6	7	8	9
Age (years)	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59
Rate (r_a)	5.28	6.06	4.37	2.57	1.61	1.43	1.00	1.00	1.00

Note that we have obtained the state vectors for the system $\boldsymbol{X}_{g,a,s}(t)$ used in the evaluation of the likelihood model via forward simulation, conditional on the model parameters of the nonlinear ODE model, ensuring that the solution points at which we evaluated the states of the system at least corresponded to the observation times $t \in \{1, \ldots, T\}$ and generally would be a finer grid than these time points. We achieved this using a specialised ODE solver as described previously in Section 3.1.

Additionally, we also define the observation equation for the likelihood corresponding to the seroprevalence observations for each age group, activity group and gender, as a function of the nonlinear ODE system state and model parameters, which were specified according to a beta distribution specified in Equation (13):

$$\begin{aligned} Y_{g,a,s}(t) &= g(\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(t)) \\ &= \frac{P_{g,s,a}}{S_{g,s,a} + I_{g,s,a} + G_{g,s,a} + P_{g,s,a} + N_{g,s,a}}. \end{aligned} \tag{13}$$

We treat the scale parameter A_Y of this beta prior as a random variable and estimate this in the posterior inference. The shape parameter, denoted by B_Y, is obtained by moment matching given the sampled scale parameter and the observations obtained from the current forward projection trajectory:

$$B_Y = A_Y \left(\frac{1}{Y_{g,a,s}(t)} - 1 \right). \tag{14}$$

We may then combine this likelihood and prior structure to obtain the posterior distribution of the model parameters, given the observations. We give the full posterior distribution of interest in Equation (15), and this comprises the likelihood model in Equation (10) and the prior model in Equation (9):

$$\begin{aligned} &p(\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr | \boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T)) \\ &\quad \propto \mathcal{L}(\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(1), \ldots, \boldsymbol{X}_{g,a,s}(T); \boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T)) \\ &\qquad \times p(TRm)\, p(TRf)\, p(WIPm)\, p(WIPf)\, p(DWTm)\, p(DWTf)\, p(DAIm)\, p(DAIf)\, p(PSCm)\, p(PSCf) \\ &\qquad \times p(DIm)\, p(DIf)\, p(\Sigma)\, p(A_Y)\, p(EPSa)\, p(EPSr). \end{aligned} \tag{15}$$

The resulting posterior distribution therefore has 16 model parameters. At each time point t, the forward simulated ODE state vectors $\boldsymbol{X}(t) \in \mathbb{R}^{360}$, because of two sexes, nine age groups, four activity groups and five compartments. Hence, the total dimension explored in the simulation performed in the results section is $360 \times T$, where we set $T = 120$.

Next we demonstrate how to perform inference under this Bayesian model formulation. In particular, we are interested in the Bayesian point estimators corresponding to the posterior mean (MMSE) and the posterior mode (MAP) estimates, as well as the distribution properties of the posterior. To explore these, we must resort to a numerical procedure to draw samples from the posterior distribution. The class of methods we consider in this paper involves combining the forward simulation procedure for solving the nonlinear ODE system, given a set of model parameters, with an AdMCMC algorithm to propose a new set of model parameters given the history of proposed parameter vectors. We present the details of the AdMCMC methodologies considered in Section 4.

4. Adaptive Markov chain Monte Carlo strategies combined with forward simulation

In this section, we present details for the AdMCMC algorithm that we will combine with the forward simulation algorithm in order to sample from the posterior distribution given in Equation (15). In particular, we first introduce the background of an AdMCMC algorithm before detailing the adaptation strategy we explore in this paper on the basis of the adaptation rules developed in [41, 44].

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In essence, we first construct a MCMC proposal distribution to sample the static posterior parameters, denoted by vector $\boldsymbol{\Theta} = [\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr]$. Then, conditional on these model parameters proposed, we obtain the state trajectories for the ODE HPV epidemic model, given by $\boldsymbol{X}_{g,a,s}(1:T) = [\boldsymbol{X}_{g,a,s}(1), \ldots, \boldsymbol{X}_{g,a,s}(T)]$, which we generate using forward simulation. The parameter vector $\boldsymbol{\Phi}$ parameterises the MCMC proposal distribution. The idea of AdMCMC methods is to learn appropriate values for $\boldsymbol{\Phi}$ recursively utilising the previous samples of the Markov chain that have been accepted under the MCMC accept–reject mechanism. We achieve this on-line, adapting according to the support of the posterior distribution, thereby allowing the Markov chain to discover and explore the regions of the posterior distribution that have the most mass. Through this on-line adaptive learning mechanism, the Markov chain proposal distribution can significantly improve the acceptance rate of the Markov chain, enabling efficient mixing and improving the samples obtained from the posterior.

In this paper, we consider a popular adaptation scheme proposed in the literature and analyse its ability to explore the very high dimension of the posterior distribution developed in the nonlinear HPV epidemic model. Before presenting the details of the adaptation scheme for the Markov proposal, we first present the generic algorithm developed for sampling from the posterior in Equation (15). In the following sequence of steps for the jth iteration of the AdMCMC forward simulation algorithm, we will update the state of the Markov chain from $\boldsymbol{\Theta}^{(j-1)}$, with corresponding states $\boldsymbol{X}^{(j-1)}_{g,a,s}(1:T)$, to parameter vector $\boldsymbol{\Theta}^{(j)}$ with associated state trajectories $\boldsymbol{X}^{(j)}_{g,a,s}(1:T)$. We summarise this algorithm subsequently for one step of the AdMCMC forward project algorithm:

1. Sample $\boldsymbol{\theta}^* \sim q([\boldsymbol{\theta}](j-1), \cdot)$ from an AdMCMC proposal constructed using previous Markov chain samples $\{\boldsymbol{\Theta}^{(1)}, \ldots, \boldsymbol{\Theta}^{(j-1)}\}$.
2. Solve the nonlinear ODE system (2)–(6) by running a forward simulation of the nonlinear ODE solver, conditional on proposed parameter vector $\boldsymbol{\theta}^*$, to obtain the state of the ODE system, $\boldsymbol{X}_{g,a,s}(1), \ldots, \boldsymbol{X}_{g,a,s}(T)$, which correspond to the observations $\boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T)$.
3. Accept the proposed new Markov chain state comprising $\boldsymbol{\theta}^*$ with acceptance probability given by

$$\alpha\left(\boldsymbol{\theta}^{(j-1)}, \boldsymbol{\theta}^*\right) = \min\left(1, \frac{\mathcal{L}(\boldsymbol{\theta}^*; \boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T))\, p(\boldsymbol{\theta}^*) q\left(\boldsymbol{\theta}^{(j-1)}, \boldsymbol{\theta}^*\right)}{\mathcal{L}\left(\boldsymbol{\theta}^{(j-1)}; \boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T)\right) p\left(\boldsymbol{\theta}^{(j-1)}\right) q\left(\boldsymbol{\theta}^*, \boldsymbol{\theta}^{(j-1)}\right)}\right)$$

where we evaluate this acceptance probability utilising the expressions developed in Sections 3.2 and 4.1. These steps are repeated for $j \in \{1, \ldots, J\}$.

4.1. *Adaptive Metropolis*

To complete the specification of the methodology utilised, we present the internal adaptation strategy we consider in this paper based on the adaptive Metropolis algorithm detailed in [44]. This is a variant of the approach proposed in [43], which develops a Random Walk Metropolis–Hastings that estimates the global covariance structure from the past samples.

Under an adaptive Metropolis algorithm, the proposal distribution is based on a Gaussian mixture kernel detailed in [44]. The proposal, $q(\boldsymbol{\theta}^{(j-1)}, \boldsymbol{\theta}^*)$, involves an adaptive Gaussian-mixture Metropolis proposal, one component of which has a covariance structure that is adaptively learnt on-line as the algorithm explores the posterior distribution. For iteration j of the Markov chain, the proposal is

$$q_j\left(\boldsymbol{\theta}^{(j-1)}, \cdot\right) = \gamma \mathcal{N}\left(\boldsymbol{\theta}^*; \boldsymbol{\theta}^{(j-1)}, \frac{(2.38)^2}{d}\Sigma_j\right) + (1-\gamma)\mathcal{N}\left(\boldsymbol{\theta}^*; \boldsymbol{\theta}^{(j-1)}, \frac{(0.1)^2}{d} I_{d,d}\right). \quad (16)$$

Here, $\boldsymbol{\Phi} = \Sigma_j$ is the current empirical estimate of the covariance between the parameters of $\boldsymbol{\theta}$, estimated using samples from the Markov chain up to time $j-1$. Small positive constant γ is usually taken equal to 0.05 [44]. The theoretical motivation for the choices of scale factors 2.38, 0.1 and dimension d are all provided in [44] and are based on optimality conditions presented in [69]. We note that the update of the covariance matrix can be done recursively on-line via the following recursion (as detailed in [70]).

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5. Synthetic data analysis

In this section, we first study the performance of the AdMCMC Forward simulation methodology in a synthetic data example. To perform this study, we utilised model parameters arbitrarily selected as

$$(TRm, TRf, WIPm, WIPf, DWTm, DWTf, DAIm, DAIf, PSCm, PSCf, \Sigma, A_Y, EPSa, EPSr) = (0.9, 0.9, 0.95, 0.85, 0.15, 0.3, 3.2, 3.4, 0.5, 0.6, 5.0, 2.0, 0.5, 0.5) \quad (17)$$

and distributed as shown in Table III. Note that we omit *DIm* and *DIf* because we decided to assume a life-long immunity for all individuals in the population. This simplification can easily be removed and would not modify our estimation procedure or models developed.

With an initial population size of 10 000, we simulated trajectories of system (2)–(6) over annual time steps for 120 years ($t \in [0, 120]$), and every 10 years we calculated the synthetically generated 'true' state and a noisy set of observations for each age group under the specified statistical models in Equation (10). We took these ODE state trajectories and the observations as the 'true' synthetic data. Next we ran 100 000 iterations of the AdMCMC forward projection sampler to obtain samples from the posterior distribution conditional on these synthetically generated observations.

