**Technical Appendix**

**Model Equations:**

The state variables in the model equations are represented by the values

\[ X^{h,p,v}_{k,l} \]

Which denotes a class of the population where the subscripts \( k \) and \( l \) refer to sex (\( k=1 \) for men and \( k=2 \) for women) and sexual activity class (\( l=1,\ldots,4 \)) respectively, and the superscripts \( h \), \( p \), and \( v \) refer to HSV-1 infection status, HSV-2 infection status and vaccination status, respectively. Here \( h=1 \) is those who are HSV-1 positive and \( h=2 \) are those who are HSV-1 negative; \( p=0 \) are those uninfected with HSV-2, \( p=1 \) those with primary HSV-2 disease, \( p=2 \) and \( p=5 \) those with a latent HSV-2 infection, \( p=3 \) and \( p=6 \) with recurrent symptomatic HSV-2 viral shedding and \( p=4 \) and \( p=7 \) those with asymptomatic viral shedding. The division of those with latent infection and viral shedding into two categories allows for different rates of viral shedding and disease in a subset of the population, which can serve two functions. First, it could be used to explore the idea that some individuals experience less severe infections than others. Alternatively it could allow for a fraction of those vaccinated to experience an altered pattern of reactivation. The three vaccination states are \( v=1 \) unvaccinated, \( v=2 \) protected by vaccine but allowing breakthrough infections and \( v=3 \) protected by vaccine against all exposures.

