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ORIGINAL ARTICLE

Mathematical Study of a Staged-Progression HIV Model with Imperfect Vaccine

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Abstract A staged-progression HIV model is formulated and used to investigate the potential impact of an imperfect vaccine. The vaccine is assumed to have several desirable characteristics such as protecting against infection, causing bypass of the primary infection stage, and offering a disease-altering therapeutic effect (so that the vaccine induces reversal from the full blown AIDS stage to the asymptomatic stage). The model, which incorporates HIV transmission by individuals in the AIDS stage, is rigorously analyzed to gain insight into its qualitative features. Using a comparison theorem, the model with mass action incidence is shown to have a globally-asymptotically stable disease-free equilibrium whenever a certain threshold, known as the *vaccination reproduction number*, is less than unity. Furthermore, the model with mass action incidence has a unique endemic equilibrium whenever this threshold exceeds unity. Using the Li-Muldowney techniques for a reduced version of the mass action model, this endemic equilibrium is shown to be globally-asymptotically stable, under certain parameter restrictions. The epidemiological implications of these results are that an imperfect vaccine can eliminate HIV in a given community if it can reduce the reproduction number to a value less than unity, but the disease will persist otherwise. Furthermore, a future HIV vaccine that induces the bypass of primary infection amongst vaccinated individuals (who become infected) would decrease HIV prevalence, whereas a vaccine

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with therapeutic effect could have a positive or negative effect at the community level.

Keywords HIV/AIDS · Staged progression · Vaccination reproduction number · Global stability

1. Introduction

Since its appearance in the 1980s, the human immuno-deficiency virus (HIV) remains a major global menace. In addition to accounting for nearly 20 million deaths so far, an estimated 36–40 million people live with the disease, and the HIV pandemic continues to inflict a major socio-economic burden on many developing nations (World Bank, 1997; Fleck, 2004; WHO, 2004).

There is a growing body of opinion that curtailing the global spread of HIV requires an effective vaccine (Chang et al., 2003; Esparza and Osmanov, 2003). Owing to the global HIV vaccine enterprise (Klausner et al., 2003) and related initiatives, several candidate HIV vaccines are currently undergoing clinical trials (see Burton et al., 2004; Zinkernagel, 2004 and the references therein). However, these efforts are unlikely to yield an effective vaccine soon. The current expectation is that such a vaccine would be imperfect. That is, it may be effective in some, but not all, people and/or may offer protection that wanes with time. The vaccine may also offer some therapeutic benefits by altering the clinical course of the disease (Shiver et al., 2002; Lee et al., 2004; Shiver and Emini, 2004). There is a need, therefore, to evaluate the potential community-wide impact of such a vaccine.

Several authors have, over the last two decades, used mathematical models to assess the potential impact of an imperfect HIV vaccine (see, for example, McLean and Blower, 1993; Blower and McLean, 1994; Corbett et al., 2003; Del Valle et al., 2004; Smith and Blower, 2004) using relatively simple compartmental models. The aforementioned models do not, however, incorporate some other important aspects of HIV disease such as the staged-progression nature of the disease, where HIV-infected individuals pass through sequential infection stages; being highly infectious during primary infection (first few weeks of infection), having low infectivity in the asymptomatic phase (lasting many years) and becoming more infectious in the AIDS stage. Staged progression models are considered in Hyman et al. (1999), Perelson and Nelson (1999), and McCluskey (2003) but these do not incorporate the use of a vaccine. Another important aspect that is often ignored in HIV modeling is the role of individuals with AIDS in HIV transmission. For instance, the models in McLean and Blower (1993), Blower and McLean (1994), Del Valle et al. (2004), and Smith and Blower (2004) assume that individuals with AIDS do not contribute in further spread of HIV. However, epidemiological evidence supports the hypothesis that AIDS patients are capable of, and do engage

in, risky sexual behavior such as having multiple sexual partners or inconsistent condom use (Nicolosi et al., 1994; O'Brien et al., 1994; Lansky et al., 2000). Although, Elbasha and Gumel (2006) presented an HIV vaccine model that considers both staged progression and transmission by AIDS patients (in addition to other vaccine and HIV features), their study does not include the possible vaccine-induced bypass of primary infection and reversal from AIDS to chronic stage of infection. Furthermore, no global stability results were presented in Elbasha and Gumel (2006).

This study complements and extends the aforementioned studies by formulating, and rigorously analyzing, a new deterministic model for HIV transmission dynamics in the presence of an imperfect vaccine. The model, which incorporates the staged-progression nature of HIV disease and HIV transmission by individuals in the AIDS stage, allows the assessment of an imperfect vaccine with various characteristics. These characteristics include waning protective immunity and incomplete vaccine-induced protection (efficacy less than 100%). Furthermore, since an HIV vaccine is expected to reduce the transmissibility of vaccinated infected individuals (break-through infections) by reducing their viral load (see Smith and Blower, 2004 and the references therein), and noting the positive correlation between viral load and infectiousness (see, for instance, Gray et al., 2003; Baggeley et al., 2005), this model assumes that an imperfect HIV vaccine could offer a therapeutic effect by converting vaccinees in the highly infectious AIDS stage into the less infectious asymptomatic stage. Furthermore, it is assumed that the vaccine could also induce a bypass of primary infection in break-through infections, where a proportion of vaccinated infected individuals move straight to the asymptomatic (chronic) stage. In summary, in addition to carrying out a detailed qualitative analysis of a relatively comprehensive HIV transmission model, one of the main novelties of this study is that it allows for the assessment of the impact of two new expected vaccine-related characteristics, namely: therapeutic effect and vaccine-induced bypass of primary infection.

The paper is organized as follows. The model is formulated in Section 2, and the vaccination reproduction number is defined and calculated in Section 3. Qualitative results for the global asymptotic stability of the disease-free equilibrium in the mass action case are also reported in Section 3. In Section 4, the existence of the endemic equilibrium of the mass action model, and its global asymptotic stability are investigated for a reduced model. In this case, an expression for the threshold fraction of individuals needed to be vaccinated to attain herd immunity in the community is also given. Numerical simulation results are reported in Section 5.

2. Model formulation and basic properties

Following Hyman et al. (1999), the population being studied is assumed to be a small, high-risk subset of a larger population. It is further assumed that the

larger population is relatively free of HIV and provides a constant source of uninfected individuals entering the high-risk population. The model monitors the temporal dynamics of the high-risk population, which is sub-divided into the sub-populations of unvaccinated ($S_u(t)$) and vaccinated ($S_v(t)$) susceptible individuals, HIV-infected individuals in primary ($I_1(t)$), secondary ($I_2(t)$) and AIDS ($I_3(t)$) stages of infection. The total high-risk population is $N(t) = S_u(t) + S_v(t) + I_1(t) + I_2(t) + I_3(t)$. As noted by Hyman et al. (1999), such a formulation could be applied to a homosexual community of a major city (e.g. the San Francisco gay community).

The unvaccinated susceptible sub-population ($S_u(t)$) is increased by the daily recruitment of uninfected sexually-active individuals from the larger embedding population (at a rate Π) and by waning of vaccine-induced immunity (at a per capita rate ω). The sub-population is decreased by infection, which may be acquired via horizontal transfer from infected individuals in any of the three infected classes, by vaccination (at a per capita rate ξ) and by natural death (at a per capita rate μ). The natural death parameter (μ) also includes the rate at which individuals leave the high-risk population due to migration or other reasons not directly related to HIV infection. Let $C(N)$ be the average number of contacts sufficient to transmit infection in unit time per infective individual in the population (of size N) with $C'(N) \geq 0$. Then, the number of new infections in unit time is $C(N)SI/N$, where S and I represent the populations of susceptible and infected individuals, respectively. It is convenient to define the transmission probability per contact, $\beta(N)$, as $\beta(N) = C(N)/N$ with $\beta(N) > 0$ for $N > 0$. The term $\beta(N)I_1$ is the force of infection from the primary infection stage, that is the average number of contacts with infected individuals in the primary stage *per* unit time. The parameter $0 \leq \eta_2 < 1$ accounts for the assumed reduced infectivity of infected individuals in the secondary infection stage (due to their low viral load). Similarly, a modification parameter η_3, with $0 \leq \eta_3 \leq 1$, is used alongside β to model the transmission rate from individuals in the AIDS stage (it is assumed that individuals in the AIDS stage make a similar number of effective contacts as individuals in the primary infection stage). The term $\beta(N)(I_1 + \eta_2 I_2 + \eta_3 I_3)$ thus gives the total force of infection, and the incidence (the number of new cases per unit time) from the unvaccinated susceptible individuals is given by the product of this with S_u. The rate of change of S_u is

$$\frac{\mathrm{d}S_u}{\mathrm{d}t} = \Pi + \omega S_v - \beta(N)\left(I_1 + \eta_2 I_2 + \eta_3 I_3\right) S_u - \xi S_u - \mu S_u. \tag{1}$$

