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Methodologies for Modeling the Impact of a Preventive AIDS Vaccine in Developing Countries: Recent Studies

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Methodologies for Modeling the Impact of a Preventive AIDS Vaccine in Developing Countries: Recent Studies

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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.

Contents

Acronyms and Abbreviations

AIDS	Acquired immunodeficiency syndrome
CSW	Commercial sex worker
HIV	Human immunodeficiency virus
IAVI	International AIDS Vaccine Initiative
IDU	Intravenous drug user
SAAVI	South African AIDS Vaccine Initiative
SADC	South African Development Community
VE_I	Vaccine effect on infectiousness
VE_P	Vaccine effect on progression
VE_S	Vaccine effect on susceptibility
WHO	World Health Organization

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 developing countries.

In late 2004 and early 2005, IAVI commissioned two interrelated 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 preventive 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 behavioural 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 preventive efficacy and lifelong protection, and so they specifically consider future vaccines with only low to moderate efficacy and a limited duration of protection.

This paper by Jane Rowley describes and compares the methodologies used to model the long-term impact of a preventive AIDS vaccine in developing countries, 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 behaviours.

The companion review by John Stover and Katherine Willson (IAVI Policy Research Working Paper #5, October 2005) 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, behavioural reversals and epidemic type. It summarizes the conclusions of these modeling efforts and compares results by combining two very important characteristics of any vaccination programme, preventive 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.

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

Public health policymakers charged with deciding which prevention strategies to support to control the HIV epidemic need a good understanding of the potential benefits over time of both existing and new tools and approaches. Preventive AIDS vaccines are one of the new technologies under development. In order to understand the potential impact an AIDS vaccine might have on the control of the HIV epidemic in a particular setting, policymakers need information on issues such as:

- the relationship between a vaccine's properties (e.g., the efficacy of the vaccine, manner of protection, and the duration of protection) and its impact over time;
- which immunization strategies and levels of coverage will have the greatest impacts given the vaccine's characteristics and the current state of the epidemic;
- how AIDS vaccines compare with other prevention interventions and strategies; and
- how to combine the different prevention options in the most effective way.

One tool that has been particularly helpful in assessing the impact of different interventions on the spread of infectious diseases is mathematical modeling. Mathematical models provide a framework that can be used to explore how a particular intervention, or combination of interventions, may affect the spread of the disease. They are particularly valuable because of the non-linear transmission dynamics that result in indirect protective effects for individuals who do not receive the intervention.[1]

A number of models have been developed that explore different aspects of the transmission dynamics of HIV at the population level. This review focuses on a subset of this work – those models that have been specifically developed and/or tailored to look at the medium- to long-term impact (defined as ten years or more) of a preventive AIDS vaccine in developing countries. Appendix 1 provides the abstracts from those papers that have explored the potential impact of an AIDS vaccine in developed countries or in particular population groups and are not included in this paper.

The AIDS vaccine models that are the focus of this review have been used to explore a number of different topics (see Box 1). In particular, researchers have looked at how the characteristics of a vaccine and how it is used affect its impact over time. In addition, there has been considerable discussion about the *potential* for behavioural reversals as a result of vaccination (also known as disinhibition) and what impact behaviour changes, such as a reduction in use of condoms or increase in sexual partners, may have on the epidemic.

[1] See Anderson, R.M. and May, R.M. (1992). Infectious Diseases of Humans: Dynamics and Control. Oxford University Press for a general discussion of the structure and use of mathematical models; and Edmunds, W.J., Medley, G.F., & Nokes, D.J. (1999). Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective. *Stat Med. 8(23)*, 3263-82 for a more specific discussion of the use of models for making public health decisions.

Box 1. Examples of the topics explored to date

Vaccine properties

- Duration of protection
- Level of protection
- Type of protection (take† or degree‡)
- Other types of protection (protect against infection, reduce infectiousness, protect against disease progression)

Use of the vaccine

- Which population groups to target (e.g., by age or sexual activity) and how often to vaccinate
- Consequences of disinhibition or behaviour change following the introduction of the vaccine
- Synergies with other prevention or treatment programmes

† A "take"-type vaccine provides a percentage of the vaccinated population with complete protection

‡ A "degree"-type vaccine provides only partial protection to those vaccinated and hence some vaccinated individuals may become infected

II. The models

A total of five published models were identified that have been used to examine the medium- to long-term impact on the HIV epidemic of introducing a preventive AIDS vaccine in a developing country setting (see Table 1). In addition to these models the South African AIDS Vaccine Initiative (SAAVI) has contracted the Centre for Actuarial Research at the University of Cape Town[2] to model the impact of an AIDS vaccine. This work is on-going and whilst no preliminary results are available, the project is scheduled to be completed by the end of 2005.

[2] More information on this group can be found on the SAAVI website (www.saavi.org.za). The objective of this work is to develop a mathematical model capable of:

- Assessing the most appropriate strategy for distributing AIDS vaccines in South Africa when supply is limited.
- Identifying the total demand for vaccination in South Africa, for both short-term scenarios (vaccination targeted at particular groups) and long-term scenarios (no supply-side constraints).
- Identifying the total demand for vaccination in other Southern African Development Community (SADC) countries, for long-term scenarios.
- Evaluating the potential long-term demographic and epidemiological effects of vaccination in SADC countries.

Table 1. Models addressing the medium- to long-term impact of an AIDS vaccine in developing countries

Model	Countries currently applied to or under development	Reference
Imperial College	Zimbabwe	Garnett *et al.*, 2003 Stover *et al.*, 2002
iwgAIDS	Uganda Thailand	Seitz, 2003 Stover *et al.*, 2002
HIV VaccSim	Kenya Brazil China Peru Thailand	Barth-Jones *et al.*, 2002 Barth-Jones *et al.*, 2003
Rakai	Uganda	Gray *et al.*, 2003
Nagelkerke and De Vlas	India	Nagelkerke and De Vlas, 2003

Each of these models is a simplification of our complex real world and was developed specifically to address a particular question or set of questions. As a result, when interpreting a model's outputs it is essential to have a good understanding of the model's structure. Table 2 highlights some of the key characteristics of the five models. The models differ considerably in their structure and level of detail (see Box 2), and as a result, some models are better than others for answering particular types of questions.

Box 2. Examples of some of the differences between the various models

- The number of viral transmission routes included and how they are incorporated:
  - Sexual (e.g. heterosexual, homosexual)
  - Blood or blood products (e.g., intravenous drug use, blood transfusions, other blood products)
  - Mother-to-child
- The level of detail in modeling the age structure of the population
- How mixing between different population groups is handled (e.g., between ages and sexual activity groups) and the balancing algorithms used
- The indicators and time frame used to assess the impact of the vaccine
- The types of vaccination strategies implemented and how they are implemented
- The handling of disinhibition
- The range of prevention and treatment programmes included and how interactions between interventions are incorporated

Table 2. Key characteristics of the five published models

	Imperial College	IwgAIDS	HIV VaccSim	Nagelkerke & De Vlas	Rakai
Transmission routes included	Heterosexual: Yes Other sexual: No Perinatal: Yes IDU: No Blood: No	Heterosexual: Yes Other sexual: Yes Perinatal: Yes IDU: Yes Blood: Yes	Heterosexual: Yes Other sexual: No Perinatal: Estimated based on HIV prevalence, probability of perinatal transmission and number of new births. IDU: No Blood: No	Heterosexual: Yes Other sexual: No Perinatal: Estimated based on HIV prevalence, probability of perinatal transmission and number of new births. IDU: No Blood: No	Heterosexual: Yes Other sexual: No Perinatal: No IDU: No Blood: No
Age structure	Fully age structured	Fully age structured	Limited	None	Limited
Handling of sexual mixing	Sexually active males and females are divided into 4 sexual activity classes based on rates of partner change and into seven 5-year age classes risk classes	A continuous risk formulation incorporates age-specific parameters, by stratification for type and concurrency of partnerships (long- and short-term, single-encounter) and contact rates (entropy distributions for high risk and low risk)	Sexually active males and females are divided into 2 risk classes (high and low) based on levels of risk activity	Sexually active males and females are divided into 2 risk classes (high and low) based on levels of risk activity	Estimates of sexual contacts with HIV-negative partners based on empirical data from Rakai
Handling of viral transmission over HIV incubation period	Incubation period divided into four compartments (3 asymptomatic and one symptomatic) with different probabilities of viral transmission	Not clear	Incubation period divided into four compartments (asymptomatic, primary, pre-AIDS, and AIDS) with different probabilities of viral transmission	Incubation period divided into three compartments (early stage, late stage, AIDS) in base scenarios probability of viral transmission assumed to be the same in all stages	No differentiation
Inclusion of interactions between HIV and other STIs	No	Yes	No	Yes	No
Inclusion of HIV treatment	No	No	No	Not in vaccine modeling paper	Yes

A. *Imperial College model (Garnett et al., 2003; Stover et al., 2002)*

The Imperial College model is based on modeling work done by Garnett, Anderson and others at Imperial College and the University of Oxford. In 2002 the model was expanded by Geoff Garnett and colleagues, with support from The World Bank and the European Commission, to explore the epidemiological impact of a preventive AIDS vaccine with a range of pre-defined properties in the context of a generalized epidemic as observed in Zimbabwe and other countries in sub-Saharan Africa.

i) Model structure

The Imperial College Model is an age-structured deterministic[3] compartmental model that incorporates both demographic and epidemiological processes to describe the spread of HIV in a population through heterosexual sex and from mother to child. In the model, the population is stratified by age (5-year age groups), sex, infection status, sexual activity and rates of sexual partner change. Individuals are assumed to be sexually active between the ages of 15 and 50. This age range is then broken down into four sexual activity classes and seven 5-year age groups. Individuals are assumed to stay in the same sexual activity class throughout their life although rates of sexual partner change vary with age. Sexual mixing is assumed to be slightly more assortative (i.e. like mix with like) than random,[4] and to ensure that the number of sexual partnerships formed by men and women balance, both sexes are assumed to alter their behaviour equally.

