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Research article

Dynamics of HSV-2 infection with a therapeutic vaccine

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ABSTRACT

Herpes-Simplex Virus type 2 (HSV-2) is a lifelong infection, which has infected over 400 million individuals aged 15-49 years, worldwide. While the disease can be treated with episodic and suppressive antiviral drugs to reduce the rate of recurrence (i.e., symptomatic disease) and viral shedding, none of the currently available therapies can clear the virus from the body of an infected person. A number of therapeutic vaccine platforms are currently in development in order to achieve similar effects to treatment. Due to the inadequate data from clinical trials of therapeutic vaccines, modeling efforts to quantify the impact of vaccination have been limited. In this study, we propose a compartmental deterministic model for the dynamics of HSV-2 to evaluate the effect of a potential vaccine candidate with the inclusion of a booster dose. Despite its simplicity that may not address the complexity of HSV-2 disease, the model shows that targeting symptomatic infection for vaccination is the most effective strategy in the long-term. This conclusion is based on the assumption of an optimal vaccine efficacy, conferring immunity levels that prevent viral shedding and recurrence transiently. Our model provides a framework for developing a computational system to include more heterogeneous characteristics of the disease and individuals, and investigate effectiveness and cost-effectiveness of vaccination scenarios when clinical data become available.

1. Introduction

Herpes-Simplex Virus type 2 (HSV-2) is a lifelong infection commonly associated with genital herpes [1, 2]. The virus does not trigger an effective immune response due to the lack of viral protein expression, and therefore clearance through adaptive immunity is not achievable. Rates of HSV-2 infections remain high, especially in individuals between 15-49 years of age [1]. There is a wide diversity of the clinical spectrum of HSV-2 disease [3], including asymptomatic and symptomatic manifestations, with painful genital lesions [4, 5]. While the infection following exposure can be asymptomatic, it can be infectious (i.e., can shed virus) and develop to symptomatic disease [6]. The first symptomatic episode is the most severe episode, and can be returned to asymptomatic stage using antiviral treatment [4, 7].

Most individuals with initial episode of symptomatic HSV-2 experience recurrences, and the frequency can reach 6 or more episodes every year [8]. Recurrence rates are especially high in individuals with an extended first episode of symptomatic disease. Men with genital HSV-2 infection experience about 20% more recurrences than do women, which can contribute to the higher rate of transmission from men to women than from women to men [8].

Symptomatic HSV-2 can be treated with episodic and suppressive antiviral treatments [9, 10, 11]. Although none of the currently available therapies can clear the virus from the body of an infected person, they generally suppress the symptoms. Treatment can reduce the severity and duration of symptoms, decrease viral shedding and neonatal herpes, facilitate healing of lesions, and lower the risk of complications and long-term sequelae [12]. Suppressive treatment is generally offered to patients with frequent recurrences and can be taken over several years to reduce the frequency of symptomatic recurrence [9, 10, 11].

Because treatment does not prevent shedding (although it may reduce its rate on average), there has been a surge of interest in developing therapeutic vaccines [13, 14, 15, 16, 17]. These vaccines may be targeted towards HSV-2 patients to act as suppressive treatment in order to extend the length of inter-episodic period (i.e., reducing the frequency of recurrences) while preventing virus shedding [18]. However, due to the limited data from clinical trials of HSV-2 therapeutic vaccines, modeling efforts have been limited in evaluating the impact

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of vaccination. Previous mathematical models have mainly investigated the potential impact of a prophylactic HSV-2 vaccine [19, 20, 21, 22, 23], while accounting for the population-level effectiveness of vaccination and the relative reduction in HSV-2 prevalence over time. Previous work suggests that the HSV-2 epidemic is most sensitive to changes in behavioral responses and to the probability of transmission during the asymptomatic stage, even in the presence of vaccine [19]. It has also been shown that therapeutic vaccines are likely to outperform prophylactic vaccines over time [21, 22]. We found only one modeling study on the effect of a therapeutic vaccine [21], concluding that vaccination can substantially reduce the prevalence of disease if a significant portion of asymptomatic HSV-2 patients are vaccinated each year.

In this study, we propose a compartmental deterministic model for the dynamics of HSV-2 for the effect of therapeutic vaccination, with the inclusion of a booster dose. The proposed model is relatively simple with few parameters, and does not address the complexity of the disease and variability in individual and infection characteristics. However, it can be used illustrate the potential effect of vaccination and build the foundation for future studies that involve more heterogeneous characteristics of the disease and individuals. We analyze the model and simulate it stochastically to show the effect of vaccination on the prevalence of HSV-2 over time in various scenarios including primary and booster vaccination. The novelty of this model relates to its structural components that allow for vaccination of primary symptomatic that is shown to be the most severe episode [24, 25], and booster vaccination with transient vaccine protection effects on recurrence [18]. These important components were absent in the previous work [21]. Using our model, we show that in contrast with previous work [21], therapeutic vaccination of HSV-2 infection may be most effective when targeted towards symptomatic infection with highest possible rates rather than asymptomatic.

2. The basic model

To develop a vaccination mode for HSV-2 infection dynamics, we first consider a simple model where vaccination is targeted towards only infected individuals who develop symptomatic infection. In this model, the total population (N) is divided into four classes of susceptible (S), symptomatically infectious (I), asymptomatically infectious (A), and vaccinated individuals (D). We do not consider any recovered class as HSV-2 is a life-long infection. For this study, we assume a highly effective vaccine that can reduce the frequency of recurrence (i.e., developing symptomatic disease), and prevent virus shedding during the vaccine-induced protection. We assumed newly infected individuals develop primary symptomatic infection following exposure. Symptomatic cases either receive suppressive treatment or vaccination. Those who are treated with suppressive drugs move to the asymptomatic class A and may still contribute to disease spread with a lower rate compared to symptomatic cases. Those who are vaccinated during symptomatic stage move to the class D and do not contribute to the spread of disease for the duration of vaccine-induced protection. Summarizing the above dynamics, the model can be expressed by the following system of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta S(I+\delta A) - \mu S \\
\frac{dI}{dt} &= \beta S(I+\delta A) - (\gamma+\xi)I + \eta A - \mu I \\
\frac{dA}{dt} &= \gamma I - (\eta+\mu)A + \theta D \\
\frac{dD}{dt} &= -(\mu+\theta)D + \xi I
\end{aligned} \tag{1}$$

where μ is the rate of natural death assumed to be the same as the birth rate for simplicity of the analysis (i.e., keeping the total population $N = S + I + A + D$ constant), β is the baseline transmission rate of symptomatically infectious individuals, δ is the relative transmissibility of asymptomatic infection compared to symptomatic infection, γ and ξ are the rates of suppressive treatment and vaccination for symptomatic infection, respectively, η is the rate of recurrence, and θ is the rate of loss of vaccine-induced immunity.

