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The Epidemiological Impact of an HIV/AIDS Vaccine in Developing Countries

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Technical Annex 1.

The potential impact of prophylactic HIV vaccination as a function of vaccine properties: Results of the Imperial College Model

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Executive Summary

The influence of a vaccine with a range of different properties has been explored in a mathematical model of the spread of HIV in a heterosexual population, reflecting the generalized epidemics observed in sub-Saharan Africa. A number of key conclusions can be derived from this work:

- 1) A vaccine with a low (i.e. 50%) efficacy can have a significant epidemiological impact.
- 2) The effectiveness of the vaccine is markedly reduced if its duration of protection is short relative to the age range over which high risk behaviours are maintained.
- 3) For a rapid turn around in the incidence of HIV infection a 'catch-up' vaccination programme amongst sexual active adults would be desirable.
- 4) The type of protection provided by the vaccine has an influence on the problem of increasing risk behaviour in response to vaccination. If the vaccine reduces the risk of acquiring infection per exposure then its beneficial effects can be overturned. Alternatively, if a fraction of the population is protected from all challenges, then any increase in risk cannot lead to the infection of the protected individuals, and the aggregate effect of the vaccine is unlikely to be undermined by behavioural reversals.
- 5) Targeting can be the most effective vaccine strategy per vaccinated individual, but may not be the most effective use of a vaccine. Targeting is less likely to be appropriate for a 'leaky' vaccine where the number of challenges influence the chances of a breakthrough infection.

Introduction

Historically vaccines have been introduced assuming that they are highly efficacious. However, as the immunological challenges of vaccine development increase then it is likely that the efficacy of vaccine products will decline. It is conceivable that the first generation of HIV vaccines with an efficacy demonstrable in vaccine trials will not have extremely high efficacy. The acceptability of low efficacy vaccines will depend upon three main factors: their cost; the willingness of individuals to accept a less efficacious product; and the epidemiological effectiveness expected and demanded by decision makers if a vaccine is to be used. The work presented here uses a mathematical model to explore the epidemiological impact of vaccines with a range of predefined properties in the context of a generalized HIV epidemic as has been observed in Zimbabwe and other countries of sub-Saharan Africa. To parameterize the model we focus on demographic and behavioural variables from rural Zimbabwe. The impact of the vaccines is compared, along with the potential impact of other population level changes in patterns of risk for HIV infection.

General Theory

Many of the implications of vaccine success and failure and its relationship to changing patterns of risk can be explored through analytical solutions of simple models for a general sexually transmitted disease. Here the basic reproductive number, R_0 , defined as the number of new infections caused when an infection enters an entirely susceptible population is an important measure, often conceptually described as the product of the mean rate of sexual contact, the mean transmission probability and the mean duration of infectiousness (Anderson and May, 1991).

The protection provided by a vaccine which reduces the incidence of infection in a trial can reflect a variety of biological effects and two extremes can be defined to illustrate this point. First a vaccine may protect a fraction of recipients from all challenges (termed 'take') or, second, vaccine may protect everyone from a fraction of challenges (termed 'degree') (Smith et al, 1984). If we define V_t as coverage with a vaccine providing total protection with a take efficacy e_t then we can derive a solution for the endemic prevalence of infection p . We can also include a parameter describing the change in one of the parameters within the basic reproductive number I . This could, for example, reflect an alteration in the rate change of sexual partners, with a value of 1 implying that the number remains constant 2 that it doubles and 0.5 that it halves.