In the model, an individual's risk of infection through heterosexual transmission depends upon the probability of sexual transmission from an infected partner to an uninfected partner (which depend upon the sex and stage of infection of the infected partner) and the probability of having an infected sexual partner (which depend upon the sex, age and sexual activity class of the susceptible partner and the sexual mixing patterns in the population). In the case of mother-to-child transmission, the probability of an infant being infected depends on the stage of infection of the mother.

ii) Vaccine properties

Two different types of vaccine protection were modeled – degree and take[5] – and for both types of protection it was assumed that the vaccine lost efficacy at a constant rate with an average duration of protection of 5 years, 10 years or lifelong.

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[3] In a deterministic model events are not subject to chance. Two runs using the same input parameters and starting conditions will give the same results. In stochastic models chance is taken into account.
[4] For example, to reflect the empirically observed age bias in the choice of sexual partners by sex, 50% of the partnerships of men over 25 years old are with women 6 to 10 years younger than themselves and vice-versa.
[5] A "take"-type vaccine provides a percentage of the vaccinated population with complete protection whilst a "degree"-type vaccine provides only partial protection to those vaccinated and hence some vaccinated individuals may become infected.

iii) Vaccination strategies

A number of vaccination strategies were explored in which individuals were targeted based on age and/or sexual activity. In addition, different rates of reaching particular coverage levels in the population were investigated.

Vaccine-related disinhibition was investigated by assuming either a decline in condom use or an increase in partner change rates.

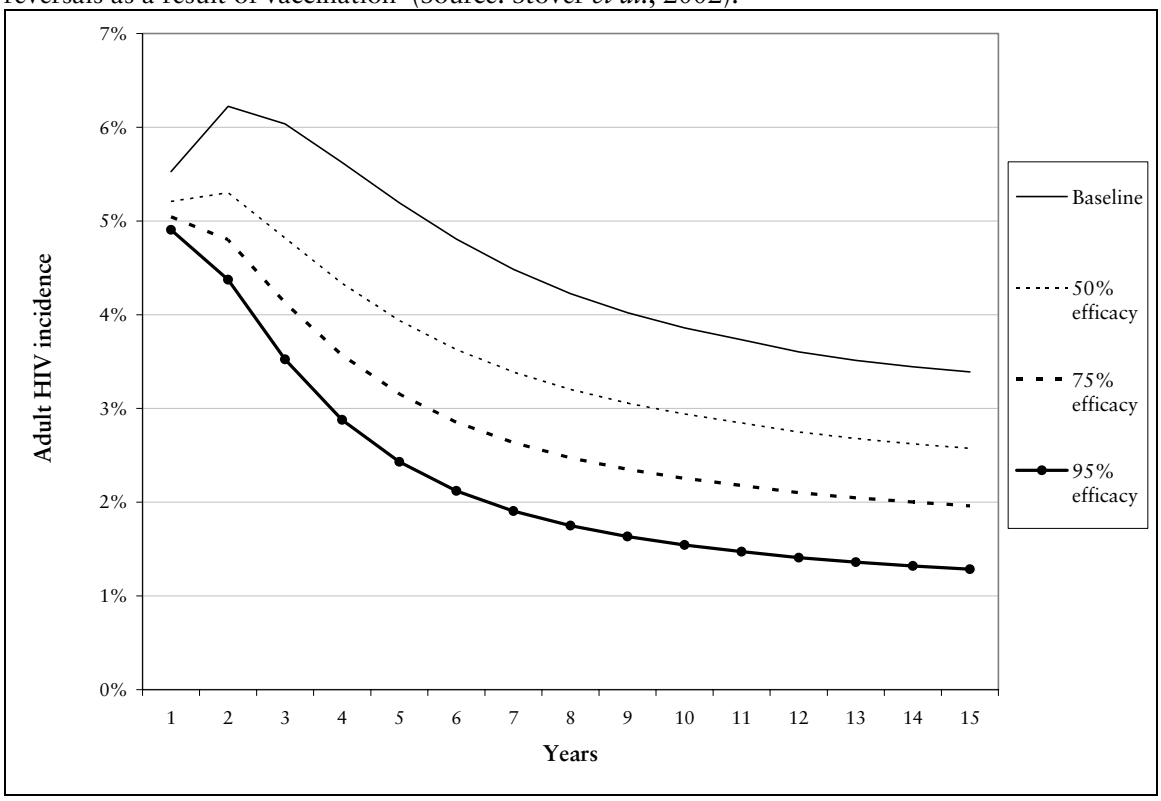
iv) Epidemiological scenario

Parameter values were based on demographic, epidemiologic and behavioural variables from rural Zimbabwe. The simulations provide an example of a heterosexual epidemic in a rural area where prevalence rises to a high level (around 25% in adults) and stabilizes at around 20 to 25%. In the vaccine simulations the vaccine was introduced during the explosive phase of the epidemic (i.e., when peak incidence and prevalence were rising rapidly).

v) Results

The papers present a number of figures showing the impact of vaccine efficacy, duration of protection and different vaccination strategies on the prevalence and incidence of HIV. Figure 1 shows estimated HIV incidence in rural Zimbabwe for a degree-type vaccine assuming 10 years duration of protection, 65% coverage in the general adult population after 5 years, and no behavioural reversals. In this scenario, a vaccine with moderate efficacy (50%) has a significant epidemiological impact, and 15 years after the vaccine is introduced, the incidence of HIV is 25% lower than it would have been in the absence of the vaccine.

Figure 1. Annual incidence of HIV in rural Zimbabwe in the absence of a vaccine and after the introduction of a vaccine providing degree-type protection. Note: In all vaccine simulations it was assumed that: the vaccine provided ten years duration of degree-type protection; the vaccination programme reached 65% coverage of adults after five years; and there were no behavioural reversals as a result of vaccination (Source: Stover *et al.*, 2002).



In addition the authors highlight that:

- The impact of a take-type vaccine targeted at the general adult population is slightly greater than that of a degree-type vaccine, and the lower the efficacy of the vaccine the greater the difference.
- For vaccines with a short duration of protection, re-vaccination is ideal, though it may still be possible to have a marked impact on HIV incidence if the vaccine protects individuals when they are at highest risk of infection. In other words, it is important to ensure that the vaccine is given to individuals so that they are protected when they are at highest risk.
- The earlier and the quicker a vaccine is introduced, the greater its impact on the incidence of HIV.
- Targeting can be the most efficient vaccine strategy per vaccinated individual but overall may not be the most effective use of a vaccine in terms of minimizing the spread of the epidemic. Targeting, in particular, is less appropriate for a degree-type vaccine where the number of challenges influence the chances of breakthrough infections.
- The consequences of behaviour reversals depend upon the scale of behaviour change and who changes behaviour. For example, the outcome is worse if behaviour reversals occur throughout the population rather than only in vaccinated individuals.

- The impact of behavioural reversals also depends upon the type of protection (degree or take) provided by the vaccine. With a degree-type vaccine an increase in risk behaviours (i.e., reduction in condom use or increase in number of sexual partners) in vaccinated individuals increases the likelihood of all becoming infected. However, with a take vaccine, an increase in risk behaviours has no effect on vaccinated individuals who are fully protected.
- HIV interventions are not mutually exclusive, and combining interventions can have a better (or worse) than additive impact on the incidence of HIV depending upon the starting conditions and the scale and intensity of the interventions.

B. *iwgAIDS model (Seitz, 2003; Stover et al., 2002)*

The iwgAIDS model was developed in the early 1990s by a US Interagency Working Group to explore the impact of the HIV epidemic in developing countries.[6] In 2002, Steve Seitz from the University of Illinois, with support from The World Bank and the European Commission, expanded and updated the model to explore the epidemiological impact of a preventive AIDS vaccine in a mature epidemic and the consequences of different vaccine strategies.

i) Model structure

The iwgAIDS model is a computational model incorporating all the major routes of HIV transmission (sexual [heterosexual, homosexual, bisexual]; intravenous drug use [stimulant and/or opiate]; mother-to-child; and blood) within a fully articulated demographic model that includes modules for fertility, mortality and migration. The model is age-structured and stratified by region (rural or urban), sex, marital status, sexual preference and infection status. A continuous risk formulation incorporates age-specific parameters stratified for type and concurrency of partnerships (long-term, short-term, single-encounter) and contact rates. Transmission cofactors, such as other sexually transmitted diseases and sexual practices, are also incorporated.

