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Population level impact of an imperfect prophylactic HSV-2 vaccine

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Abstract

Background—The continuation of developing HSV-2 prophylactic vaccines requires parallel mathematical modeling to quantify the impact on the population of these vaccines.

Methods—Using mathematical modeling we derived three summary measures for the population impact of imperfect HSV-2 vaccines as a function of their efficacies in reducing susceptibility (VE_S), genital shedding (VE_P), and infectivity during shedding (VE_I). In addition, we studied the population level impact of vaccine intervention using representative vaccine efficacies.

Results—A vaccine with limited efficacy of reducing shedding frequency ($VE_P=10\%$) and infectivity ($VE_I=0\%$) would need to reduce susceptibility by 75% ($VE_S=75\%$) to substantially reduce the sustainability of HSV-2 infection in a population. No reduction in susceptibility would be required to reach this target in a vaccine that decreased shedding by 75% ($VE_S=0\%$, VE_P

$=75\%$, $VE_I=0\%$). Mass vaccination using a vaccine with imperfect efficacies ($VE_S=30\%$, $VE_P=75\%$, and $VE_I=0\%$) in Kisumu, Kenya in 2010 would decrease prevalence and incidence in 2020 by 7% and 30% respectively. For lower prevalence settings, vaccination is predicted to have a lower impact on prevalence.

Conclusion—A vaccine with substantially high efficacy of reducing HSV-2 shedding frequency would have a desirable impact at the population level. The vaccine's short-term impact in a high prevalence setting in Africa would be a substantial decrease in incidence, whereas its immediate impact on prevalence would be small and would increase slowly over time.

Keywords

Keywords: Herpes simplex virus; mathematical modeling; prophylactic vaccines; summary measures; vaccine efficacy

Introduction

Herpes simplex virus type-2 (HSV-2) infection is highly prevalent in sub-Saharan Africa [1–10] and around the globe [11–13]. The broad spread of HSV-2 is further complicated by the common mode of transmission and the synergistic epidemiologic pattern that it shares with Human Immunodeficiency Virus (HIV). HSV-2 positive and HSV-2/HIV co-infected persons have a higher risk of contracting HIV infection [14–16], and of transmitting HIV [17,18], respectively. The estimated proportion of HIV infections attributable to HSV-2 in areas with a high HSV-2 prevalence such as sub-Saharan Africa is approximately 25% [19]. Therefore, controlling HSV-2 could have a substantial population-level impact on HIV incidence in sub-Saharan Africa.

HSV-2 vaccines have gained more focus after the recent failure of HSV-2 suppression therapy to limit HIV spread in three randomized-controlled trials [20–22]. An ideal HSV-2 prophylactic vaccine would induce sterilizing immunity and prevent HSV-2 acquisition in susceptible populations. Meanwhile, imperfect [23] prophylactic HSV-2 vaccines could partially reduce HSV-2 acquisition in vaccinees, and/or partially reduce infectivity of those who get infected after vaccination, by either reducing their shedding frequency or viral load during shedding episodes. Because the effectiveness of a licensed vaccine is not known, mathematical modeling can determine the population-level impact of various combinations of protection regarding three biologic aspects of disease: susceptibility, shedding frequency, and infectivity while shedding.

Two prophylactic recombinant vaccines have completed phase III clinical trials and achieved limited success in protecting against HSV-2 acquisition [24–26]. A third vaccine that uses the full-length of gD with bupivacaine recently underwent successful testing in a safety and immunogenicity trial [27].

Because the current HSV-2 strategies target reduction in shedding as a primary outcome along with the classical target of susceptibility reduction [26,28], the results of future clinical trials of vaccines will provide vaccine efficacies in terms of reduction in susceptibility and shedding frequency. These efficacies are obtained for individuals during the short period of the clinical trial. Therefore, the criteria for a favorable vaccine at the population level will not be directly obtained from these trials.

Our goal in this study was to estimate the population-level impacts of prophylactic HSV-2 vaccines using mathematical modeling. We introduced a model for HSV-2 in which the different aspects of prophylactic HSV-2 vaccines were parameterized to study their effects. While previous HSV-2 models [29,30] studied population-level impact of HSV-2 vaccines

in the United States, we estimated the impact of vaccination at the population level in a representative setting of hyperendemic HIV and HSV-2 epidemic in sub-Saharan Africa (Kisumu, Kenya). The impact of vaccination was estimated in terms of impact on prevalence, incidence, and infections averted per vaccination procedure.

