Could disease-modifying HIV vaccines cause population-level perversity?

Robert J Smith and Sally M Blower

Most current candidate HIV vaccines seem to produce little protection against infection, but reduce viral load and slow the decline in CD4 lymphocyte numbers. Such disease-modifying vaccines could potentially provide important population-level benefits by reducing transmission, but could possibly also increase transmission. We address the following question: could disease-modifying HIV vaccines cause population-level perversity (ie, increase epidemic severity)? By analysing a mathematical model and defining a new quantity—the fitness ratio—we show that disease-modifying vaccines that provide only a low degree of protection against infection and/or generate high fitness ratios will have a high probability of making the epidemic worse. However, we show that if disease-modifying vaccines cause a 1·5 $\log_{10}$ reduction in viral load (or greater) then perversity cannot occur (assuming risk behaviour does not increase). Finally, we determine threshold surfaces for risk behaviour change that determine the boundary between beneficial and perverse outcomes; the threshold surfaces are determined by the fitness ratio, the proportion of the population that are "successfully vaccinated", and the degree of change of risk behaviour in unvaccinated infected individuals. We discuss the implications of our results for designing optimal vaccination control strategies.

Lancet Infect Dis 2004; **4:** 636–39

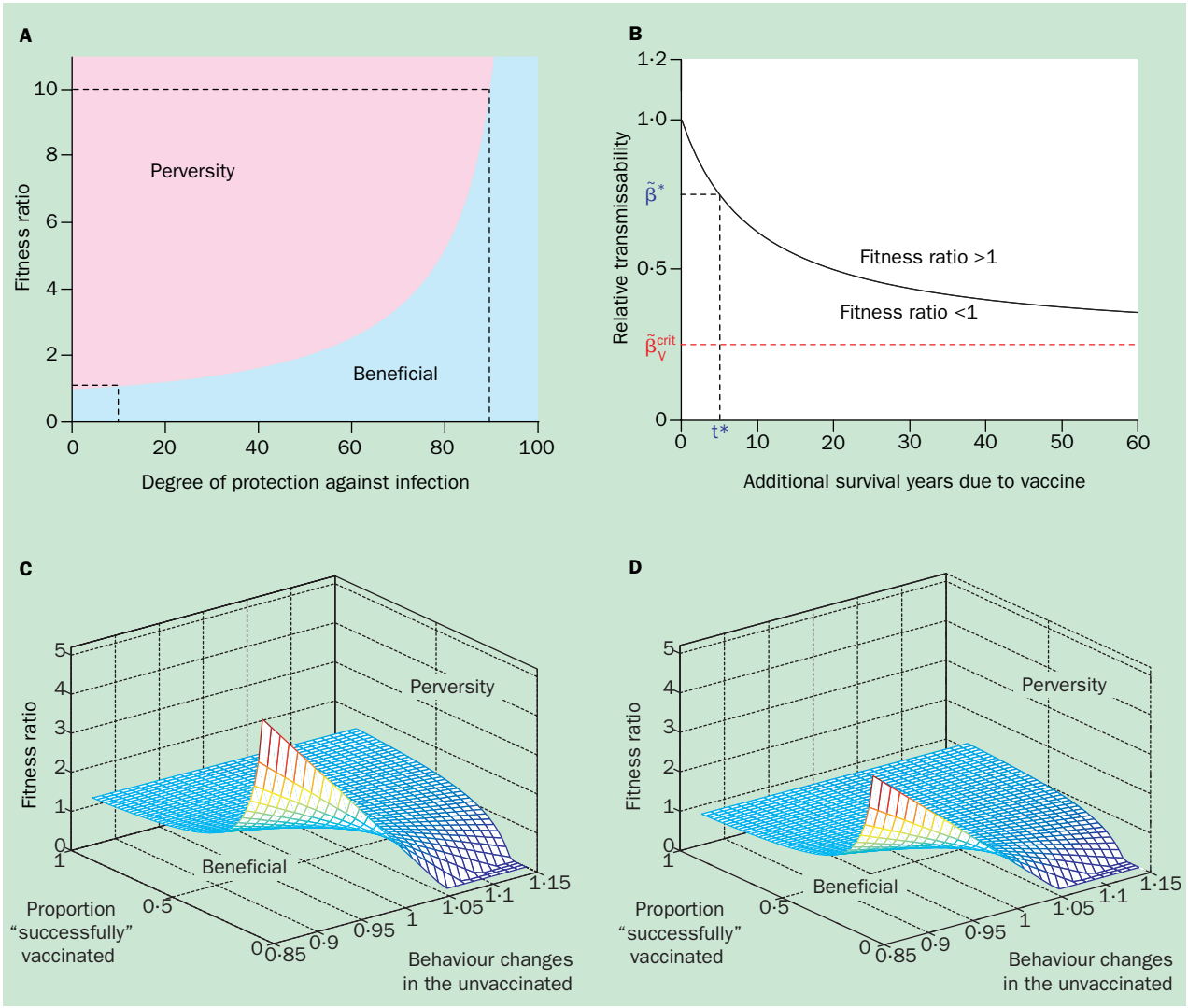
Recently there has been a call for a global HIV vaccine enterprise.[1] There is an urgent need to create and evaluate systematically more candidate HIV vaccines;[2] however, there remain substantial challenges to developing such vaccines.[3] Disappointingly, the only HIV vaccine that has been tested in phase III trials failed to show efficacy.[4] Several candidate vaccines are currently in phase I and II clinical trial evaluation.[5] Most seem to permit infection, but exert their protective effect by reducing viral load and slowing the decline in CD4 lymphocyte numbers.[6–8] Such imperfect vaccines could provide important benefits by delaying HIV progression and reducing transmission.[9] These vaccines can be described as disease-modifying vaccines. The hope is that they will be at least moderately effective, and will be made available to regions of the world that request them.[1,10] However, there is a concern that when these vaccines become available, people who are vaccinated might increase their risk behaviour.[11] Hence, there is a concern that use of such disease-modifying vaccines may have an unintended consequence and increase the severity of the HIV epidemic. This concern has been evaluated previously by Blower and colleagues[12–16] for imperfect prophylactic HIV vaccines that do not modify disease progression. Here, we use a mathematical model to address the following question: could disease-modifying HIV vaccines cause population-level perversity (ie, increase epidemic severity)?

