Potential Public Health Impact of Imperfect HIV Type 1 Vaccines

Roy Anderson and Matthew Hanson
Department of Infectious Disease Epidemiology, Imperial College, University of London, St. Mary’s Campus, London, United Kingdom

The potential public health impact of imperfect human immunodeficiency virus (HIV) type 1 vaccines was examined by use of deterministic mathematical models of virus transmission. Imperfect vaccines are defined as those that act to favorably alter the typical clinical course of disease in those immunized who acquire infection. The properties examined include a lengthened incubation period; reduced virus load, which acts to lower infectiousness; reduced susceptibility on exposure to infection; and an increase in risk behaviors by those vaccinated. Analyses suggest that, although imperfect vaccines would struggle to block transmission via cohort vaccination of those entering the sexually active age classes, they could have a substantial public health impact, as measured by reduced prevalence and mortality induced by acquired immunodeficiency syndrome (AIDS), provided the case reproductive number of HIV-1 among vaccinated individuals ($R_{0v}$) was less than that among unvaccinated individuals ($R_{0u}$). This requires that any lengthening in the incubation period and, hence, the time period over which an infected vaccine recipient can transmit to susceptible sex partners, as well as any increase in risk behaviors, are more than offset by other effects, such as reduced susceptibility to infection and reduced infectiousness. Numerical studies based on a more complex model, which included representation of age, sex, heterogeneity in sexual activity, variable infectiousness, and different mixing patterns between risk groups, were used to confirm the general insights gained from a simple deterministic model.

Progress toward the development of a safe and effective vaccine to protect against HIV-1 infection has been slow since the virus was first discovered and the etiology of AIDS was defined, 2 decades ago. The reasons are many and varied and include high antigenic diversity within HIV populations, the high rates of mutation and recombination of the virus, and, until recently, limited investment in vaccine research and development by governments, international donor agencies, and the major pharmaceutical companies.

In the past few years, however, the volume of research in this field has increased rapidly, in part because of the universal recognition of the urgent need for such a tool. The relentless spread of the virus throughout most regions of the world has not been halted in the majority of settings by other interventions, such as education, cofactor sexually transmitted disease (STD) treatment, increased condom use, and community-based antiretroviral therapy. As of July 2004, surveillance data compiled by the Joint United Nations Programme on HIV/AIDS (http://www.unaids.org) suggest that 35–43 million people are living with HIV infection. Progress in the development of an HIV vaccine also is due to advances in basic research, which are increasingly generating deeper insight into the nature and effectiveness of the human immune response to HIV-1 infection.

At present, 30 trials of HIV-1 vaccines are ongoing, and several are pending for late 2004, involving 19 different countries on 6 continents. Most trials are in phase 1; VaxGen’s 2 trials (in North America and Thailand) are the only phase 3 studies to have been completed, but the results have been disappointing (http://www.vaxgen.com). The majority of the trials use clade B strains, but a few candidate vaccines (especially among the newer ones) are based on clades A, C, D, and E (see International AIDS Vaccine Initiative at http://www.iavi.org).
In the history of vaccine development and community-wide use to combat the spread and impact of infectious agents, very high efficacy has been a necessary condition for licensing and use in most instances. Typical examples are those widely used to protect against measles, mumps, and rubella viruses. Phase 3 efficacy trails for these vaccines suggested that >90% of those immunized by 1 round or a short course of immunization are protected against infections that induce overt clinical symptoms [1]. Furthermore, available evidence suggests that the duration of protection induced by vaccination typically is long (perhaps lifelong for many vaccines against the antigenically conserved viruses).

For candidate HIV-1 vaccines, the expectations are more modest. Indeed, some fear that phase 3 trials of the early candidates may reveal very low protective efficacy. The first results from VaxGen’s phase 3 trial in North America, for a sample of 5009 individuals, recently reported an efficacy value of 3.8%, although an encouragingly high efficacy value was recorded for a smaller sample of minority individuals (78% among black volunteers [n = 314], compared with a placebo) (http://www.vaxgen.com). In those partially immunized, the duration of protection is unknown at present. It may be short owing to the continued evolution of the virus within the community—that is, antigenic variants that evade the immunological response induced by the vaccine may arise or may already be present. However, experimental work involving primate models and early results from phase 2 trials of candidate products tentatively suggest that some benefits may accrue in those vaccinated who acquire infection, in terms of reduced virus load and, concomitantly, slower progression to AIDS. For example, work by Rose et al. [2] that uses a vaccine containing HIV gag and env in an attenuated vesicular stomatitis virus vector did not protect against infection in macaques when challenged with SHIV89.6P given 3 or 6 months after vaccination. However, the vaccine did protect against disease. After 2 years of follow-up, the vaccinated animals (7 in total) remained healthy, with low or stable virus loads.