This system admits two steady states, namely the disease-free equilibrium (DFE) $E_0 = (N, 0, 0, 0)$ and the endemic equilibrium (EE) $E_* = (S_*, I_*, A_*, D_*)$. The latter can be analytically obtained as follows. Solving the fourth and the third equations of (1) at the steady state, we find:

$$I_* = \frac{\mu+\theta}{\xi} D_*, \quad A_* = \frac{D_*}{\mu+\eta}\left[\gamma\frac{\mu+\theta}{\xi} + \theta\right].$$

Upon substitution of the above quantities respectively into the second and first equations of (1), we get:

$$S_* = \frac{(\gamma+\xi+\mu)(\mu+\theta)(\mu+\eta) - \eta\gamma(\mu+\theta) - \theta\xi\eta}{\beta[(\mu+\theta)(\mu+\eta) + \delta\gamma(\mu+\theta) + \delta\xi\theta]},$$

$$D_* = \frac{\mu(N-S_*)\xi(\mu+\eta)}{\beta S_*[(\mu+\theta)(\mu+\eta) + \delta\gamma(\mu+\theta) + \delta\xi\theta]}.$$

Nonnegativity of the populations is ensured, except for D_* which requires $S_* \le N$. This condition explicitly becomes:

$$R_c = \frac{\beta N[(\mu+\theta)(\mu+\eta+\delta\gamma) + \delta\xi\theta]}{\mu[(\gamma+\eta+\mu)(\mu+\theta) + \xi(\mu+\theta+\eta)]} \ge 1. \tag{2}$$

2.1. Stability of the DFE

For the stability of the DFE, we investigate the Jacobian of the system given by:

$$\widetilde{J} = \begin{pmatrix} -\beta(I+\delta A) - \mu & -\beta S & -\beta\delta S & 0 \\ \beta(I+\delta A) & \beta S - (\gamma+\xi+\mu) & \beta\delta S + \eta & 0 \\ 0 & \gamma & -(\eta+\mu) & \theta \\ 0 & \xi & 0 & -(\theta+\mu) \end{pmatrix} \tag{3}$$

At the DFE, we find that one eigenvalue of the Jacobian evaluated at E_0 is explicitly known as $-\mu$. For establishing stability, we use the Routh-Hurwitz criterion on remaining submatrix of order three, $\widetilde{J}_{E_0}$.

Denoting the principal minors of $\widetilde{J}_{E_0}$ by $\widetilde{\Delta}_0$, with further indices corresponding to the elements of the diagonal that pertain to them, the first condition on the trace can be written as

$$\begin{aligned}
\mathrm{tr}(\widetilde{J}_{E_0}) &= \sum_{k=1}^{3} \Delta_{0,k} < 0, \\
\widetilde{\Delta}_{0,1} &= \beta N - (\gamma+\xi+\mu), \\
\widetilde{\Delta}_{0,2} &= -(\eta+\mu), \\
\widetilde{\Delta}_{0,3} &= -(\theta+\mu).
\end{aligned}$$

The sum of the minors of order two becomes

$$\begin{aligned}
\widetilde{M}_2 &= \widetilde{\Delta}_{0,12} + \widetilde{\Delta}_{0,13} + \widetilde{\Delta}_{0,23}, \\
\widetilde{\Delta}_{0,13} &= (\mu+\theta)(\gamma+\xi+\mu-\beta N) > 0, \\
\widetilde{\Delta}_{0,12} &= (\mu+\eta)(\gamma+\xi+\mu-\beta N) - \gamma(\beta\delta N + \eta) > 0, \\
\widetilde{\Delta}_{0,23} &= (\mu+\theta)(\mu+\eta).
\end{aligned}$$

For the determinant we must have:

$$-\det(\widetilde{J}_{E_0}) = (\mu+\theta)\widetilde{\Delta}_{0,12} - (\beta\delta N + \eta)\theta\xi > 0.$$

In addition, the condition

$$-\mathrm{tr}(\widetilde{J}_{E_0})\widetilde{M}_2 > -\det(\widetilde{J}_{E_0}) \tag{4}$$

must be satisfied.

Now, from the trace, explicitly we have

$$N < \frac{\gamma+\xi+\eta+\theta+3\mu}{\beta}, \tag{5}$$

while the condition on the determinant can explicitly be rewritten as

$$R_c = \frac{\beta N[(\mu+\theta)(\mu+\eta+\delta\gamma)+\delta\xi\theta]}{\mu[(\gamma+\eta+\mu)(\mu+\theta)+\xi(\mu+\theta+\eta)]} < 1. \tag{6}$$

However, condition (5) can be neglected as it is already implied by (6), in view of the fact that the upper bound for N obtained from (6) is smaller than the one implied by (5), because the following inequality is satisfied:

$$\mu[(\gamma+\eta+\mu)(\mu+\theta)+\xi(\mu+\theta+\eta)]$$
$$< (\gamma+\xi+\eta+\theta+3\mu)[(\mu+\theta)(\mu+\eta+\delta\gamma)+\delta\xi\theta].$$

Thus, the sole conditions for stability of the DFE turn out to be (6) and (4). On comparing it with (2), a transcritical bifurcation between E_0 and E_* is seen to exist, [26], for which the two equilibria are mutually exclusive.

2.2. Stability of the EE

Stability of E_* can be assessed in the same way. The diagonal entries of the Jacobian can be simplified using the equilibrium equations, in particular we find

$$\widetilde{J}_{*,11} = -\mu\frac{S_*}{N}, \quad \widetilde{J}_{*,22} = -\frac{A_*}{I_*}(\beta\delta S_* + \eta),$$
$$\widetilde{J}_{*,33} = -\frac{1}{A_*}(\gamma I_* + \theta D_*), \quad \widetilde{J}_{*,44} = -\xi\frac{I_*}{D_*}.$$

The condition on the trace is easily seen to be satisfied:

$$-\mathrm{tr}(\widetilde{J}_{E_*}) = \sum_{k=1}^{4}\widetilde{J}_{*,kk} > 0.$$

Moreover for the minors of order 2, we find

$$\widetilde{\Delta}_{*,12} = \widetilde{J}_{*,11}\widetilde{J}_{*,22} + \beta^2(I_* + \delta A_*)S_* > 0,$$
$$\widetilde{\Delta}_{*,23} = \widetilde{J}_{*,22}\widetilde{J}_{*,32} - \gamma(\beta\delta S_* + \eta),$$
$$\widetilde{\Delta}_{*,13} = \widetilde{J}_{*,11}\widetilde{J}_{*,33} > 0,$$
$$\widetilde{\Delta}_{*,14} = \widetilde{J}_{*,11}\widetilde{J}_{*,44} > 0,$$
$$\widetilde{\Delta}_{*,24} = \widetilde{J}_{*,22}\widetilde{J}_{*,44} > 0,$$
$$\widetilde{\Delta}_{*,34} = \widetilde{J}_{*,33}\widetilde{J}_{*,44} > 0,$$

so that their sum is

$$\widetilde{M}_{*,2} = \sum_{\substack{k,l=1\\k<i}}^{4}\widetilde{\Delta}_{*,ki}.$$

Those of order 3 are

$$\widetilde{\Delta}_{*,123} = \widetilde{J}_{*,11}[\widetilde{J}_{*,22}\widetilde{J}_{*,33} - \gamma(\eta+\beta\delta S_*)] + \beta^2\delta S_*(\delta A_* + I_*)(\gamma + \widetilde{J}_{*,33}),$$
$$\widetilde{\Delta}_{*,124} = \widetilde{\Delta}_{*,12}\widetilde{J}_{*,44},$$
$$\widetilde{\Delta}_{*,234} = \widetilde{\Delta}_{*,23}\widetilde{J}_{*,44} + \xi\theta(\eta+\beta\delta S_*),$$
$$\widetilde{\Delta}_{*,134} = \widetilde{J}_{*,11}\widetilde{J}_{*,33}\widetilde{J}_{*,44}.$$