$$p = 1 - \frac{1}{R_0 \cdot I} - V_t \cdot e_t$$

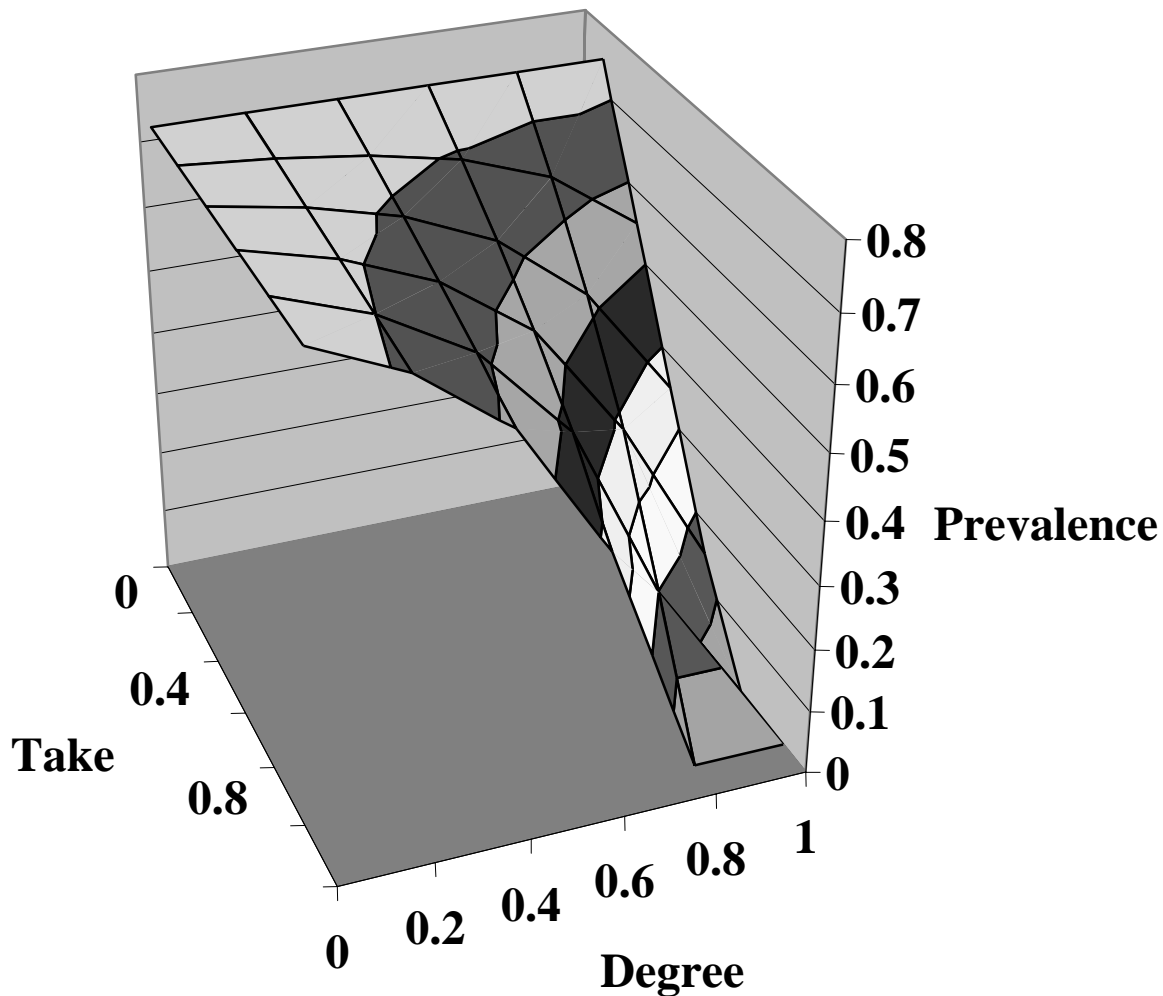
Further, if we define V_d as coverage with a vaccine providing degree protection with efficacy e_d then we can derive a solution for the endemic prevalence of infection p for this vaccine. The solution for p in this case is

$$p = 1 - \frac{1}{R_0 \cdot I \cdot (1 - V_d \cdot e_d)}$$

These are the solutions for the two extreme influences of a vaccine. It can easily be seen that if our vaccine provides ‘take’ type protection then there is a linear decrease in the prevalence of infection, whereas if it provides ‘degree’ type protection there is a nonlinear decrease. Furthermore, the scale of behavioural reversals works in direct opposition to degree vaccination where a coverage and efficacy of 50% would be overturned by a doubling in rates of sex partner change. Alternatively, in the case of a take type vaccine derived protection behavioural reversals work differently and are much less likely to overturn the impact of a vaccine.

If a vaccine has a combination of taking in a given fraction and providing degree type protection, then its impact is a combination of the two types (Longini & Halloren, 1999). The shape of the relationship between prevalence, take and degree for a vaccine against infection in a homogeneous population with a reproductive number of 10 is illustrated in Figure 1.