The model equations are as follows:
\[
\begin{align*}
\frac{dX_{k,j}^{h,0,1}}{dt} &= \phi_{k,j} \pi_h (1 - V_{k,j} \eta_{k,j}) - (r_{k,j} \eta_{k,j} + \mu + \lambda_{k,j}^h) X_{k,j}^{h,0,1} - f X_{k,j}^{h,0,2}, \\
\frac{dX_{k,j}^{h,0,2}}{dt} &= \phi_{k,j} \pi_h V_{k,j} \eta_{k,j} \omega_k + r_{k,j} \eta_{k,j} X_{k,j}^{h,0,1} \omega_k - (f + \mu + \lambda_{k,j}^h) X_{k,j}^{h,0,2}, \\
\frac{dX_{k,j}^{h,0,3}}{dt} &= \phi_{k,j} \pi_h V_{k,j} \eta_{k,j} (1 - \omega_k) + r_{k,j} \eta_{k,j} X_{k,j}^{h,0,1} (1 - \omega_k) - (\mu + f) X_{k,j}^{h,0,3}, \\
\frac{dX_{k,j}^{h,1,1}}{dt} &= \psi_{k_h,1} \lambda_{k,j}^h X_{k,j}^{h,0,1} - (\mu + \sigma_{h,1}) X_{k,j}^{h,1,1}, \\
\frac{dX_{k,j}^{h,1,2}}{dt} &= \psi_{k_h,2} \lambda_{k,j}^h X_{k,j}^{h,0,2} - (\mu + \sigma_{h,2}) X_{k,j}^{h,1,2}, \\
\frac{\partial X_{k,j}^{h,2,v}(t, \tau)}{\partial t} + \frac{\partial X_{k,j}^{h,2,v}(t, \tau)}{\partial \tau} &= -(\gamma_{k_h,1,1,v}(\tau) + \gamma_{k_h,1,2,v}(\tau) + \mu) X_{k,j}^{h,2,v}(t, \tau) + \alpha_{k_h,1,1,v} X_{k,j}^{h,3,v}(t, \tau) + \alpha_{k_h,1,2,v} X_{k,j}^{h,4,v}(t, \tau), \\
X_{k,j}^{h,2,v}(t, 0) &= \delta \left[ X_{k,j}^{h,1,v}(t) \sigma_{h,v} g_{1,v} + \lambda_{k,j}^h X_{k,j}^{h,0,1}(t)(1 - \psi_{k_h,1}) g_{2,v} \right], \\
X_{k,j}^{h,3,v}(t, 0) &= \delta \left[ X_{k,j}^{h,1,v}(t) \sigma_{h,v} (1 - g_{1,v}) + \lambda_{k,j}^h X_{k,j}^{h,0,1}(t)(1 - \psi_{k_h,1})(1 - g_{2,v}) \right], \\
X_{k,j}^{h,3,v}(t, 0) &= X_{k,j}^{h,4,v}(t, 0) = X_{k,j}^{h,7,v}(t, 0) = 0, \\
\frac{\partial X_{k,j}^{h,5,v}(t, \tau)}{\partial t} + \frac{\partial X_{k,j}^{h,5,v}(t, \tau)}{\partial \tau} &= -(\gamma_{k_h,2,1,v}(\tau) + \gamma_{k_h,2,2,v}(\tau) + \mu) X_{k,j}^{h,5,v}(t, \tau) + \alpha_{k_h,2,1,v} X_{k,j}^{h,6,v}(t, \tau) + \alpha_{k_h,2,2,v} X_{k,j}^{h,7,v}(t, \tau), \\
\frac{\partial X_{k,j}^{h,6,v}(t, \tau)}{\partial t} + \frac{\partial X_{k,j}^{h,6,v}(t, \tau)}{\partial \tau} &= \gamma_{k_h,1,1,v}(\tau) X_{k,j}^{h,2,v}(t, \tau) - (\mu + \alpha_{k_h,1,1,v}) X_{k,j}^{h,3,v}(t, \tau), \\
\frac{\partial X_{k,j}^{h,7,v}(t, \tau)}{\partial t} + \frac{\partial X_{k,j}^{h,7,v}(t, \tau)}{\partial \tau} &= \gamma_{k_h,2,1,v}(\tau) X_{k,j}^{h,5,v}(t, \tau) - (\mu + \alpha_{k_h,2,1,v}) X_{k,j}^{h,6,v}(t, \tau), \\
\frac{\partial X_{k,j}^{h,7,v}(t, \tau)}{\partial t} + \frac{\partial X_{k,j}^{h,7,v}(t, \tau)}{\partial \tau} &= \gamma_{k_h,2,2,v}(\tau) X_{k,j}^{h,5,v}(t, \tau) - (\mu + \alpha_{k_h,2,2,v}) X_{k,j}^{h,7,v}(t, \tau), \\
\lambda_{k,j}^h &= c_{k,j} \sum_{m=1}^{4} \rho_{k,1,m} \sum_{h=1}^{2} \left[ \frac{X_{k,j}^{h,1,v}}{N_{k,j}^{h,m}} (1 - \beta_k) \eta_{i,m} \left[ \frac{1}{\tau_{h,m}} \right] \right] + \sum_{T=1}^{u} \left[ \frac{Y_{k,j}^{h,v}(T)}{N_{k,j}^{h,m}} (1 - \beta_k) \eta_{i,m} \left[ \frac{1}{\tau_{h,m}} \right] \right], \\
Y_{k,j}^{h,v}(T) &= \sum_{T=1}^{u} \sum_{h=1}^{2} X_{k,j}^{h,1,v}(t, \tau'){J_{k,j}^{h,v}(t, \tau')}d\tau', \\
F_{k,j}^{h,v}(T) &= \sum_{T=1}^{u} \left[ cX_{k,j}^{h,3,v}(t, \tau') + X_{k,j}^{h,4,v}(t, \tau') + X_{k,j}^{h,6,v}(t, \tau') + X_{k,j}^{h,7,v}(t, \tau') \right]d\tau'/Y_{k,j}^{h,v}. 
\end{align*}
\]
### Table A1 Glossary of model parameters.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
<th>Value(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \phi_{k,l} )</td>
<td>Proportion of each cohort entering population recruited into sexual activity group ( l ).</td>
<td>( k = 1 ): 0.0055, 0.0445, 0.2, 0.75 &lt;br&gt;( k = 2 ): 0.0055, 0.0145, 0.1, 0.88</td>
</tr>
<tr>
<td>( c_{k,l} )</td>
<td>Rate of sex partner change (per year)</td>
