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ORIGINAL ARTICLE

Dynamic Modeling of Herpes Simplex Virus Type-2 (HSV-2) Transmission: Issues in Structural Uncertainty

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Abstract The sexually transmitted infection (STI) Herpes simplex virus type-2 (HSV-2) is of public health concern because it is a very common frequently unrecognized lifelong infection, which may facilitate HIV transmission. Within HIV/STI modeling, structural uncertainty has received less attention than parametric uncertainty. By merging the compartments of a "complex" model, a "simple" HSV-2 model is developed. Sexual interactions between female sex workers (FSWs) and clients are modeled using data from India. Latin Hypercube Sampling selects from parameter distributions and both models are run for each of the 10,000 parameter sets generated. Outputs are compared (except for 2,450 unrealistic simulations). The simple model is a good approximation to the complex model once the HSV-2 epidemic has reached 60% of the equilibrium prevalence (95% of the 7,550 runs produced $<10\%$ relative error). The simple model is a reduced version of the complex model that retains details implicitly. For late-stage epidemics, the simple model gives similar prevalence trends to the complex model. As HSV-2 epidemics in many populations are advanced, the simple model is accurate in most instances, although the complex model may be preferable for early epidemics. The analysis highlights the issue of structural uncertainty and the value of reducing complexity.

Keywords Mathematical modeling · Dynamic model · Model structural uncertainty · Model reduction · Herpes simplex virus type-2

1. Introduction

The sexually transmitted infection (STI) Herpes simplex virus type-2 (HSV-2) is of public health concern because it is a very common frequently unrecognized lifelong infection (Corey et al., 1983a; Corey and Handsfield, 2000), which may facilitate HIV transmission (Celum, 2004; Corey et al., 2004a; Delany et al., 2007; Freeman et al., 2006b; Nagot et al., 2007; Wald and Link, 2002; Zuckerman et al., 2007).

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As in other areas of modeling, difficulties can arise when modeling HSV-2 due to the range of uncertainties involved and these may propagate through a modeling analysis. The broader modeling literature from the medical/biological sciences highlights that there are different sources of uncertainty that may propagate through a modeling analysis (Critchfield and Willard, 1986; Doubilet et al., 1985; Isukapalli et al., 1998, 2000; Manning et al., 1996): (i) inherent or natural uncertainty (due to inevitable variability or unpredictability); (ii) structural uncertainty (due to approximations and simplifications in model formulation); and (iii) parametric uncertainty (due to discrepancies over input parameters because of the lack of accurate data). For example, in dynamic models, the structural uncertainty could be linked to the dimension of the system (i.e., the number of differential equations or state variables) or to whether the equations are linear or nonlinear. Once a particular model structure is assumed, then parametric uncertainty is concerned with the uncertainty in the coefficients of the equations.

In practice, it is difficult to separate out structural and parametric uncertainty: a structurally simple model usually requires fewer inputs and so may have less parametric uncertainty, or may instead be an oversimplified system. Inadequate understanding of the natural history and epidemiology of infection, and extrapolating or generalizing data from one group (that we have data for) to another (that we are trying to model), can also contribute to structural as well as parametric uncertainty. Furthermore, structural uncertainty can be turned into parametric uncertainty under certain scenarios. For example, a model described by a nonlinear equation can be approximated by a linear equation if the parameters of the nonlinear terms can be assumed to be very small.

Within HIV/STI modeling, the development of methods for handling structural uncertainty has received much less attention than methods for handling parametric uncertainty. A range of methods have been devised to deal with different levels of parametric uncertainty within models of different levels of complexity (Blower et al., 1991; Blower and Dowlatabadi, 1994; Cancre et al., 2000; Doubilet et al., 1985; Iman and Conover, 1982; Iman and Davenport, 1982; Iman and Helton, 1988; Isukapalli et al., 1998; Manning et al., 1996; McKay et al., 1979; Rowley, 1992; Stein, 1987; Watts et al., 2002). In terms of structural uncertainty, a few published articles have discussed the advantages and disadvantages of "simple" versus "complex" models (Anderson and Garnett, 2000; Baggaley et al., 2005; Boily and Masse, 1997; Garnett and Anderson, 1996; Vickerman and Watts, 2003). It is recognized that the complexity of the model should relate to its intended function and data availability (Garnett and Anderson, 1996). Generally, any exploration of structural uncertainty in HIV/STI modeling has tended to involve increasing complexity and then comparing the outputs with those from a simpler version of the model (Baggaley et al., 2005; Blower, 2004; Blower et al., 2004; Dietz and Hadeler, 1988; Ferguson and Garnett, 2000; Garnett et al., 2004; Kretzschmar and Dietz, 1998; Kumaranayake et al., 2006; Lipsitch et al., 2000; White and Garnett, 1999). Eames and Keeling (2002), in their simplification of a pair-wise network model, provide the only known example in HIV/STI modeling of reducing a complex model into a simpler model without losing the key aspects (Eames and Keeling, 2002).

In this paper, a model will be developed to describe the transmission and natural history of HSV-2 infection and progression. Within the context of this paper, complexity refers to the dimension of the model (i.e., the total number of state variables). A complex model is first developed and then its structure simplified in order to reduce the number of state equations. Formal model reduction methods have been widely used in the fields of systems

and control to reduce the dimension of dynamic systems (Antoulas and Sorensen, 2001). Here, the aim is to develop simpler application-driven methods to reduce the dimension of a system while retaining sufficient accuracy in the model outputs. This analysis involves comparing projections made by models of different structures rather than projecting the HSV-2 epidemic in a specific setting. The latter (described elsewhere (Foss et al., 2007)), requires first the development of an appropriate HSV-2 model structure (described here), which is then coupled with an HIV model, fitted to setting-specific prevalence data, and used to explore the bidirectional interactions between these infections.

Bayesian model averaging provides one approach for handling structural and parametric uncertainty simultaneously within a stochastic framework (Hoeting et al., 1999). However, unlike statistically-based models which fit data observations directly to empirical models, the models described in this paper are mechanistic, meaning that the Bayesian approaches for comparative evaluation of alternative sets of models of different complexities are not appropriate in this case (Spiegelhalter et al., 2002).

1.1. Previous and concurrent HSV-2 modeling

There are basically eight different HSV-2 models that have been developed (Blower et al., 1998; Fisman et al., 2002; Garnett et al., 2004; Ghani and Aral, 2005; Korenromp et al., 2002; Newton and Kuder, 2000; Schinazi, 1999; White and Garnett, 1999), although some have been revised and adapted over time and applied to several different research questions (Blower, 2004; Blower and Ma, 2004; Blower et al., 2004; Freeman et al., 2006a, 2006b; Gershengorn and Blower, 2000; Gershengorn et al., 2003; Orroth et al., 2006; Schwartz and Blower, 2005; Schwartz et al., 2007; White et al., 2004; Williams et al., 2007). There are some key differences between the model structures. Only three of these eight previous models have a separate compartment for the latent period where the infection is exclusively noninfectious (Blower et al., 1998; Garnett et al., 2004; Schinazi, 1999) and just three models distinguish between asymptomatic and symptomatic episodes (Fisman et al., 2002; Garnett et al., 2004; Newton and Kuder, 2000). Of the eight previous models (or adapted models), five, to varying degrees of complexity, incorporate a reduction in shedding over time since initial infection (Blower et al., 2004; Fisman et al., 2002; Garnett et al., 2004; Korenromp et al., 2002; White and Garnett, 1999). None of the models include separate compartments for the different types of initial infection (symptomatic/asymptomatic), or the possibility that those initially infected asymptomatically may develop symptomatic infection with recurrences only after a time delay (Corey et al., 1999; Langenberg et al., 1999). Without all these considerations, models may misrepresent the transmission dynamics of HSV-2.