The sub-population of vaccinated susceptible individuals ($S_v(t)$) is generated by the vaccination of unvaccinated susceptible individuals (at the per capita rate ξ) and diminished by infection, vaccine waning (at the per capita rate ω) and natural death (at the per capita rate μ). Here, $0 < \epsilon < 1$ accounts for the efficacy of the

vaccine-induced protection against infection (for a vaccine that offers 100% protection, $\epsilon = 1$; thus in reality $\epsilon < 1$). Since a vaccine is assumed to lead to reduction in viral load in break-through infections (Smith and Blower, 2004), it is further assumed that a proportion (δ) of vaccinated infected individuals move straight to the secondary infection stage (by bypassing the primary infection stage). It is worth noting that although there is no conclusive biological evidence supporting the vaccine-induced bypass of the primary infection stage (following HIV infection of vaccinated susceptible individuals), our model is robust enough to accommodate such; setting $\delta = 0$ accounts for the case where such accelerated transition does not occur. This case is discussed in Section 4.2. The above assumptions give:

$$\frac{\mathrm{d}S_{\mathrm{v}}}{\mathrm{d}t} = \xi S_{\mathrm{u}} - \beta(N)(1-\epsilon)\left(I_1 + \eta_2 I_2 + \eta_3 I_3\right) S_{\mathrm{v}} - \omega S_{\mathrm{v}} - \mu S_{\mathrm{v}}. \tag{2}$$

The sub-population of individuals in the primary infection stage ($I_1(t)$) is generated by the infection of susceptible individuals, and decreased by progression to the secondary infection stage (at a per capita rate σ_1) and natural death (at the per capita rate μ). This gives

$$\frac{\mathrm{d}I_1}{\mathrm{d}t} = \beta(N)\left(I_1 + \eta_2 I_2 + \eta_3 I_3\right)\left[S_{\mathrm{u}} + (1-\delta)(1-\epsilon)S_{\mathrm{v}}\right] - \sigma_1 I_1 - \mu I_1. \tag{3}$$

The sub-population of individuals at the secondary infection stage ($I_2(t)$) is generated by the infection of some vaccinated susceptible individuals (proportion δ), the progression of individuals in the primary infection stage (at the per capita rate σ_1) and via vaccine-induced conversion of individuals in the AIDS stage to the asymptomatic stage (at a per capita rate τ). It is worth emphasizing that in the absence of a cure for HIV, current anti-HIV therapeutic treatments are geared towards reducing viral load to levels consistent with the secondary infection stage (thereby elongating the lifespan of those treated individuals; see Baggeley et al. (2005) for a general review of HIV models that incorporate anti-retroviral therapy). We assume that a putative HIV vaccine could have such a characteristic. Additionally, the secondary infection class is diminished by progression to the AIDS stage (at a per capita rate σ_2) and natural death (at the per capita rate μ). Thus,

$$\frac{\mathrm{d}I_2}{\mathrm{d}t} = \beta(N)\delta(1-\epsilon)\left(I_1 + \eta_2 I_2 + \eta_3 I_3\right) S_{\mathrm{v}} + \sigma_1 I_1 + \tau I_3 - \sigma_2 I_2 - \mu I_2. \tag{4}$$

The sub-population of individuals in the AIDS stage of infection ($I_3(t)$) is generated by the progression to AIDS of individuals in the secondary infection stage (at the per capita rate σ_2). This population is diminished by the vaccine-induced therapeutic effect (at the per capita rate τ), natural death (at the per capita rate μ) and disease-induced death (at a per capita rate ψ), giving

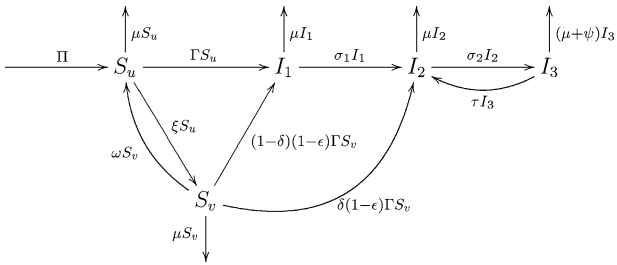

Fig. 1 Flowchart diagram for model (1)–(5).

$$\frac{\mathrm{d}I_3}{\mathrm{d}t} = \sigma_2 I_2 - \tau I_3 - \mu I_3 - \psi I_3. \tag{5}$$

A schematic description of the model, given by Eqs. (1)–(5), is depicted in Fig. 1 where $\Gamma = \beta(N)(I_1 + \eta_2 I_2 + \eta_3 I_3)$ is the force of infection on unvaccinated susceptible individuals.

By assumption, all parameters of the model are assumed non-negative with the natural death rate positive ($\mu > 0$). Since the model, consisting of Eqs. (1)–(5), monitors human populations, it is further assumed that all the state variables are non-negative at time $t = 0$ with $I_1 + \eta_2 I_2 + \eta_3 I_3 > 0$. It then follows from the differential equations that the variables are non-negative for all $t \geq 0$. Furthermore, adding Eqs. (1)–(5) gives $\mathrm{d}N/\mathrm{d}t = \Pi - \mu N - \psi I_3$. Consequently, in the absence of HIV infection, $N \to \Pi/\mu$ as $t \to \infty$ and Π/μ is an upper bound of $N(t)$ provided that $N(0) \leq \Pi/\mu$. Also, if $N(0) > \Pi/\mu$, then N will decrease to this level. Thus, the following feasible region:

$$\mathcal{D} = \{(S_\mathrm{u}, S_\mathrm{v}, I_1, I_2, I_3) \in \mathbb{R}^5_+ : S_\mathrm{u} + S_\mathrm{v} + I_1 + I_2 + I_3 \leq \Pi/\mu\},$$

is positively invariant. It is therefore sufficient to consider solutions in $\mathcal{D}$. In this region, the usual existence, uniqueness and continuation results hold for the system. In general, the model cannot be reduced to a lower dimensional model without making additional assumptions on the parameters.

3. Stability analysis of disease-free equilibrium

3.1. Local stability

The model has a disease-free equilibrium (DFE), obtained by setting the right-hand sides of (1)–(5) to zero, given by

$$\mathcal{E}_0 : \quad (S_\mathrm{u}^*, S_\mathrm{v}^*, I_1^*, I_2^*, I_3^*) = \left(\frac{(\omega+\mu)\Pi}{\mu(\mu+\xi+\omega)}, \frac{\Pi\xi}{\mu(\mu+\xi+\omega)}, 0, 0, 0\right). \tag{6}$$

Following van den Driessche and Watmough (2002), the linear stability of $\mathcal{E}_0$ is obtained using the next generation matrix for the system (1)–(5) as follows. Using the notation in van den Driessche and Watmough (2002) and the variables I_1, I_2 and I_3, the non-negative matrix F and the non-singular M-matrix V, for the new infection terms and the remaining transfer terms respectively, are given by

$$F = \begin{pmatrix} \beta(N^*)S^* & \beta(N^*)\eta_2 S^* & \beta(N^*)\eta_3 S^* \\ \beta(N^*)\delta(1-\epsilon)S_v^* & \beta(N^*)\delta(1-\epsilon)\eta_2 S_v^* & \beta(N^*)\delta(1-\epsilon)\eta_3 S_v^* \\ 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \sigma_1+\mu & 0 & 0 \\ -\sigma_1 & \sigma_2+\mu & -\tau \\ 0 & -\sigma_2 & \tau+\mu+\psi \end{pmatrix},$$

with $N^* = S_u^* + S_v^* + I_1^* + I_2^* + I_3^* = \Pi/\mu$ and $S^* = S_u^* + (1-\delta)(1-\epsilon)S_v^*$. The *vaccination reproduction number*, denoted by $\mathcal{R}_{vac}$, is then given by $\mathcal{R}_{vac} = \rho(FV^{-1})$ where ρ denotes the spectral radius (dominant eigenvalue). It follows that

$$\mathcal{R}_{vac} = Q_1\left[\frac{1}{\sigma_1+\mu} + \frac{\eta_2\sigma_1(\tau+\mu+\psi)}{\det V} + \frac{\eta_3\sigma_1\sigma_2}{\det V}\right] + \frac{Q_2}{\det V}\left[\eta_2(\tau+\mu+\psi)+\eta_3\sigma_2\right](\sigma_1+\mu), \tag{7}$$

where $\det V = (\sigma_1+\mu)\left[(\mu+\psi)(\sigma_2+\mu)+\mu\tau\right]$ and the quantities Q_1 and Q_2 are defined by

$Q_1 = \beta(N^*)S^* = \beta(N^*)\left(S_u^* + (1-\delta)(1-\epsilon)S_v^*\right)$ and $Q_2 = \beta(N^*)\delta(1-\epsilon)S_v^*$.

Thus, using Theorem 2 of van den Driessche and Watmough (2002), the following result is obtained.

Lemma 1. *The disease-free equilibrium $\mathcal{E}_0$ of (1)–(5), given by (6), is locally-asymptotically stable if $\mathcal{R}_{vac} < 1$ and unstable if $\mathcal{R}_{vac} > 1$.*

In the absence of vaccination (so that parameters $\xi = \tau = 0$, and hence $S_v^* = 0$), the reproduction number $\mathcal{R}_{vac}$ reduces to

$$\mathcal{R}_0 = \frac{\Pi\beta(N^*)}{\mu}\left[\frac{1}{\sigma_1+\mu} + \frac{\eta_2\sigma_1}{(\sigma_1+\mu)(\sigma_2+\mu)} + \frac{\eta_3\sigma_1\sigma_2}{(\sigma_1+\mu)(\mu+\psi)(\sigma_2+\mu)}\right], \tag{8}$$

where $\mathcal{R}_0$ is the *basic reproduction number* (see Anderson and May, 1991; Brauer and Castillo-Chavez, 2000; Hethcote, 2000; van den Driessche and Watmough, 2002) associated with the model (1)–(5) in the absence of any anti-HIV control measure.

