Role of Herd Immunity in Determining the Effect of Vaccines against Sexually Transmitted Disease

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Background. Vaccination programs provide both direct protection to those immunized and herd immunity, which is indirect protection of those who remain susceptible, owing to a reduced prevalence of infections.

Methods. The well-understood impact of vaccination against ubiquitous childhood infections is compared with that of vaccination against sexually transmitted infections (STIs), and theoretical insights are derived from a review of mathematical modeling studies.

Results. Typically, a large fraction of cases of STIs are acquired by those with modest risk, and these cases could be prevented by low-efficacy vaccines. If coverage is good, vaccination of only one sex can protect the other sex. Candidate vaccines against human papillomavirus (HPV) and genital herpes are in the final stages of testing. The former is likely to be highly efficacious for a limited number of disease-causing HPV types, and the latter has provided protection against disease in women who initially were seronegative for both herpes simplex virus (HSV) type 1 and HSV-2, with 73% efficacy. In models, this vaccine had a substantial impact when infectiousness was assumed to be reduced along with incidence of disease.

Conclusion. With such vaccines on the horizon, the requirements for vaccine delivery need to be considered, particularly who should be vaccinated and at what age.

The success of vaccination programs in the eradication, elimination, and control of infectious diseases has predominantly involved the “simple” viral diseases associated with childhood [1]. Our ability to readily develop highly efficacious vaccines against these infections is not an accident: because they naturally induce effective and lasting acquired immunity, persistence of these infections requires large populations with sufficient new births of susceptible hosts [2]. Infections also can persist within populations when acquired immunity is prevented through mechanisms such as antigenic variation [3], lack of antigens [4], or limited systemic contact [5]. Since sexual intercourse provides limited contacts for potential transmission, sexually transmitted infections (STIs) often display such characteristics. The challenge in developing vaccines against diseases in which the infection avoids the immune system is great, and success is likely to be limited, when it is possible at all. Thus, rather than thinking about the elimination of STIs through vaccination, a more appropriate approach would be to consider the control of sexually transmitted diseases (STDs) by means of vaccines of limited efficacy.

Despite many challenges, new vaccines against STIs are in the final stages of development. A genital herpes vaccine has been shown to protect women who were seronegative for herpes simplex virus (HSV) type 1 and HSV-2 and has entered a pivotal phase 3 trial [6], and a human papillomavirus (HPV) vaccine is in phase 3 trials [7]. A proof-of-concept trial for an HPV-16 vaccine has already shown excellent efficacy [8], which contradicts the view, expressed above, that STI vaccines will have low efficacy, presumably because HPV infection should lead to effective type-specific acquired immunity if it is sufficiently invasive and not carried chronically. In light of these advances, it is worth considering how the theory used to guide the use of childhood vaccines differs from that for STI vaccines.

An important consideration for vaccines is that their protective effect extends beyond the vaccinated individual to others in the population. This effect, called “herd immunity,” can be captured in simple theory de-
scribing the impact of vaccination [9]. This simple theory is inadequate for STIs, which have extreme heterogeneity in the risks of acquiring and transmitting infection. Nonetheless, modest extensions to the simplest models allow some insight into general rules about the impact of vaccines on the epidemiology of typical STIs. Despite many shared characteristics, the epidemiology of STIs does vary, and the characteristics of STI vaccines probably will as well. This variety is well illustrated by what we know of well-advanced vaccine candidates against HSV and HPV infections [8, 10]. Thus, it is important to consider the impact of vaccines with specific profiles in the context of the epidemiology of the particular infections.

HERD IMMUNITY: WHAT IS IT AND WHAT DOES IT ACHIEVE?