Finally,

$$\det(\widetilde{J}_{E_*}) = \widetilde{J}_{*,44}\widetilde{\Delta}_{*,123} + \theta\xi[\widetilde{J}_{*,11}(\eta+\beta\delta S_*) + \beta^2\delta S_*(\delta A_* + I_*)].$$

Thus, letting also

$$\widetilde{M}_{*,3} = \sum_{\substack{k<i<\ell\\k,i,\ell=1}}^{4}\widetilde{\Delta}_{*,ki\ell},$$

for the fourth order characteristic equation stemming from the Jacobian evaluated at E_*, the remaining Routh-Hurwitz conditions become:

$$-\widetilde{M}_{*,3} > 0, \quad \mathrm{tr}(\widetilde{J}_{E_*})\widetilde{M}_{*,2}\widetilde{M}_{*,3} > \widetilde{M}_{*,3}^2 + \det(\widetilde{J}_{E_*})(\mathrm{tr}(\widetilde{J}_{E_*}))^2, \quad \det(\widetilde{J}_{E_*}) > 0. \tag{7}$$

Conditions (7) are necessary and sufficient for the stability of the EE of the basic model (1).

3. The full model

To expand the basic model, we divided the population into seven classes to include vaccination of asymptomatic infection and booster vaccination of those who have received primary vaccination during their symptomatic infection. These classes are denoted by S (susceptible), I (symptomatic infection), A (asymptomatic infection), D_I (vaccination of symptomatic infection), D_A (vaccination of asymptomatic infection), A_V (asymptomatic infection of previously vaccinated individuals), and D_{IB} (booster vaccination). We express the model with the following system of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta S[I + \delta(A + A_V)] - \mu S\\
\frac{dI}{dt} &= \beta S[I + \delta(A + A_V)] + \eta(A + A_V) - (\gamma + \xi + \mu)I\\
\frac{dA}{dt} &= \gamma I + (1-p)\theta D_I - (\eta + \xi_A + \mu)A\\
\frac{dD_I}{dt} &= \xi I - (\theta + \mu)D_I\\
\frac{dD_A}{dt} &= \xi_A A - (\nu + \mu)D_A\\
\frac{dA_V}{dt} &= \theta D_{IB} + \nu D_A - (\eta + \mu)A_V\\
\frac{dD_{IB}}{dt} &= p\theta D_I - (\mu + \theta)D_{IB}
\end{aligned} \tag{8}$$

where ξ_A is the rate of vaccination for asymptomatic infection, p is the fraction of primary vaccinated individuals who receive a booster dose, ν is the rate of loss of vaccine-induced immunity for asymptomatic infection, and other parameters are the same as those defined in the basic model. In this model, the total population is $N = S + I + A + D_I + D_A + A_V + D_{IB}$.

From equations (8), we can deduce some implications to show that only two equilibria are possible. The first equation yields that $S = 0$ is impossible, as $N \neq 0$. Then $I = 0$ implies that $A = D_I = A_V = 0$, and therefore $D_A = D_{IB} = 0$. It can therefore be seen that the model (8) admits only a disease-free (DFE) equilibrium and an endemic one, given by:

$$E^0 = (N, 0, 0, 0, 0, 0, 0), \quad E^* = (S^*, I^*, A^*, D_I^*, D_A^*, A_V^*, D_{IB}^*).$$

To establish the stability of these equilibria, we calculate the Jacobian of (8):

$$J = \begin{pmatrix}
J_{11} & -\beta S & -\beta\delta S & 0 & 0 & -\beta\delta S & 0\\
J_{21} & J_{22} & \beta\delta S + \eta & 0 & 0 & \beta\delta S + \eta & 0\\
0 & \gamma & J_{33} & (1-p)\theta & 0 & 0 & 0\\
0 & \xi & 0 & -(\theta+\mu) & 0 & 0 & 0\\
0 & 0 & \xi_A & 0 & -(\mu+\nu) & 0 & 0\\
0 & 0 & 0 & 0 & \nu & -(\mu+\eta) & \theta\\
0 & 0 & 0 & p\theta & 0 & 0 & -(\mu+\theta)
\end{pmatrix}$$

with:

$$J_{11} = -\beta[I + \delta(A + A_V)] - \mu,$$
$$J_{21} = \beta[I + \delta(A + A_V)],$$
$$J_{22} = \beta S - (\gamma + \xi + \mu),$$
$$J_{33} = -(\eta + \mu + \xi_A).$$

At E^0, one eigenvalue of J is explicit, $-\mu$. For the remaining minor, $\hat{J}_{E^0}$, we need to assess the Routh-Hurwitz conditions. The condition on the trace $-\mathrm{tr}(\hat{J}_{E^0}) > 0$ is easily stated explicitly:

$$\beta N < \gamma + \xi + \xi_A + \nu + 2(\theta + \eta) + 6\mu. \tag{9}$$

The next step consists in calculating at first the minors of all orders. For those of order two, we find

$$\begin{aligned}
&\widehat{\Delta}^0_{12} = -[\beta N - (\gamma + \xi + \mu)](\mu + \eta + \xi_A) - \gamma(\beta N + \eta),\\
&\widehat{\Delta}^0_{13} = \widehat{\Delta}^0_{16} = -[\beta N - (\gamma + \xi + \mu)](\mu + \theta),\\
&\widehat{\Delta}^0_{14} = -[\beta N - (\gamma + \xi + \mu)](\mu + \nu),\\
&\widehat{\Delta}^0_{23} = \widehat{\Delta}^0_{26} = (\mu + \eta + \xi_A)(\mu + \theta),\\
&\widehat{\Delta}^0_{24} = (\mu + \eta + \xi_A)(\mu + \nu),\\
&\widehat{\Delta}^0_{36} = (\mu + \theta)^2,\\
&\widehat{\Delta}^0_{25} = (\mu + \eta + \xi_A)(\mu + \eta),\\
&\widehat{\Delta}^0_{34} = \widehat{\Delta}^0_{46} = (\mu + \theta)(\mu + \nu),\\
&\widehat{\Delta}^0_{45} = (\mu + \nu)(\mu + \eta),\\
&\widehat{\Delta}^0_{35} = \widehat{\Delta}^0_{56} = (\mu + \theta)(\mu + \eta),\\
&\widehat{\Delta}^0_{15} = -[\beta N - (\gamma + \xi + \mu)](\mu + \eta).
\end{aligned}$$

