Predicting the Potential Individual- and Population-Level Effects of Imperfect Herpes Simplex Virus Type 2 Vaccines

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Background. The seroprevalence of herpes simplex virus (HSV) type 2 in the United States has increased dramatically since the 1970s. Vaccines are being developed to control the epidemic. We determined the potential public health impact that imperfect, preexposure HSV-2 vaccines could have on reducing the incidence of infection.

Methods. We modeled the future impact of preexposure vaccines with both prophylactic and therapeutic properties. We predicted the individual-level (cumulative number of new infections prevented per 1000 vaccinated individuals) and population-level (cumulative percentage reduction in new infections) impact.

Results. We show that the percentage reduction in incidence of infection would be relatively modest. However, HSV-2 incidence rates are extremely high; thus, we calculate that even imperfect vaccines would prevent >1 million infections in the United States within a decade after introduction. We found that vaccines would prevent 3 times as many infections per vaccinated person in a high-prevalence epidemic than in a moderate-prevalence epidemic. We also identified the vaccine characteristics that have the greatest impact on reducing the incidence of infection. We determined that vaccine take and degree of protection against infection are equally important, whereas therapeutic characteristics are unimportant.

Conclusions. Designing preexposure HSV-2 vaccines with therapeutic characteristics will have little impact on reducing the incidence of infection. HSV-2 vaccines will have a substantially greater public health impact in developing than in developed countries.
Figure 1. Flow diagram of the transmission dynamics of the herpes simplex virus type 2 epidemic with preexposure vaccines. The model specifies the rate of change over time of individuals in 6 states: unvaccinated susceptible (X), vaccinated susceptible (V), unvaccinated infected individuals who are infectious (H), vaccinated but infected individuals who are infectious (Hv), unvaccinated infected individuals who are quiescent (Q), and vaccinated but infected individuals who are quiescent (Qv). \( \pi \), entry of new susceptible individuals into the sexually active pool; \( p \), vaccine coverage rate; \( \epsilon \), proportion of vaccinated individuals in whom the vaccine takes; \( 1/\mu \), average period of acquiring new sex partners; \( \lambda \), time-dependent per capita force of infection; \( c \), contact rate; \( 1/q \), average length of viral shedding episodes; \( 1/q_v \), average duration of viral shedding episodes in vaccinated individuals; \( r \), reactivation rate; \( r_v \), reactivation rate in vaccinated individuals; \( 1/\omega \), average duration of vaccine-induced immunity in uninfected individuals; \( 1/\omega_v \), average duration of vaccine-induced immunity in infected individuals; \( \psi \), degree of protection against infection. Model assumptions are detailed in Methods. Equations and parameter definitions are detailed in Methods and in the Appendix.

A DNA vaccine that encodes gD2, which is intended to elicit HSV-specific cellular and humoral immune responses, is in phase 2 trials [14, 17]. The production of several live attenuated vaccines (less-virulent viral strains that contain deletions of key viral proteins) and replication-impaired vaccines (mutant strains that complete only a single cycle of replication or no cycles of replication, because they lack a structural protein or protein required for replication) is in progress [14, 15]. Other approaches aim to paralyze HSV immune evasion molecules such as gC [19–22] or gE and gI [22–24]. Additional potential vaccine candidates include peptide vaccines (which contain immunodominant epitopes) and heterologous viral vectors (HSV antigens incorporated into foreign viral strains) [14]. However, each approach has encountered significant challenges [17], and it is likely that any HSV-2 vaccine that is developed will be imperfect.

