

Modeling the Impact of AIDS Vaccines: A Review of the Literature

IAVI Public Policy Department

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IAVI's Policy Research Working Paper series disseminates important new research findings in order to promote the exchange of information and ideas that facilitate the effective development and global distribution of vaccines to prevent HIV infection.

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Acronyms and Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
HIV	Human immunodeficiency virus
IAVI	International AIDS Vaccine Initiative
IDU	Intravenous drug users
LAHV	Live-attenuated HIV vaccines
QALY	Quality-adjusted life year
STI	Sexually transmitted infections

Preface

Mathematical modeling and computer simulation of vaccination and other infectious disease control efforts have become powerful tools for health policy evaluation, policy dialogue, and advocacy. A number of such mathematical and computer simulation models have been developed specifically to estimate the impact of a vaccine on the AIDS epidemic. In late 2004 and early 2005, IAVI commissioned two inter-related literature reviews synthesizing and analyzing the results of these epidemiological models of the impact of AIDS vaccines in developing countries. One review focuses on modeling methodology and the other on estimates of vaccine impact. Taken together, the two papers provide an overview of modeling work done to date, the critical issues addressed, and the results generated. The two reviews are also helpful in pointing to areas where additional research and policy analysis are needed.

The vaccine models included in these reviews have considered different types of vaccine action (complete versus partial preventative protection), a range of vaccine characteristics (e.g., varying levels of vaccine efficacy with regard to preventing infection, reducing infectiousness and delaying progression to the development of AIDS, duration of vaccine-induced protection, etc.), the possibility of behavioral reversals (disinhibition) due to perceived vaccine-related protection, application in different epidemic settings, and various coverage levels and delivery/targeting strategies. Many of these modeling investigations recognize that the first generation of AIDS vaccines is likely not to have the ideal vaccine characteristics of high preventative efficacy and lifelong protection, and so they specifically consider future vaccines with only low to moderate efficacy and a limited duration of protection.

This review by John Stover and Katherine Willson synthesizes the results of ten published papers from 1990-2005 that use models to estimate the potential effects of vaccines on HIV incidence and/or prevalence. The paper reviews key topics addressed by modeling efforts, including low efficacy vaccines, duration and type of protection, behavioral reversals, and epidemic type. It summarizes the conclusions of these modeling efforts and compares results by combining two very important characteristics of any vaccination program, preventative efficacy and coverage, into a single approximate measure of “effective coverage.” Using this measure, Stover and Willson find that many of the earlier modeling efforts show similar patterns of impact, with reductions in HIV prevalence of 40-70% for modest levels of effective coverage and up to 80-90% reductions for high levels of effective coverage, 20 to 25 years after the introduction of a vaccine. Their paper concludes that the results from the models examined generally suggest that even a vaccine with low levels of effective coverage can provide significant benefits.

The companion paper by Jane Rowley (IAVI Policy Research Working Paper #6, October 2005) describes and compares the methodologies used to model the long-term impact of a preventive AIDS vaccine, focusing on five recent models. The paper discusses the differences among the models and the topics they have explored, and some of their limitations. It points to the substantial positive effects of a vaccine on HIV prevalence in a wide range of settings, as shown by most of the modeling exercises, but cautions that the extent of this will depend on such key factors as where and how the vaccine is used, its

specific characteristics, and how people respond to it in terms of their sexual and other HIV prevention behaviors.

These reviews portray a solid foundation of modeling investigations upon which IAVI and others can build to carry out further analysis of the epidemiological impact of an AIDS vaccine. As a first step in this direction, IAVI has asked the Futures Group to extrapolate from the observed relationship between effective coverage and lowered HIV incidence and prevalence, in order to estimate the potential global impact of an AIDS vaccine. Additional phases of IAVI's work may involve designing new models incorporating the latest thinking on likely types of vaccine action and new long-run projections for the global HIV epidemic that can then be used to carry out additional impact simulations at global level and in selected developing countries, in collaboration with national researchers and policymakers.

I. Introduction

A large body of literature exists on the search for an AIDS vaccine. Over the past decade, a number of researchers have looked at the potential impact of a vaccine on the AIDS epidemic. Of particular interest have been questions about the value of vaccines with moderate to low efficacy and short duration. Other questions involve the most effective strategies for using vaccines once available and the ability of mass vaccination campaigns to eradicate the epidemic.

These questions continue to be relevant today, even though the formidable scientific challenges mean that development of a useful vaccine is still likely to be a number of years away. Donors and funding agencies need to make decisions about how much of their resources to allocate to vaccine research and testing. In addition, research today on issues of vaccination strategy and coverage levels can help to prepare for crucial decisions about implementation when vaccines do become available.

This literature review is part of a larger effort by the International AIDS Vaccine Initiative (IAVI), with support from the Futures Group, to estimate the potential benefits of vaccines of different types in confronting the AIDS epidemic. This review focuses on published research describing the use of computer models to estimate the effects of vaccines in different epidemiological settings. It is limited to articles that present estimates of the impact of vaccination programs on HIV prevalence or incidence. A list of all relevant articles is provided in the appendix.

This activity used PubMed to search for articles with the keywords: AIDS, HIV, vaccine, impact, models. The search included published journal articles, reports of research organizations and abstracts of presentations at the major AIDS conferences. The search found a large number of articles that discuss the impact of AIDS vaccines, but only a subset presented analytical results of the impact on prevalence or incidence.

II. Findings

A number of researchers have investigated the potential impacts of AIDS vaccines. Some research teams have published a significant body of research using different models to investigate various issues over the past 15 years. Roy Anderson, Geoff Garnett and colleagues at Oxford University and Imperial College and Sally Blower at the University of California at Los Angeles and her colleagues are particularly notable for the volume and sophistication of their work.

A. *General conclusions*

All the articles included here address the impact of a vaccine on an AIDS epidemic. However, each uses different techniques in various epidemic settings to investigate different sets of specific issues. Among the key topics and conclusions are:

- *Low efficacy vaccines.* Since the first vaccines are likely to be much less than 100% effective, most studies included here examine the impact of vaccines with

different levels of efficacy. They generally conclude that while higher levels of efficacy are better, even low efficacy vaccines (30-50%) can significantly reduce the number of new HIV infections.

- ***Duration of protection.*** Many of the articles examine the effects of different periods of protection varying from very short (five years) to lifetime. For durations under ten years, the waning protection is as important as the effective coverage in determining the overall impact. Analyses with duration of protection of ten years or longer find similar levels of impact.
- ***Type of protection or type of action.*** Several articles, particularly McLean and Blower 1993, Garnett *et al.* 2001, Seitz 2001, Stover *et al.* 2002, Blower *et al.* 2002, and Nagelkerke and De Vlas 2003 explore the effects of vaccines with “take” type protection (where 50% efficacy means that 50% of those vaccinated are completely protected while the other 50% receive no protection) versus those with “degree” type protection (where 50% efficacy means that the probability of infection per contact is reduced by 50% for everyone vaccinated). The type of protection seems to make little difference to the overall impact in the general population or when the average risk is low. But in populations at very high risk, “degree” protection produces much less impact than “take” protection since even 50% reductions in risk may still result in high average risk in these populations.
- ***Eradication.*** McLean and Blower 1993, Blower and McLean 1994, Anderson *et al.* 1995 and Blower *et al.* 2005 use both analytic techniques and simulation models to examine the likelihood that an AIDS vaccine could eventually eradicate an epidemic. They generally conclude that eradication through vaccination programs alone will be challenging without very effective vaccines or very low levels of risk and high vaccine coverage.
- ***Behavior reversals.*** The availability of a prophylactic vaccine might lead to riskier behavior. Those who are vaccinated might believe that they are effectively protected and those who are not vaccinated may believe that most others are and that, therefore, their personal risk is low. In these situations, it is possible that people would return to the riskier behavior patterns of the past, before the threat of AIDS caused them to change their behavior. A number of papers address this issue, including Blower and McLean 1994, Garnett *et al.* 2001, Seitz 2001, Stover *et al.* 2002, Blower *et al.* 2002, Bogard and Kuntz 2002, Gray *et al.* 2003, Blower *et al.* 2003, Nagelkerke and De Vlas 2003, Smith and Blower 2004, and Anderson and Hanson 2005. They generally conclude that behavioral reversals could mitigate the gains from vaccination or even produce perverse results where the use of the vaccine results in more infections. The conclusion is that any program to implement vaccination should be accompanied by strong general prevention efforts.
- ***Disease-modifying vaccines.*** Anderson *et al.* 1991, Edwards *et al.* 1998, Barth-Jones and Longini 2002, Blower *et al.* 2003, Smith and Blower 2004, Davenport *et al.* 2004 and Anderson and Hanson 2005 also investigate the impact of vaccines that do not prevent infection but do affect viral load and disease progression. They find that while such vaccines could prevent many deaths they could result either in

more new infections if they only lengthen the period of infectiousness or they could result in fewer new infections if they also significantly reduce viral load and, thus, the level of infectiousness.