The expectation of low efficacy or of a therapeutic, as opposed to a protective, effect raises 2 questions. First, would a low-efficacy vaccine have a significant public health impact in areas of high prevalence that prevail in many countries in sub-Saharan Africa? Second, will immunization acting in more-subtle ways following a breakthrough infection in vaccinated individuals induce an impact on transmission at the population level? Many imperfect vaccines act to lengthen the incubation period of AIDS and/or reduce infectiousness to sex partners by lowering virus load! These effects could be very important in terms of public health benefit, as measured both by net HIV/AIDS–induced mortality and by incidence of HIV infection.

The first question has been addressed in past work, by use of simple and complex mathematical models of virus transmission in defined communities [3–9]. In general, the main conclusion derived from these analyses is that a low-efficacy vaccine could have significant public health benefits, provided those vaccinated do not greatly increase risk behaviors [3]. The second question has attracted less attention to date. Preliminary studies of the potential population-level impact of an immunotherapeutic agent that increases the duration of the incubation period of AIDS, however, suggest that a measurable benefit at the individual and community levels could be achieved under some circumstances [10].

In this article, we briefly review the potential impact of a low-efficacy vaccine that induces a short duration of protection. Here, we assume that no benefit accrues to those not successfully protected against infection. We then turn to the more complex question of how an imperfect vaccine with variable efficacy but a measurable impact on virus growth within the vaccinated patient who acquires infection will influence the incidence of HIV infection and HIV/AIDS-induced mortality in a given community with varying levels of cohort-based vaccine uptake. Simple and complex deterministic mathematical models were used to seek general insights into the potential impact of a vaccine with clearly defined properties. In this article, we do not examine the important question of how best to design phase 3 trials to measure the properties of an imperfect vaccine [11–14]. This problem will be addressed in a subsequent publication, but, in the Discussion, we comment briefly on some key issues that influence trial design.

**PROTECTIVE VACCINES WITH LOW EFFICACY**

The simplest deterministic models of HIV-1 transmission and the impact of vaccination are compartmental in structure, typically with 3 or 4 classes that represent susceptible, infected, and immune (vaccinated) individuals and those with AIDS (figure 1). The structure of this model is well illustrated in the work by Anderson et al. [10] and Blower and McLean [6]. They typically ignore complications related to sex, age, sexual activity class, and mixing between different activity classes [4]. The most important result derived from this type of model is a simple expression relating the critical level of cohort-based vaccination coverage required to block HIV transmission, \( R_0\), and various properties of the vaccine and the intensity of transmission. The latter is defined by the basic reproductive number \( R_0\), which measures the average number of secondary infections generated by 1 primary case of infection in a susceptible population. To block transmission by means of mass or cohort vaccination, the effective reproductive number \( R\) must satisfy \( R < 1\), where \( R\) measures the generation of secondary cases of infection in a partially susceptible community. For a vaccine that gives protection for an average of \( V\) years and that has efficacy \( \varepsilon \) (often referred to as “take” and defined as the fraction of those immunized who are fully protected at exposure) and...
when the life expectancy in the community is \( L \) years, the critical fraction of those in each cohort, \( p_c \), who are joining sexually active age classes and who must be immunized in order to halt transmission is given by

\[
p_c > \frac{(1 - 1/R_0)(1 + L/V)}{e}.
\]

The magnitude of \( p_c \) rises above unity if the duration of protection is short, even for communities with a low intensity of transmission (\( R_0 \) just above unity in value) (figure 2). In these circumstances, cohort-based vaccination would not be able to block transmission, although it could act to significantly reduce mortality and incidence of HIV infection.

The key insight revealed by equation 1 is that the average duration of protection, \( V \), is as important as vaccine efficacy, \( e \), as a determinant of the potential population-based impact of the candidate vaccine. This point is not widely appreciated by those currently involved in HIV-vaccine development and trial design. The current phase 3 trials are designed to detect a defined level of vaccine efficacy (30% efficacy as the lower confidence limit) as quickly as possible (within 3 years) (http://www.vaxgen.com). The measurement of duration of protection requires long-term follow-up of those immunized, with the time horizon defined not in years but in decades.