Accordingly, we determined the potential impact of imperfect HSV-2 vaccines, using a mathematical model of the HSV-2 epidemic and including the specific mechanisms by which a vaccine might fail. Previously, the potential public health impact of imperfect vaccines has been evaluated for both tuberculosis vaccines and HIV-1 vaccines [25–27]. These studies determined the vaccine parameters necessary for the eradication of HIV-1 [28, 29]; predicted the effect of live attenuated vaccines on
Figure 2. Population-level impact: cumulative percentage reduction in new infections. The predictions shown were generated by use of uncertainty analysis to analyze the mathematical model shown in figure 1. The model assumptions are described in Methods; model equations are listed in the Appendix. Ranges of parameters used for the uncertainty analysis are given in table 1. In the presence of a preexposure herpes simplex virus (HSV) type 2 vaccine, cumulative new infections would be prevented by a median of 18% (interquartile range [IQR], 12%–25%) after 30 years in a population with moderate HSV-2 prevalence (A) and by a median of 17% (IQR, 11%–24%) after 30 years in a population with high HSV-2 prevalence (B). Gray lines, median values (of 1000 simulations); boxes, IQRs; vertical lines, minimum and maximum values.
Figure 3. Individual-level impact: cumulative number of new infections prevented per 1000 vaccinated individuals. The predictions shown were generated by use of uncertainty analysis to analyze the mathematical model shown in figure 1. The model assumptions are described in Methods; model equations are listed in the Appendix. Ranges of parameters used for the uncertainty analysis are given in table 1. In the presence of a preexposure herpes simplex virus (HSV) type 2 vaccine, a median of 108 (interquartile range [IQR], 87–132) new infections/1000 individuals vaccinated would be prevented, after 30 years in a population with moderate HSV-2 prevalence (A) and a median of 285 (IQR, 221–349) new infections would be prevented in a population with high HSV-2 prevalence (B). Gray lines, median values (of 1000 simulations); boxes, IQRs; vertical lines, minimum and maximum values.
populations with different transmission rates [30]; and showed that HIV-1 vaccines could cause a reduction in the incidence of HIV-1 even if they had moderate efficacy and coverage levels (if risk behavior did not increase) [26]. Previous HSV-2 modeling studies have shown that the threat of antiviral resistance to HSV is low [31–33], evaluated the role of virological core groups in HSV-2 transmission [34], and estimated the impact of HSV-2 treatment on HIV-1 epidemics [35].

We constructed a new mathematical model of the HSV-2 epidemic that includes preexposure vaccines with both prophylactic and therapeutic effects. We used our model to predict the reduction in incidence that would occur as a result of the administration of imperfect HSV-2 vaccines. We evaluated 2 factors: (1) the individual-level impact (defined as the cumulative number of new infections prevented per 1000 vaccinated individuals) and (2) the population-level impact (defined as the cumulative percentage reduction in new infections). We evaluated effects at 2 prevalence levels: moderate (22%, as in gay and black communities and in some developing countries [18, 36, 37]) and high (60%, as in gay and black communities and in some developing countries [18, 36, 37]). In addition, we identified which vaccine characteristics would have the greatest impact on reducing the incidence of infection.

METHODS

Preexposure HSV-2 vaccine model. A mathematical model of the HSV-2 epidemic [31, 32] was expanded to include preexposure HSV-2 vaccines administered to new susceptible individuals as they become sexually active; this represents vaccines given to adolescents. Our new model incorporated HSV-2 infection parameters, prophylactic vaccine characteristics, therapeutic vaccine characteristics, and coverage. A flow diagram of our model is shown in figure 1. New susceptible individuals enter the sexually active pool at rate \( \pi \) and become infected according to the contact rate (\( c \)) and the time-dependent per capita force of infection (\( \lambda \). \( \lambda \) is calculated as the product of the probability of HSV-2 transmission (\( \beta \) for unvaccinated individuals and \( \beta_v \) for vaccinated individuals) and the probability of selecting an infectious partner; therefore, \( \lambda = \beta(H/N) + \beta_v(H_v/N) \), where \( N \) represents the population size of the sexually active pool. Infected individuals oscillate between the infectious viral shedding state and the noninfectious quiescent state. The length of a viral shedding episode (either symptomatic or asymptomatic) is therefore \( 1/q \). The reactivation rate (\( r \)) is calculated from the length of the viral shedding episodes and the number of viral shedding episodes (\( N_e \)): \( 1/r = 1/N_e - 1/q \). The average period of acquisition of new sex partners is \( 1/\mu \).