To the best of our knowledge, no one has yet explored how the structure of an HSV-2 model may influence model predictions. Model structure uncertainty is a neglected issue in this field but is important to consider, in conjunction with parametric uncertainty, because of the biological uncertainties surrounding HSV-2 transmission and its natural history. All the published modeling of HSV-2 has considered hypothetical populations, used data from US populations, or modeled sub-Saharan African populations. We are not aware of any modeling of HSV-2 conducted using population data from an Asian setting.

The aim of this analysis is to identify an appropriate model structure that reflects the key features of the natural history of HSV-2 infection in a simple way, using behavioral and epidemiological data from a southern Indian setting. Specifically, this paper explores

whether the following features, considered collectively, are important when modeling the transmission dynamics of HSV-2:

(1) Distinct episodes of asymptomatic HSV-2 shedding and periods of noninfectiousness;
(2) Separate states for new and old infections to represent reduced HSV-2 shedding in old infections;
(3) Assuming the first symptomatic episode occurring among asymptomatically infected individuals is most like initial symptomatic infection rather than a recurrence;
(4) Separate states for the different types of initial infection and natural history.

2. Methods

Firstly, the development of a structurally complex HSV-2 model is described and then the process by which it was simplified is explained. These two models are then compared to explore the effect of the assumptions on the model outputs.

2.1. Complex HSV-2 model structure

Figure 1 presents a flow diagram of the "complex" HSV-2 transmission model. This was developed following a review of the literature on HSV-2 and previous models, and after discussions with experts to identify common themes and key aspects to incorporate into the model (see Acknowledgments).

From the susceptible state (S), a proportion of individuals are infected at a rate λ, either symptomatically (θ) or asymptomatically ($1-\theta$), denoted by subscript 1 or 2 for symptomatic or asymptomatic initial infection, respectively. After initial infection (I) of

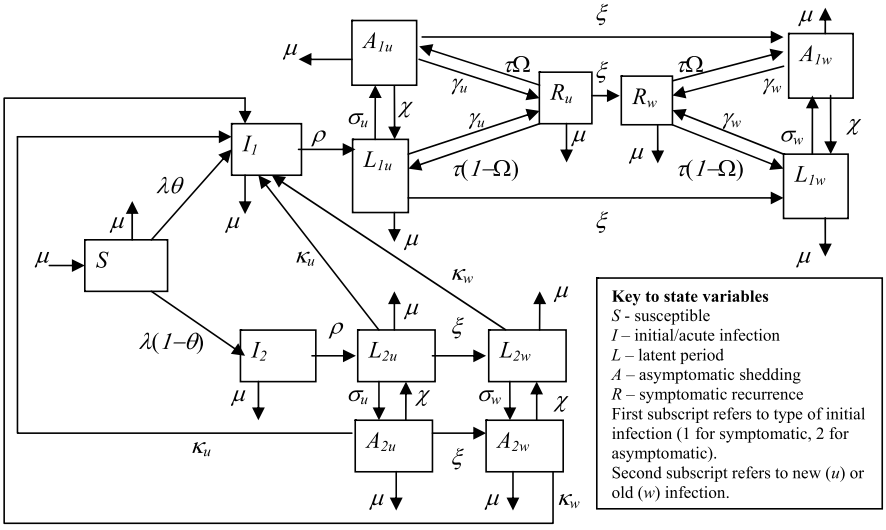

Fig. 1 Flow diagram for HSV-2 infection and progression ("complex" model).

average duration $\frac{1}{\rho}$, they enter a latent phase (L) of no shedding (noninfectious), followed by periods of infectious asymptomatic shedding (A) or symptomatic recurrences (R). The frequency and durations of these infectious episodes are denoted by σ and χ, respectively, for asymptomatic episodes, and by γ and τ for symptomatic recurrences. After a recurrence, a proportion (Ω) experience an asymptomatic shedding episode and the rest return to the latent state ($1-\Omega$). Those who were initially infected asymptomatically experience their first symptomatic episode at rate κ, following a latent or asymptomatic period, which is then modeled in the same way as initial symptomatic infection (I_1). Throughout the model, people move at a rate ξ from new to old infection states (denoted by subscripts u and w, respectively). It is assumed that people enter sex work or start buying sex at the same rate that they cease commercial sexual activity (μ) so that the population size remains constant.

The set of ordinary differential equations corresponding to the HSV-2 transmission dynamics model illustrated in Fig. 1 are as follows, replicated for each sex:

$$
\begin{aligned}
\frac{dS}{dt} &= \mu T - (\lambda+\mu)S,\\
\frac{dI_1}{dt} &= \lambda\theta S + \kappa_u(L_{2u}+A_{2u}) + \kappa_w(L_{2w}+A_{2w}) - (\rho+\mu)I_1,\\
\frac{dI_2}{dt} &= \lambda(1-\theta)S - (\rho+\mu)I_2,\\
\frac{dL_{1u}}{dt} &= \rho I_1 + \chi A_{1u} + \tau(1-\Omega)R_u - (\sigma_u+\gamma_u+\xi+\mu)L_{1u},\\
\frac{dL_{2u}}{dt} &= \rho I_2 + \chi A_{2u} - (\sigma_u+\kappa_u+\xi+\mu)L_{2u},\\
\frac{dL_{1w}}{dt} &= \xi L_{1u} + \chi A_{1w} + \tau(1-\Omega)R_w - (\sigma_w+\gamma_w+\mu)L_{1w},\\
\frac{dL_{2w}}{dt} &= \xi L_{2u} + \chi A_{2w} - (\sigma_w+\kappa_w+\mu)L_{2w},\\
\frac{dA_{1u}}{dt} &= \sigma_u L_{1u} + \tau\Omega R_u - (\chi+\gamma_u+\xi+\mu)A_{1u},\\
\frac{dA_{2u}}{dt} &= \sigma_u L_{2u} - (\chi+\kappa_u+\xi+\mu)A_{2u},\\
\frac{dA_{1w}}{dt} &= \xi A_{1u} + \sigma_w L_{1w} + \tau\Omega R_w - (\chi+\gamma_w+\mu)A_{1w},\\
\frac{dA_{2w}}{dt} &= \xi A_{2u} + \sigma_w L_{2w} - (\chi+\kappa_w+\mu)A_{2w},\\
\frac{dR_u}{dt} &= \gamma_u(L_{1u}+A_{1u}) - (\tau+\xi+\mu)R_u,\\
\frac{dR_w}{dt} &= \xi R_u + \gamma_w(L_{1w}+A_{1w}) - (\tau+\mu)R_w,
\end{aligned}
\tag{1}
$$

where λ, the rate of HSV-2 infection, is a function of all the state variables and so is time-dependent. All parameters are constant over time. T denotes the total number of sexually

active people in the population, for each sex, i.e., the sum of the 13 state variables in Eq. (1) (with definitions summarized in Appendix A). The initial conditions of the system are set so that 0.1% of female sex workers (FSWs) are experiencing initial symptomatic infection (I_1) while all other people are susceptible (S).

To focus attention on the uncertainties and complexities surrounding the biological parameters, sexual mixing behavior is modeled simply by considering only commercial penile-vaginal sex between female sex workers (FSWs) and their male clients.