Within these simple models, the nature of the vaccination program can be varied from cohort based (a fraction of those joining the sexually active age classes are immunized) to population based, in which the defined rate of vaccination of susceptible individuals is equated to the proportion of susceptible individuals being vaccinated per defined time period. The example in figure 2A illustrates cohort-based vaccination, whereas that displayed in figure 2B is based on a rate or proportion vaccinated per unit of time. The case in figure 2B was chosen to illustrate the impact of mass vaccination on the equilibrium prevalence of infection, \( \gamma \), for a vaccine with moderate efficacy that confers varying durations of protection. Mass immunization has limited impact in communities with high transmission intensity (\( R_0 = 10 \)) if the vaccine has moderate efficacy (50%) and a short duration of protection (a few years), even at high levels of coverage.

**IMPERFECT VACCINES WITH A THERAPEUTIC EFFECT**

Imperfect vaccines could act in various ways, including poor efficacy in protecting against infection. Here, however, we turn to the more complex problem of the potential public health value of a vaccine with variable efficacy that does not act to protect against infection but to slow progression to disease (perhaps by lowering the typical viral burden over the incubation period) and, hence, to improve survival once infection is acquired, in comparison with infected unvaccinated individuals. We also examined the property of reduced infectiousness in those vaccinated who subsequently acquire infection. Our aim was to seek general analytical insights from a deterministic model of simple structure that was in line with the early work by Blower and McLean [6] but included additional analytical results for the conditions under which the vaccine reduces AIDS-induced mortality and equilibrium prevalence and population density. We defined a series of new parameters to capture the assumptions outlined in the flow chart represented in figure 3. The number of stratifications of the population increases to 5: to the variables for susceptible individuals (\( X \)), infected individuals who are not vaccinated (\( Y \)), and cases of AIDS (\( A \)) are added 2 new variables, namely, those vaccinated who have not yet acquired infection (\( V \)) and who lose any protection that they have at rate \( g \) and those vaccinated who have acquired infection (\( W \)). The formal structure of the model is presented in the Appendix.

The key new assumptions relate to what happens to those vaccinated and how they acquire and transmit infection. First, we assumed that those vaccinated have a slower rate of progression to AIDS of \( \sigma \theta \) (with \( \theta \) having a value between 0 and 1) and that those infected but not vaccinated have a rate of progression of \( \sigma \). The average incubation period for the former is defined as \( I_c = 1/(\mu + \sigma \theta) \), whereas the average incubation period for infected unvaccinated individuals is defined as...
Figure 2. A, Graph showing critical proportion to be immunized with protective vaccine, \( p_c \), to block transmission of infection as a function of \( R_0 \) and the duration of protection, \( V \) (efficacy \( e = 1 \)). B, Graph showing impact of varying the duration of protection, \( V \), on the equilibrium prevalence of infection, \( y_* \), for a program that immunizes a proportion, \( p \), of susceptible individuals per year (\( R_0 = 10; e = 1 \)).

\( I_s = 1/(\mu + \sigma) \), and one hopes that \( I_s > I_v \). The parameter \( \mu \) defines the background death rate, where \( 1/\mu \) represents life expectancy in the sexually active age classes in the absence of infection. Second, the net rate at which susceptible unvaccinated individuals acquire infection is formed from 2 components, namely, infections acquired from unvaccinated and infected sex partners and those acquired from vaccinated but infected partners. The term \( \beta \) represents the probability of transmission per partner times the average rate of acquisition of new sex partners, denoting the rate at which susceptible individuals acquire infection from infected unvaccinated individuals. Vaccinated individuals could increase their risk behavior after immunization, and this possibility is denoted by the parameter \( r \), which adopts a value \( >1 \). For sexual contact between susceptible and infected vaccinated individuals, \( \beta \) is multiplied by \( r^2 \). Vaccinated but infected individuals are assumed to be less infectious, such that \( \beta \) is multiplied by a factor \( s \) (with \( s \) having a value between 0 and 1). This product determines the rate at which contacts between susceptible individuals and infected vaccinated individuals generate new infections. Third, for vaccinated individuals, 2 components again determine the rate of infection, namely, sexual contact with infected unvaccinated individuals and contact with infected vaccinated individuals. We again assume that infected vaccinated individuals are less infectious, perhaps owing to a lower average virus load, such that the transmission parameter is multiplied by factor \( s \), where \( s \) has a value between 0 and 1. In addition, for both components, we assumed that vaccinated susceptible individuals are less susceptible than unvaccinated susceptible individuals, by a factor \( q \), where \( q \) has a value between 0 and 1. Thus \( \beta \) and \( s \) are both multiplied by factor \( q \), to give the 2 component rates at which vaccinated individuals acquire infection. In short, \( q \) denotes reduced susceptibility, \( s \) denotes reduced infectiousness, and \( r \) measures increases in risk behavior among vaccinated individuals.