Recalling that $(\widehat{J}_{E_0})_{11} = \beta N - (\gamma + \xi + \mu)$, those of order three are

$$\begin{aligned}
&\widehat{\Delta}^0_{123} = -\widehat{\Delta}^0_{12}(\mu + \theta)\\
&\qquad + \xi(\beta\delta N + \eta)(1 - p)\theta,\\
&\widehat{\Delta}^0_{134} = \widehat{\Delta}^0_{146} = (\widehat{J}_{E_0})_{11}(\mu + \theta)(\mu + \nu),\\
&\widehat{\Delta}^0_{145} = (\widehat{J}_{E_0})_{11}(\mu + \eta)(\mu + \nu),\\
&\widehat{\Delta}^0_{234} = (\mu + \eta + \xi_A)(\mu + \theta)(\mu + \nu),\\
&\widehat{\Delta}^0_{235} = \widehat{\Delta}^0_{256}\\
&\qquad = -(\mu + \eta + \xi_A)(\mu + \theta)(\mu + \eta),\\
&\widehat{\Delta}^0_{236} = -(\mu + \eta + \xi_A)(\mu + \theta)^2,\\
&\widehat{\Delta}^0_{246} = -(\mu + \eta + \xi_A)(\mu + \nu)(\mu + \theta),\\
&\widehat{\Delta}^0_{345} = \widehat{\Delta}^0_{456} = -(\mu + \eta)(\mu + \nu)(\mu + \theta),\\
&\widehat{\Delta}^0_{346} = -(\mu + \nu)(\mu + \theta)^2,
\end{aligned}
\qquad
\begin{aligned}
&\widehat{\Delta}^0_{124} = -\widehat{\Delta}^0_{12}(\mu + \nu),\\
&\widehat{\Delta}^0_{125} = -\widehat{\Delta}^0_{12}(\mu + \eta),\\
&\widehat{\Delta}^0_{126} = -\widehat{\Delta}^0_{12}(\mu + \theta),\\
&\widehat{\Delta}^0_{135} = (\widehat{J}_{E_0})_{11}(\mu + \eta)(\mu + \theta),\\
&\widehat{\Delta}^0_{136} = (\widehat{J}_{E_0})_{11}(\mu + \theta)^2,\\
&\widehat{\Delta}^0_{156} = (\widehat{J}_{E_0})_{11}(\mu + \theta)(\mu + \eta),\\
&\widehat{\Delta}^0_{245} = -(\mu + \eta + \xi_A)(\mu + \nu)(\mu + \eta),\\
&\widehat{\Delta}^0_{356} = -(\mu + \eta)(\mu + \theta)^2.
\end{aligned}$$

For the order four we have

$$\begin{aligned}
&\widehat{\Delta}^0_{1234} = -(\mu + \nu)\widehat{\Delta}^0_{123},\\
&\widehat{\Delta}^0_{1235} = -(\mu + \eta)\widehat{\Delta}^0_{123},\\
&\widehat{\Delta}^0_{1236} = -(\mu + \theta)\widehat{\Delta}^0_{123},\\
&\widehat{\Delta}^0_{1345} = -(\mu + \nu)\widehat{\Delta}^0_{135},\\
&\widehat{\Delta}^0_{2346} = -(\mu + \theta)\widehat{\Delta}^0_{234},\\
&\widehat{\Delta}^0_{1456} = -(\mu + \theta)\widehat{\Delta}^0_{145},\\
&\widehat{\Delta}^0_{2345} = -(\mu + \theta)\widehat{\Delta}^0_{245},\\
&\widehat{\Delta}^0_{2356} = -(\mu + \theta)\widehat{\Delta}^0_{256},
\end{aligned}
\qquad
\begin{aligned}
&\widehat{\Delta}^0_{2456} = -(\mu + \theta)\widehat{\Delta}^0_{245},\\
&\widehat{\Delta}^0_{3456} = -(\mu + \theta)\widehat{\Delta}^0_{456},\\
&\widehat{\Delta}^0_{1245} = (\mu + \eta)(\mu + \nu)\widehat{\Delta}^0_{12} - \gamma\nu\xi_A(\beta\delta N + \eta),\\
&\widehat{\Delta}^0_{1246} = (\mu + \theta)(\mu + \nu)\widehat{\Delta}^0_{12},\\
&\widehat{\Delta}^0_{1256} = (\mu + \theta)(\mu + \eta)\widehat{\Delta}^0_{12},\\
&\widehat{\Delta}^0_{1346} = -(\mu + \theta)^2(\mu + \nu)(\widehat{J}_{E_0})_{11},\\
&\widehat{\Delta}^0_{1356} = -(\mu + \theta)\widehat{\Delta}^0_{135} - p\theta^2\xi(\beta\delta N + \eta).
\end{aligned}$$

Next, the minors of order five follow:

$$\begin{aligned}
&\widehat{\Delta}^0_{12345} = -(\mu + \eta)\widehat{\Delta}^0_{1234} + \nu\xi_A(\beta\delta N + \eta)[(1 - p)\theta\xi + \gamma(\mu + \theta)],\\
&\widehat{\Delta}^0_{12356} = -(\mu + \theta)\widehat{\Delta}^0_{1235} - p\theta^2\xi(\beta\delta N + \eta)(\mu + \eta + \xi_A),\\
&\widehat{\Delta}^0_{12346} = -(\mu + \theta)\widehat{\Delta}^0_{1234},\\
&\widehat{\Delta}^0_{12456} = -(\mu + \theta)\widehat{\Delta}^0_{1245},\\
&\widehat{\Delta}^0_{13456} = -(\mu + \nu)\widehat{\Delta}^0_{1356},\\
&\widehat{\Delta}^0_{23456} = (\mu + \theta)(\mu + \nu)\widehat{\Delta}^0_{256}.
\end{aligned}$$

To complete the task, we will calculate the sum of each class of the above minors to define the following quantities:

$$\widehat{M}^0_2 = \sum_{\substack{i,k=0\\ i<k}}^{6} \widehat{\Delta}^0_{ik}, \qquad \widehat{M}^0_4 = \sum_{\substack{i,k,\ell,m=0\\ i<k<\ell<m}}^{6} \widehat{\Delta}^0_{ik\ell m},$$

$$\widehat{M}^0_3 = \sum_{\substack{i,k,\ell=0;\\ i<k<\ell}}^{6} \widehat{\Delta}^0_{ik\ell}, \qquad \widehat{M}^0_5 = \sum_{\substack{i,k,\ell,m,n=0\\ i<k<\ell<m<n}}^{6} \widehat{\Delta}^0_{ik\ell mn}.$$

Finally we calculate the determinant:

$$\det(\widehat{J}_{E^0}) = -(\mu + \theta)\widehat{\Delta}^0_{12345} + p\theta^2(\beta\delta N + \eta)\Delta_{234}.$$

Now we can express the Routh-Hurwitz conditions for stability, in addition to (9):

$$\begin{aligned}
&C^0_2 = \widehat{M}^0_3 - \mathrm{tr}(\widehat{J}_{E^0})\widehat{M}^0_2 > 0,\\
&C^0_3 = \mathrm{tr}(\widehat{J}_{E^0})\left[\widehat{M}^0_5 - \mathrm{tr}(\widehat{J}_{E^0})\widehat{M}^0_4\right] - C^0_2\widehat{M}^0_3 > 0,\\
&C^0_4 = \widehat{M}^0_4 C^0_3 - \widehat{M}^0_2\left[\widehat{M}^0_2\widehat{M}^0_5\mathrm{tr}(\widehat{J}_{E^0}) - (\mathrm{tr}(\widehat{J}_{E^0}))^2\det(\widehat{J}_{E^0}) - \widehat{M}^0_3\widehat{M}^0_5\right]\\
&\quad + \mathrm{tr}(\widehat{J}_{E^0})[\widehat{M}^0_4\widehat{M}^0_5 - \widehat{M}^0_3\det(\widehat{J}_{E^0})] - (\widehat{M}^0_5)^2 > 0,\\
&C^0_5 = \det(\widehat{J}_{E^0})\left[\widehat{M}^0_3 C^0_3 - (\mathrm{tr}(\widehat{J}_{E^0}))^2\widehat{M}^0_2\widehat{M}^0_5 + (\mathrm{tr}(\widehat{J}_{E^0}))^3\det(\widehat{J}_{E^0})\right.\\
&\quad \left. + \mathrm{tr}(\widehat{J}_{E^0})\widehat{M}^0_3\widehat{M}^0_5\right] - \widehat{M}^0_5 C^0_4 > 0.
\end{aligned} \tag{10}$$