Herd immunity is the population-level consequence of acquired immunity among some individuals that can reduce the risk of acquiring infection among susceptible individuals. Individual immunity can be acquired either through a natural infection or through artificial inoculation with a vaccine. An understanding of the reproductive number of an infection is useful in understanding the concept of herd immunity. The basic reproductive number \( R_0 \), which determines the potential for spread of an infection, can be defined as the average number of new infections caused by 1 infected individual in an entirely susceptible population [11]. If acquired immunity is present, then the population is no longer entirely susceptible. The effective reproductive number \( R_e \) is the average number of new infections caused by an infection at time \( t \) and is the product of \( R_0 \) and the fraction of the population that is still susceptible [12]. The higher the proportion of the population that is immune, the lower \( R_e \). This is illustrated in figure 1A and 1B, which show the spread of a new infection in a host population over 2 generations. When \( R_e = 2 \), a geometric increase in infections occurs over time if there are no immune individuals (as in figure 1A); however, if 75% of the population is assumed to be immune (as in figure 1B), then most potential contacts are wasted and the infection fails to grow. Herd immunity has stopped the spread of infection and protects some otherwise-susceptible individuals (i.e., the 25% who are not immune) from being exposed to the risk of infection. This simple insight allows some important estimates to be made. If the number of infections is stable, each new case must be causing 1 more new infection, and we can calculate the endemic prevalence of infection \( y^* \) or the proportion of individuals who have experienced infection \( y^* + z^* \), in a homogeneous population, where \( y^* \) is the proportion infected, and \( z^* \) is the proportion immune. \( R_0 \) is given by \( R_0 = 1 = R_e x^* \), where \( x^* \) is the endemic fraction of susceptible individuals. This equation can be rearranged as \( x^* = 1/R_e \). Since, in the absence of acquired immunity, those who are not susceptible can be assumed to be infected, the endemic prevalence of infection is given by \( y^* = 1 - 1/R_e \). When acquired immunity is present, the prevalence of those who have experienced infection can be calculated as \( y^* + z^* = 1 - 1/R_e \), and the prevalence of infection is dependent on the relative duration of infection and acquired immunity. Then, what vaccination does to this steady-state prevalence can be considered. First, to eliminate infection, \( R_e \) must be reduced and kept to <1. If the infection has been eliminated, natural infection will no longer contribute to the reduction in the fraction of the population that is susceptible; only vaccination will contribute to this reduction. Thus, after elimination, \( x^* = 1 - p \), where \( p \) is the fraction vaccinated. The condition for elimination is \( R_e < 1 \), so that \( R_e = 1 = (1 - p)R_e \), which determines the critical threshold of coverage \( p_c \) with effective vaccination required in order to eliminate infection: thus, \( p_c = 1 - 1/R_e \). The value of the critical vaccination threshold indicates the coverage required for a vaccine to be 100% efficacious (or, if a vaccine is <100% efficacious, the product of the coverage and the efficacy), which is required for elimination of infection, and is illustrated in figure 1C. For high values of \( R_e \), high effective vaccine coverage is required for elimination, which may not be possible with low-efficacy vaccines. This raises the question of what happens to prevalence (or incidence) of infection if the critical vaccination threshold is not reached. Again, our simple relationship between \( R_e \) and \( R_0 \) is relevant. If efficacy \( e \) indicates the all-or-nothing ability of the vaccine to protect against infection, then those successfully immunized are no longer susceptible and can be included in the steady-state equations, as follows: \( R_e = 1 = R_e(1 - y^* + z^* - e p_c) \), where \( p \) is the proportion vaccinated, which can be rearranged as \( y^* + z^* = 1 - (1/R_e) - e p_c \). Therefore, a simple linear decline in prevalence occurs as vaccination coverage increases (figure 1D). The slope of the decline depends on \( R_e \) with a more-rapid decline possible from a lower value for \( R_e \). In a homogeneous population, a lower value for \( R_e \) would be associated with a lower prevalence of infection prior to the introduction of vaccination. For childhood infections, the decline can be slightly faster than a linear decline, if we take into account the increase in the average age of infection as exposure is reduced, as well as the less-frequent contact between older people than between young children [9].