- **ART.** Blower *et al.* 2003 and Gray *et al.* 2003 examine the individual and joint effects of vaccines and widespread treatment with antiretroviral therapy (ART). They conclude that widespread ART that reduces infectiousness combined with a low efficacy vaccine could reduce new infections to very low levels as long as behavioral reversals do not overwhelm the reductions in the risk of transmission per sexual act.
- **Epidemic type.** A variety of different epidemic types are examined. McLean and Blower 1993, Blower and McLean 1994, Owens *et al.* 1998 and Blower *et al.* 2002 apply their models to the epidemic among gay men. Most of the work of Anderson and Garnett as well as Porco and Blower 1998, Seitz 2001, Stover *et al.* 2002, Nagelkerke and De Vlas 2003, Gray *et al.* 2003 and Blower *et al.* 2005 looks at epidemics among the general adult population. Bogard and Kuntz 2003 analyzes an IDU epidemic and Barth-Jones and Longini 2002 analyzes an epidemic with sexual and IDU transmission.
- **Epidemic location.** Among the locations examined are San Francisco (Blower and McLean 1994, Edwards *et al.* 1998, Owens *et al.* 1998 and Blower *et al.* 2002), sub-Saharan Africa (most of the work of Anderson and Garnett), Zimbabwe (Blower *et al.* 2001, Garnett *et al.* 2001, Stover *et al.* 2002), Uganda (Gray *et al.* 2003 for Rakai, Seitz 2001 and Stover *et al.* 2002 for Kampala), South Africa (Blower *et al.* 2005), India (Nagelkerke and DeVlas 2003), Asia (Barth-Jones and Longini 2002) and Thailand (Seitz 2001 looks at Thailand and Bogard and Kuntz 2003 focuses on Bangkok).
- **Implementation strategies.** Anderson *et al.* 1995, Garnett *et al.* 2001, Seitz 2001, Blower *et al.* 2002, Stover *et al.* 2002, Barth-Jones and Longini 2002 and Nagelkerke and De Vlas 2003 look at the impact of various implementation approaches (cohort vaccination, mass vaccination, and cohort vaccination after an initial wave of mass vaccination) and target populations (highest risk populations, teenagers and easy-to-reach populations such as women attending antenatal clinics). In general, targeting to high risk groups is found to be more cost-effective but has less overall impact than general population strategies. This may suggest that vaccination should be available to everyone but that public subsidies might be targeted to the highest risk groups.
- **Conduct of trials.** McLean and Blower 1993, Koopman and Little 1995, McLean and Blower 1995 and Longini *et al.* 2001 demonstrate the importance of understanding the type of protection or vaccine action and offer advice on how trials should be conducted to collect the information necessary to understand the mode of action.
- **Subtypes.** Porco and Blower 2000 and Blower *et al.* 2005 examine epidemics with different HIV subtypes circulating and show how the differential effectiveness of a vaccine in protecting against each type affects the overall impact.

- *LAHV*. Blower *et al.* 2001 examine live attenuated HIV vaccines (LAHV) that carry some risk of producing infection as a result of vaccination. They show the conditions under which LAHV produce positive outcomes and the conditions under which the net effect could be more new infections.

B. Impact on prevalence or incidence

As explained earlier, this review is particularly focused on the potential impact of vaccines on adult HIV prevalence and incidence. Several of the papers reviewed here provide quantitative results for specific combinations of vaccine characteristics. The key characteristics are generally population coverage and vaccine efficacy. These can be multiplied together to produce an approximate indicator of effective coverage. The impact of effective coverage on prevalence or incidence is summarized below for eight of the papers providing this information.

1. McLean, A.R. & Blower, S.M. (1993). Imperfect vaccines and herd immunity to HIV. *Proceedings of the Royal Society of London, Series B*, 253, 9-13.

Analytic and modeling techniques are used to investigate the effect of different levels of efficacy and coverage of a prophylactic vaccine on herd immunity and the possibility of eradicating the epidemic. The results show that a vaccine with 100% efficacy and 10 years average duration will be equal in impact to one with 30% and lifelong protection.

Table 1. Reduction in HIV prevalence in a high risk population by 100th year of a vaccination program with a vaccine that has lifetime protection, compared to a base case of no vaccination

Coverage	Effectiveness	Effective coverage	Reduction in HIV prevalence in general population by year 100
20%	80%	16%	44%
40%	80%	32%	69%
60%	80%	48%	81%
80%	80%	64%	91%

Note: Points are read from Figure 4a in the paper for the vaccine with take protection. (The results for degree protection show less impact as a result of the very high base prevalence, 80%)

2. Anderson, R.M., Swinton J., & Garnett G.P. (1995). Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection. *Proc R Soc Lond B Biol Sci B*, 261, 147-151.

The first part of the paper analyzes the characteristics of a vaccine that can eradicate HIV transmission using a system of two levels of sexual activity with a variety of assumptions about mixing patterns between the two activity groups, and vaccine efficacy and duration of protection. It concludes that repeated blanket vaccination is the most effective approach (compared to cohort-based or targeted vaccination strategies) but that high levels of coverage are required to eradicate transmission in most epidemics.

The second part of the paper uses a more complex model to analyze the reductions in incidence that can be achieved with vaccines of low efficacy. The model is age-structured and includes distributions of incubation and infectious periods, mother-to-child transmission, and different types of sexual partnerships across age groups and activity class. The setting for the analysis is a generalized epidemic similar to southern Africa where prevalence among pregnant women reaches 30% after 10 years and then declines naturally to about 20% by the 20th year of the epidemic. Vaccination programs are assumed to start in year 10 of the epidemic. The impact of the vaccination programs stabilizes by year 25. The results are shown in Table 2.

Table 2. Reduction in HIV prevalence in the general population by the 25th year of a vaccination program with a vaccine that has an average protection of ten years, compared to a base case of no vaccination

Coverage	Effectiveness	Effective coverage	Reduction in HIV prevalence in general population by year 25
90% of highest activity group comprising 5% of the sexually active population	50%	2%	14%
90% of two highest activity groups comprising 40% of the sexually active population	50%	18%	61%
90% of sexually active population	50%	45%	78%
60% of highest activity group comprising 5% of the sexually active population	20%	1%	6%

Note: Effective coverage is calculated as the percentage of the population vaccinated multiplied by the effectiveness of the vaccine. Points read from figures 3(b) and 3(c) in paper.

The authors conclude “... that even low efficacy vaccines, that only provide protection for a few years, can save many lives if significant coverage is maintained over many years.”

- Anderson, R.M. & Garnett, G.P. (1996). Low-efficacy HIV vaccines: potential for community-based intervention programs, *Lancet*, 348, 1010-1013.