Materials and Methods

We constructed a deterministic compartmental model calibrated to describe HSV-2 transmission in presence of vaccination in different populations but focused most of our analyses on a representative sub-Saharan African population (Kisumu, Kenya). The Supplementary Information Appendix contains the details of the model and its parameterization. The model stratifies the population into compartments according to vaccination status (vaccinated or unvaccinated), sexual risk group, and stage of HSV-2 infection using eight coupled nonlinear ordinary differential equations for each risk group of the four risk groups in the model. HSV-2 pathogenesis is represented by three stages: primary, latent (*no shedding*), and reactivated (*shedding*) stages. HSV-2 is of a chronic nature, therefore the latent and reactivated stages cycle through the entire life of the infected. The shedding frequency is assumed to be at 14% of each cycle [31]. The baseline transition rates of progression from primary to latent, latent to reactivated, and reactivated to latent are derived from the duration of each stage and the shedding frequency and they are 18.3, 4.7, and 28.6 per year, respectively. Baseline transmission probabilities per coital act per HSV-2 primary, latent, and reactivated stages are 0.01, 0.00, and 0.01, respectively [19]. We considered three possible efficacies for a prophylactic HSV-2 vaccine [23]: reducing susceptibility to infection (VE_S), and for those who get infected after the time of vaccination, reducing infectivity *during shedding* episodes (VE_I) and reducing frequency of viral shedding (VE_P) (Table 1 and Supplementary Information Appendix).

We quantified the effect that variability in VE_S , VE_I , or VE_P would have on three summary measures (Appendix): basic reproduction number in a partially vaccinated population (R_{0V}), vaccine utility (Φ), and vaccinee infection fitness (Ψ). Summary measure R_{0V} quantifies the disease transmission sustainability in the partially vaccinated population such that when $R_{0V} < 1$ the vaccine would diminish HSV-2 chains of transmission in the general population. Summary measure Φ quantifies the utility of the vaccine through relative reduction in the basic reproduction number due to vaccination and reductions in prevalence and incidence [32,33] such that when $\Phi > 0$ equilibrium values of prevalence, incidence (absolute number of incident infections per year), and incidence rate (number of incident infections per susceptible individual per year) are reduced from their respective values without vaccination. Finally, vaccinee infection fitness (Ψ) is a measure of the heterogeneity in transmission introduced by vaccination [33] such that when Ψ is considerably below one ($\Psi < 1$), many fewer secondary infections are caused by the infected and vaccinated compared to infected and unvaccinated populations.

Our summary measures are appropriate tools for estimating the long-term effect of a partially efficacious vaccine. To derive each summary measure analytically, we simplified our mathematical model for a population with uniform risk behavior. In the quantitative predictions presented below, for each vaccine efficacy scenario, we assumed universal adolescent vaccination ($f=100\%$). Although it has never been proven that risk behavior compensation could accompany HSV-2 vaccination, for completeness we assumed a modest risk behavior compensation of $r=10\%$ for those vaccinated relative to baseline risk behavior. Other assumptions included a uniform average sexual-risk of two partners per year, and life-long protection upon vaccination.

To measure the short-term impact of a vaccine in a high prevalence region, we next presented a more detailed mathematical model that included heterogeneous risk behavior. This version of the model was fitted to Kisumu's prevalence data. We chose the parameter values of the model according to the best available empirical evidence of the biology and epidemiology of HSV-2 infection. In particular, recently established detailed empirical data about the pattern of HSV-2 reactivation in its clinical and subclinical form [34], played a central role in our assumptions. The behavioral parameters in the model are informed by the measurements of the Four City study [35–37]. The model's assumptions are listed in Table 2 along with their references.

Although there are substantial variations in the rate and pattern of HSV-2 reactivations [34,38,39], the critical parameter is the shedding frequency irrespective of whether the pattern is that of short but frequent reactivations or long but less frequent ones [19]; because by assumption the infectious state is manifested by shedding the virus and irrespective of the pattern of shedding. The assumption that all shedding is associated with possible transmission has not been validated, however. It is possible that only shedding above a certain quantitative threshold (such as 1000 HSV copies DNA/mL) commonly leads to transmission. A vaccine may also decrease infectivity of individual virions irrespective of their number due to increased immune surveillance in the genital tract. Vaccine efficacy of decreasing transmission during shedding VE_I accounts for both of the above possibilities.