In addition to the epidemiological, behavioural, and demographic modules, the computer programme includes a set of social dynamic modules that allow the user to compensate for shortages, such as of available spouses, from various options that reflect the realities of the legal and social culture of the society being modeled.

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[6] Stanley, E.A., Seitz, S.T., Way, P.O., Johnson, P.D. & Curry, T.F. (1991). The United States Interagency Working Group approach: the IWG model for the heterosexual spread of HIV and the demographic impact of the AIDS epidemic. In *The AIDS epidemic and its demographic consequences. Proceedings of the United Nations/ World Health Organization workshop on modelling the demographic impact of the AIDS epidemic in Pattern II countries: progress to date and policies for the future*. (eds. United Nations/World Health Organization), 119-136. United Nations, New York.

ii) Vaccine properties

Two different types of vaccine protection were modeled – degree and take – and for both types of protection it was assumed that the duration of protection decayed by a hazard function[7] whose half-life was set at 5, 10 or 50 years.

iii) Vaccination strategies

Four vaccination strategies were explored targeting:

1. All adults: 60 to 65% coverage within 5 years and maintained at this level;
2. Young adults (aged 13 to 18): 80% coverage within 5 years and maintained at this level;
3. High-risk groups between 15 and 45 years of age: 80% coverage of high-risk individuals within 5 years and maintained at this level; and
4. Mothers: 60 to 65% coverage within 5 years and maintained at this level.

Vaccine-related disinhibition was investigated by assuming either a 50% decline in condom use or a doubling of casual partner turnover rates.

iv) Epidemiological scenario

Two epidemiological scenarios were considered representing different types of epidemics:

1. Kampala, Uganda: a rapid heterosexual epidemic in an African city with considerable mixing among those engaging in casual sex and where adult prevalence peaked at around 30% in the late 1980s and then declined to between 10 and 15%.
2. Thailand: an Asian epidemic with a combination of heterosexual and intravenous drug use transmission where overall adult prevalence peaked at around 2% and was concentrated in the highest risk groups.

In the Uganda vaccine simulations, the vaccine was introduced when HIV prevalence was at its peak and HIV incidence had already declined, whilst in the Thailand simulations the vaccine was introduced when the prevalence was stable and incidence low.

v) Results

The papers present a number of figures showing the impact of vaccine efficacy, duration of protection and different vaccination strategies on the HIV epidemic. Figure 2 illustrates how HIV incidence changes over time depending on the efficacy of a degree-type vaccine, assuming 10 years duration of protection, 65% coverage in the adult population and no behavioural reversals in (a) Kampala and (b) Thailand.

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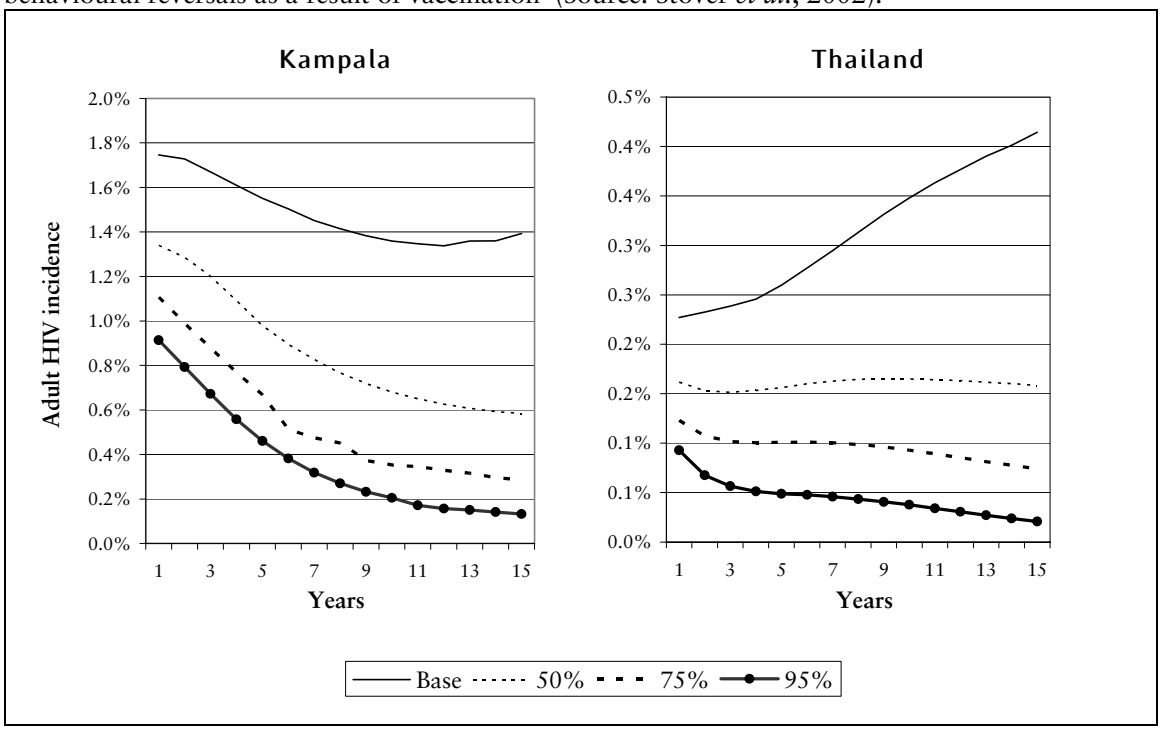
[7] Compared to a straight exponential decay, the half-life formulation results in slower extinction of coverage and hence this model is less sensitive to changes in duration.

Figure 2. Annual incidence of HIV in (a) Kampala, Uganda and (b) Thailand in the absence of a vaccine and after the introduction of a vaccine providing degree-type protection. Note: In all of the vaccine simulations it was assumed that: the vaccine provided ten years duration of protection; the vaccination programme reached 65% coverage of adults after five years; and there were no behavioural reversals as a result of vaccination (Source: Stover *et al.*, 2002).



This figure shows that a vaccine with moderate efficacy (50%) and half-life (10 years) can have a considerable impact on HIV incidence in two very different environments. In both Kampala and Thailand 15 years after the vaccine was introduced, adult HIV incidence was 50 to 60% lower than it would have been 15 years after the vaccine was introduced.

In addition, the simulations in the paper highlight that:

- Targeting the general adult population is more effective than the other three vaccination strategies considered (young adults, high-risk groups and mothers) in both Kampala and Thailand. The relative effectiveness of the other three strategies, however, differed in the two settings.
- The impact of a vaccine's duration of protection on HIV incidence depends upon both the vaccination strategy implemented (i.e., which population groups are targeted) and the epidemiological context.
- The impact of behavioural reversions on HIV incidence is sensitive to the vaccination strategy implemented, the epidemiological context, and the type of behavioural reversion that occurs (reduction in condom use or increase in casual partner turnover).

C. HIV VaccSim (Barth-Jones and Longini; 2002, Barth-Jones et al., 2003)

HIV VaccSim was developed by Daniel Barth-Jones (Wayne State) and Ira Longini (Emory University) with funding from the WHO-UNAIDS HIV Vaccine Initiative and the US Centers for Disease Control to explore optimal distribution patterns when vaccine supplies are constrained. The model has been applied to Kenya and work is under way to generate country-specific parameters for Brazil, Peru, Thailand and China.

i) Model structure

HIV VaccSim is a user-friendly deterministic compartmental model that simulates the spread of HIV in a general population. In the model presented in Barth-Jones *et al.* (2003) the focus is on a generalized African model and only heterosexual and mother-to-child transmission are included (other versions of the model include intravenous drug use – see Barth-Jones and Longini (2002)). Mother-to-child transmission is estimated based on prevalence of HIV, probability of perinatal transmission and number of new births.

The model has limited age structure – individuals enter the population as non-sexually active children (childhood stage). They then move into the pre-adolescent/adolescent stage where they are still not sexually active but can be vaccinated. Following the onset of sexual activity they move into the sexually active stage and then either die or move into the post-sexual activity stage.

Sexually active individuals are stratified into two gender-specific mixing groups based on their level of sexual partnership change – low and high.[8] Each of these groups is further stratified according to infection and immunization status. Sexual mixing between the groups is assumed to be proportional[9] and, to ensure gender balancing in sexual partnerships, the contact rates of high-risk females are assumed to vary in response to the demand of the two male mixing groups.

ii) Vaccine properties

HIV VaccSim incorporates three different types of vaccine action:

1. protecting vaccinated individuals from infection (VE_S),
2. reducing the infectiousness of vaccinated individuals who become infected and thus protecting their sexual partners against infection (VE_I), and
3. slowing disease progression in vaccinated individuals who become infected (VE_P).