Individuals not covered by the vaccine program or who are vaccinated but in whom the vaccine does not take (i.e., stimulate an immune response) join the unvaccinated susceptible population (figure 1). Susceptible individuals entering the sexually active pool are “successfully vaccinated” according to the vaccine coverage rate (\( p \)) and the fraction of the vaccinated individuals in whom the vaccine takes (\( \epsilon \)) (figure 1). These individuals are protected from infection, as long as the vaccine does not wane; however, some of these individuals will become infected because the vaccine does not provide complete protection (figure 1). The degree of immune protection is specified by \( \psi \); if \( \psi = 1 \), the vaccine provides 100% protection against infection. Individuals who have been vaccinated but who still become infected (because \( \psi < 1 \)) are afforded 3 therapeutic benefits: the average length of their viral shedding episodes is shorter, they have fewer viral shedding episodes, and they have a lower probability (than unvaccinated individuals) of transmitting infection (figure 1). Thus, vaccinated infected individuals have reduced shedding. We chose to model the possibility of therapeutic consequences of potential preexposure HSV-2 vaccines, to assess their potential importance. Vaccine-induced

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Moderate (22%) HSV-2 prevalence</th>
<th></th>
<th>High (60%) HSV-2 prevalence</th>
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<tr>
<td></td>
<td></td>
<td>10 years</td>
<td>20 years</td>
<td>30 years</td>
<td>10 years</td>
</tr>
<tr>
<td>Proportion for whom vaccine takes</td>
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<td>0.95</td>
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<tr>
<td>Coverage rate</td>
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<tr>
<td>Degree of protection against infection</td>
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<td>0.90</td>
<td>0.89</td>
<td>0.94</td>
</tr>
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<td>Length of time acquiring new sex partners</td>
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<td>-0.88</td>
<td>-0.88</td>
<td>-0.79</td>
</tr>
<tr>
<td>Vaccine duration (uninfected individuals)</td>
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<td>0.28</td>
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<tr>
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<td>0.97</td>
<td>0.97</td>
<td>0.99</td>
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<td>Length of time acquiring new sex partners</td>
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<td>-0.97</td>
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<td>-0.96</td>
</tr>
<tr>
<td>Vaccine duration (uninfected individuals)</td>
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<td>0.50</td>
<td>0.67</td>
<td>0.72</td>
<td>0.60</td>
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Table 2. Partial rank correlation coefficients, for the population-level impact (the cumulative percentage reduction in new herpes simplex virus [HSV] type 2 infections) and the individual-level impact (the cumulative no. of new HSV-2 infections prevented per 1000 vaccinated individuals).
Figure 4. Sensitivity of population-level impact to key factors. A, Increased population-level impact as the degree of vaccine-induced immune protection against infection and average duration of vaccine-induced immunity (uninfected persons) increase. Results show the cumulative percentage reduction in new infections (red, 5%–10%; black, 10%–15%; green, 15%–20%), 10 years after vaccine introduction, in a population with high herpes simplex virus (HSV) type 2 prevalence, for ranges of values for degree and duration. Median values for other parameters were used. B, Increased population-level impact as the coverage rate and vaccine take increase. Results show the cumulative percentage reduction in new infections (orange, 5%–10%; blue, 10%–15%; red, 15%–20%), 10 years after vaccine introduction, in a population with high HSV-2 prevalence, for ranges of values for coverage and take. Median values for other parameters were used.
Figure 5. Sensitivity of individual-level impact to key factors. As the degree of vaccine-induced immune protection against infection increases, the individual-level impact increases, for a population with a moderate herpes simplex virus (HSV) type 2 prevalence (A) or a population with a high HSV-2 prevalence (B). Results for 10 (green), 20 (pink), and 30 (blue) years after the introduction of the vaccines. C, Increased individual-level impact as the degree of immune protection against infection and vaccine duration increase. Results show the cumulative no. of new infections prevented per 1000 vaccinated individuals (green, 0–150; pink, 150–250; blue, 250–350), 10 years after vaccine introduction, in a population with high HSV-2 prevalence, for ranges of values for degree and duration. Median values for other parameters were used.
immunity wanes in an uninfected individual at rate \( \omega \), and therapeutic benefits of vaccination wane in an infected individual at rate \( \omega_1 \) (figure 1). Thus, different vaccine-induced immune responses can decline at different rates, as is likely [15]. The parameters \( \beta_v, q_v, r_v \), and \( N_v \) are related by the equations \( \beta_v = \alpha \beta, 1/q_v = \gamma (1/q), N_v = zN_p, \) and \( 1/r_v = 1/N_v - 1/q_v \), where \( \alpha, \gamma, \) and \( z \) are independent parameters between 0 and 1.