The paper uses a complex model of transmission dynamics to investigate the impact of low efficacy vaccines in a typical urban epidemic in sub-Saharan Africa. The model considers five vaccine characteristics: apparent efficacy, duration of protection, failure rate, reduction in infectiousness of vaccinated individuals and the change in the length of the incubation period as a result of vaccination. The authors demonstrate that eradication of the epidemic is unlikely with low-efficacy vaccines and that the duration of protection is at least as important as the efficacy. Unless vaccine duration can be extended to at least 10 years, eradication is unlikely.

Although low-efficacy vaccines may not be suitable to eradicate the epidemic they may still have value. The paper uses a model similar to the one in Anderson 1995 to investigate the impact of a low-efficacy vaccine. The model is age-stratified with multiple classes of sexual activity. It is applied to a typical epidemic in sub-Saharan Africa. This model is used to

examine the reduction in the endemic level of HIV prevalence caused by different levels of effective coverage achieved through cohort vaccination. The results for a vaccine with lifetime protection are shown in Table 3.

Table 3. Reduction in the endemic level of HIV prevalence in the general population achieved by a cohort vaccination program with a vaccine with lifetime protection compared to a base case of no vaccination

Effective cohort coverage	Reduction in HIV prevalence in general population by year 25
11%	30%
20%	44%
25%	54%
38%	70%
40%	74%
50%	81%
60%	89%
75%	96%

Note: Points read from figure 2 in paper.

The authors conclude that low-efficacy vaccines can provide a substantial benefit in generalized epidemics.

The authors also investigate the effects of vaccination programs in the presence of other prevention interventions and conclude that at all but the very highest levels of vaccination coverage the effects are likely to be additive, meaning that the impact of vaccination in reducing prevalence will be the same regardless of whether or not other prevention interventions take place at the same time.

4. Owens D.K., Edwards, D.M., & Shachter, R.D. (1998). Population effects of preventive and therapeutic HIV vaccines in early- and late-state epidemics. *AIDS*, 1998, 1057-1066.

The authors use a single risk group model of the epidemic among gay men in San Francisco to examine the effects of prophylactic and therapeutic vaccines. They examine effects when the vaccine is implemented early or late in the epidemic. The results for the prophylactic vaccine are shown in Table 4.

The authors conclude that therapeutic vaccines can produce a significant benefit in terms of years of life saved but that this effect depends heavily on whether the vaccine reduces infectiousness or not. Without a reduction in infectiousness, therapeutic vaccines would likely lead to more infections but fewer deaths. A prophylactic vaccine will have the most impact if implemented early in an epidemic but will still have a substantial impact if implemented in a mature epidemic.

Table 4. Reduction in HIV prevalence after 20 years in the gay community in San Francisco with a vaccine providing 20 years of protection

Coverage	Effectiveness	Effective coverage	Reduction in HIV prevalence in general population by year 25
75%, Vaccine implemented early in epidemic	75%	56%	65%
75%, Vaccine implemented late in epidemic	75%	56%	46%

Note: Points read from Figure 2(b) in the paper.

- Garnett, G.P. (1998). The influence of behavioral heterogeneity on the population level impact of potential prophylactic HIV-1 vaccines. *Journal of the Royal Scientific Society Series A*, 161, 209-225.

This paper elaborates on Anderson 1996 by providing additional detail on the results of the models and testing the impact of vaccines under many different circumstances including high risk populations with various rates of AIDS associated mortality and exit from high risk behavior categories. The effects of heterogeneity on sexual activity are explored and vaccine effects are compared to and combined with other prevention interventions.

- Blower, S.M., Koelle, K., & Mills, J. (2002). Health policy modeling: epidemic control, HIV vaccines and risky behavior, in *Quantitative Evaluation of HIV Prevention Programs*. Eds Kaplan and Brookmeyer. Yale University Press. 260-289.

The authors use a detailed model of vaccination response to investigate the effects of a number of vaccine characteristics on impact. They define the term “take” to be the proportion of individuals receiving a vaccine who have some level of protection and the term “degree” to be the amount of protection in terms of reduction in the probability of infection after exposure in individuals in whom the vaccine “takes.” Effective vaccination is a combination of coverage, take and degree. The paper explores the effects of simple prophylactic vaccines as well as those that not only protect against infection but also change infectiousness and duration from infection to death. It also looks at situations in which more than one type of HIV is circulating in the population and where the degree of protection can vary by subtype.

The model is used to explore the impact of various levels of coverage and efficacy on incidence of HIV in the gay community in San Francisco. It includes considerations of vaccine programs that induce reductions or increases in risky behavior. The key results are shown in Table 5.

Table 5. Reduction in HIV incidence after 25 years in the gay community in San Francisco with and without behavior change as a result of mass vaccination with a vaccine providing 20 years of protection

Coverage	Effectiveness	Effective coverage	Reduction in HIV prevalence in the gay community by year 25
With no behavior change			
90%	80%	72%	80%
90%	50%	45%	55%
50%	80%	40%	50%
50%	50%	25%	36%
With 50% reduction in risky behavior as a result of the vaccination campaign			
90%	80%	72%	94%
90%	50%	45%	86%
50%	80%	40%	85%
50%	50%	25%	80%
With 50% increase in risky behavior as a result of the vaccination campaign			
90%	50% take	45%	20%
90%	50% degree	45%	7%
50%	50% take	25%	-15%
50%	50% degree	25%	-25%

Note: Effective coverage is calculated as the percentage of the population vaccinated multiplied by the effectiveness of the vaccine. Points read from figures 13.3(a) and 13.3(b) in paper.

A vaccination program that also results in reductions in risky behavior is obviously more effective than one that does not. In this case even 50% coverage with 50% effectiveness results in a substantial reduction in incidence. In the opposite case where the vaccination program leads to a 50% increase in risky behavior the effect of the vaccine on the epidemic is drastically reduced. In the case of low coverage it results in higher incidence than the base case. The vaccine that provides take-type protection (50% of those vaccinated are completely protected while the other 50% receive no protection) produces greater impact than one with degree protection (all those vaccinated are protected in 50% of their exposures).

The authors conclude that even low efficacy vaccines at low coverage levels can have an important impact if risky behavior does not increase as a result of the vaccination program. They show the importance of combining effective prevention programs with vaccination efforts.

7. Bogard, E. & Kuntz, K.M. (2002). The impact of a partially effective HIV vaccine on a population of intravenous drug users in Bangkok, Thailand: a dynamic model. *J Acquir Immune Defic Syndr*, 29, 132-141.

This paper focuses on the effects of an HIV vaccine applied to the high prevalence setting of intravenous drug users (IDU) in Bangkok. The model includes both low and high risk IDU and allows for changing risk behavior as a result of vaccination. It uses data from IDU in Bangkok where possible, supplemented with data on IDU epidemics in the US as necessary. The model estimates endemic prevalence in this population at about 50%. The main analysis assumes that 50% of the eligible population is vaccinated each year with a vaccine that completely protects 75% of those vaccinated for an average of 10 years. The base case assumes that 5% of low risk IDU switch to high risk behavior annually. The results are shown in Table 6.

Table 6. Reduction in HIV prevalence after 40 years among IDU in Bangkok as a result of cohort vaccination with a vaccine providing 10 years of protection

Coverage by year 40	Effectiveness	Effective coverage	Reduction in HIV prevalence among IDU by year 40
58%	75%	44%	26%
58%	30%	17%	12%
50%	90%	52%	30%

Note: Coverage is 50% of those eligible each year. After 40 years this results in 58% of IDU being vaccinated.

In this population vaccination has only about one-third the impact as found in other studies of generalized epidemics. Even with a 100% effective vaccine, prevalence is only reduced by 34% because of the inflow of new susceptibles into the population each year, the very high risk of transmission without protection and the waning effect of protection. Increasing the duration of protection to 50 years instead of 10 years on average triples the impact, making it similar to the results found in other studies for generalized epidemics.

The results are not very sensitive to assumptions about changing risk behavior when vaccine efficacy is assumed to be 75% but are more sensitive with lower levels of efficacy.