Impact of Vaccination (simple theory)



Which type of action, take or degree, can we expect from an HIV vaccine? In the past it has generally been assumed that vaccines provide a ‘take’ protection – either individuals sero-convert or they don’t (Smith et al, 1984). This may also be true for HIV where the protection may depend upon eliciting a particular type of immune response (e.g. cytotoxic cellular immunity, T-helper immunity or antibodies). Alternatively, heterogeneous genotypes of the virus, or the dose of virus within the challenge, may overcome the vaccine derived immune response for a fraction of exposures. This might particularly apply if protective immune responses operate within the mucosa and are able to prevent infection.

Model Structure

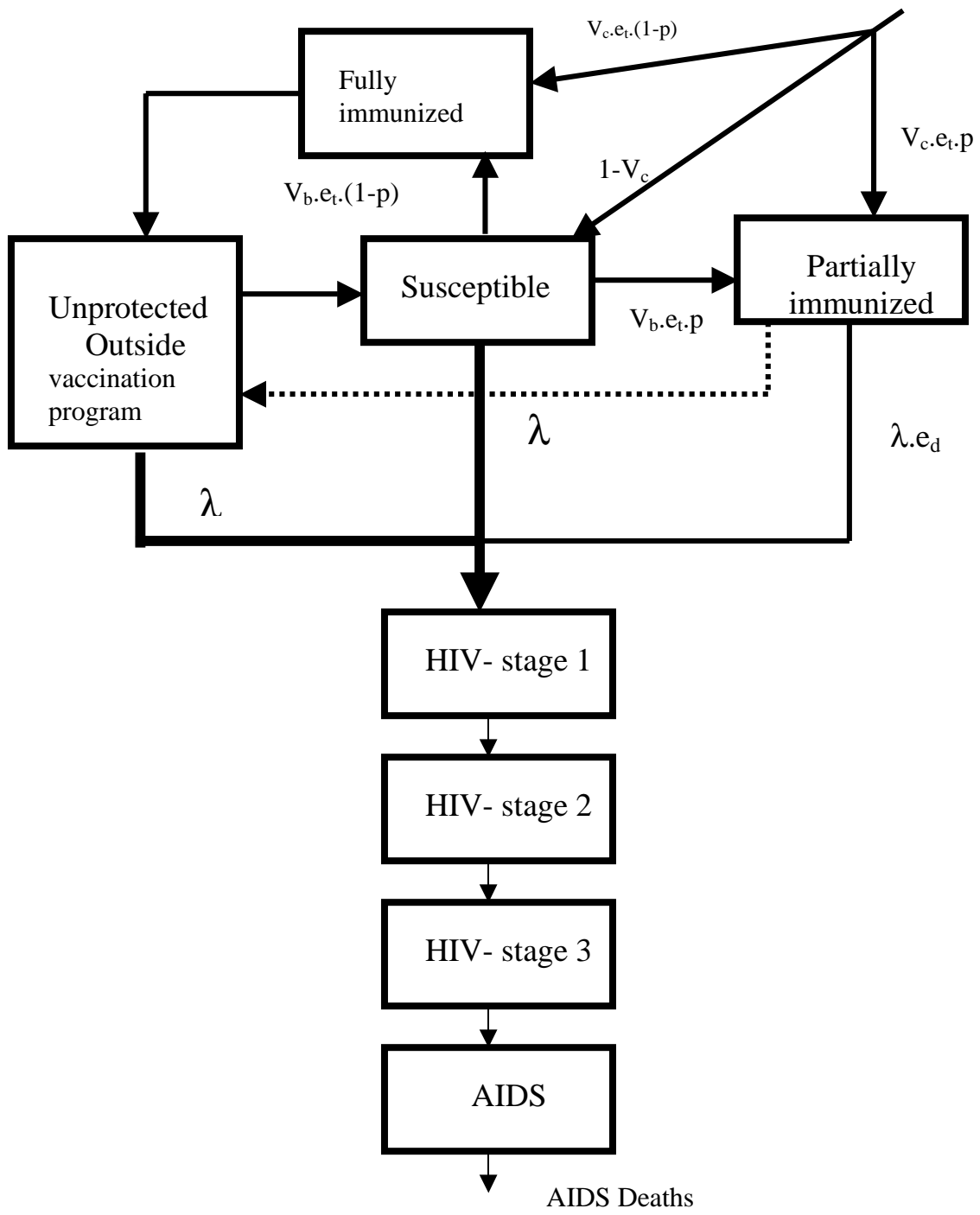
The transmission dynamics of HIV in a heterosexual population is described in an age, sex and sexual activity stratified model, where the population is additionally stratified according to rates of sexual partner change (Garnett & Anderson, 1993; 1994; Garnett 1998). A range of vaccine behaviours has been incorporated into this modeling framework as described illustratively in Fig. 2.