Initial conditions were set such that the vaccine is introduced when the susceptible, infectious, and quiescent populations (in the absence of the vaccine) are at equilibrium. Model equations are given in the Appendix. The model was analyzed to predict the individual- and population-level impact of HSV-2 vaccines for 2 prevalence levels: moderate (22%) and high (60%).

**Uncertainty and sensitivity analyses.** Numerical analyses yielded the predicted impact of imperfect preexposure HSV-2 vaccines over a 30-year period. To account for uncertainty in parameter values, we sampled parameter ranges using latin hypercube sampling [38]. Each parameter was assigned a probability distribution function, as described elsewhere [31, 33, 34, 38]. Table 1 indicates the parameter ranges used for the uncertainty analysis. Simulations were run 1000 times (with a unique parameter set for each simulation) for both the moderate- and high-prevalence epidemics. Individual- and population-level effects were calculated.

To determine key parameters, time-dependent sensitivity analyses were done by calculating partial rank correlation coefficients (PRCCs), as described elsewhere [31, 38]. PRCCs were calculated by use of the 1000 values for each parameter, from the latin hypercube sampling table, and the 1000 outcome values for either the individual- or population-level effect. Coefficients with the greatest magnitude (>0.5 or less than −0.5) indicated parameters with the largest effects on the outcome variables.

**Parameter estimates.** Parameter ranges are given in table 1. HSV-2 infection parameters (\( \beta, N_p, \) and \( 1/q \)) were set to ranges consistent with current data on HSV-2 pathogenesis [5, 39–42]. Vaccine duration parameters (\( 1/\omega \) and \( 1/\omega_1 \)) were varied independently, each ranging from 10 to 20 years, on the basis of the durations of current vaccines for smallpox, polio, and diphtheria [25, 43]. Vaccine parameters were varied widely, to reflect a wide range of hypothetical HSV-2 vaccines: coverage level (\( p \)) from 30% to 90%, take (\( \epsilon \)) from 30% to 100%, and degree (\( \psi \)) from 30% to 100%. We assumed that HSV-2 vaccines would be able to reduce the viral transmission rate by 30%–100% (thus, \( \alpha \) varied uniformly between 0 and 0.7). We assumed that HSV-2 vaccines might be able to reduce the number of viral shedding episodes and the episode length by 30%–90%; thus, we set the values of \( \gamma \) and \( z \) to vary uniformly between 0.1 and 0.7. The average length of time acquiring new sex partners was assumed to range from 10 to 20 years [34]. The size of the sexually active pool is \( N = X + V + H + H_v + Q + Q_v \). The rate at which new susceptible individuals enter the sexually active pool is \( \pi = \mu N \). The contact rate (\( c \)) is derived from prevaccine equilibrium conditions (see Appendix).
RESULTS

Predicting the Population-Level Impact of Preexposure HSV-2 Vaccines

The population-level effects of the vaccines, even after 30 years, would be relatively modest for populations with either moderate or high seroprevalence. Results from our uncertainty analysis showed that, when the initial prevalence of HSV-2 was moderate, the population-level impact of preexposure vaccines would increase steadily over time (figure 2A). After 10 years, a median of 8% (interquartile range [IQR], 5%–12%) of new HSV-2 infections would be prevented, reaching a median of 18% (IQR, 12%–25%) by year 30 (figure 2A). In a population with a high initial prevalence, the population-level effect would increase more quickly and would plateau at a median of 17% (IQR, 11%–24%) by year 30 (figure 2B). In this population, it would be only 8 years before the incidence would be reduced by one-tenth. Much of the vaccine effect (median reduction, 14% [IQR, 9%–19%]) would be realized within 15 years. In the long term, preexposure vaccines would have the same effect on populations with moderate prevalence and those with high prevalence (figure 2).