The effect differs for a vaccine that is able to protect, to a certain extent, everyone receiving it. In that case, the measure efficacy represents the reduction in risk of a breakthrough infection given a challenge, where an individual exposed to more challenges will be more likely to be infected [13]. For this “degree”-type protection [14], the probability of transmission from those infected to those who have been vaccinated is reduced, which reduces \( R_e \) in a different manner. In this case, \( y^* + z^* = 1 - [1/(R_e(1 - e p_c))] \), and a nonlinear decline in prevalence occurs as coverage or effectiveness increases (figure 1D).
Figure 1. Effect of herd immunity on the spread of an infection in a homogenous population. A. Schematic illustration of 2 generations of spread of an infection with a basic reproductive number ($R_0$) of 2, when no individuals in the population have immunity. A fraction (an average of one-half) of contacts of infected people (average, 4 contacts/person) leads to new infections and, thereby, a geometric increase in the size of the epidemic. B. Spread of the same infection, with the same number of contacts but with 75% of the population immune. In this case, the effective reproductive number is 0.5, and, despite the possibility of a few new infections, any new epidemic will peter out, because the proportion of immune individuals is beyond the threshold for elimination of an infection with $R_0$. C. Relationship between the critical vaccination threshold and the estimated value for $R_0$ for 3 example infections—measles, rubella, and Haemophilus influenzae type b (Hib). Successful vaccination coverage above the line will eliminate the infection. D. Possibility of reductions in prevalence below the critical vaccination threshold, for $R_0$. Two types of efficacy are illustrated: "take" type, in which the vaccine either does or does not protect an individual, and "degree" type, in which all those vaccinated are protected from a fraction of challenges.
Figure 2.  A–C, Effect of vaccination coverage on steady-state prevalence of a sexually transmitted infection, when, on recovery from infection, individuals move back into the susceptible class. On entry into the population, individuals are either susceptible or receive vaccine with take-type efficacy. The model population was stratified according to sex and 3 classes of sexual activity, defined according to rates of change of sex partners (75 new sex partners per year for the highest activity group, 5 partners/year for the second highest, and 0.2 partner/year for the lowest). Mixing was assumed to be intermediate between random and assortative. The probability of transmission per partnership was assumed to be 0.3 for transmission from men to women and 0.2 for transmission from women to men. The mean duration of infection was assumed to be 1 year. A, Vaccination of both sexes; B, vaccination of all and of the highest activity and 2 highest activity classes; and C, vaccination of women only. D, Endemic prevalence of infection after mass vaccination with a 50%-efficacious vaccine and increasing risk behavior, assuming a basic reproductive number of 3, in a homogeneous population.

To enhance the impact of the partial protection provided by the vaccine, the prevalence of circulating infection needs to be reduced, so that vaccine recipients are exposed less often.

GENERAL INSIGHTS ABOUT HERD IMMUNITY AGAINST STIs

Any vaccination program for protection against STIs will be different for 2 major reasons. First, there is extreme heterogeneity in the risk of acquiring and transmitting the infections. Second, the diseases affect sexually active adults, and severe disease often is restricted to a minority of cases, with the majority of severe consequences affecting women rather than men. These factors will influence the effects of herd immunity and the target populations to be protected by vaccination programs.

Herd immunity and those with relatively low risk of infection. Declines in the prevalence of infection can be greater at lower values of efficacy or coverage than those achieved by similar relative changes at higher values of efficacy or coverage. This can be illustrated by using a mathematical model of the spread of a curable STI in a population with no naturally acquired immunity to infection [15]. The impact on prevalence of infection is shown for different levels of vaccine coverage or efficacy in figure 2A. The implications of this pattern are 2-fold: First, substantial health gains are possible with low-efficacy vaccines; second, the elimination of STIs is extremely difficult, and improved efficacy and coverage are associated with diminishing returns. The pattern is explained by the distribution of infection within the population. Despite the majority of infections being transmitted by those with high levels of risk (i.e,
those with many sex partners), most infections are acquired by those with a low level of risk. The protection provided by a vaccine reduces the number of infections among those with low risk, among whom the reproductive potential is low. However, as the prevalence of infection is reduced, residual infections occur among those with the highest exposure to infection, who also have the greatest potential for infecting others, and these infections are the hardest to control. As patterns of mixing become more assortative, STIs will be more concentrated among those with high risk and more difficult to control.

The distribution of infection and the relative importance of some infectious individuals to the ongoing spread of infection suggests that targeting may be a cost-effective use of an STI vaccine. In the same model, the relative impact of vaccination of all is compared with that of vaccination of the very highest activity group alone and vaccination of the 2 highest activity groups (figure 2B). In this example, the parameters were defined so that a small very high risk group was important but also so that a slightly larger, “second highest activity group” generated >1 new case of infection when infected. If this group is left out, targeting fails to have the same impact as mass vaccination, whereas targeting can be as effective as mass vaccination when the whole “core group” is included. In considering targeting, questioning whether the whole core group can be identified and reached by the vaccination program is important. Experience with health interventions suggests that the identification and vaccination of high-risk groups is difficult to achieve in practice [16].