The last condition on the positivity of the determinant can be explicitly written down:

$$\begin{aligned}
\det(\widehat{J}_{E^0}) = &-\beta N\left[(\mu + \theta)^2(\mu + \eta)(\mu + \nu)(\eta + \mu + \xi_A)\right.\\
&\left. + \gamma\delta(\mu + \theta)^2(\mu + \eta)(\mu + \nu) + \delta\xi(\mu + \theta)(\mu + \eta)(\mu + \nu)(1 - p)\theta\right]\\
&- (\mu + \theta)(\mu + \eta)(\mu + \nu)\xi\eta(1 - p)\theta\\
&+ (\mu + \theta)^2(\mu + \eta)(\mu + \nu)\left[(\gamma + \xi + \mu)(\mu + \eta + \xi_A) - \gamma\eta\right]\\
&- \beta N\left[\delta\nu\xi_A(\mu + \theta)[\gamma(\theta + \mu) + (1 - p)\theta\xi]\right.\\
&\left. + p\delta\theta^2\xi(\mu + \eta + \xi_A)(\mu + \nu)\right] - \eta\nu\xi_A(\mu + \theta)[\gamma(\theta + \mu) + (1 - p)\theta\xi]\\
&- p\eta\theta^2\xi(\mu + \eta + \xi_A)(\mu + \nu) > 0.
\end{aligned}$$

Now, the above condition can be synthetically restated as

$$T_1 + T_2 + T_3 + T_4 + T_5 + T_6 > \beta N(W_1 + W_2 + W_3 + W_4 + W_5 + W_6),$$

where:

$$\begin{aligned}
&T_1 = \xi(1 - p)\theta\eta\widehat{\Delta}^0_{456} < 0,\\
&T_2 = (\gamma + \xi + \mu)(\eta + \mu + \xi_A)\widehat{\Delta}^0_{3456} > 0,\\
&T_3 = -\gamma\eta\widehat{\Delta}^0_{3456} < 0,\\
&T_4 = -\gamma\xi_A\nu\eta(\theta + \mu)^2,\\
&T_5 = -\xi\eta(1 - p)\theta\nu\xi_A(\theta + \mu),\\
&T_6 = -\xi\eta(\eta + \mu + \xi_A)(\mu + \nu)p\theta^2,
\end{aligned} \tag{11}$$

and

$$\begin{aligned}
&W_1 = (\eta + \mu + \xi_A)\widehat{\Delta}^0_{3456} > 0,\\
&W_2 = \gamma\delta\widehat{\Delta}^0_{3456} > 0,\\
&W_3 = -\xi(1 - p)\theta\delta\widehat{\Delta}^0_{456} > 0,\\
&W_4 = \gamma\xi_A\nu\delta(\theta + \mu)^2,\\
&W_5 = \delta\xi(1 - p)\theta\nu\xi_A(\theta + \mu),\\
&W_6 = \delta\xi(\eta + \mu + \xi_A)(\mu + \nu)p\theta^2.
\end{aligned} \tag{12}$$

Thus, in addition to (9) and (10), the following condition must be satisfied for stability:

$$R_c = \beta N \frac{W_1 + W_2 + W_3 + W_4 + W_5 + W_6}{T_1 + T_2 + T_3 + T_4 + T_5 + T_6} < 1. \tag{13}$$

Note in particular that if $\det(\hat{J}_{E_0})$ is positive, then $T_1 + T_2 + T_3 + T_4 + T_5 + T_6 > 0$.

We now consider the endemic equilibrium. Solving the last, fourth and fifth equations in (8), we find:

$$D_{IB}^* = \frac{p\theta}{\mu+\theta} D_I^*, \quad I^* = \frac{\mu+\theta}{\xi} D_I^*, \quad D_A^* = \frac{\xi_A}{\mu+\nu} A^*.$$

Substituting the second above equation into the third equation of (8), we find:

$$D_I^* = \frac{\eta+\mu+\xi_A}{\gamma(\theta+\mu)+(1-p)\xi\theta} \xi A^*.$$

Substituting D_I^* into the previous formula for I^*, it follows that we can express I^* in terms of A^*:

$$I^* = \Gamma A^*, \quad \Gamma = (\mu+\theta)\frac{\eta+\mu+\xi_A}{\gamma(\mu+\theta)+(1-p)\theta\xi}. \tag{14}$$

Using these results and the sixth equation in (8), we obtain:

$$A_V^* = \Psi A^*, \quad \Psi = \frac{1}{\mu+\eta}\left[\frac{\xi_A \nu}{\mu+\nu} + \xi\frac{p\theta^2}{\mu+\theta}\cdot\frac{\eta+\mu+\xi_A}{\gamma(\mu+\theta)+(1-p)\theta\xi}\right]. \tag{15}$$

Combining the first two equations in (8), we can write $S^* = \Phi A^* + N$ where:

$$\Phi = \frac{1}{\mu}[\eta(1+\Psi) - (\gamma+\mu+\xi)\Gamma].$$

On the other hand, at equilibrium, the first equation of (8) can be rewritten as:

$$\beta(\Phi A^* + N)[I + \delta(A^* + A_V^*)] = -\mu\Phi A^*. \tag{16}$$

Using (14) and (15), (16) can be rewritten as follows

$$\beta(\Phi A^* + N)[\Gamma + \delta(1+\Psi)] = -\mu\Phi$$

and explicitly as:

$$\frac{\beta}{\mu}[\eta(1+\Psi) - (\gamma+\mu+\xi)\Gamma][\Gamma + \delta(1+\Psi)]A^*$$
$$= -\beta N[\Gamma + \delta(1+\Psi)] - [\eta(1+\Psi) - (\gamma+\mu+\xi)\Gamma].$$

We then need to ensure the nonnegativity of A^*, as all other populations would then be so. From the previous result we have:

$$A^* = \mu\frac{\eta(1+\Psi) - \Gamma(\gamma+\mu+\xi) + \beta N[\Gamma+\delta(1+\Psi)]}{\beta[\Gamma+\delta(1+\Psi)][(\gamma+\mu+\xi)\Gamma - \eta(1+\Psi)]} = \frac{\hat{N}}{\beta[\Gamma+\delta(1+\Psi)]\hat{D}},$$
$$\hat{N} = \beta N[\Gamma+\delta(1+\Psi)] - \hat{D}, \quad \hat{D} = (\gamma+\mu+\xi)\Gamma - \eta(1+\Psi).$$