The authors conclude that a vaccine with 75% efficacy can have a significant impact in an IDU population and even a low efficacy vaccine can have important benefits. However, the impact of the low efficacy vaccine is dependent on assumptions about behavior change while the impact of the high efficacy vaccine is not.

8. Stover, J., Garnett, G.P., Seitz, S., & Forsythe, S. (2002). *The Epidemiological Impact of an HIV/AIDS Vaccine in Developing Countries*, World Bank: Washington, DC.

This study uses two different models applied to three different epidemic settings to examine the impact of vaccines with various characteristics on HIV incidence. The Imperial College Model disaggregates the population by age, sex and four classes of sexual activity. The iwgAIDS model includes a large number of population characteristics that affect the transmission of HIV (including age, sex, marital status, urban/rural residence, circumcision, prevalence of sexually transmitted infections, condom use, rates of partner change, and levels of concurrency). Characteristics vary continuously by age rather than being confined to discrete categories, as with most other models.

The Imperial College model is applied to rural Zimbabwe, while the iwgAIDS model is applied to Kampala, Uganda and Thailand. Both models are used to investigate the same vaccination programs. The base case examines the impact of a vaccine with 50% efficacy and 10 years duration of protection with 65% coverage after 5 years. Alternatives to this base case examine the effects of variations in the type of effect (take or degree), efficacy (50%, 75%, 90%), duration of protection (5 years, 10 years and lifetime), implementation strategy (targeting teenagers, high risk populations or women; cohort, cohort plus catch-up or blanket coverage), and behavioral responses (no behavioral reversals, reversals among those vaccinated, reversals among all adults). The results are shown in Table 7.

Table 7. Reduction in HIV incidence after 15 years among all adults with a vaccine providing ten years of protection

Coverage by year 5	Effectiveness	Effective coverage	Reduction in HIV incidence by year 15	Model	Setting
65%	50%	33%	24%	Imperial College	Zimbabwe
65%	50%	33%	59%	iwgAIDS	Kampala
65%	50%	33%	62%	iwgAIDS	Thailand
65%	75%	49%	41%	Imperial College	Zimbabwe
65%	75%	49%	79%	iwgAIDS	Kampala
65%	75%	49%	82%	iwgAIDS	Thailand
65%	95%	62%	62%	Imperial College	Zimbabwe
65%	95%	62%	91%	iwgAIDS	Kampala
65%	95%	62%	95%	iwgAIDS	Thailand

The iwgAIDS model applied to Kampala and Thailand shows greater impact than the Imperial College Model applied to Zimbabwe. Incidence in the base case of no vaccination is three times higher in Zimbabwe than in Kampala and 800 times higher than in Thailand, so the susceptible population in Zimbabwe is exposed to much higher risk and therefore, infection is more likely when protection wanes or is incomplete. Perhaps a more important reason for the difference lies in the structure of the models. In the iwgAIDS model risk is highest during adolescence after the initiation of sexual activity and before marriage and then drops dramatically for most of the population in the older ages. This relatively short period of high risk is more easily protected by vaccines with partial effectiveness or short duration. In the Imperial College model individuals stay in their assigned risk category for life. Although the risk profile of each category changes with age the average risk does not vary as much by age as it does in the iwgAIDS model.

The study also examines the effects of different durations of protection, targeting strategies and behavioral responses and compares the effectiveness and cost-effectiveness of vaccination with other prevention interventions. The authors conclude that even low efficacy vaccines of less than lifetime duration can have an important impact on the epidemic as long as behavioral reversal is mitigated with strong prevention programs.

9. Barth-Jones, D.C. & Longini Jr., I.M. (2002). Determining Optimal Vaccination Policy for HIV Vaccines: A Dynamic Simulation Model for the Evaluation of Vaccination Policy. *Proceedings of the International Conference on Health Sciences Simulation 2002* in Eds. Anderson JG, Katzper, 2002 Western Multiconference, January 27-31, 2002. San Antonio, Texas.

This study models an Asian epidemic where sexual transmission and IDU transmission of HIV interact. The model explicitly includes different levels of sexual activity and this detail is used by the authors to examine the effects of targeting vaccination to different population segments, particularly when vaccine supplies are limited. The results of an application for a typical Asian epidemic are shown in Table 8. This simulation uses a

vaccine that reduces susceptibility by 25%, infectiousness by 75% and disease progression by 75%.

Table 8. Reduction in HIV prevalence after 30 years among all adults in a population with both sexual and IDU transmission

Coverage	Effectiveness	Effective coverage	Reduction in HIV prevalence by year 30
75%	81%	60%	77%

Note: Points read from Figures 2 and 3 in the paper.

10. Gray, R.H., Xianbin L., Wawer, M.J., Gange, S.J., Serwadda, D., Sewankambo, N.K., Moore, R., Wabwire-Mangen, F., Lutalo, T., & Quinn, T.C. (2003). Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. *AIDS*, 17, 1941-1951.

This study analyzes the effects of ART and vaccination on HIV transmission using data from a long-term cohort study in Rakai, Uganda. Data on sexual behavior and the risk of transmission per sexual contact were derived from research conducted from 1994 to 1998 in this rural district of Uganda. The model uses stochastic techniques to simulate the number of the sexual contacts and the number of new infections that result and includes estimates of the viral load of HIV-positive individuals. The model is used to investigate the effects of vaccines with different levels of efficacy (25%, 50%, 75%) and different levels of coverage (25%, 50%, 75%, 100%). The vaccine is assumed to provide lifetime protection. The model is also used to investigate the combined effects of vaccination and expanded ART treatment. The results are shown in Tables 9a and 9b.

Table 9a. Reduction in HIV prevalence after 20 years among the adult population in Rakai, Uganda as a result of mass vaccination with a vaccine providing lifetime protection.

Coverage	Effectiveness	Effective coverage	Reduction in HIV prevalence by year 20	
			No ART	75% ART coverage
25%	50%	13%	38%	56%
50%	50%	25%	63%	72%
75%	50%	38%	81%	84%
100%	50%	50%	88%	86%

Note: Points read from Figures 3 and 4 in the paper.

Table 9b. Reduction in HIV incidence after 20 years among the adult population in Rakai, Uganda as a result of mass vaccination with a vaccine providing lifetime protection

Coverage	Effectiveness	Effective coverage	Reduction in HIV incidence by year 20	
			No ART	75% ART coverage
25%	25%	6%	3%	13%
50%	25%	13%	8%	29%
75%	25%	19%	12%	36%
100%	25%	25%	17%	49%
25%	50%	13%	9%	17%
50%	50%	25%	18%	30%
75%	50%	38%	29%	49%
100%	50%	50%	38%	62%
25%	75%	19%	15%	24%
50%	75%	38%	32%	45%
75%	75%	56%	48%	64%
100%	75%	75%	64%	80%

Note: Points taken from Table 3 in the paper.

This paper is notable in that it provides results in terms of impact on both incidence and prevalence. The findings show that over a twenty year period the impact on prevalence is 4-5 times greater than the impact on incidence at low levels of effective coverage and about 2 times greater at the highest levels of effective coverage.

This study also investigates the effects of behavioral disinhibition on vaccine impact. It shows that behavioral reversals could eliminate the benefits of the vaccine or produce a worse result in the most extreme cases.

The authors conclude that even a very low efficacy vaccine would have some positive impact on the epidemic but that at the lowest levels of effectiveness the impact would be small. However, when combined with widespread use of ART even a very low efficacy vaccine would have a substantial impact. The ideal program would combine high vaccination coverage with wide scale availability of ART and prevention programs to prevent behavioral reversals.

11. Nagelkerke, N.J.D. & De Vlas, S.J. (2003). The Epidemiological Impact of an HIV Vaccine on the HIV/AIDS Epidemic in Southern India. Policy Research Working Paper 2978. Washington, DC: World Bank, February 2003.

This paper applies a simulation model of vaccine impact to the epidemiological situation in southern India. The authors investigate the impact of vaccines that stimulate different levels of immune response at different levels of efficacy. They examine the impact of a long-lasting vaccine targeted to the general population or to high risk groups and compare these results with and without behavioral disinhibition. The results are shown in Table 10.