The impacts of the vaccine on infectiousness and disease progression were included, as these effects may be significant for some of the candidate AIDS

[8] In the generalized African model, the high-risk group for women includes both commercial sex workers (CSWs) and women engaged in significant partner change behaviour but who are not involved in commercial sex work.

[9] In proportional mixing, members of each gender select sexual partners from the opposite gender in proportion to the fraction of the total number of sexual contacts made by each opposite gender mixing group.

vaccines under development (e.g., those that reduce viral load in vaccinated individuals who become infected) and could have important public health implications.

In all of the vaccine simulations, it was assumed that the vaccine provided low protection for at least 35 years against infection (VE_S = 0.3) and moderate protection, again for at least 35 years, against transmitting the infection and disease progression (VE_I = 0.6 and VE_P = 0.6).

iii) Vaccination strategies

Nine vaccine strategies were explored that targeted individuals by risk, gender or age:

1. high-risk females only
2. low-risk females only
3. high-risk males only
4. low-risk males only
5. pre-adolescents only
6. high- and low-risk females only
7. high-risk males and high-risk females only
8. pre-adolescents, high-risk males and high-risk females only
9. pre-adolescents, high-risk males, high-risk females and low-risk females only

The particular simulations presented do not incorporate disinhibition effects. However, adjusting the model to incorporate these effects is straightforward.

iv) Epidemiological scenario

Parameter values for the Kenyan scenario were based on data from the published literature when available or estimated using unpublished data when possible. Validation analyses were conducted using surveillance data from Kenya to ensure that the simulation parameters and model configuration selected reproduced Kenya's antecedent HIV epidemic.

In the Kenyan simulations, the vaccine was introduced into the population 5 years after the initiation of the HIV epidemic.

v) Results

Barth-Jones *et al.* (2003) presents a number of figures showing the impact of different vaccination strategies on the HIV epidemic in a Kenyan context. Figure 3 compares the impact of nine different vaccination strategies on infections prevented in a total population of 100,000. In figures A and B there is only enough vaccine to vaccinate 500 people each year (0.5% of the population) whilst in C and D there is enough to vaccinate 7,500 people (7.5%).

These results highlight that:

- The population-level impact of a vaccination programme over time can vary dramatically depending on the vaccination strategy implemented.
- The strategy of vaccinating high-risk females appears to be the best approach in terms of cases prevented per person vaccinated both when vaccine resources are quite limited and when they are more plentiful.
- If optimally distributed, even a small quantity of vaccine that provides low levels of protection against infection can have a dramatic impact on preventing HIV infections.
- It is important to be clear when assessing different vaccination strategies what criteria are to be used to measure impact (e.g., number of HIV infections prevented or number of HIV infections prevented per 100 people vaccinated) and the time horizon for assessing impact.

Figures 3A-D show projections of the number of HIV infections prevented in a Kenyan type epidemic by a vaccine providing low protection against infection (VE_S = 0.3) and moderate protection against transmitting the infection and disease progression (VE_I = 0.6 and VE_P = 0.6). The vaccine was assumed to be introduced into a population of 100,000 people at Year 5 and to provide 35 years of protection. Figures A and C record total HIV infections prevented whilst B and D record HIV infections prevented per 100 persons vaccinated. In A and B the total annual vaccine allocation was 500 doses whilst in C and D it was 7,500 (Barth-Jones *et al.*, 2003).

Figure 3A. Total HIV infections prevented with annual vaccine allocation for 500 persons; VE_S = 0.3, VE_I = 0.6

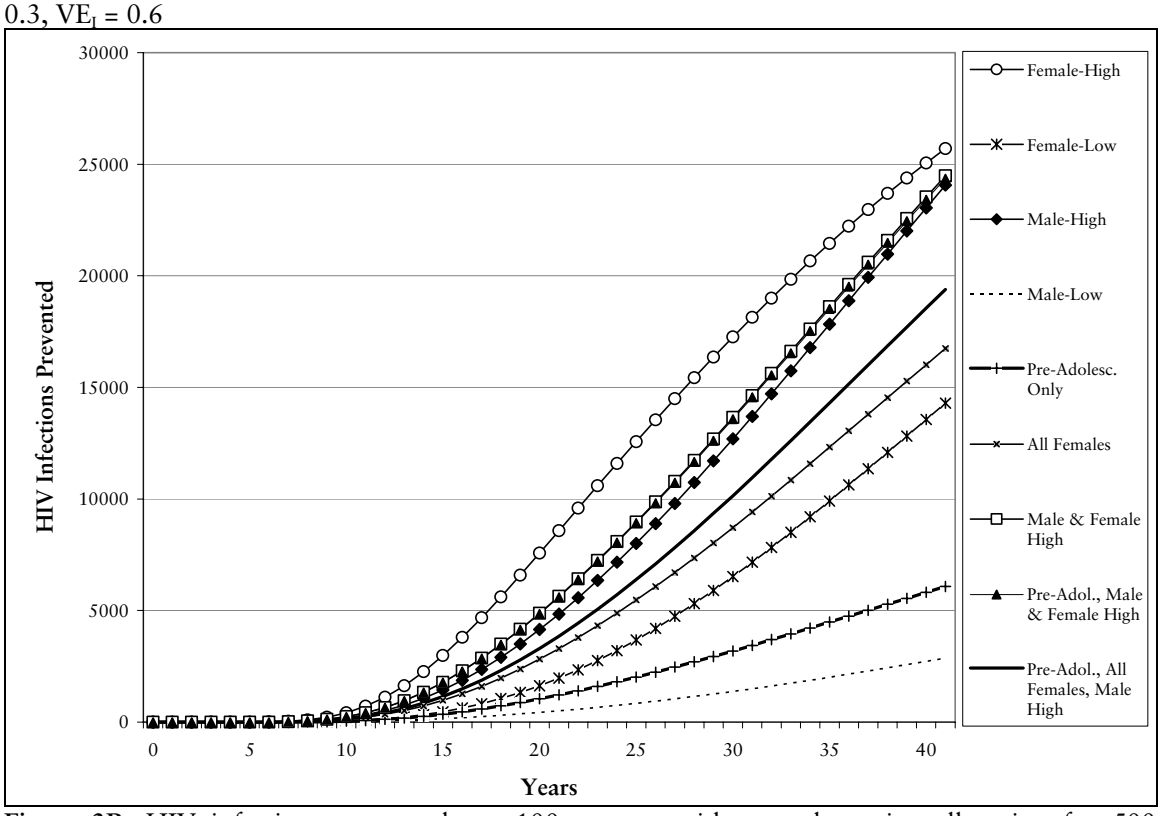


Figure 3B. HIV infections prevented per 100 persons with annual vaccine allocation for 500 persons; VE_S = 0.3, VE_I = 0.6

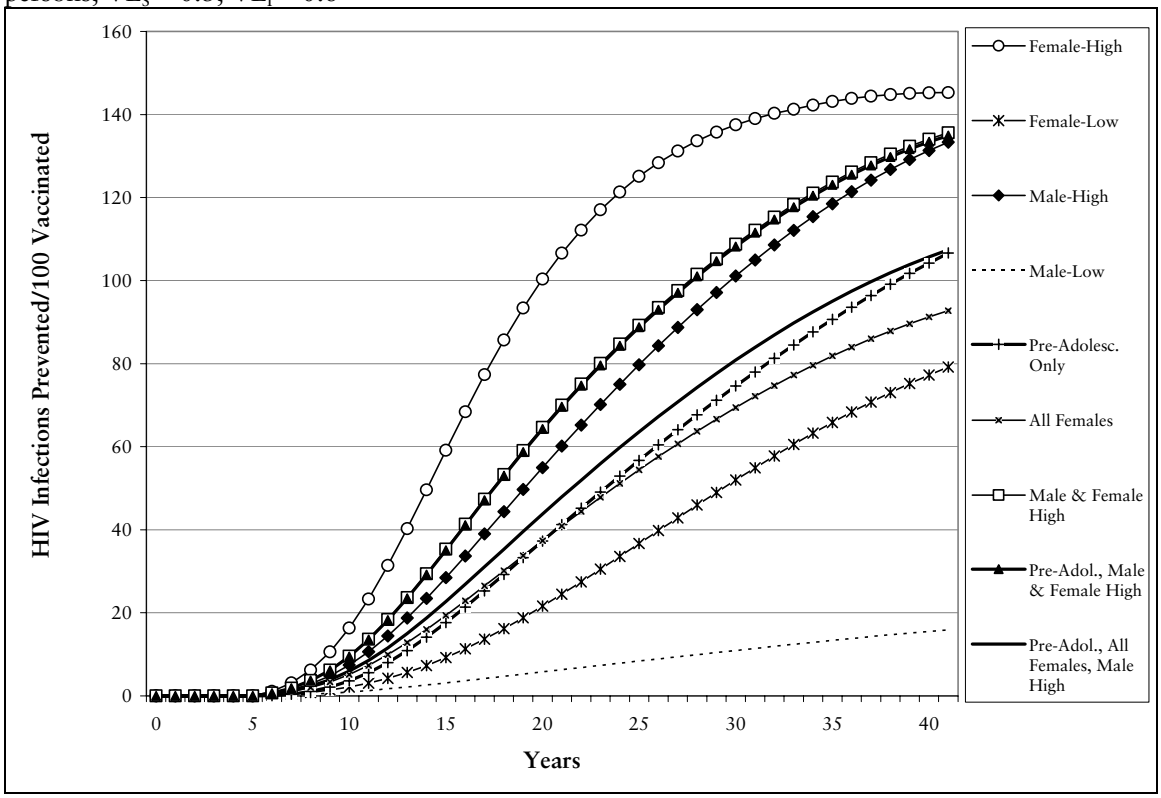


Figure 3C. Total HIV infections prevented with annual vaccine allocation for 7,500 persons; VE_S = 0.3, VE_I = 0.6