Predicting the Individual-Level Impact of Preexposure HSV-2 Vaccines

Uncertainty analysis of our model showed that, after 10 years, the vaccines would prevent a median of 50 (IQR, 38–63) infections/1000 individuals vaccinated in a population with moderate initial prevalence (figure 3A). Individual-level impact would increase with time, and, after 30 years, a median of 108 (IQR, 87–132) infections/1000 individuals vaccinated would be prevented (figure 3A). In a high-prevalence population, the individual-level effect would be substantially larger and would increase more rapidly with time (figure 3B). After 5 years, a median of 125 (IQR, 91–159) infections/1000 individuals vaccinated would be prevented, and, after 10 years, a median of 194 (IQR, 144–242) infections/1000 individuals vaccinated would be prevented. After 20 years, a median of 259 (IQR, 197–318) infections/1000 individuals vaccinated would be prevented. The maximum public health impact would be attained after 30 years, when the vaccines would prevent a median of 285 (IQR, 221–349) infections/1000 individuals vaccinated, or nearly 3 new infections for every 10 individuals vaccinated (figure 3A).

Our predictions show that both the population- and the individual-level impact of preexposure HSV-2 vaccines would increase over time. The same HSV-2 vaccines, administered to control epidemics of either moderate or high prevalence, would have approximately the same population-level effects but different individual-level effects. For every 10 individuals vaccinated, 1 new infection would be prevented in a moderate-prevalence epidemic, whereas ∼3 new infections would be prevented in a high-prevalence epidemic; thus, the individual-level impact would be 3-fold greater in a high-prevalence epidemic.

Sensitivity Analysis

Population-level impact of preexposure HSV-2 vaccines. Using time-dependent sensitivity analysis, we identified the key factors that increased (or decreased) the population-level impact. The key vaccine characteristics that increased the population-level impact were the magnitude of the take effect ($\varepsilon$, PRCC = 0.95; year 30) and the magnitude of the degree of protection against infection ($\phi$, PRCC = 0.89, for moderate HSV-2 prevalence; PRCC = 0.93, for high HSV-2 prevalence; year 30) (table 2). Not surprisingly, the population-level impact increased as the coverage level increased ($p$, PRCC = 0.94, year 30). The average length of time that an individual spent acquiring new sex partners (i.e., the average period during which they have the potential to transmit HSV-2) decreased the potential population-level impact ($1/\mu$, PRCC = −0.88, for moderate HSV-2 prevalence; PRCC = −0.73, for high HSV-2 prevalence; year 30). PRCC changed little over 30 years; the only parameter that increased in significance was the vaccine duration in uninfected individuals ($1/\omega$), which increased from 0 initially to 0.48 at year 30 (table 2). It is noteworthy that the following parameters were not important: number of episodes ($N_e$), episode length ($1/q$), transmission probability ($\beta$), and the reduction in these values induced by the vaccines ($N_{v,0}$, $1/q_v$, and $\beta_v$).

The interaction and trade-off between 2 vaccine characteristics are shown in figure 4. Figure 4A shows the effect of degree of protection against infection and average duration of protection due to the vaccine on the population-level impact. As expected, vaccines that induce a high degree of protection against infection and have a slow waning of vaccine-induced immunity would cause greater reductions in incidence (15%–20%) than vaccines with low degrees of protection and short duration of immunity (5%–10%) (figure 4A). For example, a vaccine with a degree of protection against infection of 80%–100% that lasts (on average) 20 years and is administered in 2010 would reduce new infections by 15%–20% by 2020. However, a vaccine with a degree of protection against infection of 30%–50% that lasts (on average) 10 years and is administered in 2010 would reduce new infections by only 5%–10% by 2020. A 90%–100% protective vaccine of short duration would perform well (15%–20% reduction), but a vaccine of long duration but with a low degree of protection would be less effective (5%–10% reduction), which indicates that degree is a substantially greater determinant of the impact of HSV-2 vaccines than is vaccine duration (as shown in table 2). Results were similar for populations with either moderate or high prevalence.

The effect of vaccine coverage rates and vaccine take on the reduction in new infections, after 10 years, is shown in figure

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The population-level impact depends on both take and coverage. For example, vaccines that have a 50% take, administered to 50% of the sexually active population, would reduce new infections by up to 10%; vaccines that have a 90% take administered to 90% of the population, however, could reduce new infections by >20%. Impact of Imperfect HSV-2 Vaccines