Table 10. Reduction in HIV prevalence after 25 years among the adult population in Southern India as a result of mass vaccination with a vaccine providing 25 years of protection

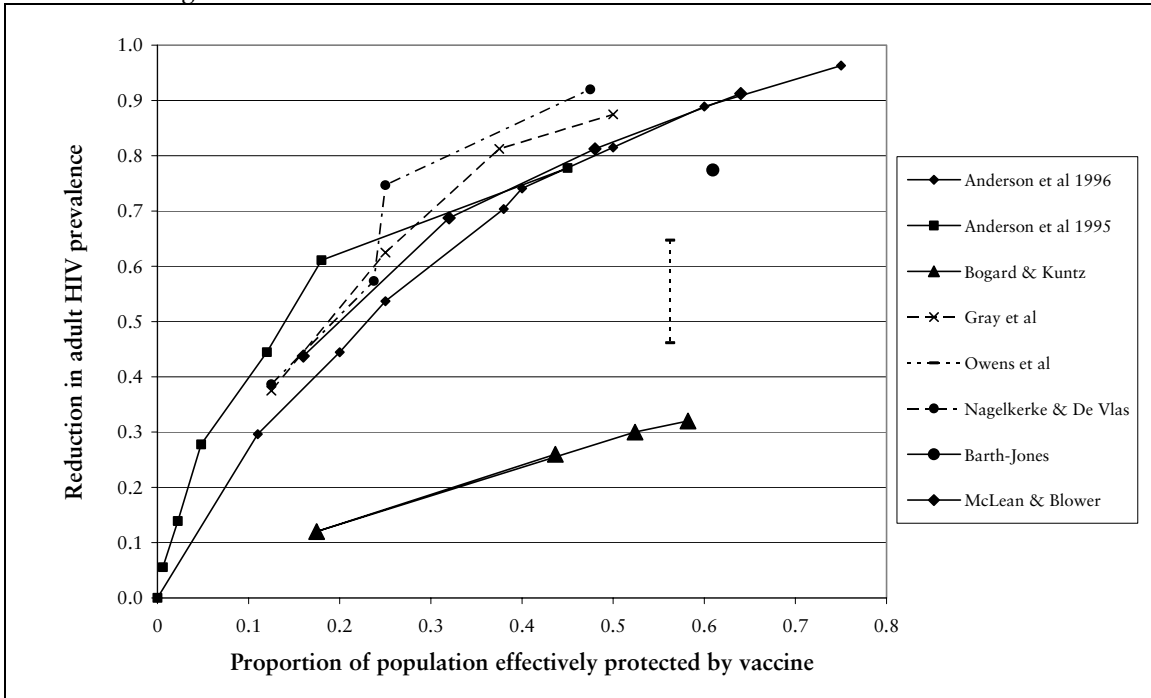
Coverage	Effectiveness	Effective coverage	Type of impact	Reduction in HIV prevalence by year 25
50%	25%	13%	Take	39%
50%	48%	24%	Take	57%
50%	50%	25%	Degree	75%
50%	95%	48%	Degree	92%

The authors also show that targeting vaccines to 90% of sex workers and their clients would have a similar impact as targeting 50% of all adults. The effects of disinhibition are investigated by repeating the analysis shown in Table 10 with the assumption that condom use would drop to zero in the presence of the vaccination program. In this case the impact of vaccination is reduced by about half.

III. Conclusions

The potential impact of AIDS vaccines on prevalence and incidence depends on the characteristics of the vaccine and the epidemic setting. Coverage and vaccine efficacy are the most important characteristics. By combining these two characteristics into a single approximate measure of effective coverage, we can compare the results of the studies reviewed here with regard to their preventive vaccine efficacy. (Most of the studies examined here assume impacts through reduced susceptibility to infections, though some incorporate the possible impacts of an AIDS vaccine that acts by lowering infectiousness and/or disease progression). It should be noted, however, that by focusing exclusively on the preventative vaccine effects, the impact of these preventative effects will be confounded with the impacts of vaccine effects lowering on infectiousness and/or disease progression) Figure 1 shows the results in terms of impact on prevalence, and Figure 2 shows the results for impact on incidence.

Figure 1. Impact of an AIDS vaccine on adult HIV prevalence after 20-25 years as a function of effective coverage



The simulations by MacLean and Blower 1993, Anderson *et al.* 1995, Anderson *et al.* 1996, Barth-Jones and Longini 2002, Nagelkerke and De Vlas 2003 and Gray *et al.* 2003 show similar patterns of impact, reaching around 80% reductions in prevalence after 20 to 25 years. Three of these studies refer to generalized epidemics in sub-Saharan Africa with prevalence without vaccines at 18% (Anderson *et al.* 1995), 27% (Anderson *et al.* 1996) and 17% (Gray *et al.*) and assume that protection lasts for 10 years (Anderson *et al.* 1995) or for life (Anderson *et al.* 1996 and Gray *et al.*). MacLean and Blower 1993 modeled a very high risk population with prevalence at 80% at the time of the vaccination program. The Nagelkerke and De Vlas study looks at southern India where the epidemic is assumed to peak at 7.5% prevalence without effective prevention. The Barth-Jones and Longini study looks at an Asian epidemic where HIV prevalence is initially high among sex

workers and IDU and gradually spreads to the general population. Prevalence in the general population is about 4% when a vaccine becomes available, but increases to 30% after 30 years without the vaccine and rises only to 7% if a vaccine is available. Similar impacts occur for the IDU and sex worker populations. The results from Bogard and Kuntz are based on an IDU population in Bangkok and show much lower impact. This may be because the very high level of average risk in this population (prevalence is 50% in the base case) reduces the protective effect of an imperfect vaccine. The duration of protection in the Bogard and Kuntz analysis is 10 years. The results for a vaccine with lifetime protection were three times greater, which would make them similar to the results from Anderson and Gray. The results from Owens *et al.* apply to the gay population in San Francisco where prevalence is 13-17%. Owens *et al.* also assume an average protection of 10 years. It is not clear from the information provided in the papers why the impact reported by Owens does not seem to follow the pattern of the other four studies.

Figure 2. Impact of an AIDS vaccine on adult HIV incidence as a function of effective coverage.