At the age of 15 years we assume adolescents enter the at risk sexually active population. Here they can receive vaccine if a ‘cohort vaccination’ policy is operating. A fraction V_c receive the vaccine at this stage. The vaccine can take in a fraction of the population to provide complete protection – this provides one measure of efficacy e_t . Alternatively the vaccine can provide partial protection where a fraction of exposures lead to breakthrough infections. The fraction of exposures that do not lead to infection provide a second measure of efficacy – degree efficacy e_d . An alternative to cohort vaccination is a ‘blanket’ vaccination policy during which all individuals are vaccinated at a given level of coverage each year. The implications of a particular coverage needs consideration as in such cases there is a cumulative increase in the proportion of the population vaccinated, such that after t years of vaccination a fraction equal to the expression $1 - e^{-V_b \cdot t}$ of those continuously in the population will have received vaccine.

The Vaccine is assumed to loose efficacy at a specified, constant rate – leading to a mean duration of protection that is the inverse of this rate with an assumed exponential distribution of durations of protection. (NB. This assumption could increase the importance of loss of protection as does the assumption made in the current version of the model that individuals remain in a given sexual activity class throughout their sexually active lifespan.) If, on loss of vaccine protection, individuals re-enter the susceptible population they will remain at risk of infection when cohort vaccination is operating., whereas, with blanket vaccination they could rapidly be re-immunized, perhaps unrealistically. Hence, a category of susceptibles outside of the vaccination program allows for an average delay until booster vaccination becomes appropriate.

The details of the model equations, in which the population was stratified according to sex, age and sexual activity, and the parameter values used, are defined and reviewed in earlier publications (Garnett and Anderson, 1993a; 1994). The model was used to explore the influence of certain vaccine properties in earlier publications (Anderson et al, 1996; Anderson & Garnett, 1996; Garnett 1998), but has been elaborated here to increase the range of circumstances represented. A detailed description of the model follows.

Fig. 2



Model Equations

The population is categorised according to HIV infection as, susceptible $X_{kl}(a,t)$; fully protected by vaccine $P_{kl}(a,t)$; partially protected by vaccine $Q_{kl}(a,t)$; unprotected by vaccine but not ‘eligible’ to receive vaccine $U_{kl}(a,t)$. The population is stratified according to sex ($k = 1$ for men and $k = 2$ for women), sexual activity (with four groups $l = 1, \dots, 4$) defined according to rate of sexual partner change and, age (a). HIV infection is described by the flow of incident cases through four compartments, three representing asymptomatic HIV-1 infection ($Y_{1kl}(a,t)$; $Y_{2kl}(a,t)$; $Y_{3kl}(a,t)$) and one AIDS ($A_{kl}(a,t)$). This is illustrated in Figure 2 and serves two functions. First, it allows for a long and variable incubation period and second it allows parameters to vary for individuals at different stages of infection. In the current application the transmission probability, both between heterosexual partners and between mothers and infants can vary according to the stage of infection. The variation in transmission probabilities is biologically related to the observed high viraemia in the early and late stages of HIV infection

$\mu_k(a)$ is the age specific death rate. The boundary conditions at age zero (see Garnett and Anderson, 1994) depend on the fertility rate of the population of reproductive aged women and the proportion of infants born infected (see Gregson, et al (1994) for an exploration of the demographic impact of HIV using this framework). Once people develop AIDS they suffer an additional AIDS associated mortality rate ($\alpha(a)$).