Individual-level impact of HSV-2 vaccines. Time-dependent sensitivity analyses were also used to identify the key parameters with the greatest impact at the individual level. In contrast to the population-level results, vaccine coverage and take rates were not key determinants of the individual-level impact. The average duration of vaccine-induced immunity in uninfected individuals was important and increased as time progressed (1/μ, PRCC = 0.72, for moderate HSV-2 prevalence; PRCC = 0.82, for high HSV-2 prevalence; year 30) (table 2). Similar to the population-level results, the degree of protection against infection was very important (ψ, PRCC = 0.97, for moderate HSV-2 prevalence; PRCC = 0.99, for high HSV-2 prevalence; year 30) (table 2). The average length of time acquiring new sex partners was also a key factor (1/μ, PRCC = −0.97, for moderate HSV-2 prevalence; PRCC = −0.94, for high HSV-2 prevalence; year 30). However, vaccine characteristics that gave therapeutic benefits—such as reducing the number of episodes, episode length, or transmission probability—were not important. Thus, our results indicate that therapeutic characteristics of preexposure HSV-2 vaccines that prevent infection will be unimportant in determining both the population-level and the individual-level impact.

Figure 5 shows the effect of key vaccine characteristics on vaccine impact at the individual level. As expected, the impact increases as the degree of protection against infection increases, for populations with either moderate or high HSV-2 prevalence (figure 5A and 5B). For example, in an epidemic with moderate prevalence, a vaccine affording a degree of protection against infection of 50% would prevent up to 148 new infections/1000 vaccinated individuals after 30 years, whereas a perfect vaccine (100% degree of protection) would prevent >210 new infections/1000 vaccinated individuals after 30 years (figure 5A). In high-prevalence epidemics, a vaccine affording 30% protection against infection would prevent 150–206 new infections/1000 vaccinated individuals after 30 years, whereas a vaccine affording 95% protection would prevent 302–529 new infections/1000 vaccinated individuals over the same period (figure 5B).

Figure 5C shows the interaction of degree of protection against infection and average duration of vaccine-induced immunity, 10 years after the introduction of vaccines, in a high-prevalence epidemic. As seen on the population level, vaccines that offer greater degrees of protection against infection and longer durations give better results at the individual level as well. For example, a vaccine with a degree of protection against infection of 90%–100% that lasts >15 years and is administered in 2010 would prevent 250–350 new infections/1000 individuals vaccinated by 2020. However, a vaccine affording only 40% protection that lasts <15 years would prevent only ~150 new infections/1000 individuals vaccinated over the same period. Results were similar for populations with either moderate or high prevalence.

DISCUSSION

Using our results, we can make predictions on the potential impact that imperfect preexposure vaccines would have on the HSV-2 epidemic. Given the current rate of new infections in the United States [44], imperfect preexposure HSV-2 vaccines would prevent a median of 15,908 (IQR, 10,332–23,452) new infections after 1 year. After 5 years, a median of 370,640 (IQR, 241,080–533,000) infections could be prevented. Within 9 years, even imperfect HSV-2 vaccines would prevent >1 million infections. In developing countries, where the prevalence of HSV-2 is much higher, as it is in certain communities—such as gay men and black persons—we predict that it would be only 8 years before the number of new infections is reduced by one-tenth.

Our results are relevant to HSV-2 vaccine development. We have determined that, if preexposure vaccines also have additional therapeutic characteristics, these characteristics will have little additional impact on reducing incidence. Thus, it appears to be unnecessary to try to design preexposure HSV-2 vaccines with therapeutic characteristics. We have also shown that it is equally important to optimize the take and degree of protection against infection. Current vaccine development efforts for uninfected individuals should be directed along these lines. Strategies that target essential proteins required for viral replication or that interrupt the establishment of latency would be valuable toward this goal [15, 17].

Our results shed light on what we would expect to see in vaccination programs. It is important to recognize that the infections prevented may be among either vaccinated or unvaccinated individuals. Not surprisingly, we found that the average length of time during which individuals acquire new sex partners is also strongly correlated with the prevention of infections; this obvious result reiterates the importance of interventions that reduce risk behavior. The effects of vaccination would change over time. Individual-level impact in epidemics of moderate prevalence will be fairly low initially but will increase over time. Therefore, vaccination programs will appear to become more efficient with time. We have found that HSV-2 vaccines would prevent 3 times as many infections per vaccinated person in high-prevalence epidemics than in moderate-prevalence epidemics. This is not surprising, given that there are more infections occurring in high-prevalence populations; it suggests that vaccines targeted at higher-risk populations would prevent more infections. Because there is likely to be some mixing between members of moderate- and high-prev-
ence populations, such a targeted vaccination strategy might prevent more infections. Previously, it has been suggested that vaccinating only high-risk individuals with the gD2-alum-MPL vaccine would not be effective in reducing incidence; however, this result was found because this specific HSV-2 vaccine is only protective against clinical disease and is only effective in HSV-seronegative women [45].