3.2. Interpretation of vaccination reproduction number

Let T_j be the average duration that an individual spends in class I_j per visit to this class. Then from Eqs. (3)–(5), it follows that $T_1 = 1/(\sigma_1 + \mu)$, $T_2 = 1/(\sigma_2 + \mu)$ and $T_3 = 1/(\tau + \mu + \psi)$.

Associated with an infected individual is a random walk that describes the individual's passage through the infective stages. This walk continues until the individual leaves the active population, and may begin in one of two ways (see Fig. 1). Either the individual, upon infection, enters I_1 and, assuming survival, proceeds to I_2, or the individual may bypass I_1 and enter directly into I_2 (if vaccinated). In either case, the random walk continues with the individual moving back and forth between I_2 and I_3 until leaving the active population.

Near the disease-free equilibrium, the fraction of new infections that enter into I_1 is

$$f_1 = \frac{S^*}{S_{\mathrm{u}}^* + (1-\epsilon)S_{\mathrm{v}}^*},$$

with the remaining fraction

$$f_2 = \frac{\delta(1-\epsilon)S_{\mathrm{v}}^*}{S_{\mathrm{u}}^* + (1-\epsilon)S_{\mathrm{v}}^*},$$

entering directly into I_2. Of those entering into I_1, a fraction

$$g_{12} = \frac{\sigma_1}{\sigma_1 + \mu},$$

survive, proceeding to I_2. Thus, the fraction of infected individuals that pass through I_1 is f_1 and the fraction that pass through I_2 is $f_1 g_{12} + f_2$.

For an individual in I_2, the probability of proceeding to I_3 and then returning to I_2 is

$$g_{232} = \left(\frac{\sigma_2}{\sigma_2 + \mu}\right)\left(\frac{\tau}{\tau + \mu + \psi}\right).$$

Thus, given that an individual has reached I_2 initially, the expected number of visits to I_2 is

$$\begin{aligned} v_2 &= 1 + g_{232} + g_{232}^2 + \cdots \\ &= \frac{1}{1 - g_{232}} \\ &= \frac{(\sigma_2 + \mu)(\tau + \mu + \psi)}{(\sigma_2 + \mu)(\tau + \mu + \psi) - \sigma_2 \tau}. \end{aligned}$$

Additionally, since a fraction

$$g_{23} = \frac{\sigma_2}{\sigma_2 + \mu},$$

of individuals in I_2 proceed to I_3, the expected number v_3 of visits to I_3, given that an individual has reached I_2 is

$$v_3 = g_{23}\ v_2 = \frac{\sigma_2(\tau + \mu + \psi)}{(\sigma_2 + \mu)(\tau + \mu + \psi) - \sigma_2\tau}.$$

Let T_j^{total} be the expected total time that a newly infected individual spends in I_j, $j = 1, 2, 3$. Then,

$$\begin{aligned}
T_1^{\text{total}} &= f_1\ T_1 \\
&= \frac{S^*}{S_{\text{u}}^* + (1-\epsilon)S_{\text{v}}^*}\ \frac{1}{\sigma_1 + \mu}, \\
T_2^{\text{total}} &= (f_1 g_{12} + f_2)\ v_2\ T_2 \\
&= \frac{\left(\left(\frac{\sigma_1}{\sigma_1 + \mu}\right) S^* + \delta(1-\epsilon)S_{\text{v}}^*\right)(\tau + \mu + \psi)}{(S_{\text{u}}^* + (1-\epsilon)S_{\text{v}}^*)((\sigma_2 + \mu)(\tau + \mu + \psi) - \sigma_2\tau)} \\
&= \frac{(\sigma_1 S^* + \delta(1-\epsilon)S_{\text{v}}^*(\sigma_1 + \mu))\left(\tau + \mu + \psi\right)}{\left(S_{\text{u}}^* + (1-\epsilon)S_{\text{v}}^*\right)\det V},
\end{aligned}$$

and

$$\begin{aligned}
T_3^{\text{total}} &= (f_1 g_{12} + f_2)\ v_3\ T_3 \\
&= \frac{\left(\left(\frac{\sigma_1}{\sigma_1 + \mu}\right) S^* \ +\ \delta(1-\epsilon)S_{\text{v}}^*\right)\sigma_2}{(S_{\text{u}}^* + (1-\epsilon)S_{\text{v}}^*)((\sigma_2 + \mu)(\tau + \mu + \psi) - \sigma_2\tau)} \\
&= \frac{\sigma_1\sigma_2 S^* \ +\ \delta(1-\epsilon)S_{\text{v}}^*(\sigma_1 + \mu)\sigma_2}{(S_{\text{u}}^* + (1-\epsilon)S_{\text{v}}^*)\det V}.
\end{aligned}$$

Finally, the rate at which a single infected individual in I_j produces new infections in a wholly susceptible population (near the disease-free equilibrium), is $\beta(N^*)\eta_j(S_{\text{u}}^* + (1-\epsilon)S_{\text{v}}^*)$ (where $\eta_1 = 1$). Thus, new infections occur at a rate

$$\begin{aligned}
&\beta(N^*)(S_{\text{u}}^* + (1-\epsilon)S_{\text{v}}^*)(T_1^{\text{total}} + \eta_2 T_2^{\text{total}} + \eta_3 T_3^{\text{total}}) \\
&\quad = Q_1\frac{1}{\sigma_1 + \mu} + Q_1\eta_2\frac{\sigma_1(\tau + \mu + \psi)}{\det V} + Q_1\eta_3\frac{\sigma_1\sigma_2}{\det V} \\
&\qquad + Q_2\eta_2\frac{(\sigma_1 + \mu)(\tau + \mu + \psi)}{\det V} + Q_2\eta_3\frac{(\sigma_1 + \mu)\sigma_2}{\det V} \\
&\quad = \mathcal{R}_{\text{vac}}.
\end{aligned}$$

Hence, $\mathcal{R}_{\text{vac}}$ can be interpreted as the average total number of new infections caused by a single infected individual, introduced into a susceptible population in which some individuals have been vaccinated.

3.3. Global stability for mass action model

In $\mathcal{D}$, since $N \leq \Pi/\mu$, it follows from (1) that

$$\begin{aligned}\frac{\mathrm{d}S_{\mathrm{u}}}{\mathrm{d}t} &\leq \Pi + \omega S_{\mathrm{v}} - (\xi + \mu)S_{\mathrm{u}},\\ &\leq \Pi + \omega(\Pi/\mu - S_{\mathrm{u}} - I_1 - I_2 - I_3) - (\xi + \mu)S_{\mathrm{u}},\\ &\leq \frac{(\omega + \mu)\Pi}{\mu} - (\mu + \xi + \omega)S_{\mathrm{u}} = (\mu + \xi + \omega)(S_{\mathrm{u}}^* - S_{\mathrm{u}})\end{aligned}$$

Thus, if $S_{\mathrm{u}} > S_{\mathrm{u}}^*$, then $\mathrm{d}S_{\mathrm{u}}/\mathrm{d}t < 0$; hence $S_{\mathrm{u}} \leq S_{\mathrm{u}}^*$ provided that $S_{\mathrm{u}}(0) \leq S_{\mathrm{u}}^*$. Similarly, from (2) and using the above bound, $\mathrm{d}S_{\mathrm{v}}/\mathrm{d}t \leq -(\omega + \mu)S_{\mathrm{v}} + \xi S_{\mathrm{u}}^* = (\omega + \mu)(S_{\mathrm{v}}^* - S_{\mathrm{v}})$ so that if $S_{\mathrm{v}} > S_{\mathrm{v}}^*$, then $\mathrm{d}S_{\mathrm{v}}/\mathrm{d}t < 0$; hence $S_{\mathrm{v}} \leq S_{\mathrm{v}}^*$ provided that $S_{\mathrm{v}}(0) \leq S_{\mathrm{v}}^*$. It follows from these bounds that the region

$$\mathcal{D}_* = \{(S_{\mathrm{u}}, S_{\mathrm{v}}, I_1, I_2, I_3) \in \mathcal{D} : S_{\mathrm{u}} \leq S_{\mathrm{u}}^*,\ S_{\mathrm{v}} \leq S_{\mathrm{v}}^*\},$$

is also positively invariant and attracts all solutions in $\mathcal{D}$. In fact, it can be shown that each solution in $\mathcal{D}$ either enters $\mathcal{D}_*$ in finite time or limits to $\mathcal{E}_0$.

From now on, we consider a special case of (1)–(5) with $C(N) = \beta N$, thus $\beta(N) = \beta$, a positive constant, which is the mass action coefficient. This gives the following model (the mass action model):

$$\begin{aligned}\frac{\mathrm{d}S_{\mathrm{u}}}{\mathrm{d}t} &= \Pi + \omega S_{\mathrm{v}} - \beta\,(I_1 + \eta_2 I_2 + \eta_3 I_3)\,S_{\mathrm{u}} - \xi S_{\mathrm{u}} - \mu S_{\mathrm{u}},\\ \frac{\mathrm{d}S_{\mathrm{v}}}{\mathrm{d}t} &= \xi S_{\mathrm{u}} - \beta(1-\epsilon)\,(I_1 + \eta_2 I_2 + \eta_3 I_3)\,S_{\mathrm{v}} - \omega S_{\mathrm{v}} - \mu S_{\mathrm{v}},\\ \frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta\,(I_1 + \eta_2 I_2 + \eta_3 I_3)\,[S_{\mathrm{u}} + (1-\delta)(1-\epsilon)S_{\mathrm{v}}] - \sigma_1 I_1 - \mu I_1,\\ \frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta\delta(1-\epsilon)\,(I_1 + \eta_2 I_2 + \eta_3 I_3)\,S_{\mathrm{v}} + \sigma_1 I_1 + \tau I_3 - \sigma_2 I_2 - \mu I_2,\\ \frac{\mathrm{d}I_3}{\mathrm{d}t} &= \sigma_2 I_2 - \tau I_3 - \psi I_3 - \mu I_3.\end{aligned} \tag{9}$$

Although standard incidence, where $\beta(N)$ is proportional to $1/N$, is often preferred for sexually-transmitted diseases (Hethcote, 2000), the use of mass action seems plausible since the total size of the target group used in the numerical simulations of this paper (the San Francisco gay community) is small (64,000 people)

and stays relatively constant during the simulations period (thereby justifying the use of mass action incidence).