<td>Derived from the overall mean of 2 and ratio of activity in men 80:20:4:8:1</td>
</tr>
</tbody>
</table>
| \( \rho_{k,l,m} \) | Probability for someone of sex \( k \), activity group \( l \), that a partner is from group \( m \). | Derived from the proportions in activity groups, rates of partner change and mixing parameter \( \varepsilon = 0.2 \).
| \( s \) | Proportion of unprotected sex acts remaining in the presence of disease. | Assumed to be 0.5 (i.e. there is a 50% reduction in risky exposures associated with disease episodes). |
| \( N_{k,m} \) | The number of people of sex \( k' \) in activity group \( m \). | Number summed over HSV-1, HSV-2 and vaccination status. |
| \( \beta_{k} \) | The transmission probability per unprotected sex act when virus is shed from sex \( k' \) to sex \( k \). | Adjusted to generate observed prevalences: \( \beta_1 = 0.09 \), \( \beta_2 = 0.015 \). |
| \( \rho_{l,m} \) | Number of unprotected sex acts per partnership between people in activity groups \( l \) and \( m \). | \( n_{1,m} = 4; n_{2,m} = 12; n_{3,m} = 48; n_{4,m} = 104; n_{5,m} = 104 \); |
| \( \sigma_{h,v} \) | Recovery rate from primary disease. | \( \sigma_{h,v} = 1/7 \) (days) |
| \( T \) | Years since acquiring infection | \( T_0 \): start of year, \( T_a \): end of year |
| \( \tau' \) | Time since infection |
| \( \pi_{h} \) | The proportion of those entering the sexually active population with HSV-1 infection \( (h=1) \) and without HSV-1 infection \( (h=2) \). | \( \pi_1 = 0.6; \pi_2 = 1 - \pi_1 = 0.4 \) |
| \( \nu_{k,l} \) | The fraction of each cohort immunized | \( \nu_{1,l} = 0.0 \) for \( l = 1, \ldots, 4 \) except Fig. 5b. \( \nu_{2,l} = 0.5 \) for \( l = 1, \ldots, 4 \) except Fig. 5a. |
| \( \eta_{k,h} \) | The take of the vaccine | \( \eta_{k,1} = 0.0; \eta_{k,2} = 1.0 \) |
| \( r_{k,l} \) | The catch-up rate of immunization per susceptible per year. | \( r_{1,l} = 0.0 \) for \( l = 1, \ldots, 4 \) except Fig. 5b. \( r_{2,l} = 0.05 \) for \( l = 1, \ldots, 4 \) except Fig. 5a. |
| \( f \) | Rate of loss of vaccine protection per year | \( f = 0.0 \) |
| \( \mu \) | Rate of exit from the sexually active population. | \( \mu = 1/30 \) (years) |
| \( \phi_h \) | Proportion immunised that remain susceptible to infection | Estimated from vaccine trials |
| \( \psi_{k,h,v} \) | Proportion of those infected who develop primary disease | \( \psi_{1,1,v} = 0.21; \psi_{2,1,v} = 0.38; \psi_{1,2,v} = 0.3; \psi_{2,2,v} = 0.54. \) |
| \( \rho_{k,h,p',d,v} \) | Rate per year of reactivation, by sex and HSV-1 status, ‘pathogenesis group, symptoms and vaccine status | Derived from equations (see text) |
| \( \gamma_{k,h,p',d,v} \) | Rate of recovery per year, by sex and HSV-1 status, ‘pathogenesis group, symptoms and vaccine status | Mean duration of symptomatic episodes 6 days and asymptomatic episodes 2 days. |
| \( \alpha_{k,h,p',d,v} \) | Rate of recovery per year, by sex and HSV-1 status, ‘pathogenesis group, symptoms and vaccine status | Mean duration of symptomatic episodes 6 days and asymptomatic episodes 2 days. |
| \( g_{d,v} \) | Fraction suffering recurrences after primary disease \( (d=1) \) or on initial asymptomatic infection \( (d=2) \) | \( g_{d,1}; g_{d,2} \) depends upon vaccine efficacy. |
| \( \varepsilon \) | Pattern of mixing \( (0= \text{random}; 1= \text{assortative}) \) | \( \varepsilon = 0.2 \) |
The risk of acquiring HSV-2 per susceptible per year is dependent upon the sex, sexual activity class and the HSV-1 sero-status of the susceptible individual and is represented by the value:

\[ \lambda_{k,l}^h \]

which is a function the partner change rate, pattern of sexual partner choice and the infectious state of sex partners. In the equation for the derivation of the force of infection the value \( Y_{k',m}^{h,v} \) is the cumulative number of those infected post primary disease, and \( F_{k',l}^{h,v} \) is the number of those infected, post-primary shedding virus and still sexually active. The patterns of sexual activity of one sex are constrained by the activity in the other sex. For simplicity and clarity we chose to specify the overall mean rate of sex partner change, \( c \), the fraction of men and women recruited into each sexual activity group, \( \phi_{k,l} \), which we assume they remain within, and a ratio of sexual activity amongst the men, \( ratio_i \). From these values and the pattern of mixing, \( \varepsilon \), the rates of partner change per year of each group, \( c_{k,l} \), can be calculated.

\[
c_{1,l} = ratio_l \frac{\varepsilon}{\sum_l (\phi_{1,l} ratio_l)}
\]

\[
\rho_{k,l,m} = c_{1,l} \delta_{l,m} + (1 - c) \frac{c_{k,m} \phi_{km}}{\varepsilon}
\]

\[
c_{2,l} = \frac{\phi_{1,l} \rho_{1,l,m} \varepsilon c_{1,m}}{\rho_{2,l,m} \phi_{2,l}}
\]

where \( \delta_{lm} \) is the identity matrix. Based on studies of reported partner characteristics in the U.S. [11,12] a pattern of mixing close to random (\( \varepsilon=0.2 \)) was chosen for the simulations presented.

On infection a fraction of the population, which depends upon their prior HSV-1 infection and vaccination status, develop primary disease. The remainder enter the latently infected class, which has two categories. This instantaneous ‘incidence’ (the incidence over the time step of numerical model solutions) provides the boundary conditions of the partial differential equations describing infection with respect to time and time since infection. As described above the division of the population into two categories, ‘pathogenic groups’, on infection can serve two functions (1) If some individuals are more disposed to symptomatic
and asymptomatic viral shedding this distinction can be represented. (2) Alternatively, if it is assumed that the use of vaccine alters risks of disease and asymptomatic shedding in only a fraction of those immunised the effect of vaccine can be reflected by the parameter values for the different pathogenic groups. In the light of observed patterns of disease and asymptomatic viral shedding, the second use predominates in the results presented here because it allows for a vaccine to have a partial effect on susceptibility to infection and a further partial effect on susceptibility to disease.

The proportion of the population developing primary disease was assumed to depend upon prior HSV-1 status and sex observed in a prospective cohort. Langenberg and colleagues [3] record that 29/92 men (31.5%) and 28/63 women (44.4%) developed primary disease and that 27/29 (28%) of HSV-1 positive and 30/60 (50%) of HSV-1 negatives developed disease. Assuming that the relative risk of disease in HSV-1 infected and uninfected women is the same then the proportion of each class experiencing primary disease can be derived.

Rates of recurrences and asymptomatic shedding events were assumed to occur at a rate, which depended upon time since infection, with a number of assumptions explored.