In Figure 2, we present the posterior estimates for the ODE epidemic static model parameters (calibration performance) under the Bayesian model constructed in Section 3. We illustrate this performance for the model parameters that describe the rates of transmission between states as well as those that quantify the statistical uncertainty we model in the sexual mixing matrix. We estimate each of these parameters on the basis of observations generated for the number of new diagnoses (incidence) and seroprevalence utilising prior specifications derived from previous literature studies. The important features of this synthetic study are that we can illustrate that our AdMCMC forward projection sampling methodology is able to generate samples from the resulting high-dimensional posterior efficiently and that the estimated posterior parameter MMSE values and 95% posterior CI contain, in all cases, the 'true' model parameters utilised to generate the data. These results demonstrate that the AdMCMC forward project estimation procedure we developed is working accurately in this controlled synthetic study. The estimation of state trajectories also confirms this. We show an example of estimated state trajectories for the total number of men in every disease state in Figure 3. For all simulated time steps and for each disease state, we observe that the 'true' trajectory is contained within the 95% posterior CI for the aggregated trajectory, and, in addition, the estimated mean trajectory is in agreement with the 'true' aggregated trajectory. Furthermore, we can also provide analysis of the calibration performance as a function of the observed data versus estimated model fits to incidence and seroprevalence per age group. We compared the 95% posterior CIs of the simulated forecast posterior calibrations with the 'true' synthetically generated observations and found them in good agreement, as depicted in Figures 4 and 5, for the number of new genital warts diagnoses and the seroprevalence by age and gender.

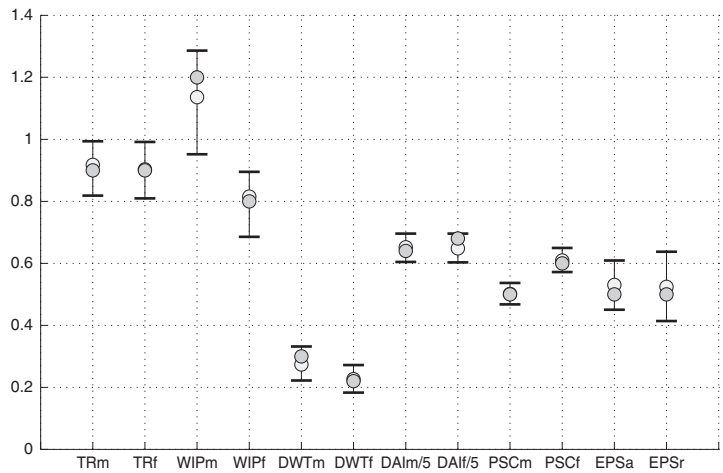

Figure 2. 'True' model parameters (grey circles) for synthetic study versus estimated model parameters (light grey circles) and error bars (95% posterior CI) for the model corresponding to the combined HPV-6 and HPV-11 case.

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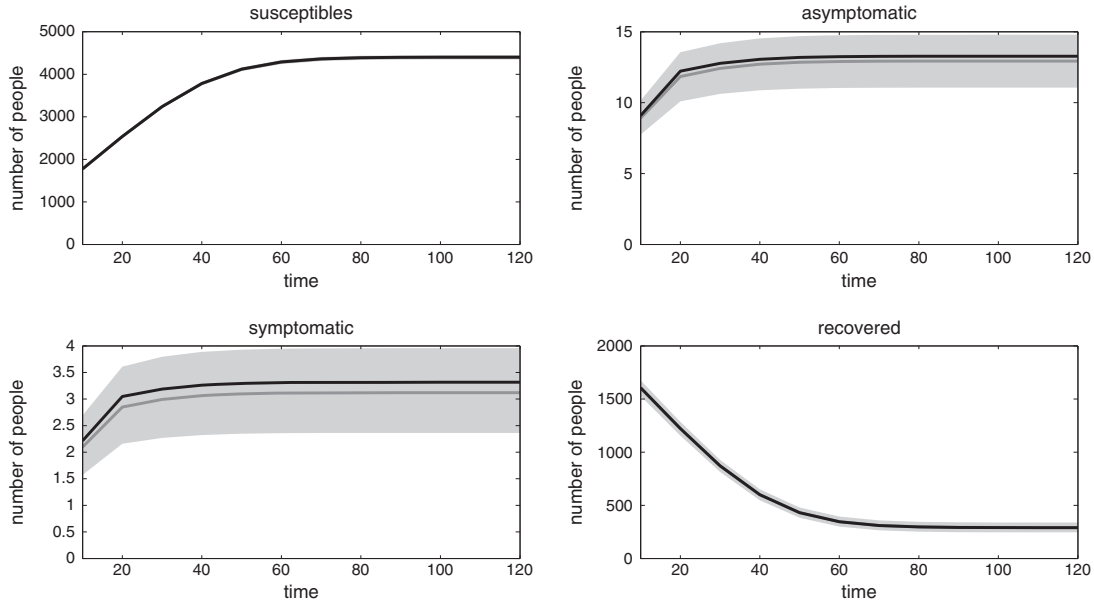

Figure 3. State trajectories for men in every disease state (synthetic case, combined HPV-6 and HPV-11): 'true' trajectories (black line), MMSE (grey line) and 95%CI (shaded area); note that in the presented case the trajectories for seropositive and seronegative men coincide, so it is convenient to call men in either state 'recovered'.

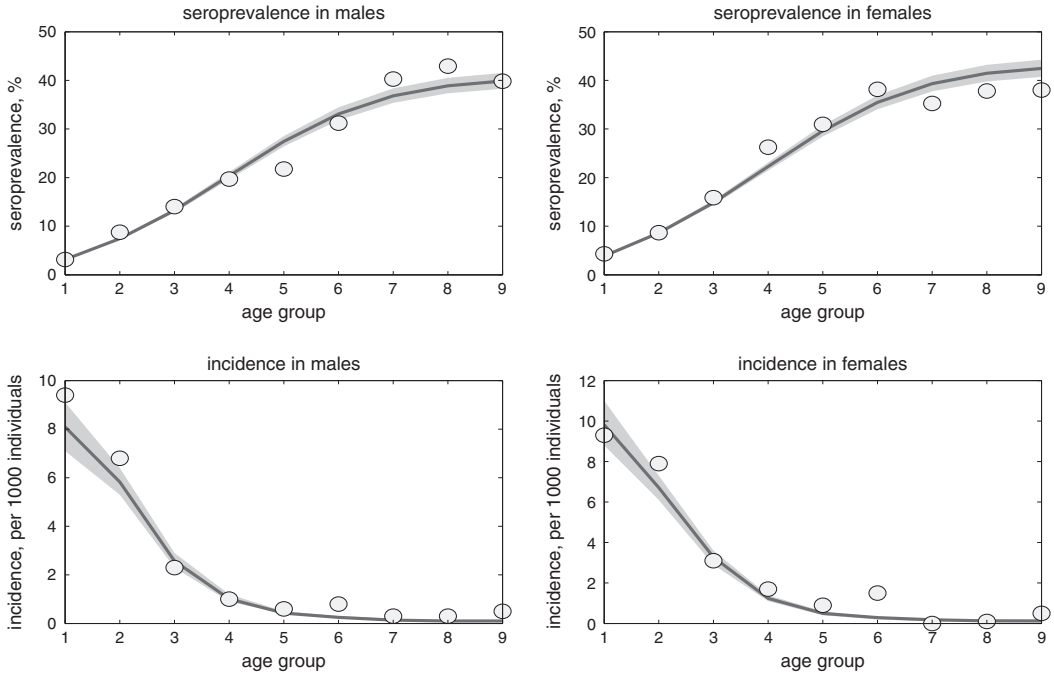

Figure 4. Calibration for synthetic case at time point $t = 30$ (combined HPV-6 and HPV-11): MMSE (solid line) and 95%CI (shaded area).

6. Calibration to the real data and results

In this section, we undertook statistical estimation and performed calibration of the ODE model to the real data observations for HPV-6, HPV-11 and HPV-6 and HPV-11 combined. We maintained the assumption that the duration of immunity is life-long for all individuals because we found that as immunity was chosen closer to permanent the calibration became consistently better. We measured this with

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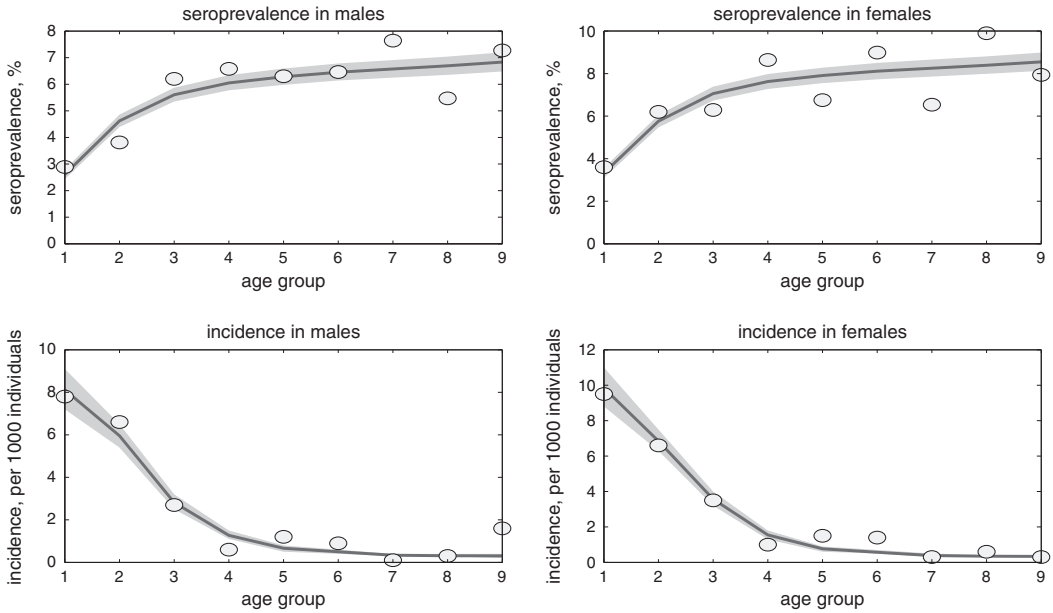

Figure 5. Calibration for synthetic case at time point $t = 120$ (combined HPV-6 and HPV-11): MMSE (solid line) and 95%CI (shaded area).