The above mass action model has a disease-free equilibrium, given by $\mathcal{E}_0$ in (6). Furthermore, the following global stability result holds, showing that, for the mass action model, the disease dies out for $\mathcal{R} < 1$, where

$$\mathcal{R} = Q_1 \left[\frac{1}{\sigma_1 + \mu} + \frac{\eta_2 \sigma_1 (\tau + \mu + \psi)}{\det V} + \frac{\eta_3 \sigma_1 \sigma_2}{\det V} \right] + \frac{Q_2}{\det V} \left[\eta_2 (\tau + \mu + \psi) + \eta_3 \sigma_2 \right] (\sigma_1 + \mu). \tag{10}$$

In (10), $Q_1 = \beta \left(S_{\mathrm{u}}^* + (1-\delta)(1-\epsilon) S_{\mathrm{v}}^* \right)$, $Q_2 = \beta \delta (1-\epsilon) S_{\mathrm{v}}^*$ and all other variables and quantities are as defined before. We give a proof that directly uses a comparison theorem; alternatively the method of the Theorem in Section 3 of Castillo-Chavez et al. (2002) can be used.

Theorem 1. *The disease-free equilibrium of the mass action model* (9)*, given by* $\mathcal{E}_0$ *in* (6)*, is globally asymptotically stable if* $\mathcal{R} < 1$.

Proof. All solutions starting in $\mathcal{D}_*$ remain in $\mathcal{D}_*$, and all other solutions approach $\mathcal{D}_*$. Thus, it may be assumed that

$$0 \le S_{\mathrm{u}}(t) \le S_{\mathrm{u}}^* \quad \text{and} \quad 0 \le S_{\mathrm{v}}(t) \le S_{\mathrm{v}}^* \quad \text{for all} \quad t \ge 0. \tag{11}$$

Consequently, since $\beta(N^*) = \beta$, the last three equations of (9) can be expressed in the following differential inequality

$$\begin{pmatrix} \dfrac{\mathrm{d}I_1(t)}{\mathrm{d}t} \\ \dfrac{\mathrm{d}I_2(t)}{\mathrm{d}t} \\ \dfrac{\mathrm{d}I_3(t)}{\mathrm{d}t} \end{pmatrix} \le (F - V) \begin{pmatrix} I_1(t) \\ I_2(t) \\ I_3(t) \end{pmatrix}. \tag{12}$$

Consider the linear ODE system given by equality in (12). If $\mathcal{R} < 1$, then $\rho(FV^{-1}) < 1$ (see Section 3.1), which is equivalent to $F - V$ having all its eigenvalues in the left-half plane (van den Driessche and Watmough, 2002). It follows that the linear system given by equality in (12) is stable whenever $\mathcal{R} < 1$, and hence $(I_1(t), I_2(t), I_3(t)) \to (0, 0, 0)$ as $t \to \infty$ for this linear ODE system. Consequently, after using a standard comparison theorem (Lakshmikantham et al., 1989, p. 31; Smith and Waltman, 1995, Theorem B.1; Appendix B), the variables $(I_1(t), I_2(t), I_3(t)) \to (0, 0, 0)$ as well for the nonlinear system given by the last three equations of (9). Returning now to the first two equations of (9) and substituting $I_1 = I_2 = I_3 = 0$ in these equations gives a linear system with $S_{\mathrm{u}}(t) \to S_{\mathrm{u}}^*$

and $S_v(t) \to S_v^*$ as $t \to \infty$. Thus, $(S_u(t), S_v(t), I_1(t), I_2(t), I_3(t)) \to (S_u^*, S_v^*, 0, 0, 0)$ as $t \to \infty$ for $\mathcal{R} < 1$, so that $\mathcal{E}_0$ is globally asymptotically stable if $\mathcal{R} < 1$.

The public health implication of the above result is that HIV will be eliminated from the community if the anti-HIV measures adopted can bring $\mathcal{R} < 1$. It is worth noting that the result of Theorem 1 holds for any non-decreasing $\beta(N)$ (i.e., $\beta(N) \leq \beta(N^*)$ in $\mathcal{D}_*$), but the proof technique does not work for the standard incidence function since in that case, the inequality (12) no longer holds. Thus, unlike the vaccination models in Kribs-Zaleta and Velasco-Hernández (2000), Arino et al. (2003), Corbett et al. (2003), and Elbasha and Gumel (2006), the mass action model (9) does not undergo the phenomenon of backward bifurcation where the disease-free equilibrium co-exists with a stable endemic equilibrium when $\mathcal{R} < 1$. The absence of backward bifurcation in (12) may be attributed to the mass action assumption that has been made.

4. Existence and stability of endemic equilibrium

4.1. Existence of endemic equilibrium for mass action model

Positive endemic equilibria (steady states with $I_1, I_2, I_3 > 0$) of the mass action model cannot easily be expressed cleanly in closed form. Here, we provide a technique for determining such solution(s). Define

$$G^{**} = \beta\,(I_1^{**} + \eta_2 I_2^{**} + \eta_3 I_3^{**}), \tag{13}$$

as the force of infection at an endemic equilibrium (the average number of contacts with infectives *per* unit time, assuming that the infectives are at an endemic equilibrium). Then, the equations in (9) at endemic equilibrium can be simplified to:

$$\begin{aligned}
S_u^{**} &= \frac{\Pi\,[(1-\epsilon)G^{**} + \mu + \omega]}{K_0}, \qquad S_v^{**} = \frac{\xi\Pi}{K_0},\\
I_1^{**} &= \frac{G^{**}\Pi\,[(1-\epsilon)G^{**} + \mu + \omega + (1-\delta)(1-\epsilon)\xi]}{K_0(\sigma_1+\mu)},\\
I_2^{**} &= \frac{(\tau+\mu+\psi)\left[\delta(1-\epsilon)G^{**}S_v^{**} + \sigma_1 I_1^{**}\right]}{(\sigma_2+\mu)(\psi+\mu)+\mu\tau},\\
I_3^{**} &= \frac{\sigma_2\left[\delta(1-\epsilon)G^{**}S_v^{**} + \sigma_1 I_1^{**}\right]}{(\sigma_2+\mu)(\psi+\mu)+\mu\tau},
\end{aligned} \tag{14}$$

where $K_0 = [(1-\epsilon)G^{**} + \mu](G^{**} + \xi + \mu) + (G^{**} + \mu)\omega$. Using (14) in (13) and simplifying gives

$$G^{**} = \frac{\beta\Pi G^{**}}{K_0 \det V}\left\{K_1 K_2 + \frac{\delta(1-\epsilon)(\sigma_1+\mu)K_3\xi}{\sigma_1}\right\}, \tag{15}$$

where

$$K_1 = (\sigma_2 + \mu)(\mu + \psi) + \mu\tau + K_3,$$
$$K_2 = (1-\epsilon)G^{**} + \mu + \omega + (1-\delta)(1-\epsilon)\xi,$$
$$K_3 = \sigma_1\eta_2(\tau + \mu + \psi) + \sigma_1\sigma_2\eta_3.$$

The positive (endemic) equilibria of (9) can then be obtained by solving for G^{**} in (15) and substituting the result into (14). Clearly, $G^{**} = 0$ is a fixed point of (15), which corresponds to the disease-free equilibrium $\mathcal{E}_0$. For $G^{**} \neq 0$, (15) can be simplified to:

$$a_0(G^{**})^2 + a_1 G^{**} + a_2 = 0, \tag{16}$$

where

$$\begin{aligned} a_0 &= 1 - \epsilon, \\ a_1 &= \left[\xi + \mu - \beta\Pi\left(\frac{1}{\sigma_1 + \mu} + \frac{K_3}{\det V}\right)\right](1-\epsilon) + \mu + \omega, \\ a_2 &= \mu(\mu + \xi + \omega)(1 - \mathcal{R}). \end{aligned} \tag{17}$$

Since all model parameters are assumed nonnegative with $\mu > 0$ and $0 < \epsilon < 1$, it follows from (17) that $a_0 > 0$ and $a_2 < 0$ for $\mathcal{R} > 1$. Thus, the quadratic equation (16) has a unique positive root when $\mathcal{R} > 1$. Alternatively, noting that $\mathcal{R} < 1$ implies $\beta S_u^*/\det V\big(\det V/\sigma_1 + \mu + K_3\big) < 1$, it follows (by substituting for S_u^*) that $\xi + \mu - \beta\Pi\big(1/\sigma_1 + \mu + K_3/\det V\big) > 0$, so that the coefficient $a_1 > 0$. Thus, for $\mathcal{R} < 1$, all three coefficients of the quadratic (16) are positive, so that the quadratic has no positive root when $\mathcal{R} < 1$. Furthermore, for $\mathcal{R} = 1$, it follows that $a_2 = 0$ and $a_1, a_0 > 0$. Consequently, the mass action model (9) cannot exhibit backward bifurcation at $\mathcal{R} = 1$ (this is in line with the global stability result of $\mathcal{E}_0$ in Theorem 1). Thus, we have established the following result.