Results

Summary measures of vaccine impact at the population level

Increasing any of the vaccine efficacies of reducing susceptibility (VE_S), shedding frequency (VE_P), or infectivity during shedding (VE_I) from 0% to 100% produces steadily increasing positive vaccine utility (Φ) suggesting an increasingly beneficial vaccine at the population-level in terms of prevalence and incidence (Figure 1). Increasing any of the vaccine efficacies also produces steadily decreasing basic reproduction number with vaccination (R_{0V}) suggesting more limited infection transmission and a decreasing fraction of the partially vaccinated population who can sustain the transmission of the disease. The vaccinee infection fitness (Ψ) does not depend on the vaccine efficacy of reducing susceptibility (VE_S), but decreases steadily with increasing the vaccine efficacies VE_P or VE_I . The steadily decreasing infection fitness manifests an increasing impact on the transmission dynamics of the disease by decreasing the number of secondary infections produced by infected and vaccinated individuals compared to infected and unvaccinated individuals in the partially vaccinated population.

Figure 1 A displays that for a vaccine with a limited efficacy of reducing shedding frequency of $VE_P=10\%$ and no efficacy in reducing infectivity i.e. $VE_I=0\%$, the basic reproduction number with vaccination (R_{0V}) crosses the threshold of sustainability around a high value of the vaccine efficacy of reducing susceptibility of $VE_S=75\%$. The vaccinee infection fitness remains flat at $\Psi = 0.99$ for all values of the vaccine efficacy of reducing susceptibility to HSV-2. These scenarios show that for a desirable population-level impact, an HSV-2 vaccine must reduce susceptibility by 75% if its effects on reducing shedding and infectivity during shedding in a vaccinated and infected host are limited.

However, as shown in Figure 1B, if $VE_I=0\%$ as in Figure 1A, an increase in VE_P to 75% renders the vaccine more beneficial at much smaller values of VE_S . The vaccinee fitness drops to 0.28 due to the higher VE_P and the basic reproduction number with vaccination drops below sustainability threshold for all values of VE_S . These results suggest that one way to accomplish desirable population-level impact is to have a vaccine that reduces shedding frequency beyond 75% in addition to its protective effects against acquisition. The

long-term benefits of such a vaccine are substantial even at low values of the vaccine efficacy of reducing susceptibility.

In contrast to Figure 1A and B, Figure 1C and D show how Ψ decreases steadily by increasing VE_P at two different values of VE_S of 10% and 30%, respectively. The more optimistic scenario shown in Figure 1D with $VE_S=30\%$ and at $VE_P=75\%$ predicts that the vaccine will be 8% more beneficial in terms of Φ than if the vaccine has only 10% efficacy of reducing susceptibility as in Figure 1C (Φ increases from 0.74 to 0.80). Also R_{0V} drops from 0.89 to 0.70 suggesting less sustainable disease in the population. The population-level impacts at $VE_S=10\%$ and $VE_P=10\%$, and $VE_S=30\%$ and $VE_P=75\%$, can increase further if the vaccine also has non-negligible protection against infectivity (VE_I) as shown in Figure 1E and F, respectively. It is notable that VE_I must be very high (greater than 70%) if $VE_S=10\%$ and $VE_P=10\%$ in order for the sustainability threshold to be crossed.

However, our predictions show that a vaccine with efficacy of reducing shedding frequency as high as 75% combined with efficacy of reducing susceptibility as low as 30% would be definitely and substantially beneficial in a population with an average of two sexual partners per year. Even though such an imperfect vaccine would not stop new HSV-2 infections among the vaccinated because of its low efficacy of reducing susceptibility, it still would effectively impact the dynamics of disease transmission. Moreover, it would render the number of secondary infections produced by infected and vaccinated individuals to one-quarter of the number produced by those infected and unvaccinated. The moderate risk compensation assumed here at 10% will not undermine the utility of such vaccine.