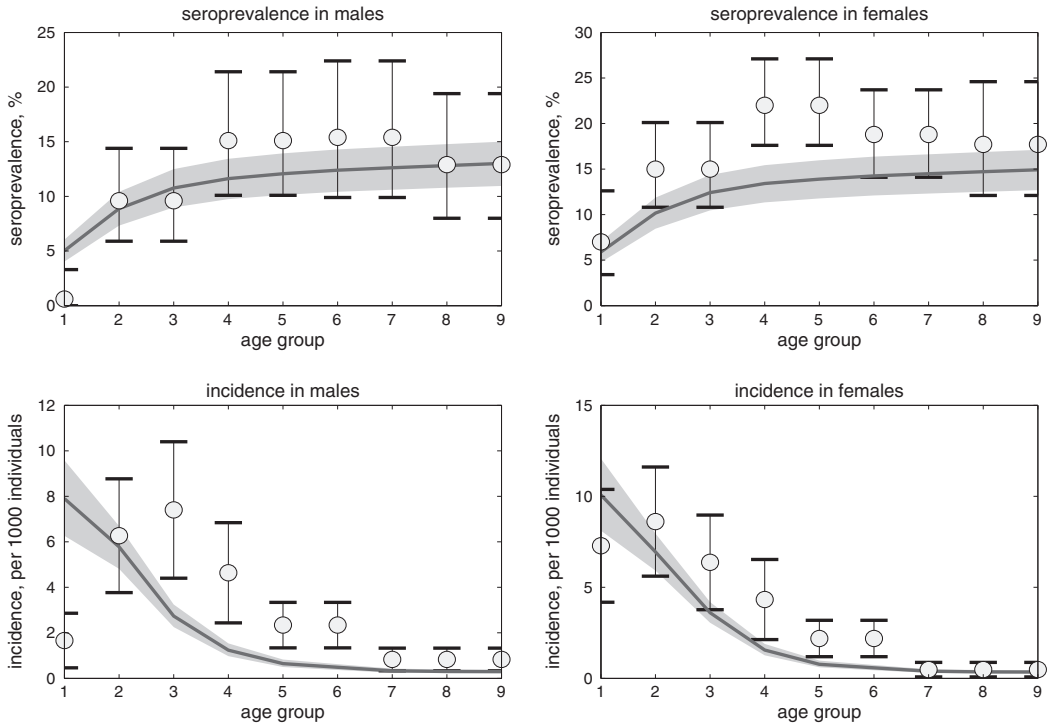

Figure 6. Calibration for HPV-6: MMSE (solid line) and 95%CI (shaded area). The circles and associated error bars denote the reported real data (mean values and 95%CI).

respect to the predictive performance of the posterior MMSE and associated posterior 95%CI obtained from the model for each age group and gender for seroprevalence and number of new genital warts diagnoses (incidence).

The first results we consider are for HPV-6 (Figure 6). The seroprevalence calibration is good for all age groups except the youngest men and women in age groups 4 and 5. At this point, it is appropriate to note that all data recordings and observations we obtained for the men in age group 1 can be questioned.

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We are inclined to think that the reported numbers do not represent the real-life situation as they suggest that both seroprevalence and incidence are much lower among men in this age group compared with the women of the same age. Considering the reported sexual partner acquisition rates (Table VI), which are the same for men and women in age group 1, there is no apparent reason to believe that this should be true, and the reported numbers may simply be due to young men being reluctant to seek medical assistance. Another possible explanation could be that men in age group 1 have sexual partners primarily of their own age who are not infected with HPV, whereas women from age group 1 have sexual partners from older age groups who are likely to be infected. As for the women aged 30–39 years, their high seroprevalence level was not captured by the model with the prior distributions specified as in Table III. Regarding incidence, we were able to obtain a reasonable fit for both women and men. The calibration for HPV-11 for seroprevalence was accurate (Figure 7) although not for the youngest men and women. A similar result was observed for the combined HPV-6 and HPV-11 data (Figure 8), with the calibration to genital warts incidence somewhat worse than to seroprevalence.

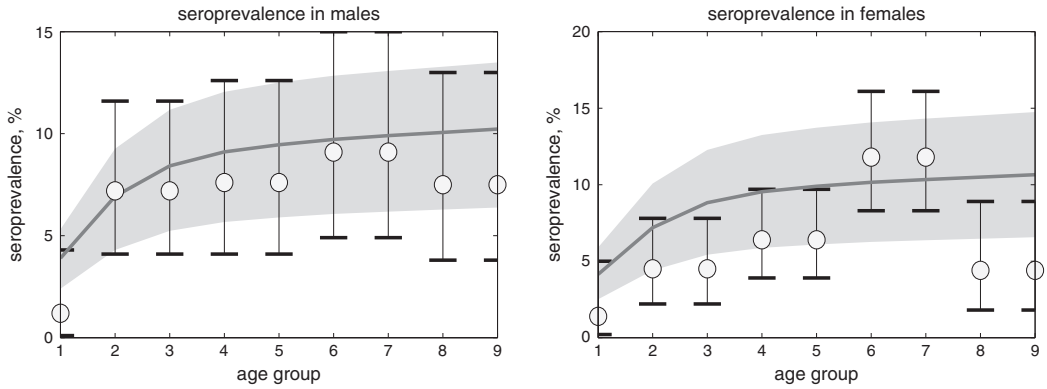

Figure 7. Calibration for HPV-11: MMSE (solid line) and 95%CI (shaded area). The circles and associated error bars denote the reported real data (mean values and 95%CI).

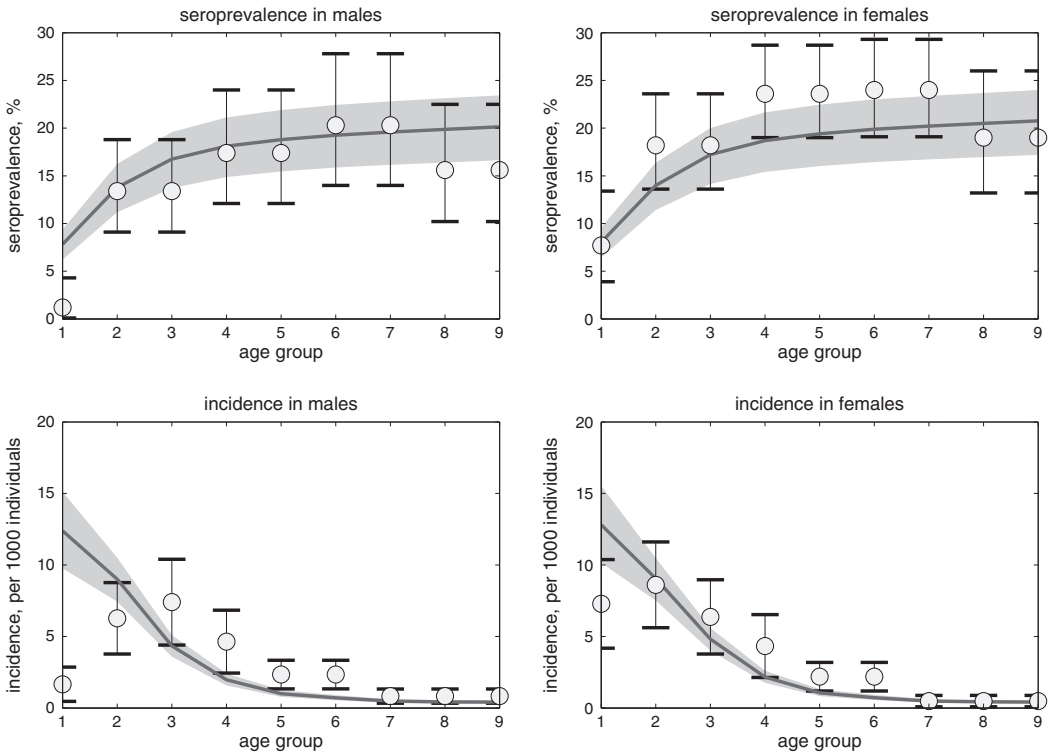

Figure 8. Calibration for combined HPV-6 and HPV-11: MMSE (solid line) and 95%CI (shaded area). The circles and associated error bars denote the reported real data (mean values and 95%CI).

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7. Impact of vaccination via the posterior predictive distribution

In this section, we demonstrate how to further develop the modelling framework provided for the calibration of the models developed for HPV-6 and HPV-11 to incorporate a statistical analysis of the impact of vaccination. Having undertaken a calibration via AdMCMC forward projection methodology presented in Section 4, we obtain an empirical estimation of the posterior distribution for the model parameters presented in Table I and the associated posterior estimates for the states at time T when the last observation was taken prior to a vaccination treatment. We can represent this information by the empirical estimation of the marginal posterior distribution

$$p(\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(T) | \boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T)),$$

using the N samples from the Markov chain generated by the AdMCMC forward projection algorithm. We can then utilise this empirical distribution to obtain the posterior predictive distribution, given by the resulting Monte Carlo approximation:

$$\begin{aligned}
&p(\boldsymbol{O}_{g,a,s}(T+1), \ldots, \boldsymbol{O}_{g,a,s}(T+\tau) | \boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T)) = \\
&\int p(\boldsymbol{O}_{g,a,s}(T+1), \ldots, \boldsymbol{O}_{g,a,s}(T+\tau) | \mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(T), \ldots, \boldsymbol{X}_{g,a,s}(T+\tau)) \\
&\quad \times p(\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(1), \ldots, \boldsymbol{X}_{g,a,s}(T) | \boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T)) \\
&\mathrm{d}\mathbf{TR}\, \mathrm{d}\mathbf{WIP}\, \mathrm{d}\mathbf{GWT}\, \mathrm{d}\mathbf{DAI}\, \mathrm{d}\mathbf{PSC}\, \mathrm{d}\mathbf{DI}\, \mathrm{d}\Sigma\, \mathrm{d}A_Y\, \mathrm{d}EPSa\, \mathrm{d}EPSr = \\
&\frac{1}{J} \sum_{j=1}^{J} p(\boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T) | \{\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(1), \ldots, \boldsymbol{X}_{g,a,s}(T)\}^j).
\end{aligned} \tag{18}$$

Here we obtain the quantities

$$p(\boldsymbol{O}_{g,a,s}(1), \ldots, \boldsymbol{O}_{g,a,s}(T) | \{\mathbf{TR}, \mathbf{WIP}, \mathbf{GWT}, \mathbf{DAI}, \mathbf{PSC}, \mathbf{DI}, \Sigma, A_Y, EPSa, EPSr, \boldsymbol{X}_{g,a,s}(1), \ldots, \boldsymbol{X}_{g,a,s}(T)\}^j)$$

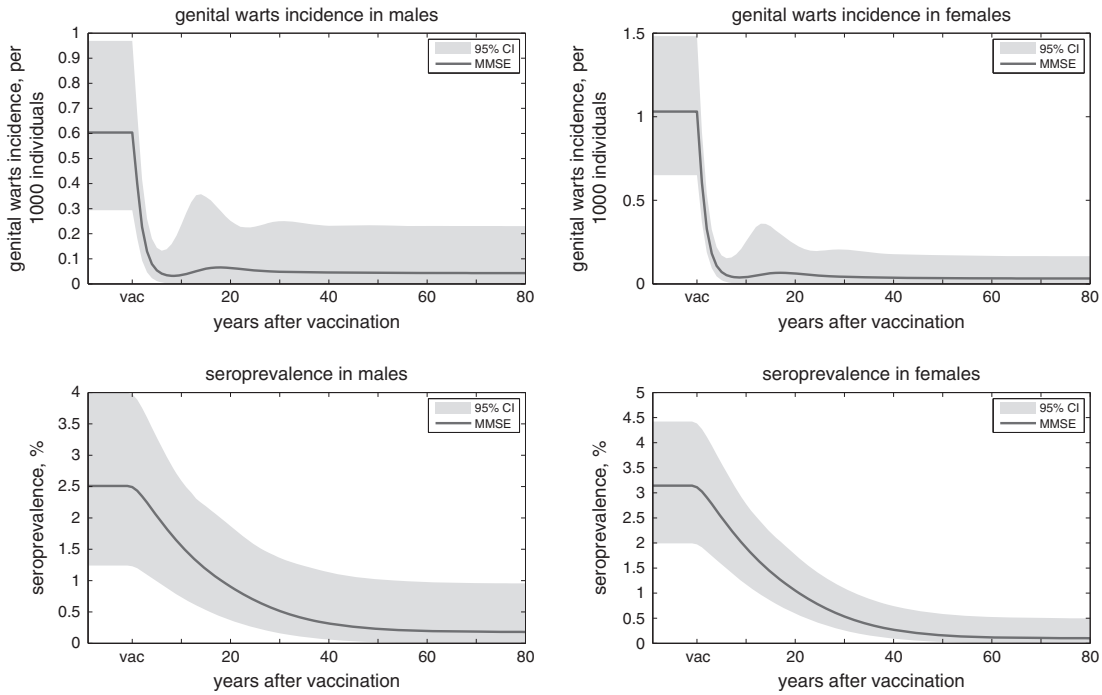

Figure 9. Posterior predictive distribution for vaccine response: MMSE (solid line) and 95%CI (shaded area).