The average number of secondary HIV infections caused by an infected individual is defined by the aggregate measure, the basic reproduction number R_0. R_0 is calculated as the product of three factors: the probability of transmission, the average rate of acquisition of new sex partners, and the duration of infection (ie, the time from infection to death). Here we analyse a previously published HIV vaccine model,[12–17] and assess only the effects of mass vaccination. In previous work we have modelled the public-health impact of using both HIV vaccines and antiretrovirals.[18]

Individuals who are vaccinated with disease-modifying vaccines have the potential to become infected and cause secondary infections. These individuals may have a reduced per-partnership transmission probability, but will have increased life expectancy (ie, survival time). We define the average number of secondary HIV infections caused by an infected vaccinated individual as R_V. The value of R_V is determined as the product of three factors: the probability of transmission (from a vaccinated infected individual), the average rate of acquisition of new sex partners (by a vaccinated infected individual), and the duration of infection (ie, the time from infection to death in a vaccinated infected individual). Thus any vaccine that increases the value of R_V (for example, by increasing the length of the asymptomatic period without reducing the probability of transmission) would increase both the incidence of infection and the AIDS death rate. We then define the relation between R_0 and R_V as the fitness ratio f, where $f=R_V/R_0$. By using a mathematical model,[12–17] and assuming that risk behaviour does not change, we determine (see website appendix, http://image.thelancet.com/extras/04ID3004webappendix.pdf) that perversity will occur if $f>1/1-\psi$, where ψ is the degree of protection against infection provided by the disease-modifying vaccine ($\psi>0$).

RJS and SMB are at the Department of Biomathematics and UCLA AIDS Institute, David Geffen School of Medicine at UCLA, Westwood, CA, USA.