Analytical insights on equilibrium behavior can be derived for this model by using various approximations (see equations A2 and A3 in Appendix). In the absence of infection, those who leave the vaccinated class, owing to a decay in immunity, were assumed to rejoin the fully susceptible class.

The model predicts 6 types of equilibrium, defined by different parameter domains as follows: (1) the trivial state of the extinction of infection, where the basic reproductive number \( R_0 \) is less than unity \(( R_0 < 1) \); (2) \( R_0 > 1 \), with \( p = 0 \) (no vaccination; \( p \) is the proportion vaccinated) and prevalence of infection at the vaccine-free equilibrium state \( y_* \); (3) eradication of infection by vaccination, where the equilibrium prevalence of infection \( y_* = 0 \); (4) the first of 3 states of the persistence of infection under vaccination, with \( y_1^* < y_*^* \) and population size in the presence of vaccination \((N_1^*) \) greater than that in the absence of vaccination \((N_0; N_0^*>N_*) \); (5) prevalence of infection under vaccination greater than that under no vaccination \((y_1^*>y_*^*) \), with increased population size \((N_1^*>N_0^*) \); and (6) the perverse outcome of increased prevalence of infection but decreased population size, with cohort-based vaccination.
Imperfect HIV-1 Vaccines

Figure 3. Flow chart of action for a vaccine with variable duration of protection, when vaccinated individuals can acquire infection (see Appendix for explanation of equations and parameters).

$\gamma^* > \gamma^*; N^* < N^*$. These various outcomes are presented schematically in figure 4.

Eradication of infection by mass cohort vaccination will always be difficult to achieve when an imperfect vaccine is used, even if vaccination does have significant impact on infectiousness in immunized individuals who acquire infection. Formally, the critical fraction that must be immunized, $p_c$, in order to block transmission is given by

$$p_c > \frac{(1 - 1/R_0)(1 + V/v)}{e(1 - R_\infty/R_0)} .$$

Here, $L$ is life expectancy in the absence of AIDS, $e$ is vaccine efficacy, $V$ is the average duration of vaccine protection (i.e., $1/\gamma$), and the expressions for the basic reproductive numbers are given in the Appendix. For moderate transmission intensity and short to medium duration of vaccine protection, the value of $p_c$ exceeds unity; hence, each cohort must be repeatedly immunized in order to block transmission.

Although eradication is difficult to achieve with an imperfect vaccine, mass cohort-based vaccination can have a significant public health impact. Cohort vaccination will always act to reduce the prevalence of infection, $\gamma^*$, and the net AIDS-induced mortality, provided $R_\infty < R_0$. Another way of expressing this condition is as follows:

$$1 > qsr^2I_\infty/I_n .$$

This makes clear the complex interplay between the impact of the vaccine on infectiousness ($s$), susceptibility ($q$), and risk behavior ($r$) and the ratio of the respective average incubation periods of AIDS in vaccinated and unvaccinated infected individuals. An imperfect vaccine would be hoped to decrease infectiousness and susceptibility by a significant amount (by at least a factor of 2) and to increase the average incubation period, $I_n$, by decreasing virus load in vaccinated individuals. The critical boundary between a beneficial effect and a detrimental outcome is plotted in figure 5A for various ranges of the parameters defined in equation 2. An effective imperfect vaccine, therefore, is one that reduces the reproductive number of the virus ($R_0$) for vaccinated individuals as much as possible below that pertaining to unvaccinated individuals ($R_0$).

Some guidance on the nature of the relationship between decreased viral burden and duration of incubation can be derived from longitudinal studies of changes in virus load in individuals with known dates of seroconversion. Plots of mean virus load versus time to AIDS suggest an inverse relationship, with low virus loads associated with longer incubation periods (figure 5B) [15–18]. In the absence of information on how any specific candidate vaccine acts at present, the relationship plotted in figure 5B suggests that a vaccine that induced a 2-log decrease in average virus load could greatly lengthen the incubation period of AIDS.