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using the samples from the AdMCMC forward projection calibration then use them to forward project the ODE solver to obtain estimates of $\boldsymbol{O}_{g,a,s}(T+1), \ldots, \boldsymbol{O}_{g,a,s}(T+\tau)$, conditional on sampled parameters and states at time T.

We present the results of this analysis in Figure 9. Here we present the posterior predictive distribution and predictive 95% posterior CI for the incidence of HPV-6 and HPV-11 combined in the population after a vaccination. The vaccination scheme, commenced at the time $T + 10$, assumes that 80% of all 15 to 19-year-old women previously not vaccinated (age group 1) receive a single dose of vaccine each year. The effect of the vaccine is exclusively in reducing the force of infection on a vaccinated individual by 90% compared with that on an individual belonging to the same age and sexual-activity group who has not been vaccinated.

The results presented in this section have demonstrated how to incorporate the information that was obtained from the posterior calibration of the HPV-6 and HPV-11 models to observed data, to predict the vaccine response post calibration to a given equilibrium in the epidemic model within the population. They demonstrate the resultant new equilibrium level for incidence of HPV that would arise post-vaccination and the time taken to reach a new equilibrium level post-vaccination.

8. Conclusion

In this paper, we developed a novel combination of a compartmental HPV-6 or HPV-11 ODE transmission model and a Bayesian statistical modelling framework. We investigated the possibility of calibrating the model to available seropositivity [31] and genital warts incidence [30] data. We then demonstrated how to perform posterior predictive inference related to impact of vaccination on the modelled population.

The estimation of the ODE model was achieved via AdMCMC-based sampling methodology based around adaptive Metropolis coupled with a forward projection ODE solver to perform the joint challenge of sampling the static model parameters together with the estimated latent ODE states from transience to equilibrium. This was required in order to perform the evaluation of the rejection stage of the MCMC algorithm.

In each case, our aim was to ensure that the models developed were both parsimonious, with respect to the number of parameters utilised to parameterise the ODEs describing the evolution of the disease epidemic for HPV-6 and HPV-11, and sufficiently flexible to statistically calibrate the ODE compartmental model to the observed number of new genital warts diagnoses and seroprevalence per age group.

In addition, we maintain that the introduction of the approach we develop for modelling seropositivity and its interpretation in the context of the poorly understood implications of seroconversion are in line with now widespread views relating to HPV epidemic modelling. In particular, we assumed that only a person who recovered from either an asymptomatic HPV infection or genital warts, and is not susceptible, can be seropositive.

An attempt to calibrate to the seroprevalence data was of interest because there were no such data available for Australia until they were presented in [31]. Additionally, we were not aware of any published models calibrated to both seroprevalence and genital warts incidence data. Taking into account that all the data are necessarily prone to various errors, we considered a calibration process successful if the simulated observation values were found within the reported 95%CI for the real data.

We have demonstrated that a reasonable calibration for the ODE epidemic model under consideration could be achieved only if some of the model parameters were allowed to take values beyond the ranges specified for them using currently available literature. We believe that this may be due to one or any combination of the following reasons: an insufficient level of HPV natural history detail incorporated in the model; poor quality of the available data; and the uncertainty in interpretation of these data in the context of compartmental ODE models. Also, we have found that we can observe a notably better calibration if we modify the assumptions we made about seropositivity in favour of a somewhat controversial notion that the seropositive status should persist regardless of an individual's disease state and if we consider relatively short (up to 10 years) durations of immunity for both men and women. However, in this case the ODE system we had to deal with appeared to be stiff, and the solver we used was significantly slower to complete solutions. An improvement to the quality of calibration can also be ensured by the introduction of different durations of immunity for different age groups. One concern with this extension to the model is the parsimony of the model because the introduction of separate durations of immunity for all age groups involves the necessity to deal with at least nine new parameters with non-informative prior distributions (or 18 new parameters if we want to improve the calibration further

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and assume different durations of immunity for men and women). Not only would one question, in such settings, the ability to accurately estimate such parameters in practice because of the observational data properties and the amount of observation data, but there would also be important statistical questions to be addressed relating to over parameterisation of the model, over fitting of the model and parsimony. Because the intention of this work was to utilise parsimonious and interpretable models, we feel that the model assumptions introduced were warranted to illustrate the properties of our estimation methodology. In addition, the extension of this methodology to working with additional parameterisations is trivial and easily incorporated into our estimation framework. Therefore, we decided, on the basis of the observed data under analysis, that it was prudent to maintain the parsimonious model representation developed.

On the other hand, we would like to emphasise that our proposed estimation methodology based around AdMCMC forward projection is automated and easily extended to facilitate any number of additional model parameters. This is in contrast to other approaches already proposed in the literature that may suffer from the curse of dimensionality under such parameter extensions. For example, had we utilised a basic Metropolis–Hastings sampler with a non-adaptive proposal mechanism and not the adaptive Metropolis methodology we developed for this solution, then the tuning of the resulting transition kernel would be affected by such changes and would have to be performed again under each such model change. This would entail a significant computational burden in performing the model calibration under each change. In addition, it may result in a serious practical hurdle to overcome in re-design of the proposal mechanism in the Metropolis–Hasting sampler in order to facilitate efficient mixing in such high-dimensional sampling frameworks.

We also note that our method is favourable relative to other approaches that are not Markov chain based solutions. For example, Latin hypercube sampling solutions that calibrate epidemic ODE models using grids over regions of the parameter space will suffer when the parameter space is significantly increased; see examples in HIV epidemic models such as [71]. We note that under such approaches, an increase in the parameter space by an additional m dimensions to represent the new model parameterisation would require a grid to be placed over an additional m dimensional space; such significant increases in dimension may cause such approaches to fail because of the super-linear (exponential) increase in volume associated with adding the extra m dimensions to the parameter space. For each such grid point, such techniques would then require a complete iteration of the ODE solver to stationarity, incurring significant additional computational cost for such model changes, even when sparse grid-based techniques are used. Often this cost results in little benefit as regions of the parameter space of little significance to the most likely calibration points must be explored. This is in contrast to our AdMCMC-based procedure, which focuses computational effort on regions of the parameter space proportional with how probable, with respect to the posterior support, they are to contribute to suitable calibrations of the ODE epidemic model.

The AdMCMC forward projection methodology developed is flexible in any dimension and under any model change, learning on-line the appropriate parameter subspaces to focus computational effort as dictated by a statistically consistent combination of both prior belief on rates of population movement between states and observed evidence. Therefore, we are able to clearly quantify the probability weighted distribution of plausible calibration regions in the high-dimensional parameter space using the samples we obtained from the posterior constructed. This is in contrast to previous literature that tries to get such information heuristically from procedures such as sensitivity analysis of the ODE structure to different parameter regions, again incurring significant computational effort. Furthermore, at best such approaches can only produce what is termed the 'variability or the prediction imprecision' in the outcome variables that is due to the uncertainty in estimating the input values. It is important to note that such quantifications are not statistically based measures of prediction uncertainty, whereas the predictive performance we developed under our Bayesian framework can be directly interpreted as the predictive distribution of the model, again providing advantages of our proposed Bayesian estimation approach in interpretation of the results.

Appendix A. Sexual mixing matrix

This appendix provides details on the mathematical specification of the sexual mixing matrix and the parameterisation of the stochastic matrix that we develop. Sexual mixing matrices are widely used in modelling of sexually transmitted diseases, and their main purpose is to describe how certain characteristics of an individual define his or her sexual activity (i.e. the rate of sexual partner change). These characteristics typically are the age and/or sexual-activity group an individual belongs to.

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To construct a sexual mixing matrix, we generally need to perform the following:

1. Derive relative sexual partner change rates from sexual behaviour data; these rates have to be stratified by age groups and sexual-activity groups. Note that in our paper we skipped this step and reused the rates presented in [16].
2. Specify probabilities of sexual partnerships between individuals from different age groups and sexual-activity groups on the basis of assumed degrees of assortativity (see subsequent text for details). The degrees of assortativity are typically estimated from sexual behaviour survey data. However, these estimations are always very rough and speculative as the surveys are limited in their ability to quantify personal preferences in the choice of sexual partners by respondents.
3. Adjust the probabilities according to age-specific features of sexual mixing. For example, this can be an increase in probabilities that young women have much older male partners.
4. To ensure that these adjustments do not cause discrepancies in the rates of partner change between groups (i.e. to ensure that the adjusted rate at which women from some group change male partners from another group is the same as the rate at which these men change partners from the mentioned group of women), re-scale the original partner change rates. These should form a sexual mixing matrix.

Notations and available data. From now on, we will denote a gender by g, the gender opposite to g by g', a sexual-activity (risk) group by s or s', and an age group by a or a'. Also, when referring to an individual of gender g who belongs to a sexual-activity group s and age group a, we will simply say 'an individual from g, s, a' for brevity.

In the equations describing our model, we have a force of infection term for every individual from g, s, a. This term is effectively a yearly rate at which an individual becomes infected, and it is defined as

$$\lambda_{g,s,a} = \beta_g \sum_{s',a'} \left\{ c^*_{g,s,s',a,a'} \frac{I_{g',s',a'}}{S_{g',s',a'} + I_{g',s',a'} + G_{g',s',a'} + P_{g',s',a'} + N_{g',s',a'}} \right\}, \tag{A.1}$$

where β_g is the transmission probability per partnership, that is, the probability that a susceptible person of gender g will get infected from his or her infectious partner of gender g'; $c^*_{g,s,s',a,a'}$ is the mean per capita rate per year at which an individual from g, s, a acquires new sexual partners from g', s', a', and $I_{g',s',a'} / \left(S_{g',s',a'} + I_{g',s',a'} + G_{g',s',a'} + P_{g',s',a'} + N_{g',s',a'}\right)$ is the probability that a new sexual partner from g, s, a is infected, defined as a proportion of infected individuals in g, s, a.