Correspondence: Dr Sally M Blower, Department of Biomathematics and UCLA AIDS Institute, David Geffen School of Medicine at UCLA, 1100 Glendon Ave PH2, Westwood, CA 90024, USA. Tel +1 310 794 8911; fax +1 310 794 8653; email sblower@mednet.ucla.edu



(A) Relation between the degree of protection ψ and the fitness ratio f when behaviour does not change. For vaccines providing a medium to high degree of protection against infection, increases in the fitness ratio can still have a beneficial impact (blue region). However, for vaccines providing only a low degree of protection, even very slight increases in the fitness ratio can have a perverse impact (red region). Note that the degree of protection against infection is a fraction in the equations, but plotted as a percentage here. (B) Relation between relative transmissibility ($\tilde{\beta}_v=\beta_v/\beta_u$) and survival time, when behaviour does not change. The vaccine may reduce (or possibly increase) the transmissibility and will likely give additional years of life to the patient. Parameters used were $1/\mu=30$ years, $\beta_U=0{\cdot}1$, and $1/\gamma_U=10$ years. A vaccine that gives t^* additional survival years will produce a beneficial outcome if its relative transmission rate satisfies $\tilde{\beta}_v<\tilde{\beta}_v^*$. Here $\tilde{\beta}_v^*$ is the relative transmission probability that corresponds to a fitness ratio of 1 when the vaccine gives t^* additional survival years. However any transmission rate satisfying $\tilde{\beta}_v<\tilde{\beta}_v^{crit}=0{\cdot}25$ will ensure a beneficial outcome, regardless of the number of additional life years due to the vaccine. (C) Epidemic control strategies for a vaccine providing only a 25% degree of protection when vaccinated infected individuals decrease risky behaviour by 15%. (D) Epidemic control strategies for a vaccine providing only a 25% degree of protection when vaccinated infected individuals increase risky behaviour by 15%.

Conversely, we determine that if the fitness ratio is less than one (ie, $0<f<1$), then population-level perversity is not possible and the HIV vaccine will always have a beneficial impact.

Figure 1A shows the quantitative relation we found that exists between the degree of protection against infection provided by the vaccine and the fitness ratio. For a high efficacy vaccine (eg, one that offers a 90% degree of protection against infection) the epidemic-level impact will always be beneficial (ie, transmission will decrease) if the fitness ratio is below 10 (figure 1A). Thus, infected vaccinated individuals would have to generate ten times as many secondary infections as infected unvaccinated individuals to cause a perverse outcome; hence, under these conditions, population-level perversity would be extremely unlikely. However, a vaccine that provides only a very low to moderate degree of protection against infection and has a low fitness ratio would lead to perversity (figure 1A). For example, an HIV vaccine that provides only a 10% degree of protection against infection and has a fitness ratio greater than just 1·1 leads to perversity. Studies of current candidate disease-modifying vaccines indicate that they may generate only low degrees of protection against infection. Our results show that—if these current candidate vaccines are used—then

infected vaccinated individuals would have to generate only 1·1 times as many secondary infections as infected unvaccinated individuals to cause population-level perversity. Thus, our results clearly demonstrate that disease-modifying vaccines that provide only a low degree of protection against infection and/or generate high fitness ratios will have a high probability of making the HIV epidemic worse.

The fitness ratio will be determined by the effect that the vaccine has on reducing viral load; reducing the viral load both reduces the probability of transmission per partnership[19] and increases survival time.[20] Low fitness ratios are beneficial, and reduce the probability of population-level perversity. Thus, we evaluated what type of disease-modifying vaccines would generate low fitness ratios (figure 1B). As the vaccine increases survival time without proportionally decreasing the probability of transmission per partnership, the fitness ratio will increase; hence the likelihood of a perverse outcome will also increase (figure 1A). The threshold fitness ratio f=1 is shown as the black curve. Above this curve, infected vaccinated individuals generate more secondary infections than infected unvaccinated individuals. Below this curve, infected vaccinated individuals generate fewer secondary infections than infected unvaccinated individuals. We found that an HIV vaccine that gives t^* additional survival years will produce a beneficial outcome if its relative transmission probability satisfies $\tilde{\beta}_v < \tilde{\beta}_v^*$. Here $\tilde{\beta}_v^*$ is the relative transmission probability corresponding to a fitness ratio of 1 when the vaccine gives t^* additional survival years. We determined (see website appendix) that there is a critical value for the reduction in the transmission probability due to the vaccine β_v^{crit} (figure 1B). Our results reveal that if disease-modifying vaccines reduce the per-partnership transmission probability by three quarters or more, the fitness ratio will always be less than 1 (ie, a perverse outcome cannot occur). A vaccine which offers a 1·5 $\log_{10}$ mean drop in viral load will reduce the per-partnership transmission probability to 26% of the per-partnership transmission probability in those without the vaccine (see website appendix). If this reduction occurs, even a disease-modifying vaccine that adds 60 additional years of life will not produce a perverse outcome. Hence our results demonstrate that decreasing the per-partnership transmission probability is critical. We strongly recommend that disease-modifying vaccines that significantly increase life expectancy, but do not substantially decrease the per-partnership transmission probability should not be used for epidemic control.