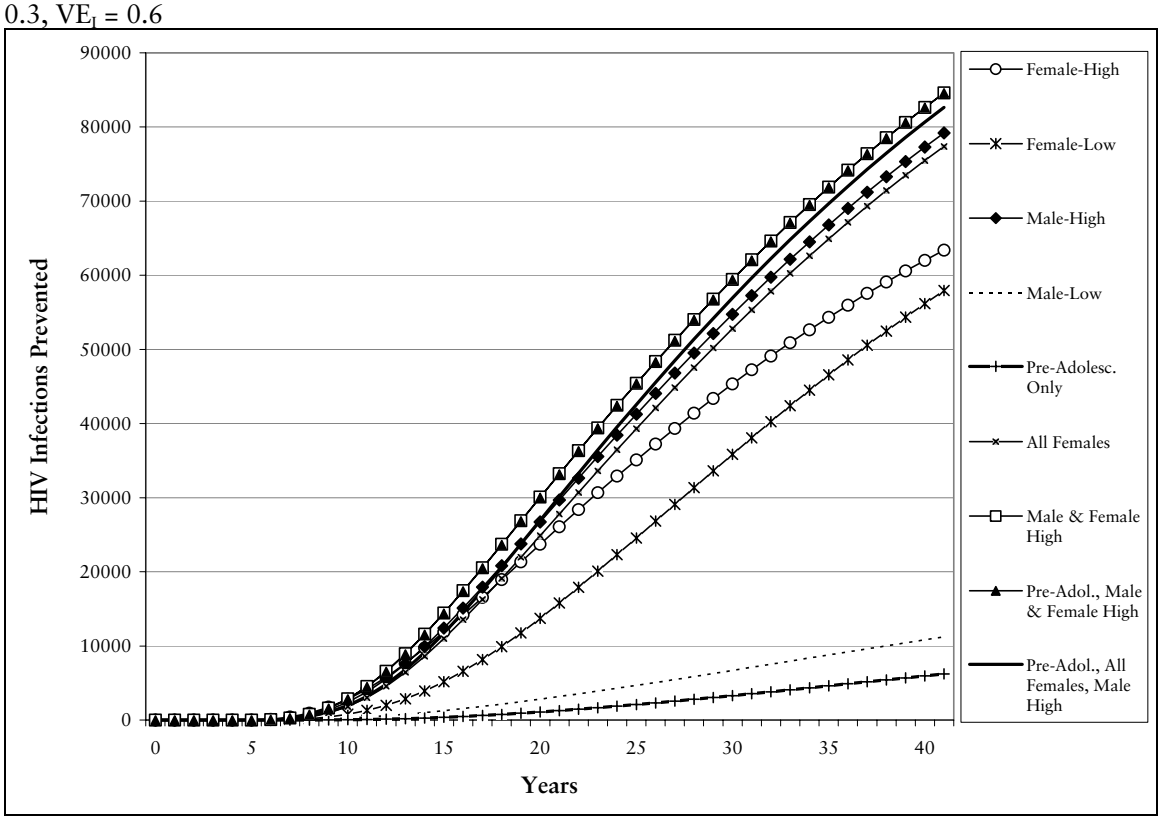
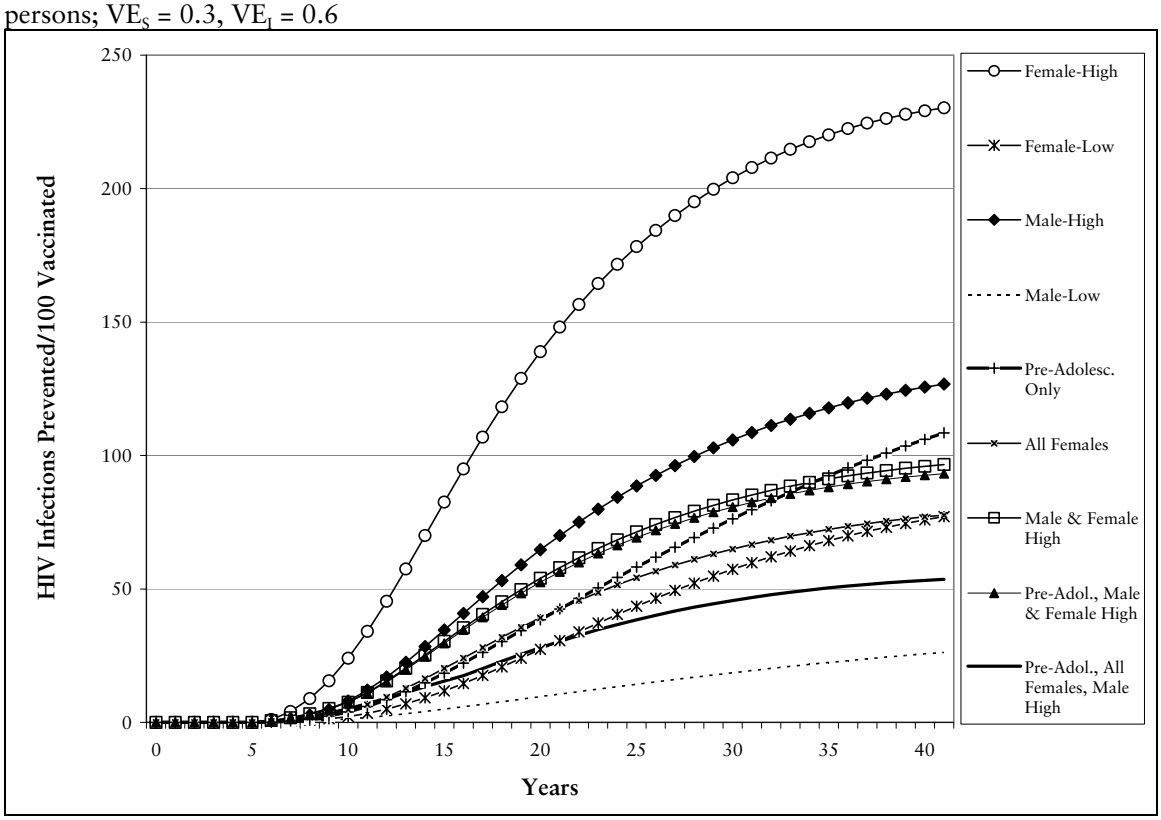


Figure 3D. HIV infections prevented per 100 persons with annual vaccine allocation for 7,500 persons; VE_S = 0.3, VE_I = 0.6



D. Nagelkerke and De Vlas model (Nagelkerke and De Vlas, 2003)

Nicol Nagelkerke and Sake De Vlas (Erasmus University), with support from The World Bank and the European Commission, extended a model they had originally developed to compare different types of behavioural interventions and antiretroviral treatment[10] to look at the epidemiological impact of an AIDS vaccine in Southern India.

i) Model structure

The model is a dynamic deterministic compartmental model that simulates the spread of HIV in the sexually active population. The model has no age structure and assumes that the spread of HIV is primarily heterosexual and driven by commercial sex. No other routes of viral transmission are included.

Individuals move between two gender-specific risk groups. For women the two groups are commercial sex workers (CSWs) and low-risk women, and for men the groups are clients of CSWs and low-risk men. Each of these groups is then split into several sub-groups according to their infection and immunization status.

ii) Vaccine properties

Four different vaccines were considered, defined by the levels of two parameters:

- level of protection or reduction in HIV susceptibility in those giving an effective immunological response to the vaccine, which was set at 50% or 100%; and
- level of immune response or percentage of those vaccinated who have an immunological response to the vaccine, which was set at 50% or 95%.

Vaccine efficacy was defined as the product of these two parameters. In the best-case scenario, vaccine efficacy was 95% and in the worst case 25%. In all of the simulations it was assumed that the vaccine provided immunity for at least 25 years.

iii) Vaccination strategies

Two vaccination strategies were considered:

1. High risk group targeting: Both CSWs and their clients were targeted and 75% of those eligible to be vaccinated were vaccinated each year. This results in an average coverage rate of approximately 90%.