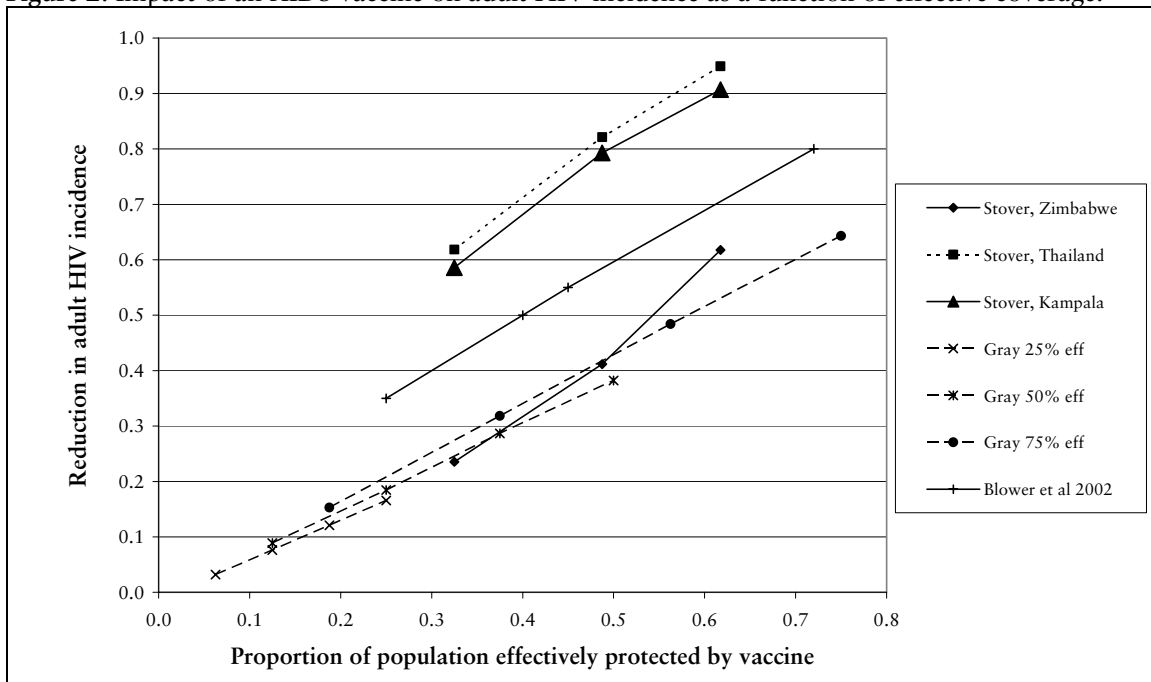


Figure 2 compares the estimated impact on incidence from Stover *et al.*, Gray *et al.* and Blower *et al.* 2002. Since Gray reports results both for prevalence and incidence, this offers a link between the two graphs. The results from Gray *et al.* for Rakai, Uganda and Stover *et al.* for rural Zimbabwe are similar. The Gray *et al.* results for prevalence are also similar to those for Anderson *et al.* 1995 and Anderson *et al.* 1996. Since the two Anderson studies applied a model like that used in Stover (Zimbabwe), the agreement is not surprising. The results from Blower *et al.* 2002 show the same slope but are somewhat larger in magnitude, while the results from Stover *et al.* for Thailand and Kampala have a similar slope and even greater magnitude. The results for Thailand and Kampala are from the iwgAIDS model that may produce higher estimates of impact because it concentrates the period of high risk more in the younger ages than do the other models.

In general, the results from these models indicate that less than perfect vaccines are unlikely to eliminate the epidemic but they do provide very significant benefits even with

low levels of effective coverage. At 25% effective coverage (which could result from a vaccine with 50% efficacy that covers 50% of the population), prevalence could be reduced by 50-60% and annual incidence could be lowered by 20-30%. If 50% percent effective coverage could be achieved, annual incidence could be reduced by 40% or more and long-term prevalence could be reduced by as much as 80%.

The implications of this conclusion are enormous. Today around five million people are being newly infected with HIV globally each year. If the wide scale implementation of a vaccine would reduce incidence by 20-40% it would avert one to two million infections a year, mostly in sub-Saharan Africa and Asia.

This paper summarizes studies published over the past 14 years. During that time there have been important changes in our understanding of the AIDS epidemic and the types of vaccines that seem most likely to be ready for implementation first. While much of the early work on vaccine modeling focused on the effects of prophylactic vaccines much of the recent research looks at vaccines which do not prevent infection but rather modify the disease by lengthening the progression period and reducing infectiousness. Rapid expansion of the availability of ART creates a different environment for vaccines that was not envisioned in the early and mid 1990s. Only a few recent studies have looked at the combination of wide spread ART and vaccination programs. Future work will focus on these new directions and improve our understanding of the important role of vaccines in confronting the AIDS epidemic.

Appendix: Literature on modeling the impact of an HIV/AIDS vaccine

1. Anderson, R.M., Gupta, S., & May, R.M. (1991). Potential of community-wide chemotherapy or immunotherapy to control the spread of HIV-1. *Nature*, 350, 356-359.

This early work looks at the impact of the use of antiretroviral therapy and therapeutic vaccines on community-prevalence of HIV. The authors use a simple model to demonstrate the relationships between enhanced survival due to treatment and the number of new infections. They conclude that treatment that lengthens the incubation period without significantly reducing the infectiousness of treated individuals would lead to more infections in a community with low levels of infection but would always produce a beneficial result in high prevalence communities such as injecting drug users.

2. McLean, A.R. & Blower, S.M. (1993). Imperfect vaccines and herd immunity to HIV. *Proceedings of the Royal Society of London, Series B*, 253, 9-13.

Analytic and modeling techniques are used to investigate the effect of different levels of efficacy and coverage of a prophylactic vaccine on herd immunity and the possibility of eradicating the epidemic. The results show that a vaccine with 100% efficacy and 10 years average duration will be equal in impact to one with 30% and lifelong protection.

3. Blower, S.M. & McLean, A.R. (1994). Prophylactic vaccines, risk behavior change and the probability of eradicating HIV in San Francisco. *Science*, 265, 1451-1454.

This paper examines the possibility of eradicating the HIV epidemic in San Francisco with a prophylactic vaccine. It describes the levels of efficacy and coverage required for eradication and looks at the impact of risk behavior changes. The authors conclude that “it is unlikely that vaccines will be able to eradicate HIV in San Francisco unless they are combined with considerable reductions in risk behaviors. Furthermore, if risk behavior increases as the result of a vaccination campaign, then vaccination could result in a perverse outcome by increasing the severity of the epidemic.”

4. Anderson, R.M., Swinton J., & Garnett G.P. (1995). Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection. *Proc R Soc Lond B Biol Sci B*, 261, 147-151.

A simulation model is used to examine the impact of low efficacy vaccines in a high prevalence setting such as southern Africa. The results show that eradication is unlikely even with very high coverage. However, significant reductions in new infections can be achieved even by vaccines with efficacy of 50% or less and duration of protection of as short as 5 years.

5. McLean, A.R. & Blower, S.M. (1995). Modeling HIV vaccination. *Trends in Microbiology*, 3, 458-463.

This paper reviews work using models and analytic techniques to examine the effects of low-efficacy vaccines and what to look for in community trials.

6. Koopman, J.S. & Little R.J. (1995). Assessing HIV vaccine effects. *Am J Epidemiol*, 142, 1113-1120.

This paper argues that vaccine trials should be assessing not only vaccine effects on new infections or disease progression but should also be examining effects on contagiousness associated with primary infection. It would be quicker to assess effects on contagiousness allowing trials to return results much more quickly than when assessing progression to AIDS or death. The paper presents a trial design to accomplish this by randomizing discordant couples into trial and control arms.

7. Anderson, R.M., & Garnett, G.P. (1996). Low-efficacy HIV vaccines: potential for community-based intervention programs, *Lancet*, 348, 1010-1013.

This article provides detailed analysis of the effects of coverage, efficacy and duration on HIV transmission within a community. Quantitative results are provided for a number of combinations of values for these parameters.

8. Garnett, G.P. (1998). The influence of behavioral heterogeneity on the population level impact of potential prophylactic HIV-1 vaccines. *Journal of the Royal Scientific Society Series A*, 161, 209-225.

This paper elaborates on Anderson 1996 by providing additional detail on the results of the models and testing the impact of vaccines under many different circumstances including high risk populations with various rates of AIDS associated mortality and exit from high risk behavior categories. The effects of heterogeneity in sexual activity are explored and vaccine effects are compared to and combined with other prevention interventions.

9. Porco, T.C. & Blower S.M. (1998). Designing HIV vaccination policies: subtypes and Cross-Immunity. *Interfaces*. 28, 167-190.

Simulation modeling is used to examine the effects of vaccines in epidemics where two sub-types of HIV are co-circulating or where one sub-type exists and a second sub-type is introduced. The analysis looks at vaccines with different levels of efficacy against each sub-type. It demonstrates several possible outcomes depending on the vaccine characteristics including complete eradication of the epidemic, control of one sub-type with replacement of the second sub-type or partial control of both sub-types.

10. Edwards D.M., Shachter, R.D. & Owens D.K. (1998). A dynamic HIV-transmission model for evaluating the costs and benefits of vaccine programs. *Interfaces*, 28, 144-166.

This study presents results from a model used to assess the costs and benefits of therapeutic and prophylactic vaccines in a population of homosexual men. They conclude that therapeutic vaccines may increase HIV prevalence unless combined with increased

condom use and that preventive vaccines are most cost-effective, particularly when implemented in the early stages of an epidemic.