Having determined conditions under which disease-modifying vaccines lead to perversity, assuming no change in risk behaviour, we now consider the case where individuals change their risk behaviour. A vaccine campaign produces four groups: (A) those who do not receive the vaccine; (B) those who receive the vaccine but the vaccine does not take; (C) those who receive the vaccine, the vaccine takes, but vaccine-induced immunity wanes over time; and (D) those who receive the vaccine, the vaccine takes, and vaccine-induced immunity does not wane over time. Risky behaviour may increase or decrease for individuals in all four groups. We consider "unvaccinated" individuals to be any members of groups A, B, or C, whereas "successfully vaccinated" individuals consist of members of group D alone. We consider the net effect of changes in unvaccinated individuals; thus, for example, if group A substantially increase their risk behaviour, compared with decreases in groups B and C, then the net effect will be an increase in risk behaviour in unvaccinated individuals. We calculated a threshold surface for risk behaviour change that determines the boundary between beneficial and perverse outcomes; the threshold is determined by the fitness ratio, the proportion of the population that are successfully vaccinated, and the degree of change of risk behaviour in unvaccinated infected individuals (figure 1C and figure 1D).

The epidemiological outcome depends strongly on the behaviour of the infected unvaccinated individuals (see website appendix) and is very sensitive for HIV vaccines that provide only a low degree of protection against infection. Figure 1C shows the threshold surface for a disease-modifying vaccine that provides only a 25% degree of protection, and calculations are made assuming that vaccinated infected individuals decrease their risky behaviour by 15%. The threshold between beneficial and perverse outcomes in figure 1C is shown by the coloured surface. Vaccines with a fitness ratio above this surface will make the epidemic worse, whereas those with a fitness ratio below the surface will improve the outcome by decreasing transmission. A perverse outcome is more likely if risky behaviour among unvaccinated people increases (figure 1C). Under these conditions, the optimal epidemic control strategy would be to maximise vaccination coverage (which will maximise S, the probability that an individual is and remains successfully vaccinated). However, if risky behaviour among unvaccinated people decreases, then the optimal epidemic control strategy would be to have low coverage levels (which will minimise S). Figure 1D shows the threshold surface for a disease-modifying vaccine that provides only a 25% degree of protection against infection; these calculations are made assuming that vaccinated infected individuals increase their risk behaviour by 15%. The optimal epidemic control strategies to avoid perversity are similar to figure 1C; however, in this case the beneficial region is slightly reduced. Thus, the outcome is strikingly more dependent on the behaviour changes in unvaccinated infected individuals than in vaccinated infected individuals.

In this analysis we have shown that under certain specified conditions, use of disease-modifying vaccines that provide only a low degree of protection against infection can lead to population-level perversity. If behavioural changes do not occur, the degree of protection that the vaccine offers, and the fitness ratio, are critical factors in determining whether the outcome will be perverse. Hence, we have shown that disease-modifying vaccines that provide only a low degree of protection against infection, but substantially increase life expectancy, are likely to make the epidemic worse. The relation of a vaccine between reducing transmission and increasing survival time will be a critical determinant of the epidemiological outcome. We have shown that a vaccine that affords a 1·5 $\log_{10}$ mean drop in

viral load will always have a beneficial impact, even if the vaccine provides 60 additional years of life.