Assuming the risk of infection is independent for each sex act and the number of sex acts is independent of infection state, the rate of HSV-2 infection over a specified timeframe for an individual of sex c ($c = 0$ for female and $c = 1$ for male), with $m_{[c]}$ partners of the opposite sex $d(= 1 - c)$, with each of whom they have n sex acts, is given by λ:

$$\lambda_{[c]} = 1 - \left\{ \sum_{q=0}^{4} \left(\frac{N_{[d][q]}}{T_{[d]}} \right) \left[1 - \Lambda_{[q]} B_{[c]} (1 - E_{\mathrm{HSV}[c]}) \right]^n \right\}^{m_{[c]}}, \tag{2}$$

where $N_{[d][q]}$ denotes the number of people of sex d who are in HSV-2 state grouping q ($q = 0$ for states S or L, $q = 1$ for state I_1, $q = 2$ for state I_2, $q = 3$ for states A, and $q = 4$ for states R), and $T_{[d]}$ is the total number of people of sex d. B is the HSV-2 transmission probability from a partner in an asymptomatic infection state to a person susceptible to HSV-2, and Λ is the multiplicative cofactor for increased HSV-2 transmission if the partner is in an initial infection state or experiencing a symptomatic recurrence (and set to zero for states S or L, and to 1 for states A). E_{HSV} is the average probability an individual is protected from HSV-2 for one sex act in a partnership:

$$E_{\mathrm{HSV}[c]} = 1 - (1 - f e_{\mathrm{HSV}})(1 - f_{\mathrm{circ}[c]} e_{\mathrm{circ\,HSV}}), \tag{3}$$

where condoms are used in a proportion f of sex acts, e_{HSV} is the per sex act HSV-2-efficacy of condoms, f_{circ} is the proportion of males who are circumcised (set to zero for females), and $e_{\mathrm{circ\,HSV}}$ is the possible protective effect of male circumcision in reducing the risk of HSV-2 acquisition among males. Equation (3) assumes condom use is independent of circumcision.

The parameter definitions and values used are shown in Appendix B and Appendix C. The natural history parameters and transmission probabilities were obtained from the literature while the behavioral and epidemiological inputs are parameterized using data from FSWs in Mysore in Karnataka, India, and data on clients from Karnataka if available or from elsewhere in India otherwise. Based on viral shedding studies, it is assumed that the probability of transmission per sex act will be highest during the first symptomatic episode, fairly high during symptomatic recurrences, and lowest during asymptomatic shedding episodes (Guinan et al., 1981; Mertz et al., 1985; Wald et al., 1997). Transmission is taken to be higher from males to females than females to males (Bryson et al., 1993; Corey et al., 2004b; Langenberg et al., 1999; Mertz et al., 1992; Wald et al., 2001).

2.2. *Reducing the complex model into a simple model*

Starting with a complex model enabled the details suggested by experts to be incorporated explicitly. The model is then reduced to a simple model that retains the key features

of the infection, but implicitly, rather than using their explicit representation as separate compartments. The outputs from these two models are then compared. If the process had instead begun with a simple model then complexity increased, it would have been difficult to parameterize the more complex model in a parallel manner to the simple model parameterization for comparison.

The model reduction process involves four steps of simplification from the "complex" model (Fig. 1) to the "simple" model (Fig. 2). First, the latent and asymptomatically shedding states are merged. Secondly, the new and old infection compartments are merged. Thirdly, a simplifying assumption is made that the first symptomatic episode experienced by those asymptomatically infected can be modeled as a symptomatic recurrence rather than as symptomatic initial infection. Lastly, the different dynamics by type of initial infection are removed.

The corresponding set of differential equations for the simple model is given below:

$$\begin{aligned}
\frac{dS}{dt} &= \mu T - (\lambda + \mu)S, \\
\frac{dI}{dt} &= \lambda S - (\rho + \mu)I, \\
\frac{dA}{dt} &= \rho I + \tau R - (\gamma + \mu)A, \\
\frac{dR}{dt} &= \gamma A - (\tau + \mu)R,
\end{aligned} \tag{4}$$

where the parameters, and λ and T are as defined previously for the complex model, except now with 4 state equations (4) (with state variable definitions summarized in Appendix D) and some "average" inputs as described below. The initial conditions of the system are set, as before, so that 0.1% of FSWs are experiencing initial infection (I) while all others are susceptible (S).

Comparing both models compartment-wise, in order to make the simple model approximate the complex model we require S to contain the same number of people in both

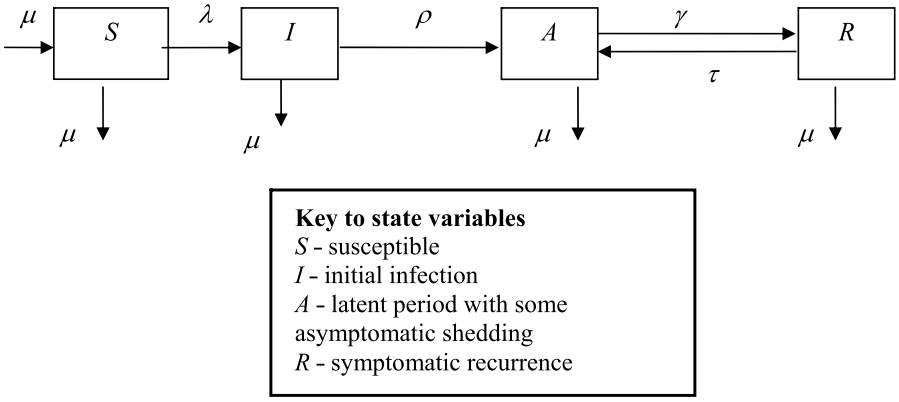

Fig. 2 Flow diagram for "simple" HSV-2 model structure.

models, and that the following holds:

$$\begin{aligned} I &= I_1 + I_2, \\ A &= L_{1u} + A_{1u} + L_{1w} + A_{1w} + L_{2u} + A_{2u} + L_{2w} + A_{2w}, \\ R &= R_u + R_w. \end{aligned} \tag{5}$$

Summing the associated complex model differential equations (1) in the same way as in (5), substituting in Eqs. (5), and equating with the simple model differential Eqs. (4), gives the following ratio required to calculate the symptomatic recurrence rate for the simple model:

$$\gamma = \frac{\gamma_u(L_{1u} + A_{1u}) + \gamma_w(L_{1w} + A_{1w}) + \kappa_u(L_{2u} + A_{2u}) + \kappa_w(L_{2w} + A_{2w})}{L_{1u} + L_{2u} + L_{1w} + L_{2w} + A_{1u} + A_{2u} + A_{1w} + A_{2w}}. \tag{6}$$

Note that γ is implicitly time-dependent and depends on γ_u, γ_w and κ_u, κ_w, respectively, as expected.

Consider mathematically the part of the transmission equation λ (Eq. (2)) that changes from the complex model structure to the simple model. For the simple model, this expression is summed over q from 0 to 3 rather than 0 to 4 ($q = 0$ for state S, $q = 1$ for state I, $q = 2$ for state A, and $q = 3$ for state R):

$$\sum_{q=0}^{q=3} \left(\frac{N_{[d][q]}}{T_{[d]}} \right) \left[1 - \Lambda_{[q]} B_{[c]} (1 - E_{\mathrm{HSV}[c]}) \right]^n. \tag{7}$$

In the simple model, those in state A are not continuously shedding asymptomatically as those in states A_{1u}, A_{2u}, A_{1w}, or A_{2w} in the complex model are. A fractional multiplicative factor, F, representing the fraction of the time in state A in the simple model that is spent asymptomatically shedding, needs to be incorporated. For the corresponding terms in expressions (2) and (7) to equate we require, by Eqs. (5), that:

$$\begin{aligned} &(L_{1u} + L_{2u} + L_{1w} + L_{2w}) + (A_{1u} + A_{2u} + A_{1w} + A_{2w}) \left[1 - \Lambda_{[3]} B_{[c]} (1 - E_{\mathrm{HSV}[c]}) \right]^n \\ &\quad = (L_{1u} + L_{2u} + L_{1w} + L_{2w} + A_{1u} + A_{2u} + A_{1w} + A_{2w}) \left[1 - F \Lambda_{[3]} B_{[c]} (1 - E_{\mathrm{HSV}[c]}) \right]^n, \end{aligned} \tag{8}$$

where $q = 3$ denotes the asymptomatic shedding states A in the complex model. If first order Taylor Series linear approximations are used for the terms of Eq. (8) that are raised to the power n, assuming the values for $\Lambda_{[q]} B_{[c]} (1 - E_{\mathrm{HSV}[c]})$ are sufficiently small (which are ≤ 0.17 for the parameter values considered here), the following requirement is obtained:

$$F = \frac{A_{1u} + A_{2u} + A_{1w} + A_{2w}}{L_{1u} + L_{2u} + L_{1w} + L_{2w} + A_{1u} + A_{2u} + A_{1w} + A_{2w}}, \tag{9}$$

which, as expected, is simply the proportion of people in A that are asymptomatically shedding, rather than experiencing a latent period. Since nothing was found in the literature to suggest a difference for males and females, the mean value for F is used, averaged over FSWs and clients. Note that F is implicitly time-dependent.