Now, $\hat{D}$ being negative implies that the numerator is positive, so that $A^* < 0$, which is not feasible. We need then to have $\hat{D} > 0$. To have $A^* \geq 0$, then $\hat{N} \geq 0$ must hold, which is equivalent to the following requirement

$$\beta N[\Gamma + \delta(1+\Psi)] > \hat{D}. \tag{17}$$

Writing explicitly this condition, we find:

$$\beta N\left\{\delta\left[1 + \frac{1}{\mu+\eta}\left(\frac{\xi_A\nu}{\mu+\nu} + \xi\frac{p\theta^2}{\mu+\theta}\cdot\frac{\eta+\mu+\xi_A}{\gamma(\mu+\theta)+(1-p)\theta\xi}\right)\right]\right.$$
$$\left. + \frac{(\mu+\theta)(\eta+\mu+\xi_A)}{\gamma(\mu+\theta)+(1-p)\theta\xi}\right\} \geq (\gamma+\mu+\xi)\frac{(\mu+\theta)(\eta+\mu+\xi_A)}{\gamma(\mu+\theta)+(1-p)\theta\xi}$$
$$- \eta\left[1 + \frac{1}{\mu+\eta}\left(\frac{\xi_A\nu}{\mu+\nu} + \xi\frac{p\theta^2}{\mu+\theta}\cdot\frac{\eta+\mu+\xi_A}{\gamma(\mu+\theta)+(1-p)\theta\xi}\right)\right]$$

Factorizing out the same common denominator $(\mu+\eta)(\mu+\nu)(\mu+\theta)[\gamma(\mu+\theta)+(1-p)\theta\xi] = -\hat{\Delta}_{456}^0[\gamma(\mu+\theta)+(1-p)\theta\xi] > 0$ on both sides of the above inequality, we obtain:

$$\beta N\left[(\eta+\mu+\xi_A)\hat{\Delta}_{3456}^0 + \delta\left\{\hat{\Delta}_{456}^0[\gamma(\mu+\theta)+(1-p)\theta\xi]\right.\right.$$
$$\left.\left. + \nu\xi_A(\mu+\theta)[(\mu+\theta)\gamma + (1-p)\theta\xi] + p\theta^2\xi(\eta+\mu+\xi_A)(\mu+\nu)\right\}\right]$$
$$\geq -\eta\hat{\Delta}_{456}^0(1-p)\theta\xi + (\gamma+\xi+\mu)(\eta+\mu+\xi_A)\hat{\Delta}_{3456}^0 - \eta\hat{\Delta}_{456}^0\gamma(\mu+\theta)$$
$$+ \eta\left\{\xi_A\nu(\mu+\theta)[\gamma(\mu+\theta)+(1-p)\theta\xi] + p\theta^2\xi(\mu+\nu)(\eta+\mu+\xi_A)\right\}.$$

Recalling (11) and (12), the latter can then be rewritten more compactly as:

$$\beta N(W_1 + W_2 + W_3 + W_4 + W_5 + W_6) \geq T_1 + T_2 + T_3 + T_4 + T_5 + T_6.$$

Existence of the positive endemic equilibrium E^* is thus ensured whenever:

$$R_c \geq 1. \tag{18}$$

Again, comparing (13) and (18), a transcritical bifurcation is seen to arise [26], under which E^* becomes locally asymptotically stable when R_0 crosses from below the critical threshold 1.

4. Stochastic structure of the full model

Applying the same compartmentalization, we developed the stochastic structure of (8). We assumed that events in this model are defined by the rates of movement between different compartments in the deterministic structure. In this framework, new infections are binomially distributed with the number of trials equal to the number of susceptibles at time t and the probability of success (i.e., infection occurs). The state of the system is defined by the integer number of individuals in each compartment, and changes discretely whenever an event occurs. These changes are summarized in Table 1.

Transition rates in Table 1 can be converted to probabilities of the corresponding event happening by considering:

$$P(\text{Event } i) = \frac{a_i}{\sum_i a_i},$$

where a_i is the transition rate of the event i. In this formulation, the time to the next event (τ) is exponentially distributed with the parameter equal to the sum of the rates for all possible events. The probability density function is given by:

$$f(\tau) = \left(\sum_i a_i\right)\exp\left(-\tau\sum_i a_i\right).$$

Using inverse transform sampling [27], we can estimate the time to the next event: for a given random variate k drawn from the uniform distribution on the unit interval $(0,1)$, τ can be estimated as $-\ln(k)/\sum_i a_i$. The state of the system is then updated according to the transitions given in Table 1 for the event occurring during the transition time τ.

5. Simulations and results

In order to investigate effect of HSV-2 therapeutic vaccination, we simulated the stochastic structure of the model (Tables 1, 2). Recent estimates indicate that the prevalence of HSV-2 is around 12% for the US population and has been relatively stable over 10 years with a slight declining trend [28]. We therefore assumed that initially 12% of the population is infected with HSV-2. To maintain this prevalence level, we chose the transmission rate $\beta = 3.7 \times 10^{-8}$, which also shows a very slight declining trend over the simulation time-horizon of 40 years in the absence of vaccination (Fig. 1).

Fixing other parameter values (see Fig. 2), we change the rate of vaccination at year 10 to show the effect of vaccination on the prevalence

Table 1. Movements of individuals between compartments according to the transition rates. The parameter r is a random variate drawn from the uniform distribution on the unit interval $(0,1)$. Other parameters are the same as those defined for the deterministic structure.

Event	Transition	Transition rate
birth	$S \to S+1$	μN
infection	$S \to S-1$ $I \to I+1$	$\beta S[I+\delta(A+A_V)]$
treatment	$I \to I-1$ $A \to A+1$	γI
recurrence	$A \to A-1$ $I \to I+1$	ηA
vaccination of symptomatic	$I \to I-1$ $D_I \to D_I+1$	ξI
loss of vaccine-induced immunity	$D_I \to D_I-1$ booster vaccine: $D_{IB} \to D_{IB}+1$ no booster: $A \to A+1$	θD_I if $r<p$ else $r \geq p$
vaccination of asymptomatic	$A \to A-1$ $D_A \to D_A+1$	$\xi_A A$
loss of vaccine-induced immunity	$D_A \to D_A-1$ $A_V \to A_V+1$	νD_A
recurrence	$A_V \to A_V-1$ $I \to I+1$	ηA_V
loss of booster immunity	$D_{IB} \to D_{IB}-1$ $A_V \to A_V+1$	θD_{IB}
death	$S \to S-1$ $I \to I-1$ $A \to A-1$ $D_I \to D_I-1$ $D_A \to D_A-1$ $A_V \to A_V-1$ $D_{IB} \to D_{IB}-1$	μS μI μA μD_I μD_A μA_V μD_{IB}

Table 2. Model parameters and their values.