Now we will start constructing a sexual mixing matrix for our model according to the approach by Garnett and Anderson [57] and its version used in [14]. In the process of construction, we should use the relevant data estimated from the results of ASHR. ASHR was a telephone survey of a random sample of about 20 000 people who were Australian residents aged from 16 to 59 years. Despite its limitations (see [50] and [16] for discussion), this survey provided important information on the sexual behaviour of Australians, and its results are currently the most representative ones available. The data we need (as suggested in [57, 72] or [55]) are the following:

- Relative sexual partner acquisition rates r_a for each age group a (the same for men and women; Table VI).
- Relative sexual partner acquisition rates r_s for each sexual-activity (risk) group s (the same for men and women; Table A.1).
- Overall sexual partner acquisition rate $\bar{c}$ for the whole population (both men and women):

$$\bar{c} = 0.437.$$

All these rates are per capita per year. If for all g, s, a we knew the rates at which an individual from g, s, a acquires new sexual partners from the entire pool of individuals of gender g' (denote them $c_{g,s,a}$),

Table A.1. Relative new sexual partner acquisition rates by sexual-activity group.

Sexual-activity group	1	2	3	4
Population in each group (%)	60	27	11	2
Rate (r_s)	1.00	4.76	24.83	105.67

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we could find the lowest of these rates,

$$c_{\min}: \ \forall g,s,a \quad c_{\min} \leqslant c_{g,s,a},$$

and divide by it all $c_{g,s,a}$ denoting the results of division by $r_{g,s,a}$:

$$r_{g,s,a} = \frac{c_{g,s,a}}{c_{\min}}. \tag{A.2}$$

These would be the relative sexual partner acquisition rates for g,s,a. We can specify them as follows

$$r_{g,s,a} = r_a \times r_s \quad \forall g,s,a. \tag{A.3}$$

We can now calculate $c_{\min}$. Note that $\bar{c}N_g$ is the number of partners of gender g' that all individuals of gender g acquire per year. This number must be equal to the total number of sexual partners of gender g' that individuals of gender g from each age and sex group acquire, so

$$\bar{c}N_g = \sum_{s,a} c_{g,s,a}N_{g,s,a} = c_{\min}r_{g,1,1}N_{g,1,1} + c_{\min}r_{g,1,2}N_{g,1,2} + \ldots = c_{\min}\sum_{s,a} r_{g,s,a}N_{g,s,a}.$$

Hence,

$$c_{\min} = \frac{\bar{c}N_g}{\sum_{s,a} r_{g,s,a}N_{g,s,a}}, \tag{A.4}$$

also, with $c_{\min}$ at hand we can easily calculate all $c_{g,s,a}$ (see (A.2)).

Proportionate and assortative mixing. Now we would like to specify $\rho_{g,s,s',a,a'}$, which are the conditional probabilities that an individual of gender g from sexual-activity group s and age group a gets a sexual partner of the opposite gender g' from sexual-activity group s' and age group a'. There are three possibilities to consider:

1. So-called 'proportionate' sexual mixing by age group or sexual-activity group; this means that $\rho_{g,s,s',a,a'}$ may be assumed equal to the proportion of partnerships 'generated' by individuals of gender g' from age group a' (and/or sexual-activity group s):

$$\rho_{g,s,s',a,a'} = \frac{\sum_{s'} c_{g',s',a'}N_{g',s',a'}}{\sum_{s',a'} c_{g',s',a'}N_{g',s',a'}} \tag{A.5}$$

or

$$\rho_{g,s,s',a,a'} = \frac{\sum_{a'} c_{g',s',a'}N_{g',s',a'}}{\sum_{s',a'} c_{g',s',a'}N_{g',s',a'}}. \tag{A.6}$$

In other words, an underlying assumption here is that more active members of gender g' have higher chances to become a new sexual partner to someone of gender g. Note that in case of proportionate mixing by both age and sexual-activity group, we should simply define $\rho_{g,s,s',a,a'}$ and a product of the right-hand sides of (A.5) and (A.6).

2. 'Assortative' mixing (also known as 'with-like' mixing); again, this can be by age or sexual-activity group or both, and if it is, for example, by age group, we define

$$\rho_{g,s,s',a,a'} = \delta_{aa'}. \tag{A.7}$$

That is, the probability of establishing a partnership is 1 if a potential partner is of the same age and 0 otherwise.

3. 'Disassortative' mixing ('with-unlike') suggests that a partnership can be formed only with someone from a different age (or sexual-activity) group.

We would like to be able to adjust the sort of mixing in our model depending on our needs. Therefore, we specify the probabilities $\rho_{g,s,s',a,a'}$ as follows

$$\begin{aligned}\rho_{g,s,s',a,a'} = &\left((1-EPSa)\delta_{aa'} + EPSa\frac{\sum_{s'} c_{g',s',a'}N_{g',s',a'}}{\sum_{s',a'} c_{g',s',a'}N_{g',s',a'}}\right)\\ &\times\left((1-EPSr)\delta_{ss'} + EPSr\frac{\sum_{a'} c_{g',s',a'}N_{g',s',a'}}{\sum_{s',a'} c_{g',s',a'}N_{g',s',a'}}.\right)\end{aligned} \tag{A.8}$$

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Parameters *EPSa* and *EPSr* help us vary the extent of assortativeness by age and sexual-activity group: if $EPSa = 0$, mixing is fully assortative by age group; if $EPSa = 1$, it is fully proportionate by age group. In a similar fashion, we can vary *EPSr* and control assortativeness by sexual-activity group.

Age-related adjustments. Here we introduce some adjustments to emphasise the effect of a steady popularity of the partnerships between older men and younger women. Let for now g denote men and g' women. We reduce the probabilities that men in age group 3 and higher have female partners of the same age:

$$\rho_{g,s,s',a,a'} \to \rho_{g,s,s',a,a'}(1-\Gamma) \quad \text{if} \begin{cases} a = a' \\ a \geqslant 3 \end{cases} \tag{A.9}$$

Similarly, we reduce the probabilities that women in age groups 1 to 5 form a partnership with men of the same age:

$$\rho_{g',s,s',a,a'} \to \rho_{g',s,s',a,a'}(1-\Gamma) \quad \text{if} \begin{cases} a = a' \\ a \leqslant 5 \end{cases} \tag{A.10}$$

To compensate for the effect of these adjustments, we increase the probabilities for men to have a female partner one age group younger but belonging to the age groups not higher than 5,

$$\rho_{g,s,s',a,a'} \to \rho_{g,s,s',a,a'} + \Gamma\rho_{g,s,s',a,a} \quad \text{if} \begin{cases} a = a' + 2 \\ a' \leqslant 5 \end{cases} \tag{A.11}$$

and also we increase the probabilities that women have one age group older men from age group 3 or higher as a partner:

$$\rho_{g',s,s',a,a'} \to \rho_{g',s,s',a,a'} + \Gamma\rho_{g',s,s',a,a} \quad \text{if} \begin{cases} a = a' - 2 \\ a' \geqslant 3 \end{cases} \tag{A.12}$$

So far, we have used the rates $c_{g,s,a}$ that describe new sexual partner acquisitions by individuals from g, s, a from the whole population of gender g'. So to find out the rates of acquisition of new sexual partners from a certain age and sexual-activity group (a' and s'), we should multiply $c_{g,s,a}$ by $\rho_{g,s,s',a,a'}$. However, now we would like to make the rates $c_{g,s,a}$ group-specific in terms of the groups that the sexual partners are selected from. This will be achieved via balancing supply and demand of sexual partners.

Balancing supply and demand. We want the following to hold for all g, s, a and g', s', a':

$$c_{g,s,a}\rho_{g,s,s',a,a'}N_{g,s,a} = c_{g',s',a'}\rho_{g',s',s,a',a}N_{g',s',a'}. \tag{A.13}$$

Here $c_{g,s,a}\rho_{g,s,s',a,a'}$ is the rate of acquisition of new sexual partners by individuals who belong to g, s, a from g', s', a', and $c_{g,s,a}\rho_{g,s,s',a,a'}N_{g,s,a}$ is the total number of new partners acquired by g, s, a from g', s', a'. So the equation simply states that the total number of new partners acquired by g, s, a from g', s', a' must be equal to the total number of new partners acquired by g', s', a' from g, s, a.

Let

$$c_{g,s,a}\rho_{g,s,s',a,a'}N_{g,s,a} \neq c_{g',s',a'}\rho_{g',s',s,a',a}N_{g',s',a'}.$$

We want to find such a multiplier B that

$$B^{\theta_1}c_{g,s,a}\rho_{g,s,s',a,a'}N_{g,s,a} = B^{\theta_2}c_{g',s',a'}\rho_{g',s',s,a',a}N_{g',s',a'}.$$

Then

$$B^{\theta_1-\theta_2} = \frac{c_{g',s',a'}\rho_{g',s',s,a',a}N_{g',s',a'}}{c_{g,s,a}\rho_{g,s,s',a,a'}N_{g,s,a}}.$$

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To keep things simple, let $\theta_1 - \theta_2 = 1$. Note that B serves as a degree of imbalance: the balance is established if $B = 1$. So, to ensure that (A.13) is true, it is enough to introduce the group-specific rates $c^*_{g,s,s',a,a'}$ to be used instead of $c_{g,s,a}$:

$$c^*_{g,s,s',a,a'} = c_{g,s,a} B^{\theta_1}, \quad c^*_{g',s',s,a',a} = c_{g',s',a'} B^{\theta_1 - 1} \tag{A.14}$$

We limit the range of value of parameter θ_1 to $[0, 1]$. Suppose the supply and demand are not balanced and $\theta_1 = 0$. Then as follows from (A.14), $c_{g,s,s',a,a'} = c_{g,s,a}$ (the rates for gender g do not get adjusted), but $c_{g',s',s,a',a} = c_{g',s',a'} B^{-1}$ (the rates for gender g' are adjusted). If $\theta_1 = 1$, it is the other way around. Consequently, θ_1 indicates to what extent individuals of each gender adjusts their sexual partner acquisition rates (i.e. we may say, sexual behaviour) in case the available supply of sexual partners does not meet demand.

At this stage, our sexual mixing matrix is fully formed.