Herd immunity protecting one sex through vaccination of the other. Vaccination of a single sex against STIs may be appropriate because of the greater risk of disease among women, the opportunities to administer vaccine during family planning or antenatal care, and the potential differences in response to vaccination. The hypothesis that the protection of one sex against a heterosexually transmitted infection also will indirectly protect the other sex is logical and is supported by modeling (figure 2C). “Take”-type protection reduces prevalence almost linearly in the directly protected sex, and is protected sex, whereas the effect of take-type protection is never overwhelmed. For degree-type protection, a simple relationship exists between the efficacy of a vaccine and how much increase in risk behavior among those vaccinated is required for the effect of the vaccine to be overturned. For a given reduction in susceptibility caused by the vaccine, an inverse-fold increase in risk behavior among those vaccinated will cancel the effects of the vaccine. If the increase in risk behavior includes all individuals, rather than just those vaccinated, then a smaller increase in risk behavior will cancel the effects of the vaccine. A take-type protection is less susceptible to increased risk behavior, since those successfully vaccinated can no longer be infected, irrespective of increases in exposure to virus. These effects are illustrated in figure 2D, in which the endemic prevalence of infection after mass vaccination with a 50%-efficacious vaccine and the relationship between prevalence and increasing risk behavior are shown (the model assumes that \( R_0 = 3 \) in a homogeneous population, so that the prevalence of infection in the absence of vaccination would be 66%). With degree-type protection, the influence of vaccination is overturned with a 100% increase in risk behavior: that is, the vaccine reduces the risk by half among everyone, and, therefore, a doubling of risk behavior cancels its effect, whereas the effect of take-type protection is never overwhelmed.

Combining herd immunity with other changes in risk. In the absence of vaccines, interventions to reduce the spread of STIs have attempted to reduce the duration of infectiousness (e.g., rapid identification of cases of bacterial STIs, for antimicrobial treatment), decrease contacts (e.g., through education programs, to reduce numbers of sex partners), or reduce the probability of transmission (e.g., through the use of condoms). These interventions all combine to reduce \( R_0 \). A vaccine with a degree-type protection similarly reduces \( R_0 \) and would combine with the other interventions to reduce incidence nonlinearly. However, a vaccine with take-type protection acts on \( R_0 \) and would have an additive influence. When an STD vaccine is added to other interventions, the combined effect can be additive or better than additive if the interventions fall short of eliminating the infection [18]. From these general insights into the relationship between vaccines and STIs we can start to consider the potential for vaccines against particular infections, especially in the light of trial results from candidate HPV and HSV vaccines.

HPV VACCINE: PROTECTING AGAINST INFECTION, TO PREVENT DISEASE

HPV is associated with both genital warts and cancer, particularly cervical cancer. Genital warts are a widespread problem but, in terms of morbidity and mortality, are dwarfed by cervical cancer, which leads to severe disease and death when left untreated and to discomfort and distress when treated or pre-
Figure 3. Schematic illustration of the relationship between natural history of infection with human papillomavirus (HPV) type 16 in women and cervical cancer. Acute infection becomes chronic in a subset of cases, which eventually can progress to disease or to recovery leading to immunity to reinfection with the same HPV type. Progress to disease is associated with histological changes, which are progressively more severe: cervical intraepithelial neoplasia (CIN) 1, CIN 2, and CIN 3 are identified by screening, leading to removal of affected tissue. These histological changes can regress as well as progress. Vaccination moves individuals from the susceptible to the immune class.
tion, and the answers to these questions will have profound implications for the use of a vaccine. On one hand, a vaccine that could generate cross-immunity against types would be greatly advantageous. As we have seen, low efficacy combined with high coverage can substantially reduce the incidence of infection in a large fraction of those at risk. Thus, cross-immunity would not have to be complete to have a substantial impact on the HPV types not included in the VLPs. However, the potential for cross-immunity raises the question of whether cross-immunity from natural infection currently limits the presence of some oncogenic types within a population [24]. At worst, a vaccine could increase the incidence of disease by releasing more pathogenic types from competition. More likely, the effects of a vaccine could be undermined by the replacement of types 16 and 18 with an organism of similar oncogenic potential, in the population [25]. For this to happen, a number of conditions have to be met. First, natural infection with HPV has to generate cross-immunity. This has not been detected and cannot be strong, given the observation of cases of reinfection with types new to an individual. However, cross-immunity would not have to be strong and, given the difficulty of detecting weak cross-immunity, is still a possibility. Second, the prevalence of an HPV type in a population has to be limited by this cross-immunity [26]. The low prevalence of types suggests that they are limited by their lack of opportunities to spread by means of sexual contacts, but they could be limited by cross-immunity among those with high numbers of sex partners, which would prevent their better establishment throughout the population. Third, the vaccine should not cause cross-immunity. Given the restricted number of antigens in the vaccine constructs, they may be less likely to generate cross-immunity; however, the vaccines are likely to be more immunogenic than natural infection, given systemic exposure and the use of adjuvants, and therefore may generate cross-immunity. Overall, the ecological impact of an HPV vaccine seems unlikely to undermine the benefits of the program but is something that will require monitoring.