2. Population targeting: Every sexually active adult was equally targeted regardless of behavioural risk group. The vaccine was launched with a 2-

[10] Nagelkerke, N.J., Jha, P., de Vlas, S., Korenromp, E., Moses, S., Blanchard, J. & Plummer, F. (2001). Modeling the HIV/AIDS epidemic in India and Botswana: the effects of interventions. Available at: http://www.comhealth.org/docs/wg5_paper4.pdf.

year vaccination campaign reaching 25% of the eligible target population each year followed by a maintenance programme that vaccinated 5% of the eligible target population annually. This results in an equilibrium situation in which approximately 50% of the sexually active population is vaccinated.

Vaccine-related disinhibition was modeled by assuming that condom use between CSWs and clients dropped from 50% prior to the availability of the vaccine to 0%.

iv) Epidemiological scenario

Model parameter values were based on data for southern India where available. The parameters chosen resulted in the prevalence in adults in 2001 being 2% and, in the absence of any intervention, increasing to 7.5% in 2033.

In the vaccine simulations it was assumed that the vaccine was first introduced in 2008.

v) Results

Table 3. Adult HIV prevalence in 2033 under four different vaccination scenarios with and without disinhibition for a vaccine providing 25 years of protection

Vaccine Scenario	Vaccine efficacy	Adult prevalence in 2033 (%)			
		High-risk groups targeted		*General population targeted*	
		No disinhibition	*Disinhibition*	*No disinhibition*	*Disinhibition*
Baseline	0	7.5	7.5	7.5	7.5
100% protection & 50% response	50	1.0	3.3	1.9	4.8
100% protection & 95% response	95	0.6	1.4	0.6	2.1
50% protection & 95% response	47.5	2.9	9.5	3.2	8.5
50% protection & 50% response	25	3.7	10.3	4.6	10.0

The simulations highlight that:

- Even for a vaccine with low efficacy (25%) there was a marked reduction in the prevalence of HIV in 2033 irrespective of which population group was targeted (high-risk groups or general population).
- If two vaccines have the same overall level of efficacy but provide different levels of protection and immune response then it is the vaccine with the higher level of protection that will have the greater impact on the prevalence of HIV.
- Targeting high-risk groups is generally more effective than targeting the general population, although under the best-case scenario (95% vaccine efficacy) the impact of the two different vaccination strategies is comparable assuming no disinhibition. Targeting high-risk groups, however, typically requires substantially fewer doses of vaccine than targeting the general population for a similar or higher impact.

- Disinhibition has the potential to undo much of a vaccine's benefits and to aggravate the epidemic, although the assumption of total abandonment of condoms by CSWs is extreme.
- Conventional HIV prevention programmes, especially those targeting CSWs, can potentially achieve results that similar to a reasonably effective vaccine and are probably less sensitive to disinhibition effects. In particular, a vaccine that conveys substantially less than full protection to those who are immunized will not prevent CSWs from getting infected, although it will delay infection. Thus targeting vaccines with low protection to CSWs is potentially less effective than providing them with highly effective vaccines or condom-based programmes.

E. Rakai model (Gray et al., 2002)

Ron Gray and colleagues at Johns Hopkins University and Makerere University constructed a model to explore the effects of antiretroviral therapy (ART) and a preventive AIDS vaccine on the number of HIV-infected persons and HIV prevalence in Uganda over a 20-year period.

i) Model structure

The model developed by Gray *et al.* consists of a stochastic simulation model of HIV transmission combined with a demographic projection model stratified into five-year age groups. The HIV transmission model simulates HIV transmission from HIV-positive to HIV-negative individuals within HIV-discordant relationships. Data from Uganda were used to estimate the probability of transmission per sex act for HIV-positive individuals (assumed to depend upon the age, gender, and viral load of the HIV-positive partner), and numbers of sexual contacts HIV-positive individuals have with HIV-negative partners. Based on this information each coital act was simulated to determine whether the HIV-negative partner either seroconverted or remained seronegative at three years. Partners who remained uninfected were recycled back into the pool of uninfected individuals, whilst those who seroconverted joined the pool of HIV-infected persons and transmissions to their HIV-negative partners were simulated.

ii) Vaccine characteristics

In the vaccine simulations it was assumed that the vaccine acts by reducing the transmission probability per coital act by between 25% and 75% in HIV-negative persons and provides at least 20 years protection.

iii) Vaccination strategies

In the simulations the vaccine was targeted at all adults and vaccine coverage was assumed to range from 0% to 100%.

Vaccine-related disinhibition was modeled by randomly increasing the number of sexual partners per individual so that the average number of sexual partners was increased by 50% or 100% among all vaccine recipients.

iv) Epidemiological scenario

Model parameter values were based on empirical data from studies in Rakai, Uganda where there is a mature, generalized HIV epidemic.

v) Results

The simulated effects of a preventive vaccine on HIV incidence in the absence of disinhibition are recorded in Table 4.

Table 4. HIV incidence per 100 person-years for a preventive vaccine with varying levels of efficacy and population coverage. In the absence of an AIDS vaccine or widespread ART, the incidence of HIV was projected to be 1.57 per 100 person-years.

Vaccine coverage	Vaccine Efficacy		
	25%	50%	75%
0%	1.57	1.57	1.57
25%	1.52	1.43	1.33
50%	1.45	1.27	1.07
75%	1.38	1.12	0.81
100%	1.31	0.97	0.56

In the paper the authors highlight that:

- A vaccine of low protective efficacy (i.e., 25%) cannot by itself control the HIV epidemic. However, combining a low efficacy vaccine with a widespread ART programme that reduces viral load in HIV-positive individuals can result in a substantial reduction in HIV incidence.
- Disinhibition can significantly reduce the impact of an AIDS vaccine and could counteract the public health impact of the vaccine and result in an increase in HIV incidence.

III. Discussion

Mathematical modeling provides a useful tool for understanding the potential impact of a preventive AIDS vaccine. In particular, the information generated by mathematical modeling provides qualitative insights into how a vaccine with pre-defined properties might affect the future course of the epidemic under different epidemiological scenarios. From the modeling work to date, it is clear that the epidemiological and demographic impact of an AIDS vaccine depends on a number of factors including: where and when the vaccine is used; the properties of the vaccine; how it is used; and how people respond to its introduction.

At present, however, the results from the modeling work thus far are illustrative rather than predictive, as the model structures and parameters are limited by our understanding of the key epidemiological, demographic and behavioural parameters determining the spread of HIV and how these parameters change over time. In addition, the real impact of a preventive vaccine will depend not only on the characteristics of the vaccine but also on

local epidemiological and socioeconomic conditions, the existing public service delivery capacity, and the willingness of individuals to be vaccinated (see Box 3.)

Box 3. Factors that need to be considered when allocating limited supplies of vaccines in a population

- The state of the HIV epidemic when vaccination is initiated;
- The relative sizes of the risks groups in the population;
- The sexual and intravenous drug use mixing behaviour between and among risk groups;
- The type of vaccine action in terms of protecting an individual from infection (take or degree);
- The impact of the vaccine on protecting against infection of sexual partners and/or on protecting against disease progression in those infected despite vaccination;
- The level of protection provided by the vaccine against the multiple subtypes of HIV circulating in the population;
- The quantity of vaccine available for distribution;
- The levels of vaccine acceptance within the risk groups;
- The feasibility of vaccine distribution to the risk groups;
- The response of vaccinated and unvaccinated individuals to the vaccine and its impact on their use of condoms and/or rates of sexual partner change; and
- The HIV control objectives of the policymakers and their time frame.

Five different models were identified that have been used to explore the potential medium- to long-term impact of a preventive AIDS vaccine in developing countries. These models, whilst sharing a number of common features, differ considerably in their structures. This poses a challenge for policy makers wanting to explore the impact of an AIDS vaccine – should they develop a new model or adapt an existing model? And if they adapt an existing model, which one to use? In making this decision it is important to consider: the structure of each model; how user friendly it is; and how open the developers of the model are to collaboration. For example, if intravenous drug use makes an important contribution to viral spread in a country, then it would be inappropriate to use a model that does not incorporate this transmission route. In addition, it is essential to allocate enough time and resources to estimate the various country-specific parameters that go into a model and to project how they will change over time. Obtaining reliable estimates for these parameter values is crucial but can be very time-consuming and may require specific field-based studies.

The modeling work to date has focused on scenario analyses in which one set of epidemiological, demographic and behavioural parameters has been used to explore how particular characteristics of a vaccine, and to whom it is targeted, result in an impact on the HIV epidemic. Uncertainties in the underlying epidemiological, demographic and behavioural parameters, however, also influence the impact of the vaccine and it is therefore important that future work incorporate both uncertainty and sensitivity analyses. This work will also help guide future research by identifying those parameters that have an important effect on the relative impact of alternative vaccine strategies and where improving our understanding is crucial.