Since Eqs. (1) are nonlinear, due to the rate of HSV-2 infection (λ) being a function of all the state variables, it was intractable to approximate the differential equations about the equilibrium or solve the system of differential equations analytically. Instead, both the complex and the simple HSV-2 models were solved numerically by programming using Borland C++ (Inprise Corporation, California, USA). The forward Euler numerical method was used with Eqs. (1) and (4) to approximate progression through the HSV-2 states over time. A time-step of one day was used as some duration parameters were a few days.

2.3. Steps in analysis

2.3.1. Parametric uncertainty analysis

For the analysis, first the HSV-2 input parameter ranges for the complex model were developed, distributions defined and correlations set (Appendix B and Appendix C). A range of values were estimated for each parameter to reflect the parametric uncertainty (uncertainty bounds). These were based on 95% confidence intervals (CIs) or minimum and maximum values from data where possible, or else based on several data estimates, sometimes requiring additional calculations. Due to lack of data about distributions of input parameters, they were assumed to be either triangular, if a middle value could be estimated or the lower and upper bounds on the uncertainty range were unlikely, or uniform otherwise. Although the correlations between the input parameters were not fully known, these were set up based on current understanding of the qualitative relationships.

Ten thousand parameter sets were selected randomly by Latin Hypercube Sampling (LHS) from all the input parameters within the estimated ranges, in order to obtain histogram distributions of each model output (via "Crystal Ball" add-in to Microsoft® Excel (2002): Software Crystal Ball 2000 Professional version 5.0 (Decisioneering Inc., 1988–2000, Denver, Colorado, USA)). Expected correlations were built into this sampling strategy. LHS was chosen because it is highly rated when compared to other methods, since it samples in a representative manner covering the full range efficiently and because it deals well with low-probability outcomes represented in input probability distributions (Blower and Dowlatabadi, 1994; Iman and Helton, 1988; Isukapalli et al., 1998; McKay et al., 1979; Stein, 1987; Sweat et al., 2000).

2.3.2. Structural uncertainty analysis

The complex model was run to equilibrium and γ and F from Eqs. (6) and (9) were output. The equilibrium prevalence was defined as the time-point at which the difference in the number of susceptible FSWs and clients each changed in the previous time-step by less than 0.00001.

Equilibrium ratio values for γ and F were used to explore the degree to which the simple model, using these values as inputs, can produce a good approximation to the outputs of the complex model when projecting the whole epidemic curve. However, in order to separate the simple model from dependency on the complex model outputs and make it more generalizable to other analyses and settings, multivariate linear regressions were performed on the inputs and outputs of the parametric uncertainty analysis undertaken on the complex model to estimate equilibrium values for γ and F. Linear regression was used for simplicity and because, intuitively, it was thought that these "average" parameters might be approximated by linear equations in γ_u, γ_w, κ_u, and κ_w for γ, and σ_u, σ_w, and χ

for F. As expected, when the standardized coefficients were ranked (using standardized units across variables), these were the parameters contributing the most to the values of γ and F (all having statistically significant predictive capability, $P < 0.001$, standard errors all ≤ 0.05), except κ_u can be ignored since it was ranked much lower. Only four regression coefficients are then required for each of the three regression equations in order to calculate the recurrence rate among females ($\gamma_{[0]}$), the recurrence rate among males ($\gamma_{[1]}$), and the proportion of those in state A who are asymptomatically shedding (F):

$$\begin{aligned}
\gamma_{[0]} &= -0.000360847 + 4.31103\kappa_w + 0.170802\gamma_{u[0]} + 0.579673\gamma_{w[0]},\\
\gamma_{[1]} &= -0.000597571 + 6.67470\kappa_w + 0.110919\gamma_{u[1]} + 0.636511\gamma_{w[1]},\\
F &= 0.0500173 + 0.227443\sigma_u + 0.876936\sigma_w - 0.0535463\chi.
\end{aligned} \tag{10}$$

The R^2 values were 0.980, 0.971, and 0.962, respectively, for $\gamma_{[0]}$, $\gamma_{[1]}$, and F, calculated using Eqs. (10).

Using Eqs. (10) to calculate the average parameter inputs required for the simple model ($\gamma_{[0]}$, $\gamma_{[1]}$ and F), both the complex and simple models were then run and their outputs compared. For this analysis, the overall prevalence of HSV-2 was the key output of interest, obtained by summing all of the state variables except S and dividing by the total population (T). If 95% of the simulations produce HSV-2 prevalence projections from the simple model that differ from the complex model projections by less than a 10% relative difference, over a specified timeframe, then the simple model is deemed acceptable.

The model outputs were compared in two different ways:

(1) Models run from start of epidemic to equilibrium
Both the complex and simple models were run from the start of the HSV-2 epidemic until reaching the equilibrium prevalence. The pair-matched outputs of these models, produced from each of the 10,000 parameter sets, were compared.

(2) Models run from start of epidemic but only output once part way into epidemic
For each model simulation, both models were run from the start of the epidemic, as in the analysis above, but set to output once the FSW prevalence reached a specific percentage of the equilibrium, named the "target." Once the target was reached, the models output at many different time-points until the equilibrium was reached, and the pair-matched outputs were compared.

3. Results

Using linear regression to estimate the symptomatic recurrence rate (γ) and proportion shedding asymptomatically (F), produced the following mean estimates and ranges (min-max) over all 10,000 simulations:

$$\begin{aligned}
\gamma_{[0]} &= 2.1 \quad (1.2\text{–}3.2) \text{ per year},\\
\gamma_{[1]} &= 2.2 \quad (1.0\text{–}3.2) \text{ per year},\\
F &= 4.6\% \quad (2.6\text{–}6.6\%).
\end{aligned} \tag{11}$$

3.1. Comparisons between outputs from simple and complex models

(1) Models run from start of epidemic

In order to compare the outputs from the simple and complex models, the relative differences are calculated, defined here as the difference in magnitude between the values output by the complex and simple models divided by the value output by the complex model. Figure 3 shows the mean (over 10,000 runs) of the relative differences in the prevalences projected by the simple and complex models from the start of epidemic (until less then 10% mean relative difference was reached).

For illustration of typical projected epidemic curves, model output prevalences of a specific simulation are plotted in Fig. 4. The relative differences between the two models are also shown. Generally, the simple model underestimates the prevalence predicted by the complex model, and it usually takes longer to reach equilibrium. In these cases, the plots also show the slow "take-off" of the epidemic when using the simple model (Fig. 4). In some other cases, the simple model first underestimates the prevalence but then begins to overestimate prevalence and reaches the equilibrium faster than the complex model, slightly overestimating the equilibrium prevalence value.