Simulated intervention

We next considered the epidemiology of intervention using vaccines in Kisumu, Kenya over a period of 10 years starting in 2010. We explored two schedules of vaccination: universal vaccination of adolescents as they enter sexual activity and mass vaccination of the sexually active population achieved within a year. We assumed vaccination using a vaccine with efficacy of reducing susceptibility to HSV-2 of $VE_S=30\%$, efficacy of reducing HSV-2 shedding of $VE_P=75\%$, and no protection against infectivity i.e. $VE_I=0\%$. Furthermore, we assumed no risk compensation ($r=0$) as perception of risk to HSV-2 infection is probably not a strong determinant of risk behavior compared to HIV in sub-Saharan Africa. By the year 2020, the adolescent vaccination would reduce HSV-2 prevalence by 3%, HSV-2 incidence and incidence rate would decrease by 21% and 23%, respectively. A total of 3842 HSV-2 infections would be averted by 2020 in Kisumu (an adult population size of 200,000) using universal adolescent vaccination.

On the other hand, mass vaccination of all susceptible persons aged 15 to 49 by the year 2020 would reduce HSV-2 prevalence, incidence, and incidence rate by 7%, 30% and 35%, respectively. A total of 8430 HSV-2 infections would be averted by 2020 in Kisumu. Figure 2A and B displays how the impact of adolescent vaccination on prevalence and incidence rate would be less than mass vaccination and would take longer to accrue due to the delay time in achieving higher vaccination coverage. As shown in Figure 2A, although the impact of either schedule of vaccination on prevalence increases over time, the effect is initially modest. Equilibrium values of prevalence, incidence, and incidence rate would be achieved beyond year 2050 and would represent a percentage decrease of 69%, 69%, and 82%, with respect to baseline values, respectively. This delay is due to the lifelong nature of HSV-2 infection where the impact on prevalence will not be substantial until the already infected population ages and leaves the sexually active population. An additional cause of the delay is that the beneficial effects of VE_P and VE_I take longer to disseminate in a population compared to that of VE_S .

Furthermore, we investigated the ten-year impact of mass vaccination intervention in 2010 on HSV-2 excess prevalence (prevalence post-intervention subtracted from prevalence pre-intervention) and computed the number of vaccinated per infection averted in populations at various levels of total HSV-2 prevalence preserving the hierarchy of sexual risk of Kisumu's settings (Figure 3). The excess prevalence is large when baseline prevalence in the absence of vaccination is high; the number of vaccinated per infection averted increases when HSV-2 prevalence in the absence of vaccination is lower. Eighteen vaccination procedures are needed per infection averted at high HSV-2 prevalence of 52%, projected for Kisumu, Kenya in 2010 which is representative of a large part of sub-Saharan Africa. This is compared to 64 vaccination procedures per infection averted for the United States at HSV-2 prevalence of 17%.

We investigated the synergy between the vaccine efficacies of reducing shedding frequency and reducing susceptibility over time. The definition of synergy is delineated in the Supplementary Information Appendix. We found that (not shown) the effects of the two efficacies VE_S and VE_P to be generally synergistic particularly in the long term. Larger value for either parameter leads to enhanced synergy. However in the short term, a slight redundancy between the two interventions is present while the transmission effects of VE_S accrue in the population. The impact of VE_P in a population is substantial only after substantial number of people are vaccinated and subsequently infected with HSV-2.

Finally, we performed sensitivity and uncertainty analyses to assess the robustness and sensitivity of our short and long-term predictions to uncertainty in the vaccine efficacies, sexual behavior parameters and risk group structure, HSV-2 progression parameters and risk compensation behaviors (Supplementary Information Appendix). We found that our short-term predictions for the impact of vaccine intervention by 2020 in terms of excess prevalence, relative reduction in incidence, and excess incidence rate are largely invariable to the assumed variations in the vaccine efficacies of reducing infectivity and shedding frequency, or behavioral and HSV-2 progression parameters. However, the predicted excess prevalence and incidence rate as well as the reduction in incidence show substantial variability in the short-term to the assumed variation in the vaccine efficacy of reducing susceptibility. This is expected as in the short-term it is mainly VE_S that is driving the impact of the vaccine.