Lemma 2. *The mass action model* (9) *has a unique positive (endemic) equilibrium if and only if* $\mathcal{R} > 1$.

4.2. Stability of endemic equilibrium of reduced mass action model

To simplify the calculations associated with the unique endemic equilibrium of the mass action model, we consider a special case of (9) with no bypass of primary infection ($\delta = 0$), no HIV transmission by AIDS patients ($\eta_3 = 0$) and the vaccine does not offer a therapeutic effect ($\tau = 0$). This gives the following (reduced mass

action model):

$$\begin{aligned}
\frac{\mathrm{d}S_{\mathrm{u}}}{\mathrm{d}t} &= \Pi + \omega S_{\mathrm{v}} - \beta\left(I_1 + \eta_2 I_2\right) S_{\mathrm{u}} - \xi S_{\mathrm{u}} - \mu S_{\mathrm{u}},\\
\frac{\mathrm{d}S_{\mathrm{v}}}{\mathrm{d}t} &= \xi S_{\mathrm{u}} - \beta(1-\epsilon)\left(I_1 + \eta_2 I_2\right) S_{\mathrm{v}} - \omega S_{\mathrm{v}} - \mu S_{\mathrm{v}},\\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta\left(I_1 + \eta_2 I_2\right)\left[S_{\mathrm{u}} + (1-\epsilon)S_{\mathrm{v}}\right] - \sigma_1 I_1 - \mu I_1,\\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \sigma_1 I_1 - \sigma_2 I_2 - \mu I_2,\\
\frac{\mathrm{d}I_3}{\mathrm{d}t} &= \sigma_2 I_2 - \psi I_3 - \mu I_3.
\end{aligned} \tag{18}$$

Since AIDS patients do not interact with the rest of the population, I_3 can be determined from the last equation in (18), and this equation decouples. For this reduced model, the associated vaccination reproduction number (obtained from $\mathcal{R}|_{\delta=\eta_3=\tau=0}$) is

$$\mathcal{R}^{(r)} = \frac{\beta\Pi(\sigma_2 + \mu + \eta_2\sigma_1)\left[\omega + \mu + (1-\epsilon)\xi\right]}{\mu(\mu + \xi + \omega)(\sigma_1 + \mu)(\sigma_2 + \mu)}.$$

Define $\mathcal{D}_0 = \left\{(S_{\mathrm{u}}, S_{\mathrm{v}}, I_1, I_2, I_3) \in \mathcal{D}_* : I_1 = I_2 = I_3 = 0\right\}$ (which is the stable manifold of the DFE).

Theorem 2. *For $\mathcal{R}^{(r)} > 1$, the unique endemic equilibrium of the reduced mass action system (18) is globally-asymptotically stable in $\mathcal{D}_* \setminus \mathcal{D}_0$ if $\eta_2 = 0$ and either*

$$\omega < \mu \quad \textit{and} \quad \sigma_1 < \mu + \xi, \tag{19}$$

or

$$\sigma_1 < \mu + \omega. \tag{20}$$

Proof. For $\mathcal{R}^{(r)} > 1$, the omega limit set of each solution of (18) that intersects $\mathcal{D}_* \setminus \mathcal{D}_0$ is contained in the interior of $\mathcal{D}_*$. Combining this with the fact that $\mathcal{E}^{**} = (S_{\mathrm{u}}^{**}, S_{\mathrm{v}}^{**}, I_1^{**}, I_2^{**}, I_3^{**})$ is the only equilibrium in the interior of $\mathcal{D}_*$, it is clear that any further conditions which imply that solutions limit to an equilibrium, imply that $\mathcal{E}^{**}$ is globally asymptotically stable in $\mathcal{D}_* \setminus \mathcal{D}_0$. We now demonstrate that, for $\eta_2 = 0$, $(S_{\mathrm{u}}^{**}, S_{\mathrm{v}}^{**}, I_1^{**})$ is a globally asymptotically stable equilibrium for the $(S_{\mathrm{u}}, S_{\mathrm{v}}, I_1)$ sub-system of (18). Then it follows that I_2 and I_3 approach I_2^{**} and I_3^{**}, respectively.

For $\eta_2 = 0$, the $(S_{\mathrm{u}},\ S_{\mathrm{v}}, I_1)$ sub-system of (18) is equivalent to the (S, V, I) sub-system of (2.2) of Arino et al. (2003) where the quantities $(S, V, I, R, \phi, \theta, d, \alpha, \nu, \sigma, \gamma, \beta)$ of Arino et al. (2003) are set equal to $(S_{\mathrm{u}}, S_{\mathrm{v}}, I_1, I_2, \xi, \omega, \mu, 0, 0, 1-\epsilon, \sigma_1, \beta\Pi/\mu)$ to agree with the quantities used here. Thus, Remark 5.7 of Arino et al. (2003) implies that $\mathcal{E}^{**}$ is globally asymptotically stable if (19)

holds. Note that other conditions are given in Arino et al. (2003), but for the model studied here, those conditions are more restrictive than those given here.

The proof in Arino et al. (2003) is based on the Li-Muldowney techniques (Li and Muldowney, 1995, 1996). The key step in the proof is to demonstrate the uniform asymptotic stability of systems $z' = Qz$ where $Q = P'P^{-1} + P\frac{\partial f}{\partial x}^{[2]}P^{-1}$. In this expression, $P(x)$ is a transformation matrix for which $||P^{-1}||$ is bounded, P' is the matrix constructed by replacing each entry of P with its time-derivative and $\frac{\partial f}{\partial x}^{[2]}$ is the second additive compound of the Jacobian matrix $\frac{\partial f}{\partial x}$. Here, the uniformity is over initial conditions for $x = (S_u, S_v, I_1)^T$. In demonstrating the uniform asymptotic stability, a norm is used as a Lyapunov function.

Using a similar calculation, with transformation matrix $P = \mathrm{diag}(1/I_1, 1/I_1, 1/I_1)$ and norm

$$\|z\| = \begin{cases} \max\{|z_1|,\ |z_2| + |z_3|\} & \text{if } \operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = \operatorname{sgn}(z_3) \\ \max\{|z_2|,\ |z_1| + |z_3|\} & \text{if } \operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = -\operatorname{sgn}(z_3) \\ \max\{|z_1|,\ |z_2|,\ |z_3|\} & \text{if } \operatorname{sgn}(z_1) = -\operatorname{sgn}(z_2) = \operatorname{sgn}(z_3) \\ \max\{|z_1| + |z_3|,\ |z_2| + |z_3|\} & \text{if } -\operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = \operatorname{sgn}(z_3), \end{cases}$$

we obtain the result that $\mathcal{E}^{**}$ is globally asymptotically stable if (20) holds. This calculation involves an extensive case analysis, based on the expressions for $\|z\|$. We omit the details and refer the reader to Section 5 of Arino et al. (2003), where a similar calculation is performed, and to McCluskey (2005), where the construction of such norms is described in detail.

The proof of Theorem 2 is, in fact, sufficient to show that solutions approach the endemic equilibrium with exponential speed. Thus, the result is robust under small perturbations. This means that any parameter set for which the necessary conditions are satisfied (implying that the result holds) is contained in an open neighbourhood of parameter values for which the result holds. In particular, this means that if inequality (19) or inequality (20) is satisfied, and η_2 is positive, but not too large, then the result still holds; i.e. for $\mathcal{R}^{(r)} > 1$, there is a globally asymptotically stable endemic equilibrium. Similarly, if δ, η_2, η_3, and τ are positive, but not too large, then the corresponding result holds for system (9) with $\mathcal{R} > 1$, as stated below.

Corollary. *Suppose $\mathcal{R} > 1$ and that (19) and (20) are satisfied. If δ, η_2, η_3, and τ are sufficiently small, then the unique endemic equilibrium of system (9) is globally asymptotically stable in $\mathcal{D}_* \setminus \mathcal{D}_0$.*

Extensive numerical simulations suggest that Theorem 2 and the subsequent Corollary hold even when inequalities (19) and (20) are violated. Thus, we offer the following conjecture.