Appendix B. Sensitivity to the presence of sexual activity in individuals under 15 years old

In this appendix, we illustrate our findings regarding the sensitivity of our model calibration to possible sexual activity in individuals younger than 15 years old. We introduced an additional age group into our model, which includes 10–14 years old. It is unreasonable to assume that the population in this age group is completely sexually active, so we do not expect the relative new sexual partner change rate (PCR) in the group to be close to the yearly rate of 5.2755 assigned to the 15–19 year age group.

Here we present the calibration plots corresponding to the PCR in group 1 equal to 1, 2 and 3 (Figures B.1–B.3 correspondingly), where 1 is the base PCR (Table VI).

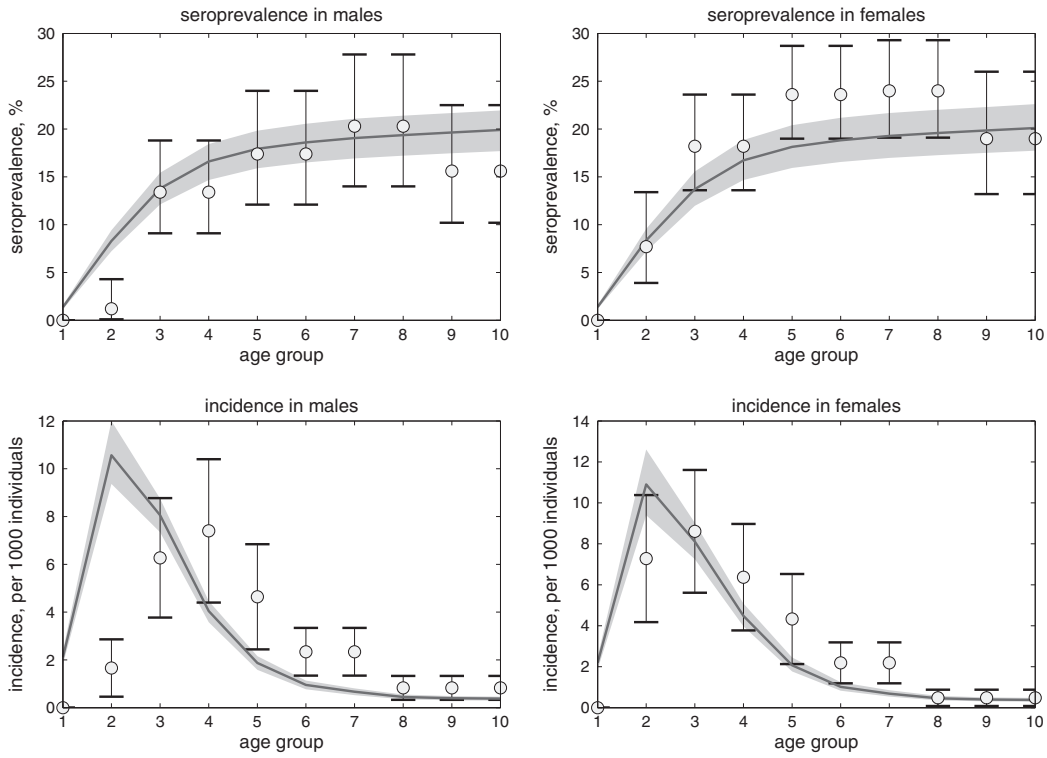

Figure B.1. Calibration plot with an additional 10–14 year-old age group (group 1); relative sexual activity in this group is 1.

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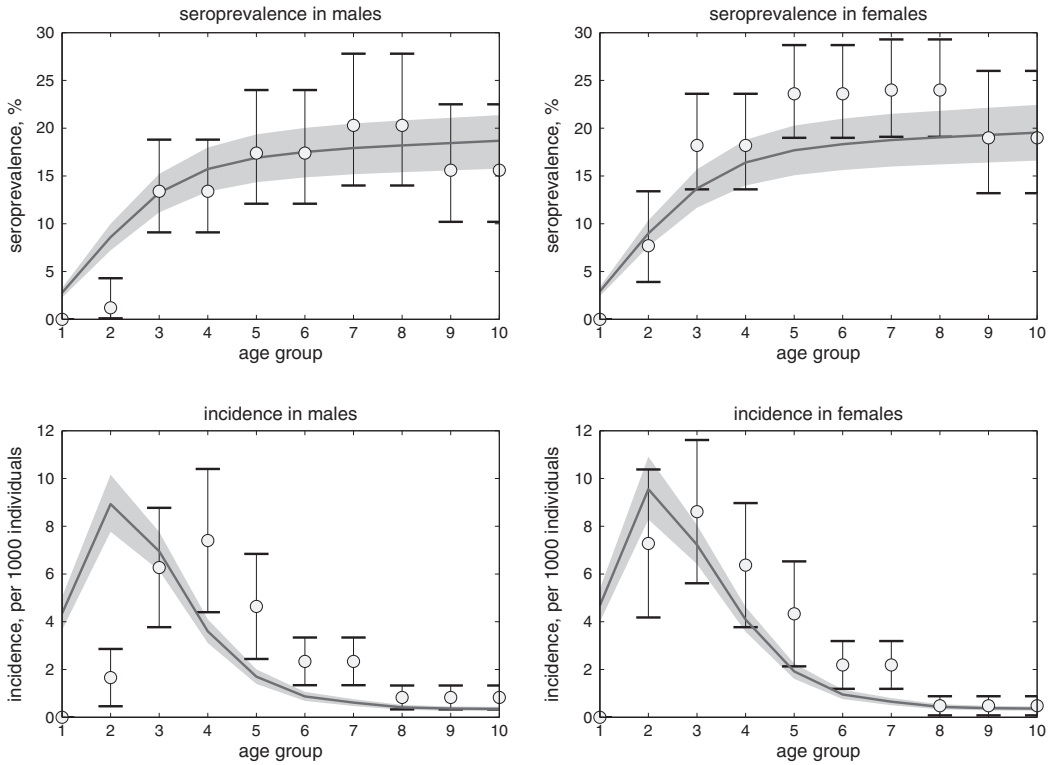

Figure B.2. Calibration plot with an additional 10–14 year-old age group (group 1); relative sexual activity in this group is 2.

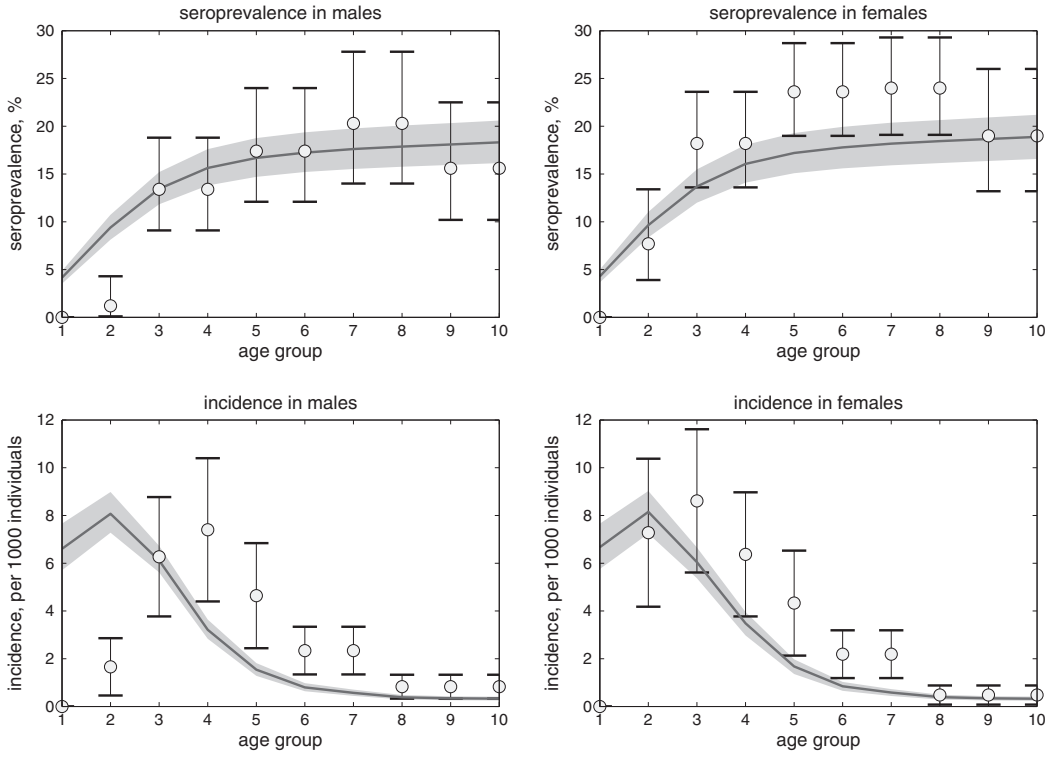

Figure B.3. Calibration plot with an additional 10–14 year-old age group (group 1); relative sexual activity in this group is 3.

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We observe that the higher the PCR in group 1, the higher are both incidence and seroprevalence in this group. Also, the higher is the proportion of individuals from age group 2 (15–19 years old) who form partnerships with individuals from age group 1 instead of individuals from age group 3 (which is considerably more active than age group 1). Indeed, we should recall that the overall PRCs are pre-specified for each age group other than 1, so any partnerships with the new age group 1 are established only at the price of reduced number of relationships with age group 3. Therefore, we see a decline in incidence in age group 2. Similarly, there is a decline in incidence in age group 3, members of which now form more partnerships with age group 5, less active than age group 2. This effect spreads to the rest of the groups, although it becomes very weak in the groups with low PCRs. Overall, the corresponding changes in seroprevalence are hardly noticeable.

Therefore, we conclude that, allowing for some nonzero level of sexual activity in the under-15 population, we would see the age-specific genital warts incidence reduced, particularly in the most sexually active age groups.

Appendix C. Sensitivity to the durations of natural immunity

This appendix studies the sensitivity to the assumption that the durations of natural immunity for men and women are life-long. We demonstrate that a reasonable choice was made for this assumption with regard to behaviour of the model.

To assess the effect of varying durations of immunity on calibration, we performed simulations for the durations of immunity ranging from 10 to 45 years. For the particular prior distributions on the durations, we first assumed that they are 10–15 years, then 15–20 years, and so on.

It is clear from Figures C.1–C.3 that as immunity lasts longer, individuals remain in state RSP (the only state containing seropositive individuals) longer; hence, we observe higher seroprevalence. At the same time, these individuals contribute less to the infected state, so we see that genital warts incidence decreases.