AIDS vaccine modeling is still in its early stages and there is a need both to improve the current generation of models and to expand the range of topics investigated. For example,

our understanding of the impact of an AIDS vaccine at the population level would be improved by:

1. *Expanding the properties of the AIDS vaccine investigated to reflect the characteristics of the vaccines currently under development.* To date, only a limited number of the potential characteristics of a vaccine have been systematically explored at a population level (e.g., duration of protection, level and type of protection) and even these have been based on stylized vaccines. Clearly there is a need to explore other characteristics in more detail based on the characteristics of the most advanced products. For example, in the case of the Merck AIDS vaccine based on an adenovirus vector, this might include exploring how (1) pre-existing immunity to the particular vector used in the vaccine may affect the effectiveness of the vaccine and (2) estimating the potential benefits from using a different vector with lower levels of pre-existing immunity.

2. *Increasing understanding of the acceptability and ease of delivering an AIDS vaccine to different potential populations.* At present, modelers have to assume *de facto* that the vaccine will be acceptable and estimate what levels of coverage can be reached in different risk groups over a particular period of time. Improving our understanding of vaccine acceptability and the challenges of delivering a vaccine to different population groups within a country should help ensure that appropriately targeted strategies are implemented.

3. *Exploring the consequence of introducing a vaccine that protects against one or more subtypes of HIV in a population where multiple subtypes of HIV are circulating.* In many countries there are a number of subtypes of HIV circulating in the population and the consequences of introducing a vaccine that provides protection against one or more of these subtypes needs to be investigated.

Mathematical modeling has an important role to play in informing policymakers about the relative merits of different HIV prevention strategies. At present, however, funding for modeling HIV programmes is limited and there is no coherent plan for investigating the range of topics that are crucial to ensure that scarce health resources are used as efficiently as possible.

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2. Barth-Jones, D.C., Chegulet, B.K., Longini, I.M., Marum, L.H., Ackers, M.L., Essenmacher, L., Esparza, J., & Mastro, T.D. (2003). Modeling the potential impact of a partially effective HIV vaccine in a generalized African HIV-1 epidemic: Evaluating strategies for HIV vaccine use. Technical Report: 03-08. Emory University, Rollins School of Public Health, Department of Biostatistics.

3. Garnett, G.P., Desai, K., Williams, J. (2003). The potential impact of a prophylactic HIV vaccination as a function of vaccine properties: Results of the Imperial College model. World Bank Policy Research Working Paper 2811 - Technical Annex 1. World Bank.

4. 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.

5. Nagelkerke, N.J.D. & De Vlas, S. (2003). The epidemiological impact of an HIV vaccine on the HIV/AIDS epidemic in Southern India. World Bank Policy Research Working Paper 2978. World Bank.

6. Seitz, S.T. (2003). The potential impact of prophylactic vaccines: Results of the iwgAIDS model. World Bank Policy Research Working Paper 2811 - Technical Annex 2. World Bank.

7. Stover, J., Garnett, G.P., Seitz, S. & Forsythe, S. (2002). The epidemiological impact of an HIV/AIDS vaccine in developing countries. World Bank Policy Research Working Paper 2811. World Bank.

Appendix: Other published studies that explore the potential impact of a preventive AIDS vaccine

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

Abstract: To combat the spread of HIV, progress on vaccine development is eagerly awaited. Haynes in this series has described the progress made so far with various vaccine types. This article describes how mathematical modelling techniques can be used to predict the likely impact of low-efficacy vaccines in community transmission of the virus. The answers are often not what one would predict by intuition alone, and they have great bearing on the likely success of such vaccination strategies.

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

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

3. 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.

Abstract: A safe and effective HIV vaccine to prevent infection and/or to moderate disease is urgently needed. Research progress has been slower than anticipated for a variety of reasons including uncertainty over which immunogen to use (i.e. recombinant subunit envelope proteins or whole HIV-1 products), confusion on which immunological markers best correlate with protection, the relevance of the HIV-1 chimpanzee model to infection in humans and the significance of the rapid evolution of HIV-1, with different clades of

the virus emerging in different parts of the world. However, what some would interpret as encouraging results, from Phase I and II trials of recombinant envelope glycoprotein vaccines, have raised the question of whether the time is right to start Phase III trials in humans with immunogens that may have low to moderate efficacy. By using mathematical models and data from epidemiological studies, we examine the potential impact of such vaccines within heterosexual communities with high rates of infection. Analyses suggest that it will be difficult to block HIV-1 transmission even with very high levels of mass vaccination. The cost of sustaining high levels of herd immunity with a vaccine of short protection duration is likely to be high. However, assessments of impact over the long duration of an HIV-1 epidemic indicate that many cases of HIV infection and associated mortality can be prevented by immunogens with efficacy of 50% or less and a five year protection duration. These analyses add some support to the view that proceeding with Phase III efficacy trials may be appropriate in high HIV transmission regions even if the consensus option on potential efficacy of the immunogen is that it will be low.

4. 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.

Abstract: The utility of live attenuated vaccines for controlling HIV epidemics is being debated. Live attenuated HIV vaccines (LAHV) could be extremely effective in protecting against infection with wild-type strains, but may not be completely safe as the attenuated strain could cause AIDS in some vaccinated individuals. We present a theoretical framework for evaluating the consequences of the tradeoff between vaccine efficacy (in terms of preventing new infections with wild-type strains) and safety (in terms of vaccine-induced AIDS deaths). We use our framework to predict, for Zimbabwe and Thailand, the epidemiological impact of 1,000 different (specified by efficacy and safety characteristics) LAHVs. We predict that paradoxically: (i) in Zimbabwe (where transmission is high) LAHVs would significantly decrease the AIDS death rate, but (ii) in Thailand (where transmission is low) exactly the same vaccines (in terms of efficacy and safety characteristics) would increase the AIDS death rate. Our results imply that a threshold transmission rate exists that determines whether any given LAHV has a beneficial or a detrimental impact. We also determine the vaccine perversity point, which is defined in terms of the fraction of vaccinated individuals who progress to AIDS as a result of the vaccine strain. Vaccination with any LAHV that causes more than 5% of vaccinated individuals to progress to AIDS in 25 years would, even 50 years later, lead to perversity (i.e., increase the annual AIDS death rate) in Thailand; these same vaccines would lead to decreases in the annual AIDS death rate in Zimbabwe.

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

Abstract: Theory is linked with data to assess the probability of eradicating human immunodeficiency virus (HIV) in San Francisco through the use of prophylactic vaccines. The necessary vaccine efficacy levels and population coverage levels for eradication are quantified. The likely impact of risk behaviour changes on vaccination campaigns is assessed. The results show it is unlikely that vaccines will be able to eradicate HIV in San

Francisco unless they are combined with considerable reductions in risk behaviours. Furthermore, if risk behaviour increases as the result of a vaccination campaign, then vaccination could result in a perverse outcome by increasing the severity of the epidemic.

6. 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.

Abstract: Mathematical models can be used as health policy tools and predictive tools. Here we review how mathematical models have been used both to predict the consequences of specific epidemic control strategies and to design epidemic control strategies. We review how models have been used to evaluate the potential impact on HIV epidemics of (i) combination antiretroviral therapies (ART) and (ii) imperfect vaccines. In particular, we discuss how models have been used to predict the potential effect of ART on incidence rates, and to predict the evolution of an epidemic of drug-resistant HIV. We also discuss, in detail, how mathematical models have been used to evaluate the potential impact of prophylactic, live-attenuated and therapeutic HIV vaccines. We show how HIV vaccine models can be used to evaluate the epidemic-level impact of vaccine efficacy, waning in vaccine-induced immunity, vaccination coverage level, and changes (increases or decreases) in risky behaviour. We also discuss how mathematical models can be used to determine the levels of cross-immunity that vaccines will need to attain if they are to be used to control HIV epidemics in countries where more than one subtype is being transmitted.

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.

Abstract: Because of the variability of HIV, the first AIDS vaccine is likely to be only partially effective. There is some concern among scientists that a low-efficacy vaccine could worsen the HIV epidemic if vaccinated individuals increase their risk behaviour under the false assumption of immunity. To address this concern, we constructed a dynamic compartmental model that simulated the course of the HIV/AIDS epidemic in a population of injection drug users in Bangkok, Thailand. The model calculated long-term HIV prevalence, number of AIDS cases, and total population size for two scenarios: vaccination programme versus no vaccination programme. We used sensitivity analyses to evaluate the impact of post-vaccination risk behaviour change on HIV prevalence. A 75% effective vaccine led to a 40-year HIV prevalence of 37% with vaccination and 50% without vaccination. Post-vaccination behaviour change had only a limited effect on the results with a 75% effective vaccine but a significant effect with a 30% effective vaccine. If 90% of low-risk individuals responded to a 30% effective vaccine with increased high-risk behaviour, the benefit of vaccination disappeared. These results agree with analyses of the epidemic among gay men. If injection drug behaviour is indeed modifiable, our findings have significant policy and planning implications.

8. Bos, J.M. & Postma, M.J. (2001). The economics of HIV vaccines: projecting the impact of HIV vaccination of infants in sub-Saharan Africa. *Pharmacoeconomics, 19*, 937-46.