Parameter	Description	Value
β	baseline transmission rate	3.7×10^{-8}
μ	birth rate	$1/(50\times365)$
δ	relative transmissibility of asymptomatic infection	0.01
γ	rate of suppressive treatment	1/17
η	rate of recurrence	1/90
ν	rate of loss of primary vaccine-induced immunity	1/730
θ	rate of loss of booster vaccine-induced immunity	1/730
ξ	vaccination rate of symptomatic infection	varies
ξ_A	vaccination rate of asymptomatic infection	varies
p	fraction of primary vaccinated individuals who receive booster dose	varies

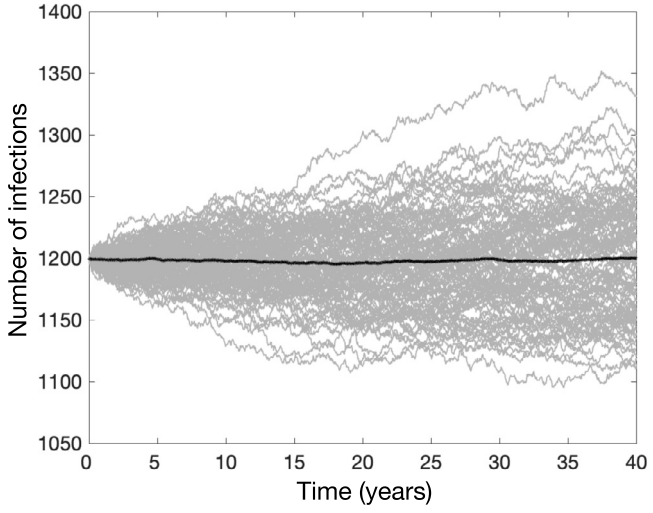

Fig. 1. Prevalence of HSV-2 in the absence of vaccination. Parameter values are: $\mu = 1/(50\times365)$, $\beta = 3.7\times10^{-8}$; $\delta = 0.01$; $\gamma = 1/17$, $\xi = 0$, $\eta = 1/90$, $\xi_A = 0$, $p = 0$. Units of parameters are per day. Initial conditions are $S_0 = 8800$, $I_0 = 1$, $A_0 = 1199$, $D_{I0} = 0$, $D_{A0} = 0$, $A_{V0} = 0$, $D_{IB0} = 0$. Gray curves represent 100 independent replicates in the stochastic simulations, and the black curve represents the average of these realizations.

of HSV-2. In the absence of booster vaccination, we observed a sharp decline in the prevalence of HSV-2 after the start of vaccination, followed by a steady decline whose level depends on the vaccination rate. Thus, the long-term disease prevalence depends on how fast individuals are vaccinated after developing symptomatic infection.

When the primary vaccination is combined with a booster dose, we observed no significant difference between the prevalence of HSV-2 in the low booster coverage ($p = 0.1$) and that in the high booster coverage ($p = 1$), especially when the rate of primary vaccination was high (Fig. 3). These simulations suggest that for a relatively high rate of vaccination of HSV-2 infected cases during symptomatic infection, a booster vaccination may not affect long-term disease prevalence. We therefore explored the effect of vaccination when asymptomatic individuals are identified and offered vaccine without considering a booster dose.

We assumed that vaccination rate of asymptomatic cases will not exceed that of symptomatic cases, i.e., $\xi_A \leq \xi$. Fig. 4 shows the total prevalence of HSV-2 following the start of vaccination. For a relatively low vaccination rate of symptomatic infection, vaccination of asymptomatic cases can lead to a lower prevalence of disease in a long-term. However, we observed an initial increase in the prevalence of HSV-2 after the introduction of vaccination when $\xi_A > 0$ (Fig. 4(a), blue curve) compared to when $\xi_A = 0$ (Fig. 4(a), black curve) followed by a faster rate of decline. The initial increase can be explained by the fact that

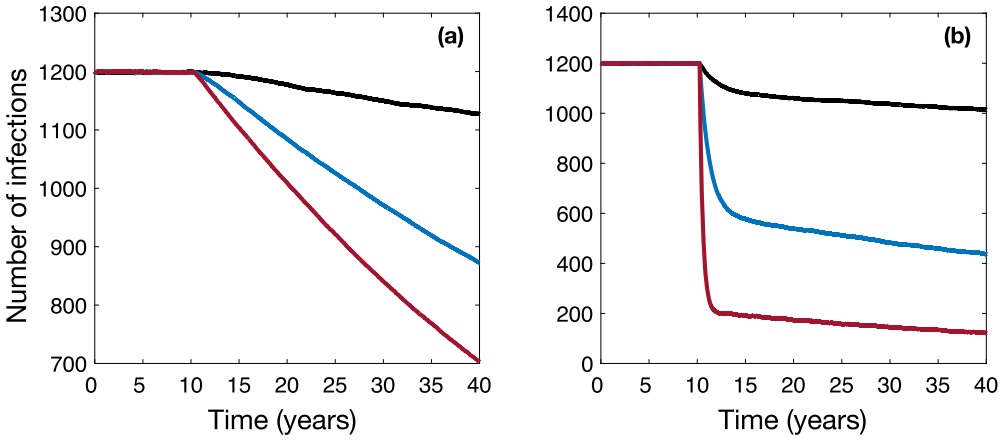

Fig. 2. Prevalence of (a): the total HSV-2 infected individuals (i.e., $I + A + D_I + D_A + A_V + D_{IB}$), and (b): the total HSV-2 individuals who can shed the virus (i.e., $I + A + A_V$) in the presence of vaccination (started on year 10 of the simulations) without a booster dose. Parameter values are: $\mu = 1/(50 \times 365)$, $\beta = 3.7 \times 10^{-8}$; $\delta = 0.01$; $\gamma = 1/17$, $\eta = 1/90$, $\xi_A = 0$, $\theta = 1/730$, $\nu = 1/730$, $p = 0$. Vaccination rate is $\xi = 0.001$ (black), $\xi = 0.01$ (blue), and $\xi = 0.1$ (red). Units of parameters are per day. Initial conditions are $S_0 = 8800$, $I_0 = 1$, $A_0 = 1199$, $D_{I0} = 0$, $D_{A0} = 0$, $A_{V0} = 0$, $D_{IB0} = 0$. Curves represent the average of 100 independent realizations.