A related question of great importance in a public health context is the degree to which infectiousness is decreased concomitant with a lowered virus load. Data are limited and derive mostly from 2 studies, by Quinn et al. [19] and Gray et al. [20]. Gray et al. [20] suggest that a 1.4 log decrease in virus load (from 4.58 to 3.23 copies/mL of plasma) lowered the probability of transmission (defined per act) by a factor of 23. This change supports the argument that an imperfect vaccine that has a substantial effect on virus load could be of great benefit. However, data presented in the article by Gray et al. [20] hint at a nonlinear relationship between virus load and the probability of transmission per act; hence, the decrease in infectiousness induced by a reduction in virus load will depend on the range of viral burden over which the change is induced. The associated increase in the incubation period, which lengthens the infectious period and could increase risk behavior, could act to offset any benefit. The quantitative detail matters, as illustrated by equation 2.
Using expressions for the equilibrium prevalence of infection (see Appendix) with and without vaccination and various parameter assignments for the ratio $q_s$ and the fraction of each birth cohort immunized, $p$, when joining the sexually active age classes, gaining some insight into quantitative aspects of the potential public health impact of an imperfect vaccine is possible. Figure 5C and 5D shows the ratio between the 2 prevalences of infection (with vaccination divided by without vaccination) for values between 0 and 1 for the fraction of each cohort vaccinated $p$ and for values between 0 to 0.5 for the ratio $q_s$. The latter range reflects a fairly modest impact of the vaccine on reducing susceptibility and infectiousness in those who acquire infection. When no change in risk is assumed, these conservative assumptions about the properties of imperfect vaccines show that these vaccines can have a very substantial public health impact, as measured by the equilibrium prevalence of HIV-1 infection. Similar conclusions emerge when population size or net AIDS-induced mortality are used as the outcome measure (figure 6B). For larger changes in the ratio $q_s$, the benefits would be much greater, as suggested by results reported by Gray et al. [20] in their study of viral burden and probabilities of transmission.

Even when the condition defined in equation 2 is not satisfied and the prevalence of infection increases over that in the unvaccinated population (because infected vaccinated individuals live longer), net AIDS-induced mortality can be decreased by mass vaccination. For example, for the conservative case in which $R_o = R_m$ and $q_s < 1$, the net AIDS-induced mortality, as reflected inversely by population size at equilibrium, is decreased when the following approximation holds:

$$q_s r^2 < \frac{I_n}{I_0} + q_s (R_o - 1)(1 - \theta).$$

This condition illustrates the complex interplay between the typical durations of the incubation period of AIDS in unvaccinated ($I_n = 1/(\sigma + \mu)$) and vaccinated ($I_v = 1/(\sigma \theta + \mu)$) individuals, transmission success ($R_o$), increased risk behaviors ($r$), and the degree to which the vaccine may influence susceptibility and infectiousness ($q_s$) (figure 6A). In short, the increased life expectancy of vaccinated infected individuals must be offset by a significant decrease in infectiousness, to prevent more infections and subsequent deaths arising from transmission events deriving from them than would be the case in the absence of vaccination.

THE MORE COMPLEX MODELS

We briefly consider the predictions of a more complex deterministic model that consists of a system of nonlinear partial differential equations representing changes over time and age for both sexes, 3 classes of infectiousness (primary HIV infec-
Figure 5.  A, Boundary relationship, as defined in equation 2, between the product of the degree of reduction in infectiousness \( q_s \) and the degree of reduction in susceptibility \( q \) for vaccinated individuals, as a function of the ratio between the length of the incubation period of AIDS in vaccinated individuals and that in unvaccinated individuals, \( I_u/I_v \), and the factor by which risk behavior increases for vaccinated individuals, \( r (r = 1 \text{ denotes no change}) \). Imperfect vaccines with properties defined by combinations of parameter values that lie below the surface of the graph led to a decrease in prevalence of infection and mortality, compared with values prior to immunization. Two regions exist above the surface of the graph, namely, one with increased prevalence and decreased mortality and the other with increased prevalence and increased mortality (see text). B, Relationships between average log10 virus load (per milliliter of plasma) and the incubation period of AIDS in a cohort of individuals in Amsterdam with known dates of seroconversion (red dots) and a simulation study based on a model of HIV-1 pathogenesis (green dots), by Fraser et al. [15]. C and D, Surfaces showing the equilibrium relationship (the exact relationship derived from numerical evaluation of the model equations) between the ratio of prevalence of HIV-1 infection after cohort vaccination and that before vaccination, \( p \); the fraction \( p \) of each cohort that was vaccinated; and the ratio \( q_s \), which denotes the product of the proportion reduction in infectiousness and the proportion reduction in susceptibility. In C, \( q \) was fixed at 0.5; in D, \( s \) was fixed at 0.5. Other parameter assignments were as follows: \( R_0 = 2.0 \), \( R_0 = 1.0 \), \( r = 1.0 \) (no increased risk behavior), \( e = 1.0 \), and \( V = 10.0 \) years.