**GENITAL HERPES VACCINE: PARTIAL EFFICACY CAN BE BENEFICIAL**

In contrast to the high efficacy found for an HPV vaccine, recent trials have demonstrated a more limited efficacy for a candidate HSV vaccine [10]. In 2 trials with HSV-discordant couples, a candidate vaccine prevented genital herpes disease, with 73% efficacy, and potentially reduced susceptibility to infection (with 42% efficacy, but the results did not achieve significance). This success was limited to women who were seronegative for both HSV-1 and HSV-2 at vaccination. The trials left some unanswered questions, the foremost of which was what happened to episodes of virus shedding in those who became infected but did not suffer disease? The question is key if we assume (as we must) that transmission to others is a function of virus shedding [27]. A further conundrum posed by the trials was the role of HSV-1, the presence of which prevented the demonstration of efficacy. However, in the placebo arms of the second trial (all subjects recruited to the first trial were HSV-1 negative), those with HSV-1 infection were extremely unlikely to acquire HSV-2, which is not reflected in populations in which infection with the 2 virus types is correlated [28, 29].

As suggested from general insights into STD vaccines, the utility of a vaccine with the observed profile is equivocal. On one hand, the vaccine will have direct benefits if it protects against infection, but the extent to which the spread of infection is reduced depends on reductions in transmissibility. To have a major indirect effect, a vaccine that reduces transmissibility has to reduce circulating virus to a point that is close to elimination. To explore the potential epidemiological impact of the candidate vaccine, a mathematical model that represented the natural history and transmission dynamics of HSV-2 in the US population was developed, and changes in susceptibility to infection, disease, and virus shedding were explored [30]. If the vaccine could reduce transmissibility through a reduction in virus shedding, then it could play a major role in controlling HSV-2 infection [30]. These findings can be explained by the relatively widespread risk of acquiring and transmitting HSV-2 infection, which has a low probability of transmission and a long duration of infectiousness. Those most likely to spread the infection further are those with a handful of sex partners but who have many sex acts with each partner. This results in a modest ability of each infection to cause further cases and a system that is readily controlled.

The results of a model similar to that published previously [30] but including an age structure found a similar impact on the incidence of HSV-2 infection among both men and women, with indirect benefits for the unvaccinated sex (i.e., men) when reasonable coverage was achieved (figure 4A). These results were generated under the assumption that only women can be vaccinated and that only 40% of women are HSV-1 negative. By targeting vaccination to those age groups with a lower prevalence of HSV-1 infection, greater effects would be possible. The potential of the vaccine has led to a pivotal phase 3 trial with mass vaccination of HSV-1– and HSV-2–negative young women. However, some key questions remain, including those about the role of HSV-1. For example, the role of HSV-1 in the spread of HSV-2 in the absence of vaccination is important in influencing the impact of the vaccine. Two alternatives were compared in simulations of the impact of the vaccine (figure 4B). In the first, prior HSV-1 infection was assumed not to influence susceptibility to HSV-2 but only to reduce the likelihood of initial disease, as has been observed previously [31]. This was compared with a situation in which prior HSV-1
infection was assumed to reduce susceptibility to HSV-2, as was observed in the placebo arm of the genital herpes vaccine trial [10]. In the second alternative, reductions in incidence that were caused by the vaccine were almost doubled. If the epidemiology of HSV-2 infection is dominated by those who are not infected with HSV-1, then a vaccine that works in this group has a greater effect than would be the case if HSV-1–infected individuals were equally involved in the epidemiology of HSV-2 infection.