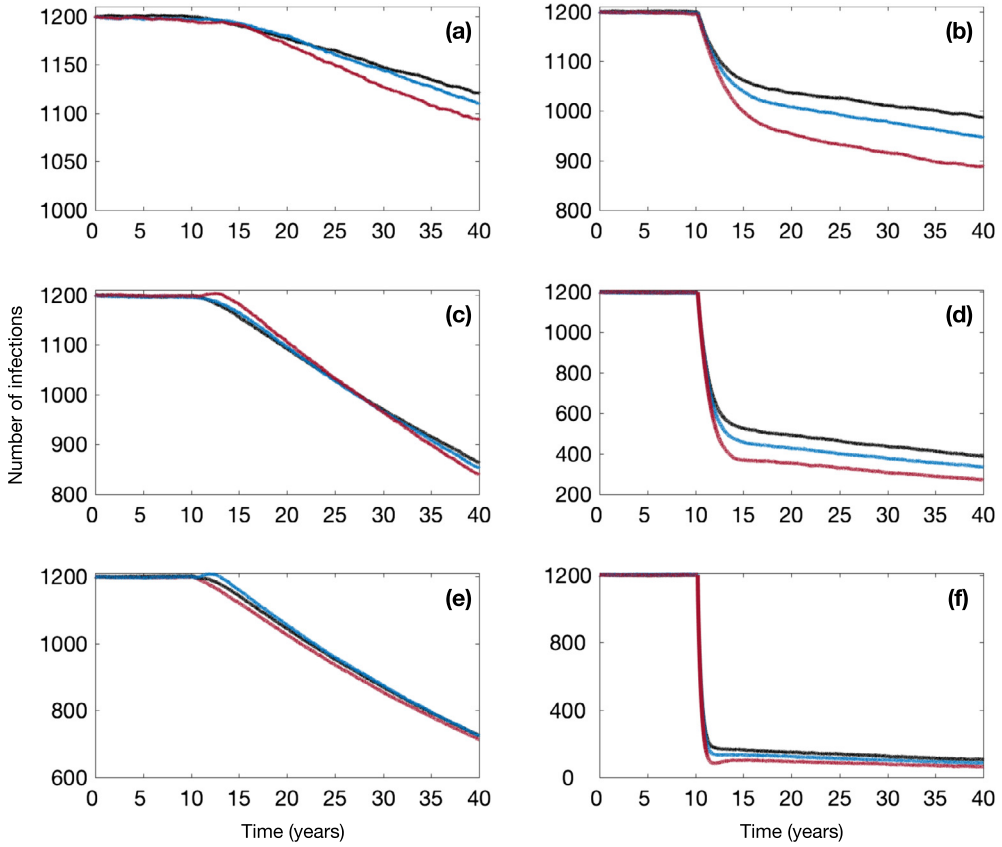

Fig. 3. Prevalence of (a, c, e): the total HSV-2 infected individuals (i.e., $I + A + D_I + D_A + A_V + D_{IB}$), and (b, d, f): the total HSV-2 individuals who can shed the virus (i.e., $I + A + A_V$) in the presence of vaccination (started on year 10 of the simulations) with a booster dose. Parameter values are: $\mu = 1/(50 \times 365)$, $\beta = 3.7 \times 10^{-8}$; $\delta = 0.01$; $\gamma = 1/17$, $\eta = 1/90$, $\xi_A = 0$, $\theta = 1/730$, $\nu = 1/730$. Vaccination rate is (a, b): $\xi = 0.001$, (c, d): $\xi = 0.01$, and (e, f): $\xi = 0.1$. Units of parameters are per day. Fraction of individuals receiving a booster dose is $p = 0.2$ (black), $p = 0.5$ (blue), and $p = 1.0$ (red). Initial conditions are $S_0 = 8800$, $I_0 = 1$, $A_0 = 1199$, $D_{I0} = 0$, $D_{A0} = 0$, $A_{V0} = 0$, $D_{IB0} = 0$. Curves represent the average of 100 independent realizations for $p = 0.1$ (black), $p = 0.5$ (blue), and $p = 1$ (red).

following the loss of vaccine-induced immunity in the A_V class, there is no booster vaccination, and therefore virus shedding can occur before recurrence. We observed similar patterns when the vaccination rate of symptomatic infection increased (Fig. 4(b, c)); however vaccinating asymptomatic infection contributed minimal or even less to reducing the total prevalence of HSV-2 (compared to the scenario in which asymptomatic infection was not vaccinated). Overall, these simulation results suggest that therapeutic vaccination of HSV-2 infection may be most effective when targeted towards symptomatic infection with highest possible rates.

6. Discussion

In this study, we developed a simple compartmental model for the dynamics of HSV-2 infection to investigate the temporal effects of a therapeutic vaccine. The goals of a therapeutic vaccine, which may be

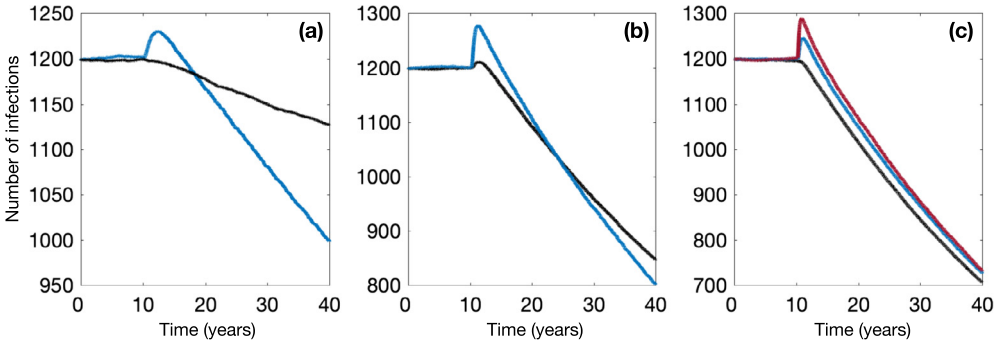

Fig. 4. Prevalence of the total HSV-2 infected individuals (i.e., $I + A + D_I + D_A + A_V + D_{IB}$), with different rates of vaccination (started on year 10 of the simulations) without booster dose: (a) $(\xi, \xi_A) = (0.001, 0)$ (black), and $(\xi, \xi_A) = (0.001, 0.001)$ (blue); (b) $(\xi, \xi_A) = (0.01, 0.001)$ (black) and $(\xi, \xi_A) = (0.01, 0.01)$ (blue); and (c) $(\xi, \xi_A) = (0.1, 0.001)$ (black), $(\xi, \xi_A) = (0.1, 0.01)$ (blue), and $(\xi, \xi_A) = (0.1, 0.1)$ (red). Parameter values are: $\mu = 1/(50 \times 365)$, $\beta = 3.7 \times 10^{-8}$; $\delta = 0.01$; $\gamma = 1/17$, $\eta = 1/90$, $\theta = 1/730$, $\nu = 1/730$, and $p = 0$. Units of parameters are per day. Initial conditions are $S_0 = 8800$, $I_0 = 1$, $A_0 = 1199$, $D_{I0} = 0$, $D_{A0} = 0$, $A_{V0} = 0$, $D_{IB0} = 0$. Curves represent the average of 100 independent realizations.

administered to individuals already infected with HSV-2 virus, are to reduce the number of recurrent symptomatic episodes and/or the rate of viral shedding. Previous studies have suggested that an HSV-2 vaccination could reduce these factors in the range of 5% to 80% after 10 years [19, 21, 29], under various assumptions and vaccine efficacy. In particular, a previous modeling study of a therapeutic vaccine [21] suggests a decline in the HSV-2 prevalence if a sizable portion of asymptomatic cases are vaccinated every year in order to prevent shedding. Since this target may not be achievable, our study suggests that targeting symptomatic infection for vaccination may be the most effective strategy. We also observed that for a relatively high rate of the primary vaccination for HSV-2 symptomatic infection, booster vaccination may not affect the long-term trend of disease prevalence in a significant measure, further highlighting the importance of primary vaccination.

Since the proposed model is relatively simple and explanatory, our results should be considered in the context of study assumptions and limitations. In particular, we considered a vaccine with perfect clinical effectiveness; that is, the vaccine was 100% effective in reducing recurrent symptomatic episodes until the vaccine-induced immunity waned, and prevented viral shedding. However, recent clinical trials suggest that vaccine would at best (given current data) reduce recurrent disease by about 50% [18]. Furthermore, clinical trials suggest that vaccine may not fully prevent viral shedding while it may reduce it by about 50%. Considering that vaccinated individuals could still contribute to viral shedding, our model could be extended to include viral shedding during vaccine-induced protection and investigate the dynamics of disease and its prevalence. Of particular importance in future studies is to evaluate whether vaccination under suboptimal effects shown in recent clinical trials [18, 30] would be a cost-effective measure to curb the incidence and prevalence of HSV-2.

Declarations

Author contribution statement

E. Venturino: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

A. Shoukat: Analyzed and interpreted the data; Wrote the paper.

S. M. Moghadas: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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