Conjecture. *The unique endemic equilibrium of the mass action model* (9) *(reduced mass action model* (18)*) is globally asymptotically stable in* $\mathcal{D}_* \setminus \mathcal{D}_0$ *whenever* $\mathcal{R} > 1$ *(*$\mathcal{R}^{(r)} > 1$*).*

4.3. Threshold fraction of vaccinated population for the reduced mass action model

Since the mass action model (9) has a globally-stable DFE for $\mathcal{R} < 1$, it follows that the reduced model (18) has a globally-stable DFE for $\mathcal{R}^{(r)} < 1$. It is instructive to determine elimination conditions in terms of the fraction (p) of the population that are vaccinated at equilibrium, which is given by $p = S_v^*/N^* = \xi/(\mu + \xi + \omega)$. This enables the determination of a critical fraction that must be vaccinated in order to achieve herd immunity, where the unvaccinated susceptible members of the community receive indirect protection due to high levels of vaccination amongst the remaining segments of the population (Hethcote, 1989; Anderson and May, 1991; McLean and Blower, 1993). Define $\mathcal{R}_0^{(r)} = \mathcal{R}^{(r)}|_{\xi=0,\omega=0} = \mathcal{R}_0|_{\beta(N)=\beta,\eta_3=0}$, the basic reproduction number associated with the reduced mass action model (18). Then $\mathcal{R}^{(r)} = \mathcal{R}_0^{(r)}(1 - \epsilon p)$. Setting $\mathcal{R}^{(r)} = 1$, and solving for the critical vaccinated fraction $p = p_c$ gives

$$p_c = \frac{1}{\epsilon}\left(1 - \frac{1}{\mathcal{R}_0^{(r)}}\right). \tag{21}$$

Threshold conditions similar to p_c have been reported by a number of authors (see, for instance, Hethcote, 1989; McLean and Blower, 1993; Blower and McLean, 1994). From (21), p_c is positive if $\mathcal{R}_0^{(r)} > 1$, marking the case in which vaccination has a positive impact on disease control by decreasing HIV prevalence. On the other hand, if $\mathcal{R}_0^{(r)} < 1$, then the disease dies out without vaccination (since the disease-free equilibrium of the vaccination-free model is globally asymptotically stable if $\mathcal{R}_0^{(r)} < 1$). For the reduced mass action model (18) with $\mathcal{R}_0^{(r)} > 1$, HIV can be eliminated from the community if the fraction of individuals vaccinated at steady-state exceeds the threshold p_c (i.e., herd immunity is achieved if $p > p_c$).

The quantity $1 - 1/\mathcal{R}_0^{(r)}$ in (21) is the minimum vaccine coverage level needed to eliminate a disease for a vaccine that offers 100% protection against infection (i.e., $\epsilon = 1$). It is clear from (21) that the lower the efficacy of the vaccine (lower ϵ), the higher the fraction of the population that needs to be vaccinated to attain herd immunity. Using the lower bound estimate of the basic reproduction number for HIV in San Francisco equal to two (Blower and McLean, 1994) (so that $\mathcal{R}_0^{(r)} = 2$), it follows that, for an HIV vaccine that offers 80% efficacy, a threshold vaccinated fraction of $p_c = 0.625$ must be attained in order to eliminate HIV from the community. Similarly, an HIV vaccine with lower efficacy, such as $\epsilon = 0.5$, would necessitate vaccinating a much larger fraction of the population to achieve

herd immunity (in this case, $p_c = 1$, requiring the vaccination of the entire population).

5. Numerical simulations and discussions

To illustrate the various theoretical results contained in this paper, the mass action model (9) is simulated using the parameter values/ranges in Table 1. The parameter values are estimated as follows. The recruitment rate (Π) models the inflow of uninfected people into the high-risk sexually-active community. Following Maclean and Blower (1993), this parameter is estimated based on the HIV transmission data in the San Francisco gay community. Here, the mean duration of sexual activity is 32 years (so that $\mu = 1/32$ per year) and the approximate size of the homosexual community is 64,000. Thus, $\Pi \approx 2000$ per year. Furthermore, for this population, the expected lifespan after diagnosis with AIDS is estimated to be 20 months (so that $\psi = 0.6$ per year); Hyman et al. estimated the mean duration of the AIDS stage to be 3 years (so that $\psi = 0.333$) (Hyman et al., 1999). For this reason, we take the average value, namely $\psi = 0.47$. McLean and Blower estimated the contact rate to be $\beta c = 0.62$ (in their notation, where c represents the average number of new partners *per* unit time). Thus, in our notation, the mass action coefficient is estimated as $\beta = 0.62 \times \mu/\Pi = 9.61 \times 10^{-6}$.

Table 1 Description and estimation of parameters for mass action model.

Parameter	Description	Estimated value/range
Π	Recruitment rate of susceptible people into the community	2000 (year)$^{-1}$
β	Mass action transmission coefficient	9.61×10^{-6}
η_2	Modification factor of transmission rate for asymptomatically-infected individuals	$\eta_2 \in [0, 1)$
η_3	Modification factor of transmission rate for AIDS individuals	$\eta_3 \in [0, 1]$
ξ	Per capita vaccination rate	variable (year)$^{-1}$
ω	Per capita waning rate of vaccine	1/20 (year)$^{-1}$
$1/\mu$	Average duration of sexual activity	32 years
δ	Fraction of infected individuals that bypass primary infection	$\delta \in [0, 1)$
ϵ	Vaccine efficacy	$\epsilon \in (0, 1)$
τ	Per capita rate of vaccine-induced reversal from AIDS to asymptomatic stage	$\tau \geq 0$ (year)$^{-1}$
σ_1	Per capita rate of progression from primary to asymptomatic stage	13 (year)$^{-1}$
σ_2	Per capita rate of progression from asymptomatic to AIDS stage	0.0885 (year)$^{-1}$
ψ	Per capita disease-induced mortality rate	0.47 (year)$^{-1}$

Note. Sources of estimates: McLean and Blower (1993) and Hyman et al. (1999).

Table 2 Effect of $\mathcal{R}$ on number of HIV cases at steady-state using $\tau = 0$.

ϵ	ξ	δ	$\mathcal{R}$	$I_1^{**} + I_2^{**} + I_3^{**}$
0.1	0.3	0.3	2.034	10100
0.3	0.3	0.5	1.683	8183
0.6	0.4	0.5	1.105	1971
0.72	0.25	0.6	1.007	152
0.73	0.25	0.6	0.991	0

Note. The Table is generated using various values of ξ, δ, ϵ with $\eta_2 = 0.3$, $\eta_3 = 0.7$ and all other parameters as in Table 1.

It is assumed that the duration of vaccine effect is 20 years (so that $\omega = 0.05$ per year). Following Hyman et al. (1999), it is assumed that the duration of the primary infection stage is 4 weeks (i.e., $\sigma_1 = 13$ per year) and 11 years for the mean duration in the asymptomatic stage ($\sigma_2 = 0.0885$). Furthermore, the modification parameters η_2 and η_3 are set at $\eta_2 = 0.3$ and $\eta_3 = 0.7$, respectively. The parameters $0 < \epsilon < 1$, $\xi > 0$, $\tau > 0$ and $0 \leq \delta \leq 1$ are variable.

The effect of the numerical size of the vaccination reproduction number for the mass action model ($\mathcal{R}$) on the total number of HIV cases is monitored firstly (by obtaining G^{**} from (16) and (17) and substituting in (14)) using combinations of the parameters in Table 1 resulting in various $\mathcal{R}$ values. Two scenarios are tabulated. One for the case $\tau = 0$ (i.e., for a vaccine that offers no therapeutic effect) (Table 2) and the other for $\tau > 0$ (Table 3). These results show that the total number of HIV infections increases with increasing $\mathcal{R}$. Furthermore, in line with the aforementioned Corollary and Conjecture, these tables show HIV persistence for values of $\mathcal{R} > 1$ and elimination for values of $\mathcal{R} < 1$. It is instructive to note that higher total number of infections are recorded for the case when $\tau > 0$ in comparison with using a vaccine with no therapeutic effect ($\tau = 0$).

Figures 2A and 2B depict the combined effect of vaccine efficacy (ϵ) and fraction of individuals vaccinated at steady-state (given by $S_v^*/N^* = \xi/(\mu + \xi + \omega)$) on the vaccination reproduction number ($\mathcal{R}$) for $\tau = 0$ and $\tau = 0.5$, respectively. These contour plots show a marked decrease in $\mathcal{R}$ with increasing vaccine efficacy and fractional vaccine coverage rate. Significantly high efficacy and fractional coverage rate are needed to eliminate the disease (achieve $\mathcal{R} < 1$). In particular, even if

Table 3 Effect of $\mathcal{R}$ on number of HIV cases at steady-state using $\tau > 0$.

τ	$\mathcal{R}$	$I_1^{**} + I_2^{**} + I_3^{**}$
100	3.340	45615
20	3.195	42584
10	3.039	39353
1	1.986	17917
0.5	1.698	12289

Note. The Table is generated using $\epsilon = 0.5$, $\xi = 0.5$, $\delta = 0.2$, $\eta_2 = 0.3$, $\eta_3 = 0.7$ and all other parameters as in Table 1.