We have analysed a simple previously published model to gain analytical insights and to understand the complexity of the population-level outcomes that will occur due to vaccination with disease-modifying vaccines and behaviour changes. Our model could be extended to include additional complexities, such as temporal changes in viral load over time within individuals or between individuals, or heterogeneity in risk behaviour. Analysis of this more complex model would yield similar results to those we have shown here, but would also provide some additional insights. Not surprisingly, we have shown that increases in risk behaviour can increase the probability of perversity; however, it is noteworthy that we found that the probability of perversity occurring is extremely sensitive to risk behaviour changes in unvaccinated infected individuals. We have also shown that the optimal epidemic-control strategy for disease-modifying vaccines that will only provide a low degree of protection against infection will differ depending on whether unvaccinated infected individuals either increase or decrease their risk behaviour. Our results show that it is critical that effective behavioural intervention strategies are tightly linked with vaccination programmes and that before any disease-modifying vaccine is widely used, the population-level impact should be carefully assessed.

In this analysis we have chosen to focus on the reproduction number, as it is a time-independent measure. It is also important to predict the effects of vaccines on the temporal dynamics of HIV epidemics, as we have done previously.[8–14,21] As we have illustrated here, mathematical models should be used as health-policy tools for predicting the future public-health impact of vaccines in controlling the global HIV pandemic.

Acknowledgments

We thank Elissa Schwartz and Romulus Breban for technical discussions. We also acknowledge financial support from NIAID/NIH (R01 AI041935) and the UCLA AIDS Institute.

Conflicts of interest

We declare that we have no conflict of interest.

References

1 Klausner RD, Fauci AS, Corey L, et al. The need for a global HIV vaccine enterprise. *Science* 2003; **300:** 2036–39.
2 Esparza J, Osmanov S. HIV vaccines: a global perspective. *Curr Mol Med* 2003; **303:** 183–93.
3 Zinkernagel RM. The challenges of an HIV vaccine enterprise. *Science* 2004; **303:** 1294–97.
4 VAXGEN vaccine trial. http://depts.washington.edu/hptu/vaxgen.htm (accessed Aug 24, 2004).
5 Burton DR, Desrosiers RC, Doms RW, et al. A sound rationale needed for phase III HIV-1 vaccine trials. *Science* 2004; **303:** 316.
6 Desrosiers RC. Prospects for an AIDS vaccine. *Nat Med* 2004; **10:** 221–23.
7 Candidate HIV-1 vaccines evaluated in uninfected adults. http://www.vrc.nih.gov/vrc/HIVCli2.pdf (accessed Aug 24, 2004).
8 Graham B. Clinical trials of HIV vaccines. *Annu Rev Immunol* 2002; **53:** 207–21.
9 Gilbert PB, DeGruttola VG, Hudgens MG, Self SG, Hammer SM, Corey L. What constitutes efficacy for a human immunodeficiency virus vaccine that ameliorates viremia: issues involving surrogate end points in phase 3 trials. *J Infect Dis* 2003; **188:** 179–93.
10 Esparza J, Chang ML, Widdus R, Madrid Y, Walker N, Ghys PD. Estimation of "needs" and "probable uptake" for HIV/AIDS preventative vaccines based on possible policies and likely acceptance (a WHO/UNAIDS/IAVI study). *Vaccine* 2003; **1621:** 2032–41.
11 Francis, DP, Heyward WL, Popovic V, et al. Candidate HIV/AIDS vaccines: lessons learned from the world's first phase III efficacy trials. *AIDS* 2003; **17:** 147–56.
12 Blower SM, McLean AR. Prophylactic vaccines, risk behaviour change and the probability of eradicating HIV in San Francisco. *Science* 1994; **265:** 1451–54.
13 Blower SM, McLean AR. AIDS: modeling epidemic control. *Science* 1995; **267:** 1252–53.
14 McLean AR, Blower SM. Modeling HIV vaccination. *Trends Microbiol* 1995; **3:** 458–63.
15 Blower SM, Koelle K, Mills J. Health policy modeling: epidemic control, HIV vaccines and risky behaviour. In: Kaplan EH, Brookmeyer R, eds. Quantitative evaluation of HIV prevention programs. New Haven, CT: Yale University Press, 2002; 260–89.
16 Blower SM, Schwartz EJ, Mills J. Forecasting the future of HIV epidemics: the impact of antiretroviral therapies and imperfect vaccines. *AIDS Rev* 2003; **5:** 113–25.
17 McLean AR, Blower SM. Imperfect vaccines and herd immunity to HIV. *Proc R Soc Lond B Biol Sci* 1993; **253:** 9–13.
18 Blower SM, Moss RB, Fernandez-Cruz E. Calculating the potential epidemic-level impact of therapeutic vaccination on the San Francisco HIV epidemic. *AID Science* 2003; **3**.
19 Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342:** 921–29.
20 Smith SM, Holland B, Russo C, Dailey PJ, Marx PA, Connor RI. Retrospective analysis of viral load and SIV antibody responses in rhesus macaques infected with pathogenic SIV: predictive value for disease progression. *AIDS Res Hum Retroviruses* 1999; **15:** 1691–701.
21 Blower SM, Koelle K, Kirschner DE, Mills J. Live attenuated HIV vaccines: predicting the trade-off between efficacy and safety. *Proc Natl Acad Sci USA* 2001; **98:** 3618–23.