The equations:

\[ \gamma_{k,h,p',l,1} = 6 - 0.8\tau \quad \text{for } \tau < 5 \]
\[ \gamma_{k,h,p',l,1} = 2 \quad \text{for } \tau \geq 5 \]
\[ \gamma_{k,h,p',l,1} = 6 - 0.8\tau \quad \text{for } \tau < 8 \]
\[ \gamma_{k,h,p',l,1} = 0 \quad \text{for } \tau \geq 8 \]
\[ \gamma_{k,h,p',l,1} = 6e^{-0.143\tau} \]
\[ \gamma_{k,h,p',l,1} = 2 + 4e^{0.223\tau} \]

were all explored for the rate of reactivation of disease, with a six fold greater rate of asymptomatic viral shedding. In the first year of infection this implies 36 days (i.e. 9.8% of the time with recurrences), because each recurrence is assumed to last for 6 days on average.
As asymptomatic shedding episodes are assumed to last 2 days on average the 6 fold greater frequency implies 72 days in the first year with asymptomatic shedding (i.e. 19.6% of the first year). These figures are commensurate with the observed isolation of viral DNA on swabs from women on 28% of 1410 days from 27 seropositive women [21]. These rates were reduced to zero in those fully protected by vaccination from disease or asymptomatic viral shedding. The rate of recovery from symptomatic disease or asymptomatic infection could potentially also vary according to a number of factors. However, the results presented here these recovery rates were assumed to be constant.

Algorithm for calculating the impact of vaccination.

For each scenario the efficacy of the vaccine in preventing infection and disease is specified. It has to be assumed that the effect on disease is a combination of a reduced incidence of infection and a reduced incidence of disease in those with breakthrough infection. To simply represent an effect on disease the rate of incidence of recurrences can be set to zero in a fraction of those vaccinated who have acquired infection \((1-g_{d,2})\). Likewise the rate of incidence of asymptomatic viral shedding episodes can be adjusted in this subset of the population to reflect assumptions about the influence of the vaccine on viral shedding. The efficacy assumed has to be translated into model parameters as follows: Of those vaccinated a fraction, equal to the efficacy against infection (e.g. 42%), are assumed insusceptible. The remainder can acquire infection and disease. Of those who acquire breakthrough infections a fraction will develop primary disease, and a further fraction will develop disease after a latent infection. Together these constitute the vaccine failures. If vaccine efficacy against disease is 73 percent it is assumed that 27 percent those protected can develop disease either primary or after recurrences. On infection they have the risk of primary disease of their sex and HSV-1 status reduced efficacy of the vaccine. It is assumed that the reduction in primary disease is one minus the complete vaccine efficacy divided by the fraction of those vaccinated who remain susceptible. Once someone has experienced primary disease it is assumed that they continue to be at risk for recurrences. The rest progress to a
latent infection, a group who are infected and have not yet had disease. The proportion of this group that can still experience episodes up to the level allowed by the efficacy of the vaccine enter the ‘pathogenic’ category and the proportion still protected against disease enter the ‘non-pathogenic’ category.

**Numerical solution**

The model is a complex analytically intractable combination of ordinary differential and partial differential equations containing integrals. The ordinary differential equations could be solved using a standard Runge-Kutta methods, whereas the partial differential equations were solved on a discretized grid with respect to time and time since infection, with numerical evaluation of integrals. Despite the models complexity it should be noted that in common with models of other sexually transmitted infection the system tends to an equilibrium with highly damped oscillations and because of the long duration of infection the model dynamics evolve slowly. Such model behaviour is relatively straightforward for numerical algorithms. Univariate sensitivity analysis was carried out during the model development to test the impact of assumptions specific to the system being modelled. For example, the patterns of recurrences, the rate of recovery from episodes and the influence of vaccine preventing all disease in some versus some disease in all. The model behaviour was found to be quantitatively, but not qualitatively altered by changes in the values explored. Model solutions were too slow to explore the full parameter space as has been done for much simpler models of STD transmission dynamics \[A1,A2\]. However, it would be expected that the key terms in these earlier explorations (i.e. those contribution to the reproductive number of infection: the duration of infectiousness, the partner change rates, patterns of mixing and transmission probabilities) would be the most significant determinants of prevalence.

**Appendix references:**