Over the long-term, substantial sensitivity in our predictions are observed with respect to the assumed variations in the vaccine efficacy of reducing shedding frequency and in the shedding frequency itself, respectively. The long-term sensitivity results attest to the role of VE_P and shedding frequency in determining the course of HSV-2 transmission in presence of vaccination over a time horizon of few decades.

Discussion

Our approach enables prediction of the potential population impact of vaccines immediately after clinical trial results are available. In the case of HSV-2, a vaccine candidate's efficacy measures are likely to become available after a clinical trial: vaccine efficacy of reducing susceptibility (VE_S) is often the primary outcome measure of most vaccine trials; but because current HSV-2 strategies also target reduction in shedding [26,28], it is now standard practice to measure the effect of all HSV-2 interventions on shedding frequency and therefore a detailed assessment of vaccine efficacy of reducing shedding frequency (VE_P) will be available as well; any effect on transmissibility during shedding as measured by VE_I will be more difficult to obtain because a quantitative virologic threshold for HSV-2 transmission is not currently known. Nevertheless, if it is assumed that VE_I is low as in our

Kisumu simulations, then the other two measures can represent a worse case scenario for a vaccine's effect in a population.

Our results underscore the relative impact of each of the vaccine efficacies at the population level, which is an important aspect of studying any imperfect vaccine. While the impact of VE_S at the population-level is immediate, the effects of VE_P and VE_I accrue over time. When VE_S is large, a small number of infections occur among vaccinees in the short term leaving little room for VE_P to impact HSV-2 infectious spread. However in the long term there is a synergy between the effects of the two efficacies and they compliment each other.

Our study has several limitations. First, it does not address heterogeneity in shedding frequency in the general population. Ranges of shedding frequency among HSV-2 infected persons are from 0% – 78% [40]. In addition, there is evidence that frequent shedders may serve as “super spreaders” irrespective of sexual risk behavior [41]. Therefore, the effect of high VE_P in this group would decrease the absolute amount of shedding more substantially than in infrequent shedding groups. Future mathematical models of vaccine efficacy would benefit from independent stratification of sexual risk behavior and shedding frequency into sub-groups. In addition, a true quantitative surrogate measure for transmission risk has not been identified as of yet. We account for the possibility that low-copy shedding may not be associated with transmission risk in our sensitivity analysis where we decrease shedding frequency, and also by incorporating VE_I , which is a measure of vaccine efficacy regarding infectivity during shedding only. Lastly our model does not incorporate age-dependent targeting of interventions nor does it allow for differences by sex in transmission probability per coital act.

In summary, if HSV-2 vaccines that are currently under development have limited efficacy against HSV-2 acquisition, but have substantial efficacy of reducing shedding frequency or infectivity, then such vaccines are likely to have a high impact on HSV-2 incidence and prevalence over several decades, and will have a more immediate strong effect on HSV-2 incidence, particularly in high prevalence populations. Conversely, a vaccine that has a modest effect on acquisition but no effect on viral shedding is unlikely to be as effective. It is therefore imperative, that all future vaccine studies evaluate the effect that a vaccine has on genital viral shedding.

Summary

Mathematical modeling is used to derive summary measures for the utility of HSV-2 vaccination and to assess the epidemiological impact of vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

HSV-2 basic reproductive number without vaccination

The HSV-2 basic reproduction number (R_0) for a population with no vaccination ($f=0$) is given by

$$R_0 = \frac{L\rho}{L+\tau_1} \left[\tau_1 t_1 + \frac{L(1-\xi)(\xi+L\chi)}{L\chi+\xi(1-\xi)} t_2 + \frac{L^2\chi\xi}{L\chi+\xi(1-\xi)} t_3 \right] \quad (\text{A.1})$$

where t_i is the transmission probabilities per partnership from HSV-2 infected individuals in HSV-2 stage i to susceptible individuals. The parameters ρ , L , τ_1 , ξ , and χ are the effective partnership acquisition rate of unvaccinated individual, the average sexual life span, the average duration of HSV-2 primary infection, average shedding frequency among infected individuals, and the average frequency of latency and reactivation cycles, respectively.