Considering the relative error of the simple model in approximating the complex model over all 10,000 runs, the approximation is often poor when it takes the models a very long time to reach equilibrium, and/or if the epidemic does not really ever "take-off" and so the prevalence at equilibrium remains very low. In 2,450 of the 10,000 runs, the simple model did not reach equilibrium within 1,000 years, or the equilibrium prevalence was less than 1% among FSWs or clients. Examining the input parameter sets producing these simulations, the only inputs with means that differed by more than 10%, compared with those over all 10,000 simulations, were the per sex act transmission probabilities (B), which were lower by at least 60%. These 2,450 runs were deemed unrealistic and removed from the subsequent analysis.

The simple model takes longer to reach equilibrium in 82% of the remaining 7,550 simulations. The equilibrium prevalences output by the complex and simple models over the 7,550 simulations are given in Table 1.

Eighty-nine percent of simulations predicted a lower FSW prevalence when using the simple model and 96% predicted a lower client prevalence, compared to the complex

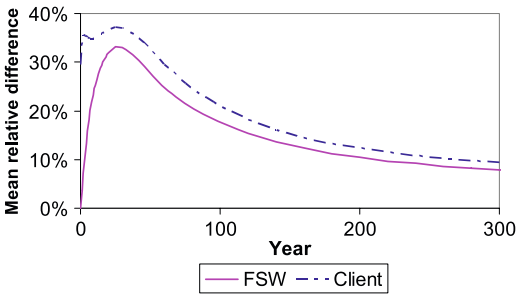

Fig. 3 Mean (over 10,000 runs) of the relative difference in female sex workers (FSWs) and client prevalences projected by the simple and complex models from the start of epidemic (until less then 10% mean relative difference was reached).

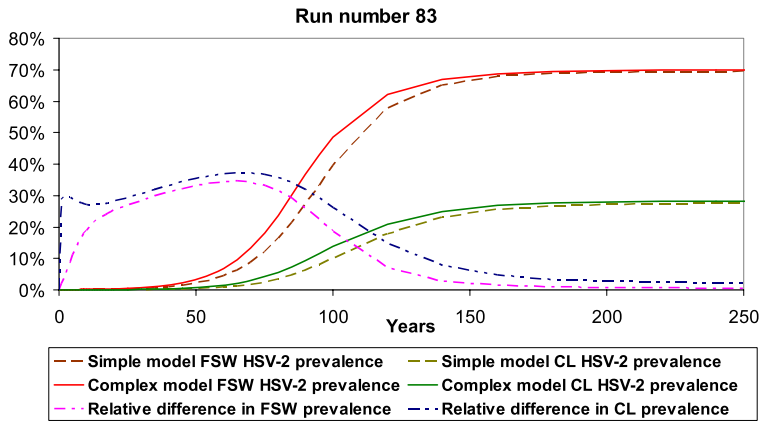

Fig. 4 Typical epidemic curves projected by the models from the start of epidemic to equilibrium. FSW, female sex workers, CL, clients. (Color figure online.)

Table 1 Comparison between complex and simple model predictions of HSV-2 prevalence at equilibrium

		Equilibrium HSV-2 prevalence			Relative difference		
		Mean	95% CI	Range (min-max)	Mean	95% CI (one-sided)	Maximum
Complex model	FSWs	75%	43–90%	33–93%	1.1%	4.0%	14%
Simple model		75%	41–90%	31–93%			
Complex model	Clients	34%	13–54%	9.3–65%	2.9%	7.0%	20%
Simple model		33%	12–53%	8.7–64%			

CI, confidence interval; FSW, female sex workers
The relative difference is defined here as the difference in magnitude between the values output by the complex and simple models divided by the value output by the complex model. The mean, maximum, and 95% CI upper bound (one-sided) are calculated over all 7,550 simulations

model. The mean relative difference in the prevalence predicted by the two models at equilibrium was less than 3%.

The inputs for those runs (of the 7,550) producing a relative error in prevalence of more than 10% were compared with those from all 10,000 runs. For FSWs, there were 17 such runs, and for clients there were 110 runs. The mean values of the inputs for these runs that differed by over 20% compared with the mean values of the inputs to all 10,000 simulations were the transmission probabilities (B), which were lower in these 17 FSW runs and the 110 client runs, and the efficacy of male circumcision against HSV-2 ($e_{\text{circ HSV}}$) was lower in the 17 FSW runs.

The findings suggest that the simple model can be used as a good approximation if used to run to equilibrium (for an equilibrium of over 1% prevalence), which is reached within 1,000 years. This suggests that for most reasonable scenarios, using a sufficiently high value for the transmission probabilities, the simple model produces a good approximation to the equilibrium prevalences.

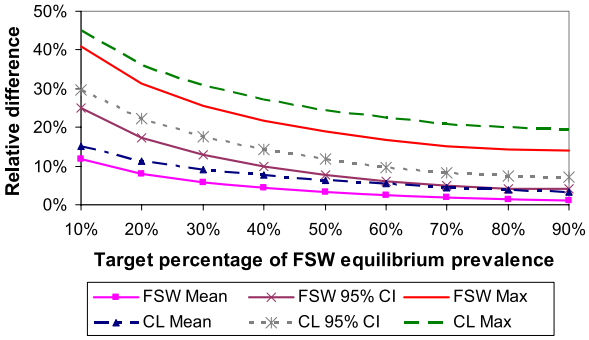

Fig. 5 Relative difference in female sex worker (FSW) and client (CL) HSV-2 prevalence projected by simple and complex models from target to equilibrium. (Color figure online.)

(2) Models run from start of epidemic but only output once part way into epidemic
Often, in STI modeling, the model is fitted to a specific prevalence and then used to project the progression of the epidemic. It can be hypothesized from the plots in the previous section (Fig. 3 and Fig. 4) that if the simple model is set to match the complex model prevalence part way though the epidemic, the projections from both models from this time-point to the equilibrium may be very similar. This hypothesis is explored here for the case where the models are run from the start of the epidemic but only output prevalence on reaching a certain level.

Figure 5 plots the mean, maximum and 95% CI upper bound (one-sided) of the relative differences when comparing the outputs from the simple and complex models over time from once a certain "target" prevalence is reached among FSWs then onto equilibrium. The mean was calculated by averaging over the 7,550 runs and over all the time-points output by the model from the target to equilibrium. The maximum and 95% CI upper bound were calculated similarly.

Although the FSW prevalences are matched at the target, the client prevalences are not, which partially explain the larger differences seen between the client outputs than the FSW outputs.

Once the epidemic reaches 60% of the equilibrium prevalence, from this point to the equilibrium, 95% of the simulations produce relative differences between the model prevalence estimates that are less than 10% for both FSWs and clients. The approximation of using the simple model improves if the prevalence comparison is made over short time-frames (such as 5 years), but is worse earlier in the epidemic, e.g., the maximum relative error across the 7,550 runs is 45% when the model outputs are compared from 10% of the equilibrium prevalence.

4. Discussion

The complex model has several features that have not previously been modeled. The main addition is the inclusion of an initial infectious period that differentiates between symptomatic and asymptomatic infection, and allowing those infected asymptomatically to develop symptomatic infection after a time delay.

This simple model offers a reduced structure that retains some of the value of the complexities implicitly, through the model reduction procedure, rather than explicitly as compartments. In this analysis, new and old infections are first considered separately in the complex model, allowing shedding rates to decline over time, and having separate compartments for symptomatic and asymptomatic initial infection. Collapsing this into the simple model, under certain conditions (outlined below), it was found that similar model projections can be obtained by using "average" values for these shedding rates, so eliminating the need for these extra compartments. It was also found generally unnecessary to model asymptomatic shedding episodes as a separate compartment, distinct from the latent state, since mathematically, these shedding episodes can be closely approximated by a parameter describing an associated proportion of the latent state shedding asymptomatically. This simple structure is supported by recent findings of more frequent shorter HSV-2 asymptomatic reactivations occurring during the "latent" stage than previously thought (Mark et al., 2007). Additionally, the first symptomatic episode occurring among asymptomatically infected individuals can essentially be modeled as a recurrence.