The more complex model structures permit analysis of the costs and benefits associated with different vaccine-delivery programs. Cost is a key issue in the design and implementation of any intervention to reduce the impact of HIV infection in countries in sub-Saharan Africa. An imperfect vaccine can be used in a variety of ways, including mass vaccination of the entire population (the most costly approach) and, at the other end of the cost spectrum, a highly targeted program for those most at risk (perhaps related to age, sex, and sexual activity class or some surrogate marker of activity, such as attendance at an STD clinic or involvement in commercial sex work).
Targeting may involve hidden costs related to the identification of those most at risk. When considering design issues, simplicity of implementation should be a major priority for resource-poor settings. With a vaccine that may confer a degree of protection for only a limited period of time, the age at which vaccination is administered also is of importance. We first examine the issues of who to vaccinate and at what age. The outcome criteria were defined as the number of lives saved over a 20-year period, per dose of vaccine administered. In most scenarios examined, vaccination was introduced as a cohort program for defined age groups before or soon after they join the sexually active age classes.

Analyses suggested that the best impact would be achieved by targeting women 15 years of age and men 25 years of age (i.e., before the majority start sexual activity, considering the potentially short duration of protection of 10 years for imperfect vaccines). This optimum was very much influenced by the prevailing pattern of sexual activity for both sexes. Data from Zimbabwe, used to set the parameters of the model, revealed an early start to sexual activity among women and a later start among men [21]. The pattern of mixing also was of importance, with women typically having older male partners. For complete cohort coverage, vaccines can have an important impact, with 1–2 deaths prevented per 10 doses of vaccine administered, given a reasonable degree of suppression of infectiousness in those vaccinated who acquire infection. However, a perverse outcome can occur for vaccines with poor efficacy, if suppression of infectiousness is very limited (s > 0.9, for the negative numbers in figure 7B).

The lengthened incubation period of AIDS in those vaccinated who subsequently become infected enhances the overall transmission of HIV-1 and, hence, its demographic impact [4]. Increased risk behavior also acts in this manner.

Extensive numerical studies of the behavior of models have suggested that targeting to the highest 2 sexual activity classes for both sexes is highly beneficial in terms of deaths prevented per dose of vaccine, even when vaccination is started late in the epidemic (i.e., at endemic equilibrium). With the best vaccines (10-year duration of protection and high suppression of infectiousness), 4–5 deaths can be prevented per 10 doses of vaccine administered.

Figure 7 records contour plots of deaths prevented, with a focus on the degree to which vaccination lengthens the incubation period of AIDS (θ; values from 0.3 to 1 examined), reductions in infectiousness (s), and the average duration of protection provided (γ). Two durations of protection were considered (5 and 10 years), with 2 different scenarios for risk behavior (r = 1 and r = 1.2). In all cases, 60% of individuals in all activity groups were vaccinated, at 15 years of age for women and 25 years of age for men. For measurable benefits to accrue over a 20-year time span, a long duration of effect in the vaccinated individual is desirable (a small value for θ). This is independent of changes in other vaccine-related properties. A further exploration of the impact of different properties is presented in figure 8, where contours are plotted for deaths prevented for a range of incubation periods in the vaccinated individuals (θ), of values for infectiousness (s) and proportion vaccinated (p), and of reductions in susceptibility (q). In figure 8A, variation in these parameters is given for a program targeted at the 2 highest sexual activity classes. In figure 8B and 8C, vaccination is across all activity classes (cohort

Figure 6. A. Exact relationship, derived from numerical evaluation of the model equations, between the ratio of equilibrium population size after cohort vaccination is initiated, \( N_v \), and that before vaccination, \( N^* \); the fraction \( p \) of each cohort vaccinated; and the ratio \( q_s \). Parameter assignments were as follows: \( R_0 = R_{50}, r = 1.0 \) (no increased risk behavior), \( e = 1.0, \beta = 0.3, q = 0.666, \sigma = 0.125, \alpha = 1, \) and \( \gamma = 0.1 \). B. Exact relationship, derived from numerical evaluation of the model equations, between population size after cohort vaccination is initiated at time \( t = 0 \) and the fraction \( p \) of each cohort vaccinated. Parameter assignments were as follows: \( R_0 = 2.0, R_{50} = 1.0, r = 1.0 \) (no increased risk behavior), \( \gamma = 0.1, e = 1.0, q = 0.5, s = 0.5, \beta = 0.3 \), and \( \mu = 0.025 \).
immunization, starting with 15-year-old women and 25-year-old men). Good benefits can accrue, with, for example, 2–4 deaths prevented per 10 doses of vaccine administered in an activity-targeted program (figure 8A) with a vaccine that suppresses infectiousness by 60%–90% and lengthens the incubation period by ≥60%.