11. Owens D.K., Edwards, D.M., & Shachter, R.D. (1998). Population effects of preventive and therapeutic HIV vaccines in early- and late-stage epidemics. *AIDS*, 1998, 1057-1066.

This study examines the effect of preventive and therapeutic vaccines in the HIV epidemic among gay men in San Francisco. It measures effects in terms of infections averted, HIV prevalence and quality-adjusted life years (QALY). The preventive vaccine can significantly reduce prevalence even if implemented late in the epidemic. Therapeutic vaccines could produce benefits in terms of QALYs but might lead to higher prevalence unless they also reduced infectivity. Vaccines introduced early in the epidemic show even greater advantages for preventive vaccines compared to therapeutic ones.

12. Porco, T.C. & Blower S.M. (2000). HIV vaccines: The effect of the mode of action on the coexistence of HIV subtypes. *Mathematical Population Studies*, 8, 205-229.

Results are presented from a model developed to examine the effects of a vaccine in an epidemic with two HIV subtypes or an epidemic with a single HIV subtype initially, but with a second subtype introduced later. The vaccine is assumed to have differential efficacy for the two subtypes. It assesses the conditions under which: (1) both subtypes are eradicated, (2) the endemic subtype persists and the invading subtype is eradicated, (3) the endemic subtype is eradicated and the invading subtype persists, or (4) both subtypes coexist.

13. Blower, S.M., Kirschner, D.E., Koelle, K., & Mills, J. (2001). Live attenuated HIV vaccines: predicting the tradeoff between efficacy and safety. *PNAS*, 98, 3618-3623.

Monte Carlo modeling techniques are used to examine the effects of LAHVs on the number of infections. The results show the trade-off between efficacy in preventing transmission from an infected partner and safety with regard to infection caused by the vaccine itself. Any vaccine that produces infection in more than 5% of those vaccinated would increase AIDS deaths in Thailand but could lead to a smaller number of deaths in an epidemic such as Zimbabwe.

14. Garnett, G.P., Desai, K., & Williams, J. (2001). The Epidemiological Impact of an HIV/AIDS Vaccine in Developing Countries. Technical Annex 1. The potential impact of prophylactic HIV vaccination as a function of vaccine properties: Results of the Imperial College Model. Technical appendix to Garnett, G.P., Forsythe, S., Seitz, S., Stover, J. *The Epidemiological Impact of and HIV/AIDS Vaccine in Developing Countries*, World Bank. (March 2002).

This paper describes a model designed to investigate the effects of vaccines with different characteristics on HIV incidence in Manicaland in rural Zimbabwe. The population is segregated by age, sex and sexual activity class. New entrants into the adult population (those aged 15) are assigned to one of four activity classes. Individuals stay in their assigned activity class for life, but the characteristics of the class vary with age. The model

further divides the population into four categories according to immunization status: (1) fully immunized, (2) partially immunized, (3) not immunized and (4) previously vaccinated but no longer protected by the vaccine and not yet eligible for re-vaccination. Once a person becomes infected, he or she progresses eventually to AIDS and death. The effect of a vaccine in the model is to move the vaccinated person from the susceptible (not immunized) category to the fully immunized or partially immunized category, depending on the type of vaccine. A fully immunized person is completely protected from HIV infection. A partially immunized person has a reduced probability of HIV infection. If the duration of the protection of the vaccine is not lifetime, then a person can move from the fully or partially immunized category to the previously vaccinated category, where he or she is fully exposed to the risk of HIV infection.

15. Seitz, S. (2001). The Epidemiological Impact of an HIV/AIDS Vaccine in Developing Countries. Technical Annex 2. The Potential Epidemiological Impact of Prophylactic Vaccines: Results of the iwgAIDS Model. Technical appendix to Garnett, G.P., Forsythe, S., Seitz, S., Stover, J. *The Epidemiological Impact of and HIV/AIDS Vaccine in Developing Countries, World Bank*. (March 2002).

A computational model encapsulated in the iwgAIDS software package is used to simulate prophylactic vaccine scenarios that vary vaccine efficacy (50%, 75%, 95%) and half-life of the vaccine (5-year duration, 10-year duration, 50-year duration). The vaccine scenarios focus on four target groups: adults in general, high-risk adults, teenagers and paired females during their childbearing years. Comparisons also are made with behavior interventions to change condom use, to change concurrent partners, to change casual partner turnover rates and to change STD rates. The potential impact of behavioral reversions (decreased condom use or increased partner turnover) is explored under the various vaccine scenarios. Separate analyses are provided for Kampala, Uganda and Thailand. (1) Vaccines of all efficacy levels have considerable impact on reducing cumulative HIV incidence in both contexts (Kampala and Thailand). (2) Duration of effectiveness is not uniformly important in differentially reducing cumulative HIV cases, but it is sensitive to context and target (general adult population, high risk, teenagers, mothers). (3) Targeting the general adult population is effective in both environments; targeting the others (high risk, teens, mothers) show context-specific sensitivities. (4) The lowest efficacy vaccine outperforms all other interventions except an idealistic condom intervention. (5) The impact of behavioral reversions on vaccine gains vis-à-vis cumulative HIV cases is sensitive to both context and target.

16. Tangcharoensathien, V., Kasemsup, V., Kongsin, S., Phoolcharoen, W., Pitayarangarit, S., Suraratdecha, C., & Tantivess, S. (2001). Potential demand for an AIDS vaccine in Thailand, *Health Policy*, 57, 111-139.

This paper examines the demand for AIDS vaccines in Thailand and the impact and budgetary implications of vaccination programs. Eight population groups are studied: direct sex workers, indirect sex workers, IDU in treatment, IDU out of treatment, males with sexually transmitted infections (STI), transport workers, conscripts and prisoners. Vaccines are estimated to cost from 100 Baht (3 US dollars) to 1000 Baht (29 US dollars) per dose. The authors conclude that proper policies will be required to ensure efficient and equitable consumption of vaccines.

17. Longini, Jr., I.M., Halloran, M.E., & Nizam, A. (2001). Model-based estimation of vaccine effects from community vaccine trials. *Stat Med*, 21, 481-495.

This paper uses statistical models to analyze alternative methods for analyzing the results from community trials. The authors recommend the use of a fixed effects epidemic model to get the most information from the trial data.

18. Blower, S.M., Koelle, K., & Mills, J. (2002). Health policy modeling: epidemic control, HIV vaccines and risky behavior, in *Quantitative Evaluation of HIV Prevention Programs*. Eds. Kaplan and Brookmeyer. Yale University Press. 260-289.

Mathematical models are used to predict the epidemiological consequences of a variety of HIV vaccines that are under development and include examination of the effects of behavioral reversal.

19. Bogard, E. & Kuntz, K.M. (2002). The impact of a partially effective HIV vaccine on a population of intravenous drug users in Bangkok, Thailand: a dynamic model. *J Acquir Immune Defic Syndr*, 29, 132-141.

This study models the impact of an AIDS vaccine among a high prevalence population of injecting drug users in Bangkok. "A 75% effective vaccine led to a 40-year HIV prevalence of 37% with vaccination and 50% without vaccination." Behavior change did not have much effect when vaccine efficacy was 75% but could eliminate the benefits of the vaccine if efficacy was only 25%.

20. Stover, J., Garnett, G.P., Seitz, S., & Forsythe, S. (2002). *The Epidemiological Impact of and HIV/AIDS Vaccine in Developing Countries*, World Bank: Washington, DC.