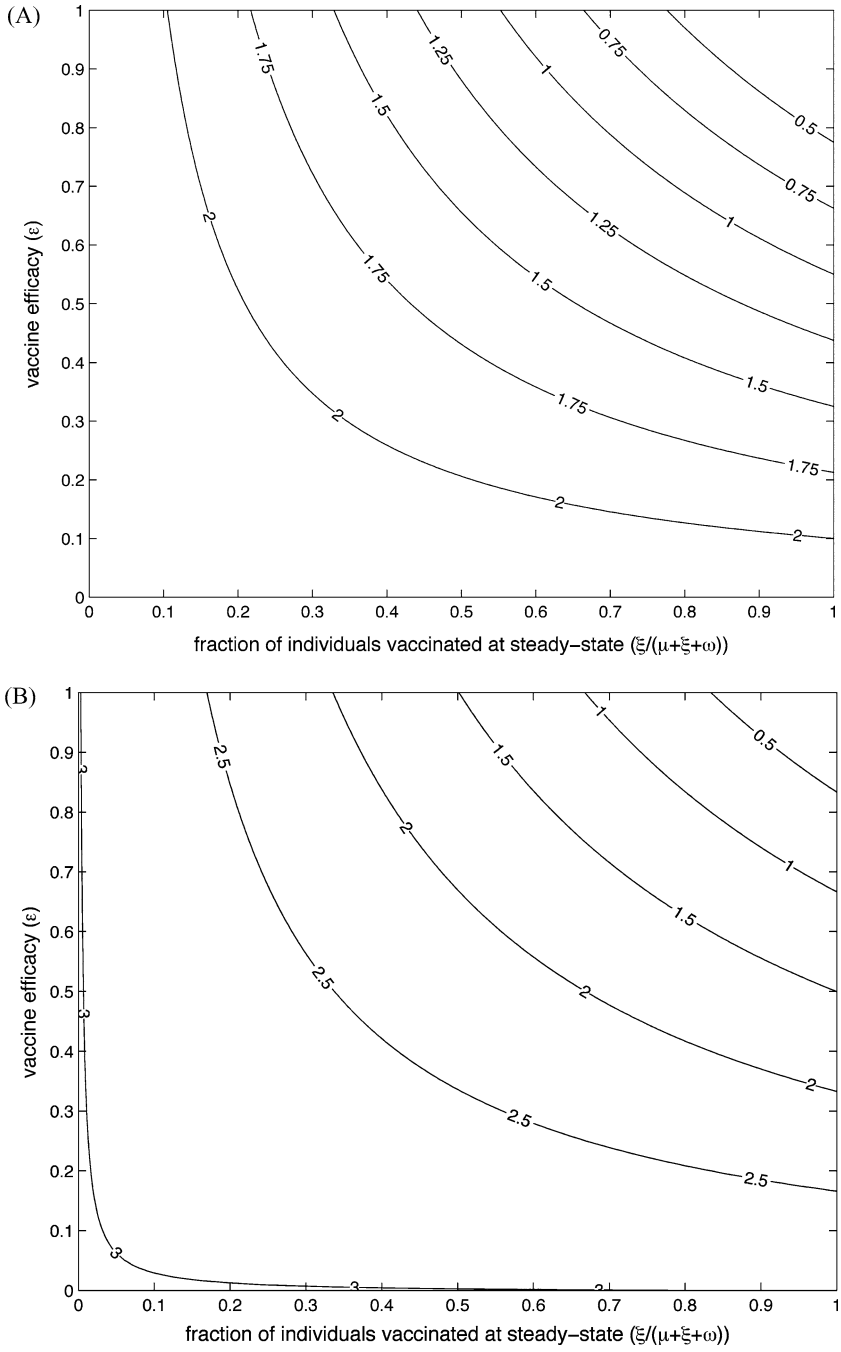

Fig. 2 Contour plots of $\mathcal{R}$ as a function of vaccine efficacy (ϵ) and fraction of individuals vaccinated at steady-state ($\xi/(\mu+\xi+\omega)$). Parameters are as in Table 1, with $\tau = 0$, $\delta = 0.3$, $\eta_2 = 0.3$ and $\eta_3 = 0.7$ (A) and with $\tau = 0.5$, $\delta = 0.3$, $\eta_2 = 0.3$ and $\eta_3 = 0.7$ (B).

80% of individuals are vaccinated at steady state (a realistic target), an efficacy level of at least 70% (for the case $\tau = 0$) or 80% (for the case $\tau = 0.5$) would be needed to effectively control HIV spread. It is worth noting that the increase in threshold efficacy needed for elimination is a consequence of using a vaccine with therapeutic benefit ($\tau > 0$).

One essential aspect of this study is that it enables the assessment of the hypothesis that an HIV vaccine could cause some infected vaccinated individuals to bypass primary infection ($\delta > 0$). We investigate the effect of this potential phenomenon. It is easy to see that

$$\frac{\partial \mathcal{R}}{\partial \delta} = -\frac{\beta \Pi (1-\epsilon)\xi}{\mu(\mu+\xi+\omega)\det V}\{\mu(\mu+\psi+\tau)(1-\eta_2)+\sigma_2[\mu(1-\eta_3)+\psi]\} < 0,$$

by the assumptions on the efficacy (ϵ) and modification parameters (η_2 and η_3). Thus, $\mathcal{R}$ is a decreasing function of δ. Since it is shown in Tables 2 and 3 that reduction in $\mathcal{R}$ corresponds to a decrease in the number of HIV cases, it follows that a future HIV vaccine that can induce a bypass of primary infection amongst vaccinated infected individuals would decrease HIV prevalence.

The effect of waning rate of the vaccine (ω) can be assessed by differentiating the expression for $\mathcal{R}$ with respect to ω. This gives

$$\frac{\partial \mathcal{R}}{\partial \omega} = \frac{\beta \Pi \xi}{\mu(\mu+\xi+\omega)^2 \det V}(A_1 + A_2 - A_3),$$

with

$$A_1 = [(\mu+\psi)(\sigma_2+\mu)+\mu\tau][\epsilon+\delta(1-\epsilon)],$$
$$A_2 = [\eta_2(\tau+\mu+\psi)+\eta_3\sigma_2][\delta\mu+\sigma_1]\epsilon,$$
$$A_3 = [\eta_2(\tau+\mu+\psi)+\eta_3\sigma_2]\delta\mu.$$

Noting that $A_3 \leq A_1$, it follows that $\mathcal{R}$ increases with increasing ω. Thus, as expected, an increase in the waning rate of vaccine would result in an increase in HIV prevalence.

The vaccine-induced therapeutic effect of converting individuals in the AIDS stage into the asymptomatic (secondary) stage is investigated. It can be shown that

$$\frac{\partial \mathcal{R}}{\partial \tau} = \frac{\beta \Pi (\sigma_1+\mu)}{\mu(\mu+\xi+\omega)(\det V)^2}\{A_4[\eta_2(\mu+\psi)-\eta_3\mu]\sigma_2\},$$

with $A_4 = \sigma_1(\omega+\mu)+\xi(1-\epsilon)(\sigma_1+\delta\mu)$. Since $0 < \epsilon < 1$, it follows that $\mathcal{R}$ is an increasing function of τ provided $\eta_3 < \eta_2(\mu+\psi)/\mu$. Figure 3 shows contours of $\mathcal{R}$ as a function of vaccine efficacy (ϵ) and vaccine-induced therapeutic effect (τ),

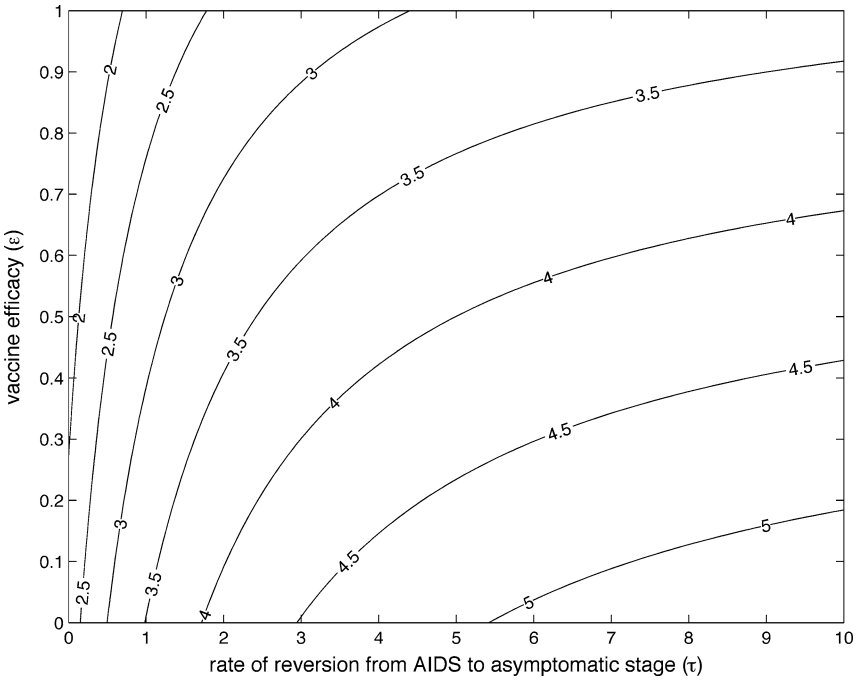

Fig. 3 Contour plot of $\mathcal{R}$ as a function of vaccine efficacy (ϵ) and vaccine-induced therapeutic effect (τ). Parameters are as in Table 1 with $\xi = 0.05$, $\eta_2 = 0.3$, $\eta_3 = 0.7$ and $\delta = 0.3$.

from which it is clear that a vaccine that induces reversal from AIDS stage to the asymptomatic stage ($\tau > 0$) must be highly efficacious to result in effective control of the epidemic in a population. Note that, in this simulation, $\eta_3 = 0.7 < \eta_2(\mu + \psi)/\mu = 4.812$ (satisfying the above inequality). Thus, although a vaccine with therapeutic effect alleviates the high morbidity and mortality suffered by vaccinated individuals in the AIDS stage (by reverting them to the asymptomatic stage), such a vaccine also results in an increase in HIV prevalence owing to its impact in extending the lifespan of infected individuals at the AIDS stage (by reverting them to the asymptomatic stage). Thus, while a therapeutic vaccine is certainly beneficial to successfully vaccinated infected individuals, its cumulative community-wide impact could be detrimental by resulting in an increase in HIV prevalence.