Overall, the numerical results generated by the more complex model confirm the general prediction of the simple structure outlined in the Appendix. Imperfect vaccines can have a very significant impact on the epidemic, provided their effect on infectiousness in infected vaccinated individuals is sufficiently high.

DISCUSSION

In the longer term, high vaccine efficacy (in the traditional, prophylactic sense) is the key goal in the development of HIV-1 vaccines. At present, however, given the wide global dissemination of the virus and its terrible toll in some regions of the world, less than perfect vaccines are likely to be considered for use in a public health context. The question of what constitutes a “useful” vaccine is not easy to answer, as illustrated by the analyses in this article. Clearly, a vaccine with no protective efficacy in the traditional sense but with a measurable impact on the clinical course of infection in infected vaccinated individuals, such as a lowered average virus load, can be very beneficial in lowering net AIDS-induced mortality and prevalence of HIV-1 infection. However, there is a fine dividing line between a beneficial and a detrimental outcome, which depends on the trade-off between a lengthened incubation period to AIDS and reduced infectiousness over this lengthened period [10].

When the possibility of increased risk behavior by those immunized is considered, the condition for a beneficial outcome is simply that the reproductive number (i.e., the generation of secondary cases) for those vaccinated who acquire infection is less than that for infected unvaccinated individuals ($R_{av} < R_0$). The magnitude of the beneficial impact, in terms of a reduction in AIDS-induced mortality, depends both on the magnitude of the difference in these 2 reproductive numbers and on the relationship between reduced susceptibility plus reduced infectiousness and increased incubation periods (see Appendix). The need to try and measure epidemiological (in defined communities) and vaccine-related parameters (for each candidate that enters phase 3 trials) as precisely as possible, is highlighted by the model's prediction of 6 possible equilibrium states for the variables prevalence of HIV-1 infection and population size, for different domains of parameter combinations.
Figure 8. Contour graphs for deaths prevented per vaccine dose, for different types of imperfect vaccines. In all 3 graphs, \( r = 1.2 \) (relative risk of behavior change for vaccinated individuals). In A, only the highest 2 activity classes were vaccinated, with \( p = 0.7 \). In B, \( q = 0.9 \) (relative susceptibility of vaccinated individuals), and \( p = 0.3 \) (proportion vaccinated, across all activity classes). In C, \( q = 0.7 \), and \( p = 0.6 \). Negative numbers reflect perverse outcomes, in which vaccination increased mortality. \( \theta \), Ratio of rates of progression to AIDS, between infected vaccinated and infected unvaccinated individuals; \( s \), relative infectiousness for those vaccinated.

The model used to derive this conclusion was simple and ignored much of the important complexity in real transmission settings. However, results of numerical studies based on a more complex model are encouraging, in the sense that obviously various forms of heterogeneity will affect the quantitative detail of benefit or detriment but not the underlying condition \( R_0 \). Careful thought on how best to measure the determinants of the magnitudes of the respective reproductive numbers must be a central part of the design of phase 3 trials. Ideally, software for trial simulations based on a stochastic framework is needed, to assess how best to measure transmission-related parameters within settings with much heterogeneity in sexual behavior and complex patterns of mixing between and within sexual activity and age classes. These are under development at present and are hoped to be capable of setting parameters to mimic trials in given communities. To achieve this, however, the development of models and parameters must influence decisions on precisely what to measure in preparatory studies for phase 3 trial sites (see HIV Vaccine Trials Network at http://www.hvtn.org). Once a candidate product is put forward for a phase 3 trial, simulators also can be used to provide guidance on optimum designs, sample sizes needed to detect defined vaccine properties, and, most importantly for an imperfect vaccine, benefits to be gained from trials of different durations.

The precise properties of an imperfect vaccine will not be easy to measure within phase 3 trial settings, in part owing to prevailing heterogeneity, not least of which is in the genetics of both the virus and the human host. As illustrated in figure 6, much heterogeneity prevails among unvaccinated individuals, with regard to the progression of disease after infection and, in particular, the fluctuations and temporal trends in virus load. Changes induced by prior immunization must be detected against this noisy background. High heterogeneity also is a feature of studies that attempt to relate virus load to the probability of transmission [20]. However, in the coming early phases of candidate-vaccine testing, measurement of this heterogeneity and the design of appropriate trials that consider this variability will be important. Given high variability in most
measures of the potential clinical impact of an imperfect vaccine, trials must necessarily involve many patients and many years of follow-up.