HSV-2 basic reproductive number with adolescent vaccination

The HSV-2 basic reproduction number in a partially vaccinated population (R_{0V}) is given by

$$\begin{aligned} R_{0V} = R_0 + & \frac{L^2\rho}{(L+\tau_1)} \frac{fT}{(L+T+rfT)} \\ & \times \left\{ (1+r)^2(1-VE_I)(1-VE_S) \left(\frac{\tau_1}{L} t_1 + t_2 \right) - \frac{\tau_1}{L} t_1 - (1-\xi)t_2 - \xi t_3 \frac{\xi^2(1-\xi)}{\xi(1-\xi)+L\chi} (t_3 \right. \\ & - t_2) + (1+r)^2(1 \\ & - VE_I)(1 \\ & - VE_S)(1 \\ & - VE_p)\xi \times \left. \left(1 - \frac{\xi(1-(1-VE_p)\xi)}{L\chi+(1-VE_p)\xi(1-(1-VE_p)\xi)} \right) (t_3 - t_2) \right\} \end{aligned} \quad (\text{A.2})$$

where VE_S , VE_p , and VE_I are the vaccine efficacy of reducing: susceptibility, shedding frequency, and infectivity *during* shedding, respectively. The parameters f , r , and T are the fraction of adolescents entering sexual activity who are being vaccinated, their relative increase in risk behavior after vaccination, and the average duration of vaccine protection, respectively.

Vaccine utility

The vaccine utility (Φ) is defined by relative reduction in the basic reproduction number due

to vaccination [32]: $\Phi = \frac{1}{f} \left(1 - \frac{R_{0V}}{R_0} \right)$ and is given by:

$$\begin{aligned} \Phi = & \frac{1}{R_0} \frac{L^2 \rho}{(L + \tau_1)} \frac{T}{(L + T + rT)} \\ & \times \left\{ \frac{\tau_1}{L} t_1 + (1 - \xi) t_2 + \xi t_3 - (1 + r)^2 (1 - VE_I)(1 - VE_S) \left(\frac{\tau_1}{L} t_1 + t_2 \right) \right. \\ & - \frac{\xi^2 (1 - \xi)}{\xi(1 - \xi) + L\chi} (t_3 \\ & - t_2) - (1 + r)^2 (1 \\ & - VE_I)(1 \\ & - VE_S)(1 \\ & - VE_p) \xi \times \left(1 - \frac{\xi(1 - (1 - VE_p)\xi)}{L\chi + (1 - VE_p)\xi(1 - (1 - VE_p)\xi)} \right) (t_3 - t_2) \left. \right\} \end{aligned} \quad (A.3)$$

Vaccinee infection fitness

The vaccinee infection fitness (Ψ) is equal to the ratio of the number of secondary infections caused by an infected vaccinated individual (R_{IV}) to the number of secondary infections caused by an infected unvaccinated individual (R_{IS}) in a partially vaccinated and infection-

free population (Supplementary Information Appendix): $\Psi = \frac{R_{IV}}{R_{IS}}$ and is given by

$$\Psi = (1 + r)(1 - VE_I) \frac{L\chi + \xi(1 - \xi)}{L\chi + (1 - VE_p)\xi(1 - (1 - VE_p)\xi)} \times \frac{\left[\xi(1 - VE_p)(1 - (1 - VE_p)\xi)(\tau_1(t_1 + t_2 + t_3) + L(2t_2 + t_3)) + L\chi(t_1\tau_1 + (3L + 2\tau_1)(t_2 - (1 - VE_p)\xi t_2 + (1 - VE_p)\xi t_3)) \right]}{\left[\tau_1\xi(t_1 + t_2 + t_3)(1 - \xi) + 3L^2\chi(t_2(1 - \xi) + t_3\xi) + L(t_1\chi\tau_1 + t_3\xi(1 + 2\chi\tau_1 - \xi) + 2t_2(1 - \xi)(\chi\tau_1 + \xi)) \right]} \quad (A.4)$$

Vaccine utility states and desirable values of summary measures

Vaccine utility was classified to *definitely beneficial* (deduced by $\Phi > 0$ [33]) if it reduces endemic equilibrium values for prevalence, incidence (absolute number of incident infection per year), and incidence rate (number of incident infections per susceptible individual per year) compared to values without vaccination. The vaccine is considered *partially beneficial* ($\Phi = 0$) if at least one but not all of these values were reduced upon achieving equilibrium after vaccination and *perverse* ($\Phi < 0$) if none of these equilibrium values were reduced after vaccination. It is desirable for vaccines to have $\Phi > 0$, $\Psi < 1$, and $R_{0V} < 1$.