Abstract: OBJECTIVES: (i) To project vaccine parameters, economic consequences and market size associated with HIV-1 vaccination of infants in sub-Saharan Africa through the Expanded Programme on Immunisation (EPI); and (ii) to assess threshold values for price and effectiveness. STUDY DESIGN AND METHODS: Cost-effectiveness analysis using a decision-analysis model linking epidemiological data with economic information. Epidemiological data on the burden of disease of HIV were obtained from the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS. The decision analysis model was constructed using estimates of lifetime chances of HIV infection. To assess threshold values for price and effectiveness, a maximum value for cost effectiveness in developing countries of $US100 was used in the base case. One-way and multivariate sensitivity analysis was performed on relevant parameters, assessing the impact of these parameters on the results of our analysis. In the base case, health benefits and consequences were discounted at a rate of 3%. STUDY PERSPECTIVE: Societal. RESULTS: According to our model, introduction of an HIV-1 vaccine in the EPI would result in the vaccination of 8717112 infants in sub-Saharan Africa per year. This corresponds to the prevention of 1839355 cases of HIV per year, gaining 16461800 disability-adjusted life years (DALYs). The cost-effectiveness ratio of the intervention would be $US3.4 per DALY gained (1998 values) at a vaccine price in the base case of $US5. At the same price the estimated size of the market would be approximately $US44536111 per year. CONCLUSION: If technological and financial problems associated with the development of an HIV vaccine can be solved, HIV vaccination in Africa could be both cost effective and potentially profitable.

9. 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.

Abstract: Studies of human immunodeficiency virus (HIV) vaccines in animal models suggest that it is difficult to induce complete protection from infection (sterilizing immunity) but that it is possible to reduce the viral load and to slow or prevent disease progression following infection. We have developed an age-structured epidemiological model of the effects of a disease-modifying HIV vaccine that incorporates the intra-host dynamics of infection, a transmission rate and host mortality that depend on the viral load, the possible evolution and transmission of vaccine escape mutant viruses, a finite duration of vaccine protection, and possible changes in sexual behaviour. Using this model, we investigated the long-term outcome of a disease-modifying vaccine and utilized uncertainty analysis to quantify the effects of our lack of precise knowledge of various parameters. Our results suggest that the extent of viral load reduction in vaccinated infected individuals (compared to unvaccinated individuals) is the key predictor of vaccine efficacy. Reductions in viral load of about 1 $\log_{10}$ copies ml^{-1} would be sufficient to significantly reduce HIV-associated mortality in the first 20 years after the introduction of vaccination. Changes in sexual risk behaviour also had a strong impact on the epidemic outcome. The impact of vaccination is dependent on the population in which it is used, with disease-modifying vaccines predicted to have the most impact in areas of low

prevalence and rapid epidemic growth. Surprisingly, the extent to which vaccination alters disease progression, the rate of generation of escape mutants, and the transmission of escape mutants are predicted to have only a weak impact on the epidemic outcome over the first 25 years after the introduction of a vaccine.

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

Abstract: We developed a dynamic model of HIV transmission to evaluate the costs and benefits of HIV –vaccine programmes in a population of homosexual men. We examined how changes in high-risk sexual behaviour and the growth pattern of the epidemic influence the cost-effectiveness of preventive vaccines and of therapeutic vaccines. We found that the effect of reduction in condom use is more important for therapeutic vaccines than for preventive vaccines. Therapeutic vaccines may increase HIV seroprevalence in the population, unless the vaccine programme is accompanied by increased condom use. Epidemic growth patterns also influence the cost-effectiveness of both vaccines, but the effects of re more pronounced for preventive vaccines, which are more cost-effective in an early-stage epidemic than in a late-stage epidemic.

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

Abstract: Theoretical results indicate that extensive coverage with low efficacy type 1 human immunodeficiency virus (HIV) vaccines could substantially reduce the incidence of HIV in developing countries. There is a non-linear relationship between effective vaccine coverage and HIV prevalence such that improved efficacy brings diminishing returns. The relative contribution of HIV-associated mortality and behavioural heterogeneity to this non-linear relationship is explored using deterministic mathematical models. If the duration of risk of acquiring HIV is long relative to the HIV incubation period then infection-associated mortality can generate the non-linear relationship. However, in its absence the same relationship results from behavioural heterogeneity. Models of HIV vaccination alongside other interventions generate qualitative results that suggest that targeted interventions lead to less redundancy in control efforts.

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

Abstract: Relatively recently, mathematical models have been applied to issues related to HIV vaccination. Significant progress has been made towards understanding how rather ineffective vaccines will perform in trials and in the community, but some areas still need research.

13. 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.

Abstract: OBJECTIVE: To evaluate the population effects of potential preventive and therapeutic vaccines in early- and late-stage epidemics in a population of homosexual men. METHODS: An epidemic model was used that simulated the course of the epidemic for a population of homosexual men in San Francisco, California. Vaccine programmes were evaluated by the number of cases of HIV averted, the effect on the prevalence of HIV, and by the gain in quality-adjusted life years (QALY) for the total population. RESULTS: In the model, a preventive vaccine prevented 3877 cases of HIV infection during a 20-year period, reduced the projected prevalence of HIV infection from 12 to 7% in a late-stage epidemic, and gained 15,908 QALY. A therapeutic vaccine that did not affect the infectivity of vaccine recipients increased the number of cases of HIV infection by 210, resulted in a slight increase in the prevalence of HIV infection from 12 to 15% in a late-stage epidemic, and gained 8854 QALY. If therapeutic vaccines reduced infectivity, their use could produce net gains of QALY in the population that were similar to gains from the use of preventive vaccines. In an early-stage epidemic, the advantage of a preventive vaccine programme relative to a therapeutic vaccine programme was markedly enhanced. CONCLUSIONS: Both preventive and therapeutic vaccine programmes provided substantial benefit, but their relative merit depended on which outcome measures were assessed. Evaluation of HIV vaccine programmes based solely on cases averted or on prevalence of HIV in the population underestimates the benefit associated with therapeutic vaccine programmes. The effect of a therapeutic HIV vaccine on the epidemic outcomes depended markedly on whether the therapeutic vaccine reduced the infectivity of the vaccine recipient. The relative merits of preventive and therapeutic vaccines depend on the stage of the epidemic. Field vaccine trials should evaluate correlates of infectivity, such as HIV viral load. HIV vaccine implementation strategies should be tailored to the dynamics of the epidemic in specific populations.

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

Abstract: We developed and used mathematical models to assess vaccine programmes for controlling tow subtypes of HIV, both for developing countries where more than one subtypes is present and for countries where only one subtype is present but other subtypes may invade. We began by formulating a model of the intrinsic transmission dynamics of the two HIV subtypes and then extended this model to include the effects of a prophylactic vaccine that provides a degree of protection against infection by one subtype and vaccine-induced cross-immunity against infection by the second subtype. Using these models we assessed the potential impact of using a prophylactic vaccine when one subtype of HIV is endemic and a second subtype is introduced into the community. In each case, mass vaccination could result in one of four possible outcomes: (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.

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

Abstract: Most current candidate HIV vaccines seem to produce little protection against infection, but reduce viral load and slow the decline in CD4 lymphocyte numbers. Such disease-modifying vaccines could potentially provide important population-level benefits by reducing transmission, but could possibly also increase transmission. We address the following question: could disease-modifying HIV vaccines cause population-level perversity (i.e., increase epidemic severity)? By analysing a mathematical model and defining a new quantity-the fitness ratio-we show that disease-modifying vaccines that provide only a low degree of protection against infection and/or generate high fitness ratios will have a high probability of making the epidemic worse. However, we show that if disease-modifying vaccines cause a 1.5 $\log_{10}$ reduction in viral load (or greater) then perversity cannot occur (assuming risk behaviour does not increase). Finally, we determine threshold surfaces for risk behaviour change that determine the boundary between beneficial and perverse outcomes; the threshold surfaces are determined by the fitness ratio, the proportion of the population that are "successfully vaccinated", and the degree of change of risk behaviour in unvaccinated infected individuals. We discuss the implications of our results for designing optimal vaccination control strategies.

16. 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.**

Abstract: Cytotoxic T lymphocyte (CTL)-based HIV vaccine concepts shown to reduce viremia and postpone disease but not to prevent infection in monkeys are currently in human phase 1 trials. To evaluate the potential efficacy of vaccines that cannot prevent HIV-1 to infect and escape immunologic control, we designed a mathematic model that correlates the level of viremia to both infectiousness and disease progression. We speculate that vaccinees will have a virologic set point and disease progression rates comparable to untreated HIV-1-infected individuals with the best prognosis. Our model (illustrated with R0 = 3) shows that a sexually active population can ultimately be reduced to 26% of its initial size as a result of AIDS-related mortality in the absence of treatment or vaccination. Start of vaccination when HIV-1 prevalence is still low might postpone the peak incidence of infection and the dramatic decline in population size by up to 22 years. In conclusion, CTL-based vaccines that do not prevent HIV-1 infection but do postpone the time to onset of AIDS have considerable potential to curb the spread of HIV-1 and to postpone high AIDS-related mortality on a population level. The number of long-term survivors is substantially increased only when vaccination is initiated early in an AIDS epidemic, however.

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