The reduced mass action model (18) was simulated using the aforementioned parameter values with $\eta_2 = \eta_3 = \delta = \tau = 0$, $\xi = 0.25$, $\epsilon = 0.2$ and different values of β so that $\mathcal{R}^{(r)} > 1$. It should be noted that with this choice of parameter values, the inequalities in (19) and (20) are violated. The results obtained, tabulated in Table 4, show the sizes of the infected classes at the unique endemic equilibrium point, to which the simulations did converge, supporting the Conjecture.

Table 4 Effect of β on $\mathcal{R}^{(r)}$ and prevalence using reduced mass action model.

β	$\mathcal{R}^{(r)}$	I_1^{**}	I_2^{**}	I_3^{**}
0.00961	40.07	150	16296	2877
0.006	25.02	148	16068	2837
0.004	16.68	145	15756	2782
0.002	8.34	136	14795	2612
0.001	4.17	118	12817	2263
0.0007	2.92	102	11099	1960
0.0003	1.25	31	3395	599
0.00025	1.04	6	690	122

Note. Parameters are as in Table 1 except: $\eta_2 = \eta_3 = \delta = \tau = 0$, $\epsilon = 0.2$, $\xi = 0.25$ and various values of β.

6. Conclusions

A five-dimensional, deterministic, staged-progression model is developed and used to assess the potential impact of an imperfect HIV vaccine in curtailing the spread of HIV in a homosexual community. The model is rigorously analyzed to investigate the existence and stability (including global stability) of the associated equilibria. Numerical simulations were carried out using reasonable sets of parameter values to assess the impact of various vaccine features and characteristics on disease control. The main findings of the study are summarized below:

(i) The model with mass action incidence has a globally-asymptotically stable disease-free equilibrium whenever the vaccinated reproduction number is less than unity. When this number is greater than one, there is a unique endemic equilibrium, which is shown to be globally asymptotically-stable for a reduced version of the model (under stated parameter restrictions). Unlike other vaccination models for HIV, this model does not undergo the phenomenon of backward bifurcation.

(ii) An imperfect HIV vaccine can eliminate HIV from a community provided it can reduce the vaccination reproduction number to values less than unity. Higher values of vaccine efficacy and coverage rate are needed to achieve elimination.

(iii) A vaccine that induces a bypass of primary infection amongst vaccinated individuals would decrease HIV prevalence.

(iv) An increase in waning rate of vaccine-induced protection results in an increase of the vaccinated reproduction number, and, hence, an increase in HIV prevalence.

(v) Whilst the use of vaccine with therapeutic benefits is beneficial to successfully vaccinated individuals, its cumulative community-wide effect may be detrimental since it can result in higher HIV prevalence.

Overall, this study shows that a future imperfect HIV vaccine, with certain desirable characteristics, can significantly help in halting the spread of HIV in a given community, such as the San Francisco gay community.

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References

Anderson, R.M., May, R.M., 1991. Infectious Diseases of Humans. Oxford University Press, London/New York.

Arino, J., McCluskey, C.C., van den Driessche, P., 2003. Global results for an epidemic model with vaccination that exhibits backward bifurcation. SIAM J. Appl. Math. 64, 260–276.

Baggeley, R.F., Ferguson, N.M., Garnett, G.P., 2005. The epidemiological impact of antiretroviral use predicted by mathematical models: A review. Emerg. Themes Epidemiol. 2, 9. (http://www.ete-online.com/contect/2/1/9). Accessed September 20, 2005.

Blower, S.M., McLean, A.R., 1994. Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco. Science 265, 1451–1454.

Brauer, F., Castillo-Chavez, C., 2000. Mathematical Models in Population Biology and Epidemiology. Texts in Applied Mathematics Series, vol. 40. Springer-Verlag, New York.

Burton, D.R., et al., 2004. A sound rationale needed for Phase III HIV-1 vaccine trials. Science 303, 316.

Castillo-Chavez, C., Feng, Z., Huang, W., 2002. On the computation of $\mathcal{R}_0$ and its role on global stability. In: Castillo-Chavez, C., with Blower, S., van den Driessche, P., Kirschner, D., Yakubu, A.-A. (Eds.), Mathematical Approaches for Emerging and Reemerging Infectious Diseases: An Introduction. The IMA Volumes in Mathematics and its Applications, vol. 125. Springer, New York, pp. 229–250.

Chang, M.L., Vitek, C., Esparza, J., 2003. Public health considerations for the use of a first generation HIV vaccine. Report from a WHO-UNAIDS-CDC consultation, Geneva, 20–21 November 2002. AIDS 17, W1–10.

Corbett, B.D., Moghadas, S.M., Gumel, A.B., 2003. Subthreshold domain of bistable equilibria for a model of HIV epidemiology. IJMMS 58, 3679–3698.

Del Valle, S., Evangelista, A.M., Velasco, M.C., Kribs Zaleta, C.M., Schmitz, S.H., 2004. Effects of education, vaccination and treatment on HIV transmission in homosexuals with genetic heterogeneity. Math. Bios. 187, 111–133.

Elbasha, E.H., Gumel, A.B., 2006. Theoretical assessment of public health impact of imperfect prophylactic HIV-1 vaccines with therapeutic benefits. Bull. Math. Biol. DOI 10.1007/s11538-005-9057-5.

Esparza, J., Osmanov, S., 2003. HIV vaccines: A global perspective. Curr. Mol. Med. 3, 183–193.

Fleck, F., 2004. Developing economies shrink as AIDS reduces workforce. BMJ 329, 129.

Gray, R., Li, X., Wawer, M., Gange, S., Serwadda, D., et al., 2003. Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. AIDS 17, 1941–1951.

Hethcote, H.W., 1989. Three basic epidemiological models. In: Gross, L., Hallam, T.G., Levin, S.A. (Eds.), Applied Mathematical Ecology. Springer, Berlin, pp. 119–144.

Hethcote, H.W., 2000. The mathematics of infectious diseases. SIAM Rev. 42(4), 599–653.

Hyman, J.M., Li, J., Stanley, E.A., 1999. The differential infectivity and staged progression models for the transmission of HIV. Math. Biosci. 208, 227–249.

Klausner, R.D., et al., 2003. The need for a global HIV vaccine enterprise. Science 300, 2036–2039.

Kribs-Zaleta, C., Velasco-Hernández, J., 2000. A simple vaccination model with multiple endemic states. Math. Biosci. 164, 183–201.

Lakshmikantham, V., Leela, S., Martynyuk, A.A., 1989. Stability Analysis of Nonlinear Systems. Marcel Dekker, Inc., New York and Basel.

Lansky, A., Nakashima, A., Jones, J., 2000. Risk behaviors related to heterosexual transmission from HIV-infected persons. Sex. Transm. Dis. 27, 483–489.

Lee, D., et al., 2004. Breakthrough infections during phase 1 and 2 prime-boost HIV-1 vaccine trials with canarypox vectors (ALVAC) and booster dose of recombinant gp120 or gp160. J. Infect. Dis. 190(5), 903–907.

Li, M.Y., Muldowney, J.S., 1995. On R.A. Smith's autonomous convergence theorem. Rocky Mount. J. Math. 25, 365–379.

Li, M.Y., Muldowney, J.S., 1996. A geometric approach to global-stability problems. SIAM J. Math. Anal. 21, 1070–1083.

McCluskey, C.C., 2003. A Model for HIV/AIDS with staged progression and amelioration. Math. Bios. 181, 1–16.

McCluskey, C.C., 2005. A strategy for constructing Lyapunov functions for non-autonomous linear differential equations. Linear Algebra Appl. 409, 100–110.

McLean, A.R., Blower, S.M., 1993. Imperfect vaccines and herd immunity to HIV. Proc. R. Soc. Lond. Series B 253, 9–13.

Nicolosi, A., Musicco, M., Saracco, A., Lazzarin, A., 1994. Risk factors for woman-to-man sexual transmission of the human immunodeficiency virus. J. Acq. Immun. Def. Synd. 7, 296–300.

O'Brien, T., Busch, M., Donegan, E., Ward, J., Wong, L., et al., 1994. Heterosexual transmission of human immunodeficiency virus type 1 from transfusion recipients to their sex partners. J. Acquir. Immune. Defic. Syndr. 7, 705–710.

Perelson, A., Nelson, P., 1999. Mathematical analysis of HIV-1 dynamics *in vivo*. SIAM Rev. 41, 3–44.

Shiver, J., Emini, E., 2004. Recent advances in the development of HIV-1 vaccines using replication-incompetent adenovirus vectors. Ann. Rev. Med. 55, 355–372.

Shiver, J., Fu, T.-M., Chen, L., Casimiro, D., Davies, M.-A., et al., 2002. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. Nature 415, 331–335.

Smith, R.J., Blower, S.M., 2004. Could disease-modifying HIV vaccines cause population-level pervasity? Lancet Infec. Dis. 4, 636–639.

Smith, H.L., Waltman, P., 1995. The Theory of the Chemostat. Cambridge University Press.

van den Driessche, P., Watmough, J., 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Bios. 180, 29–48.

World Bank, 1997. Confronting AIDS: Public Priorities in a Global Epidemic. Oxford University Press, Oxford.

WHO, 2004. The World Health Report: Changing History. World Health Organization, 1211 Geneva 27, Switzerland.

Zinkernagel, R.M., 2004. The challenges of an HIV vaccine enterprise. Science 303, 1294–1297.