HSV-2 vaccines may also be important in reducing HIV-1 infection—HSV-2 has been found to be a risk factor for the transmission of and infection with HIV-1 [46–49]. Other modalities besides preexposure vaccines could be effective in controlling herpes epidemics. Antiviral therapy has been shown to lower the risk of transmission of HSV-2 [5], and it has recently been shown that daily antiviral therapy could be very effective for epidemic-level control if virological core groups are targeted [34]. Postexposure (therapeutic) HSV-2 vaccines for infected individuals are currently in development [15, 16, 19], and their effect on the prevention of HSV-2 transmission should be carefully evaluated. The optimal way to control HSV-2 epidemics potentially involves several approaches, including preexposure vaccines, postexposure vaccines, and antiviral therapy.

In summary, our results show that the impact of imperfect preexposure vaccines on the population level may be fairly modest and reduce incidence by only 20%. However, in absolute numbers, the impact could be fairly substantial. Incidence reduction will be similar in both moderate- and high-prevalence HSV-2 epidemics. In contrast, the same vaccines will have greater impact (at the individual level) in high-prevalence than in moderate-prevalence epidemics, preventing 3 times as many infections per vaccinated person. Because the prevalence of HSV-2 has been found to be greater in developing countries, our results indicate that the same HSV-2 vaccines, if used in both developed and developing countries, would have a substantially greater individual-level impact in developing countries.

Acknowledgments

We thank the following members of Sally Blower’s research group for helpful comments and technical assistance: Erin N. Bodine, Romulus Breban, Robert Smith, and Li (Mary) Ma.

APPENDIX

The mathematical model [31, 32] is described by the equations

\[
\frac{dX}{dt} = \pi(1 - \rho e) + \omega V - (\mu + \lambda c)X ,
\]

\[
\frac{dV}{dt} = \pi pe - \mu + \lambda c(1 - \psi) V ,
\]

\[
\frac{dH}{dt} = \lambda cX - (\mu + q)H + rQ ,
\]

\[
\frac{dQ}{dt} = qH + \omega Q_v - (\mu + r)Q ,
\]

and

\[
\frac{dH_v}{dt} = \lambda c(1 - \psi)V - (\mu + q)H_v + rQ_v ,
\]

where \( X \) represents the population of susceptible individuals in the sexually active pool; \( H \) represents the population of unvaccinated, HSV-2–infected individuals who are shedding virus and therefore infectious to others; and \( Q \) represents the population that is infected but is not shedding virus and therefore is not infectious to others. \( V \) represents the population of susceptible but vaccinated individuals, \( H_v \) represents the population of vaccinated individuals who still became infected and are infectious to others, and \( Q_v \) represents the population of individuals who were vaccinated, became infected, and are not infectious to others.

The prevaccine equilibrium values for \( X(t) \), \( H(t) \), and \( Q(t) \), denoted by \( X^* \), \( H^* \), and \( Q^* \), respectively, are given by

\[
X^* = \frac{\pi}{c\beta} \left( \frac{\mu + q + r}{\mu + r} \right),
\]

\[
H^* = \frac{\pi}{\mu + r} \left( \frac{\mu + r}{\mu + q + r} - \frac{1}{c\beta} \right),
\]

and

\[
Q^* = \frac{\pi q}{\mu + r} \left( \frac{\mu + r}{\mu + q + r} - \frac{1}{c\beta} \right).
\]

The initial HSV-2 prevalence is \( \rho = (H^* + Q^*)/(X^* + H^* + Q^*) \). The contact rate, \( c \), is derived from the prevaccine equilibrium conditions and initial HSV-2 population prevalence and is therefore

\[
c = \frac{\mu + q + r}{\beta(\mu + r)(1 - \rho)}.\]
References