The findings suggest that in the vast majority of settings, the simple model is a very good approximation to the complex model when used to estimate equilibrium HSV-2 prevalence values. This requires that the transmission probabilities are not too low. With these same constraints, the simple model is also a good approximation to the epidemic curve if used after fitting the model to a prevalence value of 60% of the equilibrium prevalence, but can be a poor approximation earlier in the epidemic. The approximation of using the simple model is improved if the prevalence comparison is made over short timeframes (such as 5 years).

4.1. Limitations

Unlike Garnett et al. (2004), the models presented here do not stratify by HSV-1 infection, but instead assume, based on limited available data (Cowan et al., 2003) that the HSV-1 prevalence in the population modeled is high. Adjusted values are used to account for prior HSV-1 infection possibly increasing the likelihood of asymptomatic seroconversion (Brown et al., 1997; Brugha et al., 1997; Langenberg et al., 1999; Stanberry et al., 2002).

Another limitation is that the models do not allow for sexual behavior differences in symptomatic versus asymptomatic episodes (Rana et al., 2006). If there are substantial reductions in sexual risk behavior during recognized symptomatic episodes, then the models may overestimate the effect of symptomatic recurrences and HSV-2 prevalence.

The equilibrium HSV-2 prevalence outputs for some simulations may seem rather high for this setting. However, this paper only compares projections made by models of different structures rather than projecting the HSV-2 epidemic in Mysore. Model fitting techniques are required to deal with this issue along with the use of a combined HSV-2/HIV model (Foss et al., 2007). Combining the HSV-2 model with an HIV model enables incorporation of the possible effect of HIV increasing HSV-2 infectivity in those coinfected and potentially increasing the risk of HSV-2 acquisition in those singly infected with HIV, as well as the effects of HSV-2 on the risk of HIV acquisition and transmission (Celum, 2004; Corey et al., 2004a).

4.2. Implications for modeling

For late-stage HSV-2 epidemics, the simple model gives similar prevalence trends as the complex model. This simple model is reduced from the complex model and offers a sim-

pler structure, while still incorporating complexities implicitly by using model-calculated "average" inputs and linear regression equations. The simple model also requires less computational time per simulation.

Future work could try to identify a model reduction that better approximates the complex model earlier in the epidemic, perhaps by examining ratios in Eqs. (6) and (9) output by the complex model earlier in the epidemic or by exploring the use of other models formed during the different steps of the reduction (which could be ordered according to the dimension of the model).

The simple model structure resembles that of Newton and Kuder (2000), but without the vaccinated class and incubation period (Newton and Kuder, 2000). However, the symptomatic recurrence rate used in their model seems rather high (5.3 per year) as an average lifetime rate, and resembles more that observed in the first year of infection (Benedetti et al., 1994, 1999; Corey et al., 1983a; Corey and Wald, 1999; Diamond et al., 1999; Lafferty et al., 1987). The values in the simple model presented here are considerably lower ($\sim$2 per year). Perhaps this is because a reduction in shedding over time and a delay in onset of symptomatic shedding among those infected asymptomatically are implicitly incorporated in the simple model. When using simple model structures, it is important to adjust parameter estimates to factor in complexities or, in this example, risk overestimating the HSV-2 epidemic.

Simplifying the HSV-2 model was an important step toward future work, since the simple HSV-2 model has now been built into a large-scale population-level model of HIV/STI transmission which will be used to estimate the impact of the multisite Avahan intervention on HIV/STI transmission in southern India (Boily et al., 2007b).

The techniques presented in this paper could be considered and adapted for other modeling studies. Model simplicity is advantageous for many reasons and these techniques have shown that this may be possible without losing some of the benefits which would normally require more complex dynamic structures.

The findings show that it is possible to obtain similar prevalence projections under different model assumptions and simplifications. As the HSV-2 epidemics in many populations are advanced, the simple model may be used in most instances, although the complex model may be preferable for early epidemics. The analysis highlights the issue of model structural uncertainty, and the value of minimizing complexity. These issues are important to all those involved in modeling HSV-2, HIV, or other STI, and warrant further attention.

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Appendix A: State variables for "complex" model of the natural history of Herpes simplex virus type-2 (HSV-2)

State variable symbol	State variable definition
S	Susceptible to HSV-2
I_1	Experiencing initial symptomatic HSV-2 infection or first symptomatic episode following asymptomatic infection (infectious)
I_2	Experiencing initial asymptomatic HSV-2 infection (infectious)
L_{1u}	Latent phase (noninfectious) among those with a relatively new infection who have experienced symptoms
L_{2u}	Latent phase (noninfectious) among those with a relatively new infection who have not experienced symptoms
L_{1w}	Latent phase (noninfectious) among those with a relatively old infection who have experienced symptoms
L_{2w}	Latent phase (non-infectious) among those with a relatively old infection who have not experienced symptoms
A_{1u}	Asymptomatic shedding episode (infectious) among those with a relatively new infection who have experienced symptoms
A_{2u}	Asymptomatic shedding episode (infectious) among those with a relatively new infection who have not experienced symptoms
A_{1w}	Asymptomatic shedding episode (infectious) among those with a relatively old infection who have experienced symptoms
A_{2w}	Asymptomatic shedding episode (infectious) among those with a relatively old infection who have not experienced symptoms
R_u	Symptomatic recurrence (infectious) among those with a relatively new infection
R_w	Symptomatic recurrence (infectious) among those with a relatively old infection

Appendix B: Input parameters for natural history of Herpes simplex virus type-2 (HSV-2)

Parameter symbol	Definition	Estimated values and uncertainty ranges	Distributions and correlations	References and notes
Setting-specific inputs for population size and infection seeding:				
T	Size of total population	2,284 (2,158–2,410) FSWs, 35,381 (29,746–41,015) clients	Triangular	Using mean, min and max for number of FSWs in Mysore estimated by capture-recapture and mapping (from KHPT, 2005). For one-time clients, used mean number of one-time clients per FSW (from KHPT, 2006 data on Mysore FSWs) and divided this by NACO (2001) mean and median estimates for number of FSWs per client, then multiplied by mean number of FSWs in Mysore to get estimated number of one-time clients for Mysore FSWs. For regular clients, assumed that number of clients per day reflects multiple counting of repeat clients if multiply up over a year, then found difference per FSW between total number of commercial sex acts per year and number of one-time clients, and this difference gave number of regular client sex acts per year. Dividing this by number of sex acts with regular clients per year (from KHPT, 2006 data on Mysore FSWs) gave number of regular clients per FSW per year. Multiplying this by mean number of FSWs in Mysore gave estimated number of regular clients for Mysore FSWs. The total number of clients for Mysore FSWs was then estimated by summing the number of one-time clients and the number of regular clients. Min value is number of one-time clients only, max value is sum of number of one-time and regular clients using NACO (2001) median value for number of FSWs per client, and the main value is the mean of this min and max.
μ	Rate of starting or ceasing to sell/buy sex	0.000161 (0.000125–0.000249) per day for FSWs, 0.000105 (0.0000913–0.000130) per day for clients [i.e. FSWs sell sex for 17 (11–22) yrs and clients buy sex for 26 (21–30) yrs]	Triangular	Based on mean age start sex work and age distribution of FSWs in Mysore, it was estimated that FSWs sell sex for 17 years on average, with most selling sex for between 11 and 22 years. Similarly, client age distributions and summary statistics were used to estimate the duration men buy sex. Approximated rate cease selling or buying sex as 1/(duration sell or buy sex).