The partial differential equations are solved numerical on a discretized age-time grid where all ages are followed. However, in terms of transmission of HIV, the population is divided into 7 age groups, i , each covering 5 years of age. The first group starts with sexual maturity at age 15 years. Up until age 15 all children are described in a general susceptible class $X_k(a,t)$ or infected $Y_{k,s}(a,t)$:

$$\begin{aligned} \frac{\partial X_k(a,t)}{\partial a} + \frac{\partial X_k(a,t)}{\partial t} &= -\mu_k(a).X_k(a,t) \\ \frac{\partial Y_{k,1}(a,t)}{\partial a} + \frac{\partial Y_{k,1}(a,t)}{\partial t} &= -(\mu_k(a) + \gamma_1(a)).Y_{k,1}(a,t) \\ \frac{\partial Y_{k,s}(a,t)}{\partial a} + \frac{\partial Y_{k,s}(a,t)}{\partial t} &= \gamma_{(s-1)}(a)Y_{k,(s-1)}(a,t) - (\mu_k(a) + \gamma_s(a)).Y_{k,s}(a,t) \\ \frac{\partial A_{k,s}(a,t)}{\partial a} + \frac{\partial A_{k,s}(a,t)}{\partial t} &= \gamma_3(a)Y_{k,3}(a,t) - (\mu_k(a) + \alpha(a)).A_{k,1}(a,t) \end{aligned}$$

The boundary conditions for births are the number of children born either susceptible or infected. At age 15 there are boundary conditions for the sexually active classes and two sets of assumptions reflected the different assumptions about the action of the vaccine. For protection of a fraction from all challenges (take):

$$\begin{aligned}
X_{k,l}(15,t) &= \phi_{k,l} \cdot X_k(15 - \delta, t - \delta) \cdot (1 - V_{c,l}) \\
P_{k,l}(15,t) &= \phi_{k,l} \cdot X_k(15 - \delta, t - \delta) \cdot V_{c,l} \cdot e_t \\
Q_{k,l}(15,t) &= \phi_{k,l} \cdot X_k(15 - \delta, t - \delta) \cdot V_{c,l} \cdot (1 - e_t) \\
U_{k,l}(15,t) &= 0
\end{aligned}$$

For a vaccine which provides protection for all from a fraction of challenges:

$$\begin{aligned}
X_{k,l}(15,t) &= \phi_{k,l} \cdot X_k(15 - \delta, t - \delta) \cdot (1 - V_{c,l}) \\
P_{k,l}(15,t) &= \phi_{k,l} \cdot X_k(15 - \delta, t - \delta) \cdot V_{c,l} \\
U_{k,l}(15,t) &= 0
\end{aligned}$$

In the first it is assumed that $Q_{kl}(a,t)$, individuals are fully susceptible but not eligible for immediate revaccination and in the second that all those vaccinated are only partially protected. In this case the group represented by $Q_{kl}(a,t)$ plays no role.

Where cohort vaccination is administered in a fraction V_c . The vaccine is assumed to take in a fraction e_t or to provide partial protection. Those who the vaccine has failed to protect remain susceptible but, also are not repeatedly vaccinated until they re-enter the susceptible class at a rate ψ .

For continuous vaccination individuals are removed at a rate $V_b(a,t)$ from the susceptible to the immunised classes $P_{kl}(a,t)$ and $Q_{kl}(a,t)$, and the class in which the vaccine has waned $U_{kl}(a,t)$. This latter prevents rapid revaccination of vaccine failures through waning. For the take type vaccine the full set of equations for the state variables is:

$$\begin{aligned}
\frac{\partial X_{kl}(a,t)}{\partial a} + \frac{\partial X_{kl}(a,t)}{\partial t} &= -[\lambda_{kli}(t) + \mu_k(a) + V_{b,l}(a,t)]X_{kl}(a,t) + \sigma U_{k,l}(a,t) + \psi Q_{k,l}(a,t) \\
\frac{\partial Y_{1kl}(a,t)}{\partial a} + \frac{\partial Y_{1kl}(a,t)}{\partial t} &= \lambda_{kli}(t)[X_{kl}(a,t) + U_{k,l}(a,t) + Q_{k,l}(a,t)] - [\gamma_1(a) + \mu_k(a)]Y_{1kl}(a,t) \\
\frac{\partial Y_{skl}(a,t)}{\partial a} + \frac{\partial Y_{skl}(a,t)}{\partial t} &= \gamma_{(s-1)}(a)Y_{(s-1)kl}(a,t) - [\gamma_s(a) + \mu_k(a)]Y_{skl}(a,t) \\
\frac{\partial A_{kl}(a,t)}{\partial a} + \frac{\partial A_{kl}(a,t)}{\partial t} &= \gamma_3(a)Y_{3kl}(a,t) - [\mu_k(a) + \alpha(a)]A_{kl}(a,t) \\
\frac{\partial P_{kl}(a,t)}{\partial a} + \frac{\partial P_{kl}(a,t)}{\partial t} &= V_{b,l}(a) \cdot X_{kl}(a,t) \cdot e_t - (\mu_k(a) + f)P_{kl}(a,t) \\
\frac{\partial Q_{kl}(a,t)}{\partial a} + \frac{\partial Q_{kl}(a,t)}{\partial t} &= V_{b,l}(a) \cdot X_{kl}(a,t) \cdot (1 - e_t) - \lambda_{kli}(t) \cdot Q_{k,l}(a,t) - (\mu_k(a) + \psi)Q_{kl}(a,t) \\
\frac{\partial U_{kl}(a,t)}{\partial a} + \frac{\partial U_{kl}(a,t)}{\partial t} &= f \cdot P_{kl}(a,t) - (\mu_k(a) + \sigma + \lambda_{kli}(t))U_{kl}(a,t)
\end{aligned}$$

Whereas for a degree vaccine the equations for the state variables are:

$$\begin{aligned}
\frac{\partial X_{kl}(a,t)}{\partial a} + \frac{\partial X_{kl}(a,t)}{\partial t} &= -[\lambda_{kli}(t) + \mu_k(a) + V_{b,l}(a,t)]X_{kl}(a,t) + \sigma U_{k,l}(a,t) \\
\frac{\partial Y_{1kl}(a,t)}{\partial a} + \frac{\partial Y_{1kl}(a,t)}{\partial t} &= \lambda_{kli}(t)[X_{kl}(a,t) + U_{k,l}(a,t)] + \lambda_{kli}(t).(1 - e_d).P_{k,l}(a,t) - [\gamma_1(a) + \mu_k(a)]Y_{1kl}(a,t) \\
\frac{\partial Y_{skl}(a,t)}{\partial a} + \frac{\partial Y_{skl}(a,t)}{\partial t} &= \gamma_{(s-1)}(a)Y_{(s-1)kl}(a,t) - [\gamma_s(a) + \mu_k(a)]Y_{skl}(a,t) \\
\frac{\partial A_{kl}(a,t)}{\partial a} + \frac{\partial A_{kl}(a,t)}{\partial t} &= \gamma_3(a)Y_{3kl}(a,t) - [\mu_k(a) + \alpha(a)]A_{kl}(a,t) \\
\frac{\partial P_{kl}(a,t)}{\partial a} + \frac{\partial P_{kl}(a,t)}{\partial t} &= V_{b,l}(a).X_{kl}(a,t).e_t. - (\mu_k(a) + f + \lambda_{kli}(t).(1 - e_d))P_{kl}(a,t) \\
\frac{\partial U_{kl}(a,t)}{\partial a} + \frac{\partial U_{kl}(a,t)}{\partial t} &= f.P_{kl}(a,t) - (\mu_k(a) + \sigma + \lambda_{kli}(t))U_{kl}(a,t)
\end{aligned}$$

The force of infection $\lambda_{kli}(t)$ is the sex, age and activity specific rate of incidence per susceptible per year and is derived from the equation:

$$\lambda_{kli}(t) = \sum_{j=l}^{n_1} \sum_{m=1}^{n_2} \left[c_{klmij}^* \rho_{klmij} \frac{\sum_{s=1}^3 (\beta_{sk} Y_{sk'mj}(t))}{N_{k'mj}(t) - A_{k'm}(t)} \right].$$

The risk of infection depends upon the sex, age and activity group specific rate of sexual partner change (c_{kli}), the probability that a sexual partner comes from a particular age and activity group of the opposite sex ($\rho_{k'lmij}$), the proportion of such partners that are infected and the likelihood of transmission per sexual partnership from an infected to a susceptible (β_{sk}), which depends upon the sex and stage of infection of the infected host.