This study uses the two computer simulation models described in Garnett *et al* 2001 and Seitz 2001 to investigate the effects of various vaccine characteristics and implementation strategies on the impact and cost-effectiveness of vaccines in different contexts. A simulation model from the Imperial College is applied to data from rural Zimbabwe and the iwgAIDS model is applied to Kampala and Thailand. The models are used to investigate the effects of efficacy, duration, cost and type of protection on impact and cost-effectiveness. The models also illustrate the merits of targeting public subsidies to various population groups: all adults, teenagers, high-risk group and reproductive age women. The impact of vaccines on the epidemic is compared with the impact of other prevention interventions, such as condom use and behavior change. Finally, the models are used to explore the extent to which behavioral reversals may erode the positive benefits of the vaccine. The authors conclude that a highly effective, long-lasting, inexpensive vaccine would be ideal and could make a major contribution to controlling the HIV/AIDS pandemic. However, vaccines that do not attain this ideal can still be useful. A vaccine with 50 percent efficacy and 10 years duration supplied to 65 percent of all adults could reduce HIV incidence by 25 to 60 percent depending on the context and stage of the epidemic. Better efficacy and longer duration would provide even more impact. Programs focused on teenagers or high-risk populations have less overall impact but would provide significant benefits at much less cost than those reaching all adults. Behavioral reversals

could erode much of the benefits of vaccination programs so it will be important to combine vaccination with continued messages about the importance of safe behaviors.

21. Barth-Jones, D.C. & Longini Jr., I.M. (2002). Determining Optimal Vaccination Policy for HIV Vaccines: A Dynamic Simulation Model for the Evaluation of Vaccination Policy. *Proceedings of the International Conference on Health Sciences Simulation 2002* in Eds. Anderson JG, Katzper, 2002 Western Multiconference, January 27-31, 2002. San Antonio, Texas.

The authors present preliminary work on a simulation model that examines AIDS vaccines effects in a system of sexual and IDU transmission of HIV. The model includes difference stages of HIV infection, stratification of sexual activity by class and sexual mixing between IDU and non-IDU. The model will eventually be expanded and applied in a number of countries to examine the effects of different vaccination strategies, particularly when vaccine availability is less than demand.

22. Blower, S., Moss, R.B., & Fernandez-Cruz, E. (2003). Calculating the potential epidemic-level impact of therapeutic vaccination on the San Francisco HIV epidemic. *AIDScience*, 3, 21.

The paper investigates the impact of a therapeutic vaccine used in combination with widespread use of antiretroviral therapy in the gay community in San Francisco. Two types of vaccines were examined: one that increased survival slightly with no effect on transmission and one that increased survival and reduced transmission. The authors conclude that “over a 20 year time period the therapeutic vaccine that only increased survival had an almost negligible impact on the epidemic. However, the therapeutic vaccine that increased survival and also decreased infectiousness had a substantial impact on the epidemic: over a 20 year period this vaccine would prevent 26%-27% of HIV infections, and 9-10% of AIDS deaths in San Francisco.”

23. Blower, S., Schwartz, E.J., & Mills, J. (2003). Forecasting the future of HIV epidemics: the impact of antiretroviral therapies & imperfect vaccines. *AIDSRev*, 5, 113-125.

This paper reviews how mathematical models have been used to predict the consequences of specific epidemic control strategies and to design epidemic control strategies. This review includes both the effects of ART on epidemic trajectories as well as the impact of imperfect vaccines.

24. Gray, R.H., Xianbin L., Wawer, M.J., Gange, S.J., Serwadda, D., Sewankambo, N.K., Moore, R., Wabwire-Mangen, F., Lutalo, T., & Quinn, T.C. (2003). Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. *AIDS*, 17, 1941-1951.

This study uses data from a community cohort study in Rakai, Uganda to examine the effects of ART and HIV vaccines on transmission in that community. The cohort study provides information on behavior and on probability of transmission according to viral load. The ART program alone was estimated to reduce incidence somewhat but not enough to eradicate the epidemic. Preventive vaccines with 50% efficacy above 50% and

coverage above 50% population coverage were seen to substantially reduce the number of new infections. The combination of ART and vaccination could have a large impact even at low levels of vaccination coverage. Behavioral reversals could eliminate much of the benefits if they do occur.

25. Nagelkerke, N.J.D. & De Vlas, S.J. (2003). The Epidemiological Impact of an HIV Vaccine on the HIV/AIDS Epidemic in Southern India. Policy Research Working Paper 2978. Washington, DC: World Bank, February 2003.

This paper applies a simulation model of vaccine impact to the epidemiological situation in Southern India. The authors investigate the impact of vaccines that stimulate different levels of immune response at different levels of efficacy. They examine the impact of a long-lasting vaccine targeted to the general population or to high risk groups and compare these results with and without behavioral disinhibition. Results are also compared to the impact of other prevention interventions. The paper presents the number of vaccinations required under each strategy as a way to gauge the overall costs. The authors conclude that vaccines could have a major impact on the epidemic under any of these assumptions. However, they also caution that vaccines are not yet available. Other prevention interventions that are available now should be implemented fully to reduce transmission now.

26. van Ballegooijen, M., Bogaards, J.A., Weverline, G-J., Moerlijst, M.C., & Goudsmit, J. (2003). AIDS Vaccines that Allow HIV-1 to Infect and Escape Immunologic Control: A Mathematical Analysis of Mass Vaccination. *J Acquir Immune Defic Syndr* 34(2), 214-220.

This study evaluates the effectiveness of vaccines that do not prevent infection but do reduce viremia and prolong disease progression. They conclude that such vaccines can have a significant impact on the number of AIDS deaths but only when implemented early in an HIV epidemic.

27. Smith, R.J. & Blower, S.M. (2004). Could disease-modifying HIV vaccines cause population-level perversity? *Lancet Infect Dis.*, 4, 636-639.

This paper looks at vaccines that reduce viral load and thus have the potential to reduce transmission. The authors use a mathematical model to show that vaccines that prolong life significantly but do not have much effect on reducing transmission could make the epidemic worse. The model is used to calculate the thresholds of viral load reduction and behavior reversals in order for vaccines to have a net benefit. The authors discuss the implications of these results for the design of vaccination programs.

28. Davenport, M.P., Ribeiro, R.M., Chao, D.L., & Perelson, A.S. (2004). Predicting the Impact of a Nonsterilizing Vaccine against Human Immunodeficiency Virus. *Journal of Virology*, 78(20), 11340-11351.

The authors use a simulation model to examine the impact of a disease-modifying vaccine that reduces viral load and delays disease progression. They conclude that the most important characteristic in determining impact is the reduction in viral load caused by the vaccine. Other factors, such as the rate of disease progression and the generation and

transmission of mutant strains, are less important. The largest impact is found when vaccines are applied in areas of low prevalence and rapid epidemic growth.

29. Anderson, R., & Hanson, M. (2005). Potential public health impact of imperfect HIV type 1 vaccines. *J Infect Dis.*, 191 Suppl 1, S85-96.

Deterministic models are used to investigate the impacts of imperfect vaccines. The models are used to examine 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 ($R(0_v)$) was less than that among unvaccinated individuals ($R(0)$)." The results show that any lengthening in the incubation period or increase in risk behaviors can be more than offset by reduced susceptibility to infection and reduced infectiousness.

30. Blower, S.M., Bodine, E.N., & Grovit-Ferbas, K. (2005). Predicting the Potential Public Health Impact of Disease-Modifying HIV Vaccines in South Africa: The Problem of Subtypes. *Curr Drug Targets Infect Disord.* 2005 Jul; 5(2), 179-192.

This paper focuses on the potential impact of disease-modifying vaccines on the epidemic in South Africa where multiple subtypes of HIV are co-circulating. The authors use simulation modeling to reproduce the South African from 1940 to 2005 and project it to 2140. They predict that the epidemic will switch from one where subtype C predominates to one with a variety of subtypes. They show how the characteristics of the different subtypes are crucial to determining the amount of impact any HIV vaccine would have on the epidemic.

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IAVI-New York
110 William Street
New York, NY 10038
United States

IAVI-East Africa
Floor 16, Rahmutulla Tower
Underhill Road, PO Box 340
Nairobi, Kenya

IAVI-Europe
Postbox 15788
1001 NG, Amsterdam
The Netherlands

IAVI-India
193 Floor 4, Jorbagh
New Delhi, 110003
India