Note that if the durations of immunity are very long, let us say 40–45 years (Figure C.3), the level of seropositivity produced by the model is closer to the real-life reported level than under any other

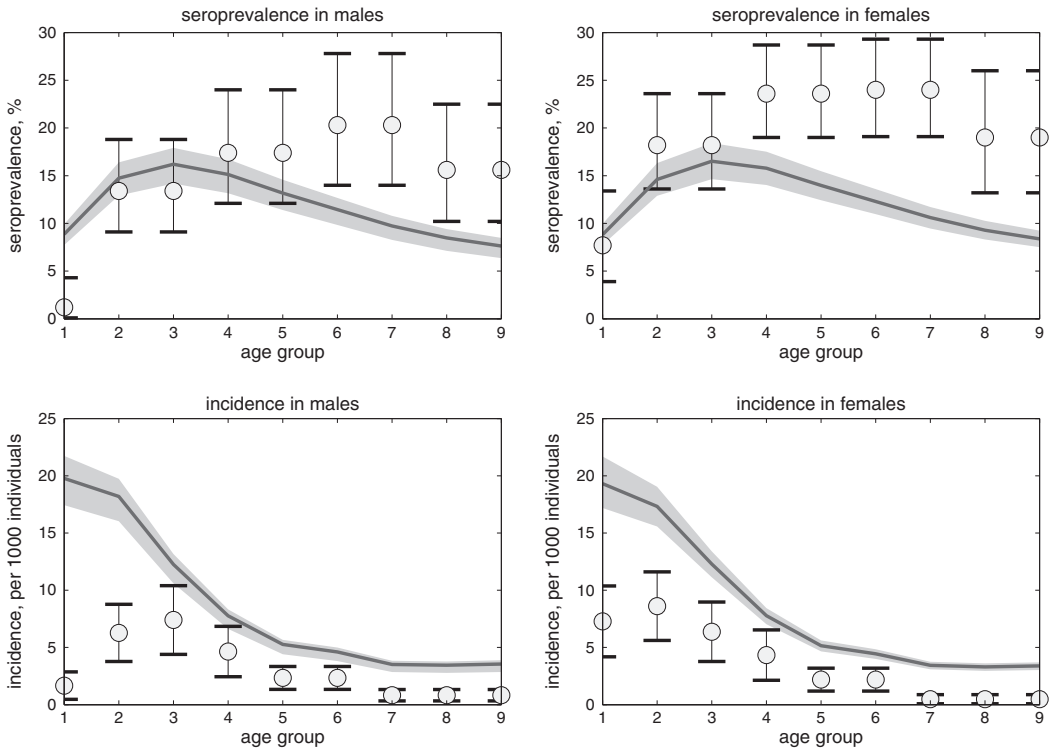

Figure C.1. Calibration plot if the durations of natural immunity for both men and women are 10–15 years.

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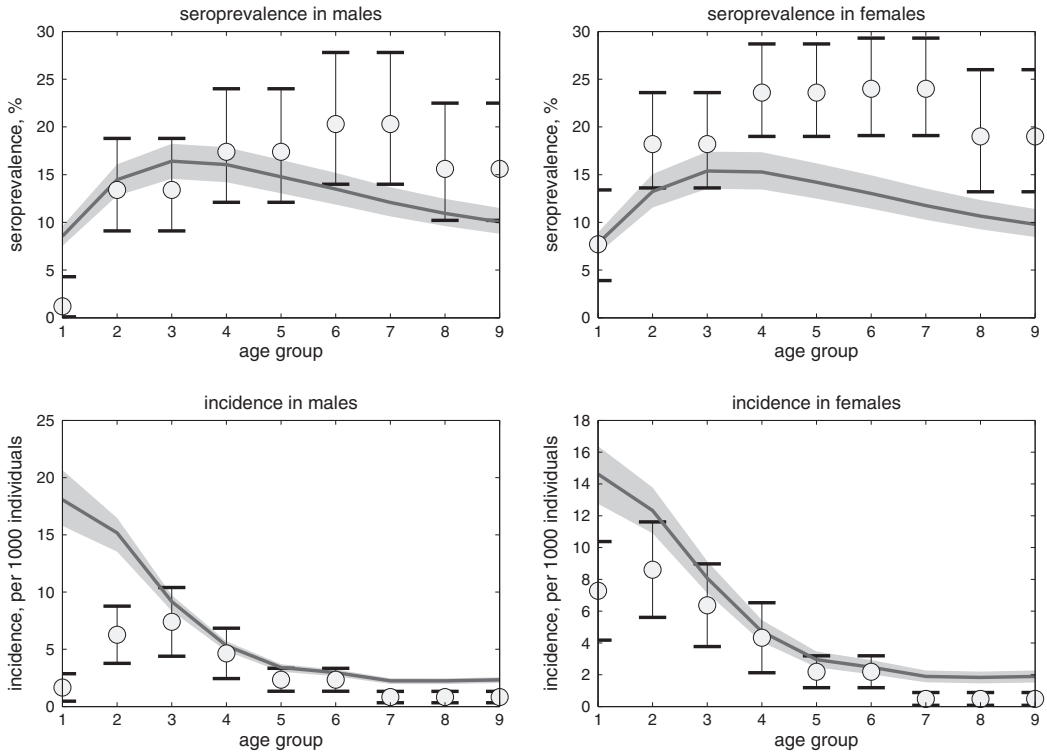

Figure C.2. Calibration plot if the durations of natural immunity for both men and women are 20–25 years.

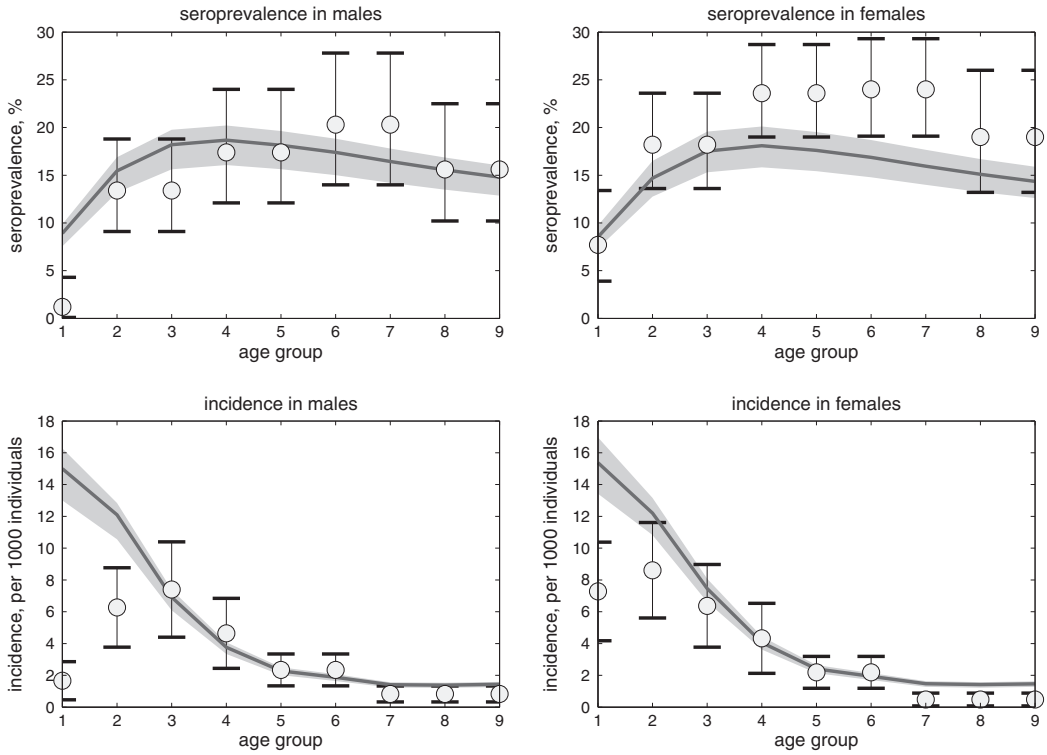

Figure C.3. Calibration plot if the durations of natural immunity for both men and women are 40–45 years.

assumed durations of immunity (Figures C.1 and C.2). Also, genital warts incidence is clearly closer to the reported values.

Therefore, our model favours long durations of immunity, and we simply set them to as long as possible to reduce the number of parameters in the model.

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Appendix D. Sensitivity to demographic changes

This appendix studies the sensitivity to the simplified population structure utilised in our model. In particular, we made it more realistic by incorporating the birth and death data for Australia published by Australian Bureau of Statistics (http://www.abs.gov.au). We assumed that age-specific death rates for men and women are constant and equal to the reported rates for 2010. This is acceptable because they did not change significantly between 2005 and 2010 (Table D.1). We also assumed a constant birth rate at 12 births per population of 1000. There was no apparent need to analyse the case when the number of men in the population is significantly different from the number of women because the official data say that the difference is not notable.

As we can see from Figures D.1 and D.2, the effect of the added complexity of population structure is clearly minor and mainly visible in the youngest age group. Considering that the observational data we deal with are particularly ambiguous for age group 1, we felt that the simplified population structure would be appropriate.

Table D.1. Australian death rates for 2005–2010, per 1000 individuals.

Age group	Male population						Female population					
(years)	2005	2006	2007	2008	2009	2010	2005	2006	2007	2008	2009	2010
15–19	0.5	0.5	0.5	0.5	0.5	0.5	0.2	0.3	0.2	0.2	0.2	0.2
20–24	0.8	0.8	0.7	0.7	0.6	0.6	0.3	0.3	0.3	0.3	0.3	0.3
25–29	0.9	0.8	0.9	0.8	0.8	0.7	0.3	0.3	0.3	0.3	0.3	0.3
30–34	1.1	1.0	1.0	1.0	1.0	0.9	0.4	0.4	0.5	0.4	0.4	0.4
35–39	1.2	1.2	1.2	1.2	1.2	1.2	0.6	0.6	0.6	0.6	0.6	0.6
40–44	1.7	1.6	1.5	1.6	1.7	1.6	1.0	0.9	1.0	0.9	0.9	0.9
45–49	2.4	2.4	2.4	2.4	2.3	2.4	1.4	1.5	1.4	1.4	1.5	1.4
50–54	3.5	3.4	3.5	3.6	3.5	3.4	2.1	2.1	2.2	2.1	2.2	2.1
55–59	5.4	5.3	5.4	5.2	5.2	5.2	3.2	3.2	3.2	3.2	3.2	3.1

Taken from the data published on-line by Australian Bureau of Statistics, www.abs.gov.au.