Appendix

We used the previously published mathematical model[12-17]. We denote by R_0 the basic reproduction number for unvaccinated individuals and by R_V the basic reproduction number for vaccinated individuals. The probability that an individual is (and remains) "successfully" vaccinated is S. From[15] we have $S = \frac{p\varepsilon\mu}{\mu+\omega}$, for vaccination coverage p, probability that the vaccine "takes" ε, average duration of immunity $\frac{1}{\omega}$ and average sexual lifespan $\frac{1}{\mu}$. An individual is defined to be "successfully" vaccinated if they are vaccinated (p), the vaccine "takes" (ε), and the vaccine-induced immunity (ω) does not wane. Thus, the total number of secondary infections caused by a single individual is

$$R_P = S(1-\psi)R_V + (1-S)R_0$$

as reported previously.[15] In the absence of behavioral changes, perversity will occur if $R_P > R_0$. Hence

$$S(1-\psi)R_V + (1-S)R_0 > R_0.$$

Since $R_V = fR_0$, we thus require

$$f > \frac{1}{1-\psi}$$

for perversity.

The basic reproduction numbers are

$$R_j = \frac{\beta_j c}{\mu + \gamma_j} \qquad (j = U, V)$$

where β_j is the per partnership transmission probability, c is the average number of sex partners per unit time and γ_j is the average progression rate to AIDS. Define

$$\beta_V^{\text{crit}} \equiv \frac{\beta_U \mu}{\mu + \gamma_U}.$$

If $\beta_V \leq \beta_V^{\text{crit}}$, then since $R_V = fR_0$, it follows that

$$f \leq \frac{\mu}{\mu + \gamma_V} < 1.$$

Thus, if the per partnership transmission probability of vaccinated infected individuals is sufficiently low, then the fitness ratio will be less than 1, for any value of γ_V. Thus, if the vaccine can reduce the per-partnership probability below the critical threshold β_V^{crit}, then any additional survival time will not result in a perverse outcome.

From[19], each log increase in viral load is associated with an increase by a factor of 2.45 in the risk of transmission; hence – by using this relationship - we can calculate the relative relationship between viral load and transmission probability. Thus, if an initial viral load w is reduced to a new viral load v, then the relationship between the corresponding per partnership transmission probabilities is

$$\frac{\beta(v)}{\beta(w)} = 2.45^{\log_{10}(v/w)}.$$

It follows that a vaccine which offers a $1.5 \log_{10}$ mean drop in viral load will reduce the viral load by a factor of $10^{-1.5}$ and hence

$$\frac{\beta(v)}{\beta(w)} = 2.45^{-1.5} = 0.261.$$

Thus, the per partnership transmission probability in those with such a vaccine will be reduced to 26.1% of the per partnership transmission probability in those without the vaccine, or just slightly greater than $\tilde{\beta}_V^{\text{crit}}$.

For perversity where the infected unvaccinated change their behavior by a multiplicative factor m_U and the infected vaccinated change their behavior by a multiplicative factor m_V, we require

$$S(1-\psi)R_V m_V + (1-S)R_0 m_U > R_0$$
$$f > \frac{1-m_U + m_U S}{S(1-\psi)m_V} \equiv z.$$

Note that

$$\frac{\partial z}{\partial S} = \frac{m_U - 1}{S^2(1-\psi)m_V}.$$

Thus if $m_U > 1$ then z is increasing with respect to S, whereas if the reverse inequality holds, then z is decreasing with respect to S. Thus, the behavior changes in the unvaccinated are a critical determinant of the epidemic control strategy for vaccines that offer a low degree of protection.