Parameter symbol	Definition	Estimated values and uncertainty ranges	Distributions and correlations	References and notes
HSV-2 biological parameters:				
θ	Proportion of those infected who have symptomatic initial infection	0.44–0.55 for women, 0.32–0.39 for men	Uniform	Ranges based on estimates from several studies (Corey et al., 1999; Cowan et al., 2003; Langenberg et al., 1999), and considering high-risk populations with high/fairly high levels of HSV-1.
ρ	Recovery rate from initial infection	0.05–0.0909 per day [i.e. duration of initial infection is 11–20 days]	Uniform	Range based on estimates from several studies (Benedetti et al., 1994; Cheong et al., 1990; Corey et al., 1983a, 1983b; Corey and Wald, 1999; Diamond et al., 1999; Koelle et al., 1992). Approximated recovery rate as 1/(duration of initial infection).
Ω	Proportion of those who have symptomatic recurrence who then have an asymptomatic shedding episode immediately following the recurrence without first experiencing a latent phase	0.5	N/A	Set as 0.5 but mathematically the value of this term does not have any effect when simplifying the model since the states L, A and R form a continuous loop.
ξ	Rate move from 'new' into 'old' infection states (denoted by subscripts u and w)	0.000548 per day [i.e. defined new infections as < 5 years since initial infection and old infections as > 5 years since initial infection]	N/A (uncertainty reflected in parameters κ, γ and σ below)	Set to define age of infection when considered 'old' rather than 'new', in order to define κ, γ and σ below.

Parameter symbol	Definition	Estimated values and uncertainty ranges	Distributions and correlations	References and notes
κ_u	Rate of onset of first episode among those asymptomatically infected (for new infections)	0.000342–0.000384 per day [i.e. 12.5–14% per year]	Uniform	Data from a study by Corey et al. (1999) suggest 8.7% per year, while Langenberg et al. (1999) suggest 15.6% per year. Mean value across these two studies is 12.5% per year (Corey et al., 1999; Langenberg et al., 1999). Experts (see Acknowledgements) suggested proportion infected asymptomatically who become symptomatic reduces each year since initial infection but most will develop symptoms within first 10 years. Starting with 16% (Langenberg et al., 1999) and reducing by 1% each year, it takes 8–9 years to get 33% remaining asymptomatic and $\geq$11 years to reach 23%. Mean rate over first 5 years is 14% and over years 5–15 is 6.5% (or 1.6% if assume those infected for >10 years who have not yet developed symptoms never will). So used range 12.5–14% per year for first 5 years and 1.6–6.5% per year for >5 years since initial infection.
κ_w	Rate of onset of first episode among those asymptomatically infected (for old infections)	0.0000438–0.000178 per day [i.e. 1.6–6.5% per year]	Uniform	
γ_u	Symptomatic recurrence rate in HIV-negatives (for new infections)	0.00822–0.0137 per day (skew so 0.00959 more likely for women and 0.0123 more likely for men) [i.e. 3.5 (3–5) per year for women and 4.5 (3–5) per year for men]	Triangular Correlated male and female recurrence rates with coefficient of +1.0	In first year since initial infection, clinically-recognized recurrence rate is 4–6 per year (Benedetti et al., 1994, 1999; Corey et al., 1983a; Corey and Wald, 1999; Diamond et al., 1999; Lafferty et al., 1987). Slightly higher rate in men than women in a couple of studies (Benedetti et al., 1999; Corey et al., 1983a), so skew 4–6 per year so that 4.5 more likely for women and 5.5 more likely for men. Over first 3 years of infection recurrence rate decreases by 0.6 per year (Benedetti et al., 1999). Assuming rate of decrease is slightly less for years 3–5, consider the 2–3 year rate as the mean in the first 5 years = 3–5 per year with skew so 3.5 more likely for women and 4.5 more likely for men.
γ_w	Symptomatic recurrence rate in HIV-negatives(for old infections)	0.00273–0.0110 per day (skew so 0.00548 more likely for women and 0.00822 more likely for men) [i.e. 2 (1–4) per year for women and 3 (1–4) per year for men]	Triangular Correlated male and female recurrence rates with coefficient of +1.0	After 5 years since initial infection, recurrence rate is 1–4 per year (Benedetti et al., 1999; Corey and Wald, 1999). Slightly higher rate in men than women in a couple of studies (Benedetti et al., 1999; Corey et al., 1983a), so skew 1–4 per year so that 2 more likely for women and 3 more likely for men.

Parameter symbol	Definition	Estimated values and uncertainty ranges	Distributions and correlations	References and notes
τ	Recovery rate from symptomatic recurrence	0.2–0.3333 per day [i.e. duration of recurrence is 3–5 days]	Uniform	Several studies suggest 3–5 days shedding with lesions (Corey et al., 1983a; Corey and Wald, 1999; Guinan et al., 1981; Wald et al., 1997, 2000, 2002b). Approximated recovery rate as 1/(duration of symptomatic recurrence). Schacker et al. (1998) found no significant difference between HIV-infected and HIV-susceptible men who have sex with men.
σ_u	Rate of asymptomatic shedding episodes(for new infections)	0.0430–0.08 per day [i.e. 15.7–29.2 per year]	Uniform	Lower bound based on data that 4.3% of days sampled detected asymptomatic shedding from any genital site (cervix or vulva) among women with primary HSV-2 (Koelle et al., 1992), which converts to 15.7 episodes per year (assuming each lasts 1 day (see χ below)). Wald et al. (1997) reported much higher rates of shedding both as detected by culture, and as detected by PCR, for a sample of 27 women within 2 years of initial infection. So these PCR values were adjusted by factor difference between Wald et al. (1997) and culture values from Koelle et al. (1992), so estimates resemble more Wald et al. (2003). This produced estimate of 15% of days shedding. It is likely that shedding rate in years 3–5 is lower than in years 1–2 and so reduced shedding rate to 12% as average rate over years 1–5, which converts to 29.2 episodes per year (assuming each lasts 1.5 days (see χ below)) over first 5 years.
σ_w	Rate of asymptomatic shedding episodes(for old infections)	0.0216–0.04 per day [i.e. 7.9–14.6 per year]	Uniform	People with genital herpes for 5–10 years appear to have about half the subclinical shedding as women with disease of < 2 years duration (Corey and Wald, 1999). So halved estimates in above row for σ_u.
χ	Recovery rate from asymptomatic shedding episode	0.6667–1 per day [i.e. duration of asymptomatic shedding episode is 1-1.5 days]	Uniform	Mean and median estimates for duration of episode of asymptomatic shedding are in the range 1–1.5 days among those with a history of genital herpes (Wald et al., 1995, 1997, 2000). Approximated recovery rate as 1/(duration of episode).