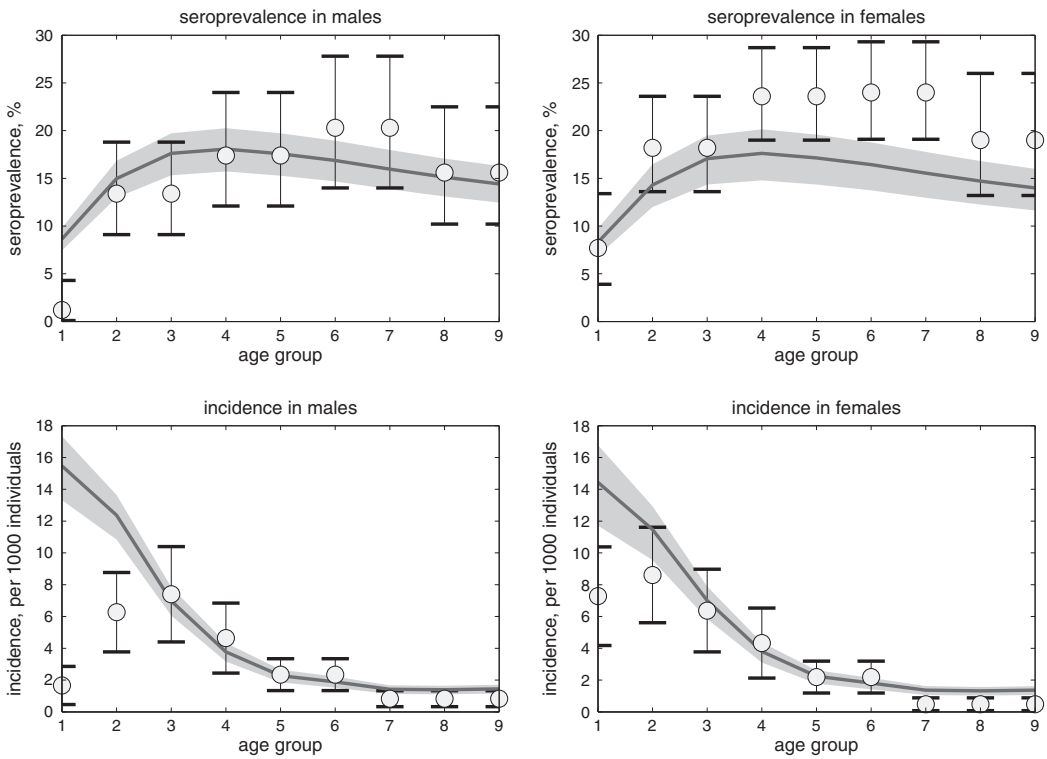

Figure D.1. Calibration plot corresponding to the simplified population structure implemented in our model.

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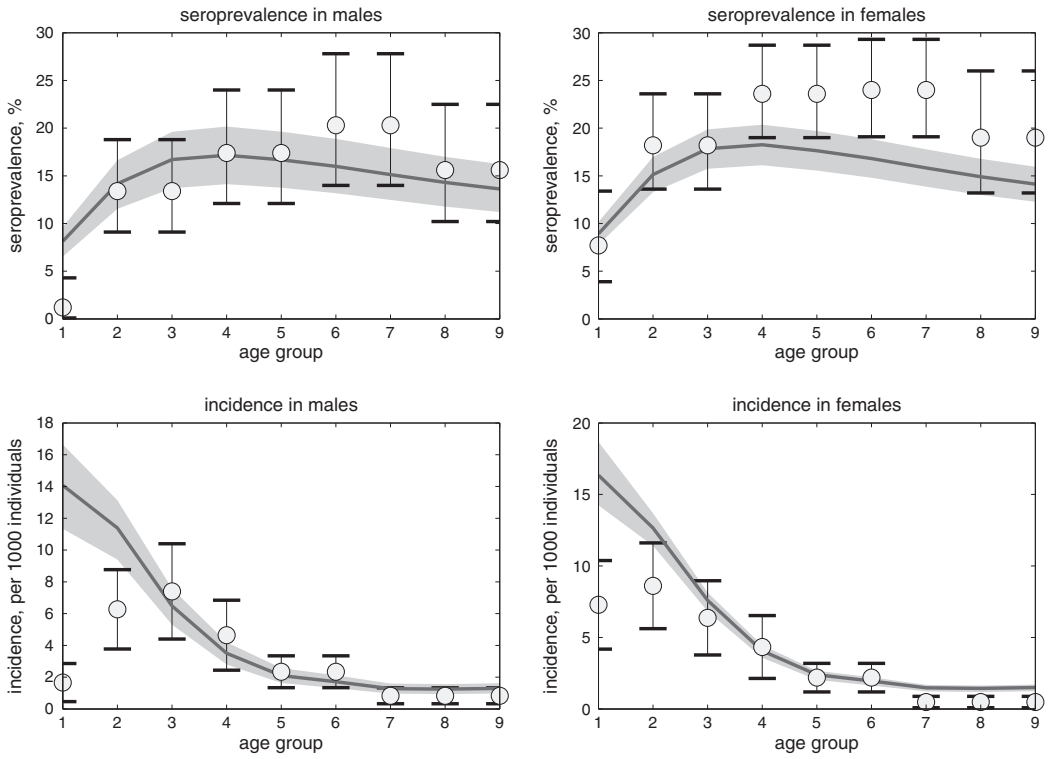

Figure D.2. Calibration plot corresponding to the case when the simplified population structure implemented in our model is extended via incorporation of age-specific Australian death rates based on the figures reported by the Australian Bureau of Statistics for 2005–2010 and national birth rate estimated for the same period. Data detailed in Table D.1.

Appendix E. Prior distributions

In this appendix, the prior specifications are developed for Case 1 (that is, on the basis of the data available in the literature; Table II).

Transmission term (TR)

This parameter is often understood as the probability of transmission of HPV infection per sexual partnership of a susceptible man with an infected woman or vice versa. There is currently no conclusive evidence to narrow down the range of possible values of this parameter to anything noticeably different from $[0, 1]$. Therefore, we chose uniform prior distributions for both TRm and TRf: $TRm \sim U(0, 1)$, $TRf \sim U(0, 1)$.

Genital warts incubation period (WIP)

We chose a gamma distribution to be used as prior on this parameter, that is, for men we have $WIPm \sim \Gamma(\alpha_m, \beta_m)$ and for women $WIPf \sim \Gamma(\alpha_f, \beta_f)$. As the most frequent incubation period observed during the studies we use the data from was not within the first month, we set the shape parameters α_m and α_f in such a fashion that the mode of the prior is not the origin, simply by $\alpha_m = \alpha_f = 2$. The remaining scale parameter is then utilised to adjust the prior to the study results reporting median durations of incubation period as detailed next.

To specify the prior distribution for the genital warts incubation period for men ($WIPm$), we used the results of a cohort study of 18–21 year-old male students attending the University of Washington [66]. Eighteen out of 418 men had incident HPV-6 infection and developed warts during the duration of the study (the mean follow-up time was 24.6 months). Among these men, the median time between incident infection and detection of genital warts was reported to be 11 months (IQR: 0–16.1 months).

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We re-calculate these durations in years by dividing them by 12 months, which produced a median of 0.916 (IQR: 0–1.341) years.

The quantile function CDF^{-1} (also known as inverse cumulative distribution function) of the gamma distribution has no closed form. However, according to the method of medians, we can find β_m solving numerically the following equation: $0.916 = CDF^{-1}(0.5; \alpha_m = 2, \beta_m)$. This gives us $\beta_m = 0.546$.

The duration of genital warts incubation period in women (*WIPf*) was provided by a study of 18–20 year-old female students of University of Washington [67]. Twenty-eight out of 41 women with incident HPV-6 infection (no HPV-11 infection) developed warts. The median incubation period was 2.9 months (IQR: 0–5.7 months). In years, this is 0.241 (IQR: 0–0.475) years. As in the preceding, according to the method of medians, this would involve solving numerically the equation $0.241 = CDF^{-1}(0.5; \alpha_f = 2, \beta_f)$ for β_m. Hence, we obtain $\beta_f = 0.144$.

Duration of treatment for genital warts (DWT)

To specify a prior distribution for this parameter, we used the data from a study [68] based on analysis of private insurance claims associated with genital warts in the USA (total 3 664 686 claims sampled, 5095 cases of genital warts identified). The mean 'duration of episode' for men was reported to be 102.6 days (95%CI: 77.8–127.4), with 237 men considered, or in years (if we divide these numbers by 365 days) this is 0.281 (95%CI: 0.213–0.349).

We assume that *DWT* for men, $DWTm \sim \Gamma(k_m, \theta_m)$. To specify the shape parameter k_m and scale parameter θ_m, we again note that the mode of the distribution would not be located at the origin, and so we set the shape parameter $k_m = 2$ and solve for the scale parameters by matching $\theta_m = 0.14$.

The same study [68] reports the mean duration of treatment for women 84.8 days (95%CI: 67.5–102.1), with 299 women considered. In years, the mean is 0.232 (95%CI: 0.185–0.28). We again assume that $DWTf \sim \Gamma(k_f, \theta_f)$ and perform the same procedure to get $k_f = 2$ and $\theta_f = 0.12$.

Duration of asymptomatic human papillomavirus infection (DAI)

We assign a Gamma distribution to this parameter: $DAIm \sim \Gamma(a_m, b_m)$ and $DAIf \sim \Gamma(a_f, b_f)$. As for the previous parameter, we set the shape parameters a_m and a_f in such a fashion that the mode of the prior is not the origin, simply by $a_m = a_f = 2$. The remaining scale parameter is then utilised to adjust the prior to previous study results reporting the median as detailed next, where we apply the method of medians.

A study of the natural history of HPV infections among men aged 18–44 years was conducted in Tucson, Arizona [49]. In total, 290 men were under observation. The findings showed that the median value of *DAI* for men (*DAIm*) for HPV-6 or HPV-11 was equal to 5.4 months (95%CI: 5.1–5.7 months). In years, this is 0.45 (95%CI: 0.425–0.475).

In the same manner as described for *WIP*, we specify $b_m = 0.268$ as the solution to $0.45 = CDF^{-1}(0.5; a_m = 2, b_m)$.

To specify *DAI* for women (*DAIf*), we used the results of a study conducted in São Paulo, Brazil [51]. The recruited 2462 women, 18–60 years old, who attended a maternal and child health programme in a low-income neighbourhood between 1993 and 1997 were followed for up to 10 years. It was found that the median duration of asymptomatic HPV-6 or HPV-11 infection was 6.0 months (95%CI: 5.7–6.9), which in years is 0.5 (95%CI: 0.425–0.575). The mean duration was 9.5 months (95%CI: 6.9–12.1) or 0.7916 (95%CI: 0.575–1.0) years. Similarly to the way we calculated b_m, $b_f = 0.472$ is obtained as the solution to $0.7916 = CDF^{-1}(0.5; a_f = 2, b_f)$.

Duration of natural immunity (DI)

Almost nothing is known about duration of natural immunity. We investigated a wide range of possible values for this parameter assuming that it is distributed uniformly (see the sensitivity analysis in Appendix C).

Probability of becoming seropositive (PSC)

We decided to assign a prior distribution $Beta(2, 2)$ to this parameter as it denotes a probability.

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