**HIV VACCINES: A MUCH-NEEDED PANACEA**

The HPV and HSV vaccines discussed raise many challenges for public health researchers and policy makers, but such challenges are to be welcomed, since they reflect genuine progress in developing vaccines against these STIs. The catastrophic incidence of HIV infection in developing countries [32] cries out for an effective vaccine, but little good news is available [33]. Nonetheless, in considering the potential impact of hypothetical HIV vaccines, we can explore the characteristics that would be required of them in particular epidemiological contexts. In earlier work, the impact of low-efficacy vaccines with a long duration of protection was considered [18, 34, 35]. Another type of vaccine failure to consider is the loss of protection over time. This can be as important as the short-term efficacy of the vaccine [36], as illustrated by the results of a model of HIV transmission, structured by age, sex, and sexual activity, after administration of a vaccine protecting against infection with a 50% take-type efficacy (figure 5). Although protection of 5 or 10 years does have an impact, the impact is far greater if the protection conferred by the vaccine is lifelong. However, another model did not find such an important role for the duration of protection [37]. In comparing these results from different models, the assumptions regarding the duration of risk behavior over the lifetime of the vaccine recipient were found to be crucial. If the duration of protection is commensurate with the duration of risk behavior, then loss of protection is not particularly important; however, if risk behavior is assumed to continue over a wide range of ages, as was assumed in the results illustrated, then loss of protection can be extremely important.

**CONCLUSION**

Preventive vaccines offer an ideal tool for the control of infectious disease. Unlike treatments, they work in advance of any disease and associated morbidity and do not rely on the identification of cases, since they can be universally administered. Unlike other preventive interventions, they do not rely
on changes in patterns of behavior. Despite these advantages, the development of STI vaccines has been slow. Compared with the testing of treatments, for which those who already have the disease can be recruited for trials, the testing of a vaccine requires the recruitment of as-yet-uninfected individuals who may or may not acquire infection, thereby increasing the scale and cost of vaccine trials. This is exacerbated if the infection is less common, as is the case with many of the bacterial STIs. Furthermore, because vaccines are used with healthy individuals to prevent disease, extremely high levels of safety are required, compared with that required for treatments, since the toxicity and harm caused by drugs often can be outweighed by the severe consequences of disease. Perhaps one of the main difficulties in developing and using vaccines is that those using and paying for them have to be motivated by the risk of an infection and disease that they have not suffered; treatment, however, is motivated by current suffering. Such hurdles perhaps explain the slow progress in development of vaccines even when a pandemic of an infection like HIV infection is perceived to be an international catastrophe.

In addition to helping design intervention strategies once vaccines become available, mathematical models of the spread of infections and their control by vaccination can play a role in vaccine development. Clearly, the models themselves cannot determine the biological properties and efficacy of vaccines, but they can explore what properties would be useful and can assist in the making of decisions about development. Furthermore, by exploring the public health role of the vaccines, the case for their development and use can be made in terms of health economics, thereby stimulating efforts at development. One key role of the models is to identify problems and questions about a vaccine and its use well in advance, so that plans can be made to investigate and overcome barriers to the successful development of vaccination programs. Such preparatory modeling of the impact of vaccines becomes particularly fruitful once candidate vaccines with defined properties are available, as has been the case for the HSV and HPV vaccines. In these cases, models of the particular infections have provided insight into the impact of behavioral heterogeneity on the effectiveness of vaccination and the impact of vaccines used for restricted sections of the population, such as women. When insights are based on understanding, the implications of changing model assumptions can be inferred, but insights based on more-detailed quantitative analysis require the further development of models and an exploration of the sensitivity of model results to assumptions and parameter values.

Acknowledgments

I thank John Williams, Ruanne Barnabus, John Stover, Steven Seitz, Neil Ferguson, and Roy Anderson for their helpful discussions.

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