Figure 1.

A set of mixed scenarios for the impact of HSV-2 vaccination. The vaccine utility (Φ), the vaccinee infection fitness (Ψ), and the basic reproduction number (R_{0v}) for a scenario versus (A) vaccine efficacy of reducing susceptibility to HSV-2 (VE_S) at $VE_P=10\%$ and $VE_I=0$, (B) vaccine efficacy of reducing susceptibility to HSV-2 (VE_S) at $VE_P=75\%$ and $VE_I=0$, (C) vaccine efficacy of reducing shedding frequency (VE_P) at $VE_S=10\%$ and $VE_I=0$, (D) vaccine efficacy of reducing shedding frequency (VE_P) at $VE_S=30\%$ and $VE_I=0$, (E) vaccine efficacy of reducing infectivity (VE_I) at $VE_S=10\%$ and $VE_P=10\%$, and (F) vaccine efficacy of reducing infectivity (VE_I) at $VE_S=30\%$ and $VE_P=75\%$. In all these plots f

$=100\%$ (fraction of adolescents vaccinated), $r = 10\%$ (risk compensation), and the vaccine is assumed to have a lifelong immunity.

Figure 2. Impacts of adolescence and mass vaccine interventions in Kisumu, Kenya administered in 2010 using a vaccine with efficacies of $VE_S=30\%$, $VE_P=75\%$, and $VE_I=0$. **(A)** Time series of prevalence values. The source of population survey data is the Four-City study [9] **(B)** Time series of incidence rate values.

Figure 3. Impact of mass vaccination in diverse HSV-2 settings having the same hierarchy of sexual risk as in Kisumu, Kenya. **(A)** Number of vaccination procedures needed per each HSV-2 infection averted at varying baseline HSV-2 prevalence levels before vaccine administration. **(B)** HSV-2 excess prevalence at endemic equilibrium (prevalence post-intervention subtracted from prevalence pre-intervention) at varying HSV-2 baseline prevalence levels. Vaccine properties are as in Figure 2.

Table 1

Prophylactic-vaccine efficacies expected to be an output of vaccine randomized controlled trials [¹, ²].

Vaccine efficacy	Definition
VE_S	Vaccine efficacy of reducing susceptibility: the relative reduction in risk of acquisition due to vaccination is given by $1 - VE_S$
VE_P	Vaccine efficacy of reducing shedding frequency: the relative reduction in the shedding frequency (given infection) due to prophylactic vaccination is given by $1 - VE_P$
VE_I	Vaccine efficacy of reducing infectivity during shedding episodes: the relative reduction in transmission probability per discordant partnership due to prophylactically vaccinating the index partner (given his/her infection and shedding) is given by $1 - VE_I$

¹ Stanberry, LR (2004) **Clinical trials of prophylactic and therapeutic herpes simplex virus vaccines.** *Herpes* 11 Suppl 3: 161A–169A.

² <http://clinicaltrials.gov/ct2/show/NCT00057330> (2009) **HerpeVac Trial for Young Women.**

Table 2

Summary of the parameters used in the model.