CI, confidence interval; FSW, female sex worker; PCR, polymerase chain reaction

Appendix C: Input parameters for rate of HSV-2 infection

Parameter symbol	Definition	Estimated values and uncertainty ranges	Distributions and correlations	References and notes
Setting-specific inputs for population size and infection seeding:				
$P_{\text{qseed}} = N/T$	Seeding prevalence of HSV-2	28.9% (6.4–43%) in FSWs at start of sex work, (10–40%) in clients	Triangular for FSWs Uniform for clients Correlated FSW prevalence with client prevalence and correlated HSV-2 seeding prevalence with HIV seeding prevalence (all correlation coefficients set as +1.0).	For FSWs, a subanalysis was conducted to estimate HSV-2 prevalence by duration of sex work, calculated using data on current age of the FSWs and their age at starting sex work (KHPT, 2006). Using mid-time-points for resulting durations meant no data estimate could be obtained exactly as women enter sex work, so linear extrapolation was used to estimate this based on mean and 95% CIs from data for 0.5 and 1 year in sex work. Data from three referral STI clinics and a reproductive tract infection clinic in Pune were used to reduce the upper bound on the HSV-2 prevalence estimates for women entering sex work in Mysore (Reynolds et al., 2003). Client HSV-2 prevalence range based on several data estimates, and calculations using client age distributions (NACO, 2001; Ramesh et al., 2003). For lower bound, data were used from general population males in northern Karnataka and low-risk males in Vellore, Tamil Nadu (Cowan et al., 2003; ICHAP, 2004/2005; National Informatics Centre, 2004). For upper bound, data from STI clinics in Pune and Mumbai, Maharashtra, and a STI clinic attached to a medical college in south India (Jacob et al., 1989; Kura et al., 1998; Reynolds et al., 2003) were used. Data from reviews of prevalences in STI clinics across India were also incorporated (Hawkes and Santhya, 2002; Sharma and Khandpur, 2004).
Behavioral inputs:				
n	Average number of sexual acts per FSW-client partnership during fixed time-period	2.1 (1.5–3.2) sex acts per year per each FSW-client partnership	Triangular Correlated to m by coefficient −0.5.	Using data on Mysore FSWs, multiplied mean number of clients per day by mean number of days work per month then by 12, then divided by the mean number of clients per FSW per year (KHPT, 2006). Range based on repeat calculation using 95% CIs from the data in combination to produce lower and upper estimates.

Parameter symbol	Definition	Estimated values and uncertainty ranges	Distributions and correlations	References and notes
m	Average number of clients per FSW over fixed time-period	213 (155–271) clients per FSW per year	Triangular Correlated to n by coefficient −0.5.	Using data on Mysore FSWs, estimated number of one-time clients per year (KHPT, 2006). Similarly, using same data set, estimated number of sex acts with regular clients per FSW per year. Assumed that mean number of clients per day reflects multiple counting of repeat clients if multiply up over a year, then found difference per FSW between total number of commercial sex acts per year and mean number of one-time clients, and this difference gave estimate for number of sex acts with regular clients per FSW per year. Dividing this by estimated number of sex acts with same FSW per regular client per year gave estimated number of regular clients per FSW per year. Range based on repeat calculation using 95% CIs from the data in combination to produce lower and upper estimates.
f	Average consistency of condom use	62% (56–65%)	Triangular	Using data on condom use reported by FSWs in Mysore (KHPT, 2006). Mean condom use (out of every 10 clients) was reported to be 61.7% (95% CI 58.8–64.5%). Mean consistency of use was also estimated as 55.8% by using the frequency distribution of consistency of condom use and assuming use 'almost every time' was 75% of the time and 'sometimes' use was 25%. 64.8% reported condom use with last client.
f_{circ}	Proportion of males who are circumcised	15% (12–18%)	Triangular	3.4% of Hindus, 97.5% of Muslims and 2.3% of other religions attending 3 STI clinics in Pune were circumcised (clinical examination) (Reynolds et al., 2004). The Census of India (2001) reports that in Karnataka 83.9% of population are Hindus, 12.2% are Muslims and 3.9% of population are of other religions. So, overall in Karnataka, approximately 83.9%*3.4%+12.2%*97.5%+3.9%*2.3% = 14.9% of males are circumcised. To obtain lower bound assumed only Muslims are circumcised. Then assumed same difference above 15% for upper bound.

Parameter symbol	Definition	Estimated values and uncertainty ranges	Distributions and correlations	References and notes
HSV-2 biological parameters:				
B and Λ	HSV-2 transmission probability per sex act and state-related cofactors	Range for transmission probability B while partner is asymptomatically shedding: 0.002–0.04 for male-to-female and 0.002–0.02 for female-to-male. Multiplicative cofactor Λ for increased transmission in state R or I: $\Lambda = 4$–6 if symptomatic in I; $\Lambda = 1$–3 if asymptomatic in I; Λ=1 if asymptomatic in state A; $\Lambda = 2.5$–3.5 if symptomatic in R. [cofactor Λ is not used if partner is HSV-2-negative]	Uniform Correlated male and female transmission probabilities to each other with coefficient of +1.0.	HSV-2 transmission probability is 0.001 per sex act when averaged over both sexes and all infection states (including latent periods) from several studies (Bryson et al., 1993; Corey et al., 2004b; Mertz et al., 1988; Wald et al., 2001). Same value also obtained by calculating ratio of Taylor Series linear approximations for HIV incidence (π) and HSV-2 incidence (λ), then substituting in values for HSV-2 incidence and prevalence and HIV incidence (Reynolds et al., 2003), and HIV prevalence (Bentley et al., 2000; Gadkari et al., 1998; Joshi et al., 2001), and HIV transmission probability (Boily et al., 2007a), to estimate the HSV-2 transmission probability. Several studies suggest that Λ in state $A < \Lambda$ in state $R < \Lambda$ in state I (Guinan et al., 1981; Mertz et al., 1985; Wald et al., 1997, 2003). Set Λ to be 1 in state A by definition. Wald et al. (2003) suggest a cofactor of 3 during symptomatic recurrences (state R) so used range 2.5–3.5. Expected Λ in initial asymptomatic infection (state I_2) to be $<$ in state R but $\geq$ in state A so used range 1–3. Expected Λ to be largest in initial symptomatic infection (state I_1) so used range 4–6. Ranges for Λ then each multiplied by the proportion of days spent shedding in each corresponding state (Langenberg et al., 1999; Wald et al., 2000, 2003), using culture and PCR estimates to provide uncertainty ranges. Multiplies then summed to give the weighted average Λ. Overall HSV-2 transmission probability estimate of 0.001 then divided by weighted average Λ to give estimated value for B. Several studies suggest that the male-to-female HSV-2 transmission probability is greater than the female-to-male transmission probability (Bryson et al., 1993; Corey et al., 2004b; Langenberg et al., 1999; Mertz et al., 1992; Wald et al., 2001). However, Wald et al. (2005) found only slightly lower rate of acquisition among men than women (no significant difference). So used same lower bound for both B but higher upper bound for male-to-female transmission.

Parameter symbol	Definition	Estimated values and uncertainty ranges	Distributions and correlations	References and notes
e_{HSV}	Per sex act effectiveness of condom against HSV-2	50–80%	Uniform	Comparing groups using condoms in <25% of sex acts with those using condoms in >75%, produced an estimated reduction in risk of HSV-2 of 45% in one study (Wald et al., 2005). In another study, overall reduction in risk among men and women was 75% (Holmes et al., 2004; Wald et al., 2001). Risk was reduced by 42% if condoms were used in >65% of sex acts (Holmes et al., 2004; Wald et al., 2002a). Would expect greater reductions in risk if compared 'always' and 'none' condom users, so used range 50–80% to approximate efficacy.
$e_{circ\,HSV}$	Per sex act efficacy of male circumcision in protecting males from HSV-2 acquisition	31% (0–87%)	Triangular	As main value used 1-RR from systematic review by Weiss et al. (2006), using also their lower bound of no protective effect. Upper bound of uncertainty range based on upper bound of 95% CI for protective effect of circumcision in period 12–21 months estimated by Auvert et al. (2005).

Appendix D: State variables for "simple" model of the natural history of Herpes simplex virus type-2 (HSV-2)

State variable symbol	State variable definition
S	Susceptible to HSV-2
I	Experiencing initial HSV-2 infection (infectious) with a proportion of people being symptomatic and the remainder being asymptomatic
A	Latent phase with a proportion of people asymptomatically shedding (infectious)
R	Symptomatic recurrence or first symptomatic episode following asymptomatic infection (infectious)

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