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APPENDIX

The equations for the model of an imperfect vaccine (figure 4) are defined as follows (also see the work by Blower and McLean [6]) for the densities of susceptible individuals \((X)\), infected individuals who are not vaccinated \((Y)\), vaccinated individuals \((V)\), infected vaccinated individuals \((W)\), and cases of AIDS \((A)\):

\[
\begin{align*}
\frac{dX}{dt} &= \Lambda(1 - p) - \mu X - \beta X \left(\frac{Y + \sigma W}{N}\right) + \gamma V, \\
\frac{dY}{dt} &= \beta X \left(\frac{Y + \sigma W}{N}\right) - \mu Y - \sigma Y, \\
\frac{dV}{dt} &= \beta X \left(\frac{Y + \sigma W}{N}\right) - \mu Y - \sigma Y, \\
\frac{dW}{dt} &= \beta Y \left(\frac{V}{N} + \sigma W\right) - \mu W - \sigma \theta W, \text{ and} \\
\frac{dA}{dt} &= \sigma Y + \sigma \theta W - (\mu + \alpha) A. \\
\end{align*}
\]  

(A1)

The model describes cohort vaccination of a fraction \(p\) of susceptible individuals entering the sexually active age classes. In reality, \(p\) is \(pe\), where \(e\) is vaccine efficacy, or “take” (values for \(e\) are between 0 and 1). Those vaccinated who acquire infection are assumed to have a longer incubation period for the development of AIDS \((\sigma > \sigma \theta\), where values for \(\theta\) are between 0 and 1); to lose protection prior to infection at a rate \(\gamma\); and to be less infectious to susceptible sexual partners by a factor \(s\), compared with infected unvaccinated individuals \((\beta > \beta s\), where values for \(s\) are between 0 and 1). Those vaccinated who have sexual contact with infected unvaccinated individuals are assumed to be less susceptible to infection than are susceptible unvaccinated individuals, by a factor \(q\), where values for \(q\) are between 0 and 1. In brief, the parameter \(q\) denotes the reduction in susceptibility of vaccinated individuals and the parameter \(s\) denotes the reduction of infectiousness (due to lowered virus load) of vaccinated individuals who acquire infection. The term \(\beta\) represents the probability of transmission per partner times the average rate of acquisition of new sex partners. The inclusion of the parameter \(r\) is to denote the potential of increased risk behaviors by those who are vaccinated (applying to both susceptible and infected vaccinated individuals). The parameter \(r\) records the degree to which risk behavior increases, where values for \(r\) are 1 (no change in risk behavior) or higher. An \(r\) value of 1.1, for example, denotes a 10% increase in risk behavior. The basic reproductive number, \(R_0\), in the absence of vaccination is \(R_0 = \beta/(\mu + \sigma)\). For a population consisting entirely of vaccinated individuals, the basic reproductive number is \(R_{0v} = \beta qs r^l(\mu + \alpha \theta)\). These expressions can be written as \(R_0 = \beta L_0\) and \(R_{0v} = \beta qs r^lL_v\), where \(L_0\) and \(L_v\) are the average incubation periods from infection to AIDS for unvaccinated and vaccinated individuals, respectively. Simple analytical expressions for the equilibrium values of the variables defined in equation A1 are difficult to derive, but approximate values (with small errors for most parameter ranges, except for high values of \(pe\)) in the limit \(\alpha \approx \infty\) (where \(\alpha\) is the rate of death among those with AIDS), for the equilibrium prevalence of HIV-1 infection \(y^*\) and population size \(N^*\), are as follows:

\[
y^* \approx \phi + pe \left(\frac{\beta \phi + \mu(1 - \phi)}{\mu + \gamma + qr\beta \phi}\right) ,
\]

(A2)

where \(\phi = 1 - 1/R_0\) and \(\psi = (R_{0v}/R_0) - 1\), and

\[
N^* \approx \Lambda \left(1 - \phi(\beta \phi + \mu)[1 + pe \frac{\psi s r(\beta - \mu + \beta \theta (qr - \psi + 1))}{\sigma s r(\mu + \gamma + qr \beta \phi)}]\right).
\]

(A3)

References

10. Anderson RM, Gupta S, May RM. The potential of community-wide...