Parameter	Value	Reference
HSV-2 transmission probability per coital act per HSV-2 stage		
Primary infection ($p_{IS(1,j) \rightarrow S(i)}$)	0.01^I	[3]
Latency ($p_{IS(2,j) \rightarrow S(i)}$)	0	(assumption)
Reactivation ($p_{IS(3,j) \rightarrow S(i)}$)	0.01	[3]
HSV-2 shedding frequency (ξ)	14% of the time	[4]
HSV-2 transition rates between stages (absence of vaccination)		
From primary to latent infection (π_1)	18.3 per year	(derived)
From latent infection to reactivation (π_2)	4.7 per year	(derived)
From reactivation to latent infection (π_3)	28.6 per year	(derived)
Behavioral and demographic data for Kisumu, Kenya		
Frequency of coital acts per HSV-2 stage:		
Primary stage (n_1)	10.6 per month	[5]
Latent stage (n_2)	11.0 per month	[5]
Reactivation stage (n_3)	7.1 per month	[5]
Duration of sexual partnerships:		
Low risk with low risk ($d_{IS(a,1) \rightarrow S(1)}$)	48 months	(representative value)
Low risk with low to intermediate risk ($d_{IS(a,1) \rightarrow S(2)} = (d_{IS(a,2) \rightarrow S(1)})$	36 months	(representative value)
Low risk with intermediate to high risk ($d_{IS(a,1) \rightarrow S(3)} = (d_{IS(a,3) \rightarrow S(1)})$	24 months	(representative value)
Low risk with high risk ($d_{IS(a,1) \rightarrow S(4)} = (d_{IS(a,4) \rightarrow S(1)})$	12 months	(representative value)
Low to intermediate risk with low to intermediate risk ($d_{IS(a,2) \rightarrow S(2)}$)	24 months	(representative value)
Low to intermediate risk with intermediate to high risk ($d_{IS(a,2) \rightarrow S(3)} = (d_{IS(a,3) \rightarrow S(2)})$	12 months	(representative value)
Low to intermediate risk with high risk ($d_{IS(a,2) \rightarrow S(4)} = (d_{IS(a,4) \rightarrow S(2)})$	6 months	(representative value)
Intermediate to high risk with intermediate to high risk ($d_{IS(a,3) \rightarrow S(3)}$)	6 months	(representative value)
Intermediate to high risk with high risk ($d_{IS(a,3) \rightarrow S(4)} = (d_{IS(a,4) \rightarrow S(3)})$	1 month	(representative value)
High risk with high risk ($d_{IS(a,4) \rightarrow S(4)}$)	1 week	[6]
Fraction of the initial population size in each risk group ($N_0(i) / N_0^{Total}$):		
Low risk	62.8%	[7]
Low to intermediate risk	22.9%	[7]
Intermediate to high risk	11.8%	[7]
High risk	1.3%	[6]
Effective new sexual partner acquisition rate:		
Low risk ($\rho_{S(1)}$)	0.18 partners per year	(representative value calibrated to the epidemic)
Low to intermediate risk ($\rho_{S(2)}$)	1.85 partners per year	(representative value calibrated to the epidemic)

Parameter	Value	Reference
Intermediate to high risk ($(\rho_{S(3)})$)	8.2 partners per year	(representative value calibrated to the epidemic)
High risk ($(\rho_{S(3)})$)	95 partners per year	(representative value calibrated to the epidemic)
Degree of assortativeness (e)	0.2	(representative value)
Duration of the sexual lifespan ($L = 1/\mu$)	35 years	[⁸ , 9]

¹ Prospective partner studies predict a value of 0.0005 [1] while time to HSV-2 studies estimate it at 0.022 [2]. Three independent rough estimates presented in [3] give 0.01.

¹ Wald, A, Langenberg, AG, Link, K, *et al.* (2001) **Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women.** *Jama* 285: 3100–3106.

² Wald, A, Krantz, E, Selke, S, *et al.* (2006) **Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition.** *J Infect Dis* 194: 42–52.

³ Abu-Raddad, LJ, Magaret, AS, Celum, C, *et al.* (2008) **Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa.** *PLoS ONE* 3: e2230.

⁴ Stamm, WE, Handsfield, HH, Rompalo, AM, *et al.* (1988) **The association between genital ulcer disease and acquisition of HIV infection in homosexual men.** *Jama* 260: 1429–1433.

⁵ Wawer, MJ, Gray, RH, Sewankambo, NK, *et al.* (2005) **Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda.** *J Infect Dis* 191: 1403–1409.

⁶ Morison, L, Weiss, HA, Buve, A, *et al.* (2001) **Commercial sex and the spread of HIV in four cities in sub-Saharan Africa.** *AIDS* 15 Suppl 4: S61–69.

⁷ Ferry, B, Carael, M, Buve, A, *et al.* (2001) **Comparison of key parameters of sexual behaviour in four African urban populations with different levels of HIV infection.** *AIDS* 15 Suppl 4: S41–50.

⁸ Abu-Raddad, LJ, Patnaik, P and Kublin, JG (2006) **Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa.** *Science* 314: 1603–1606.

⁹ Buvé, A, Carael, M, Hayes, RJ, *et al.* (2001) **Multicentre study on factors determining differences in rate of spread of HIV in sub-Saharan Africa: methods and prevalence of HIV infection.** *AIDS* 15 Suppl 4: S5–14.