It should be noted that because the vaccine is assumed to only alter susceptible recipients there are no vaccination rates explicit in the model equations for those already HIV infected. This does not imply that those infected with HIV would not receive the vaccine. From the above equations it could equally be assumed that those infected are not vaccinated or that they are.

The empirical study of patterns of sexual mixing has been developed alongside theoretical studies of their impact (Jacquez et al, 1988; Anderson et al, 1990; Garnett and Anderson 1993b; Ghani and Garnett, 1998). Here we calculate the mixing matrix following the method described in detail in Garnett and Anderson (1993a; 1994). This allows mixing to vary from assortative to random according to sexual activity ($\epsilon_{k2}=1$ for random; $\epsilon_{k2}=0$ for assortative), and according to age ($\epsilon_{k1}=1$ for random; $\epsilon_{k1}=0$ for assortative), except that there is an observed preference of older men for younger women partner the strength of which is determined by ϵ_{k3} . The mixing matrices for men are formally defined by:

$$\rho_{1lmij} = \left[(1-\varepsilon) \left\{ \left(\varepsilon_{11} \frac{\sum_{u=1}^4 (N_{2uj} c_{2uj})}{\sum_{u=1}^4 \sum_{v=1}^7 (N_{2uv} c_{2uv})} + (1-\varepsilon_{11}) \delta_{ij} \right) \left[\varepsilon_{12} \frac{N_{2mj} c_{2mj}}{\sum_{u=1}^4 (N_{2uj} c_{2uj})} + (1-\varepsilon_{12}) \delta_{ij} \right] \right\} \right]$$

for $i=j$ and $i < 2$,

$$\rho_{1lmij} = \left[\left(\varepsilon_{11} \frac{\sum_{u=1}^4 (N_{2uj} c_{2uj})}{\sum_{u=1}^4 \sum_{v=1}^7 (N_{2uv} c_{2uv})} + (1-\varepsilon_{11}) \delta_{ij} \right) + \varepsilon_{13} \left(\varepsilon_{11} \frac{\sum_{u=1}^4 (N_{2uj+2} c_{2uj+2})}{\sum_{u=1}^4 \sum_{v=1}^7 (N_{2uv+2} c_{2uv+2})} + (1-\varepsilon_{11}) \delta_{ij+2} \right) \right] \text{for}$$

$$\left(\varepsilon_{12} \frac{N_{2mj} c_{2mj}}{\sum_{u=1}^4 (N_{2uj} c_{2uj})} + (1-\varepsilon_{12}) \delta_{lm} \right)$$

$i=j+2$

$$\rho_{1lmij} = \left[\varepsilon_{11} \frac{\sum_{u=1}^4 (N_{2uj} c_{2uj})}{\sum_{u=1}^4 \sum_{v=1}^7 (N_{2uv} c_{2uv})} + (1-\varepsilon_{11}) \delta_{ij} \right] \left[\varepsilon_{12} \frac{N_{2mj}}{\sum_{u=1}^4 (N_{2uj} c_{2uj})} + (1-\varepsilon_{12}) \delta_{ij} \right]$$

for $i \neq j$ and $i \neq j+2$ or $i=j$ and $i < 2$

Here δ_{ij} refers to the identity matrix. The same pattern is used for women except that this time younger women form partnerships with older men so the value ε_{k3} moves contacts to $i=j-2$ when $i < 6$.

In the simulations presented here choice of sexual partners according to both age and sexual activity is assumed to be slightly more assortative than random - on a scale where mixing ranges from fully assortative (i.e. like with like) with a value of 0.0, to random according to supply of sexual partnerships, with a value of 1.0, mixing for the illustrated epidemic with respect to age was set at 0.5 ($\varepsilon_{11} = \varepsilon_{21} = 0.75$) and with respect to activity was set at 0.3 ($\varepsilon_{12} = \varepsilon_{22} = 0.75$). There is also an empirically observed age bias in the choice of sexual partners by sex, with older men being more likely to form partnerships with younger women. Fifty percent of the partnerships of men over 25 years old come from the age group of women 6 to 10 years younger than themselves and vice-versa ($\varepsilon_{13} = \varepsilon_{23} = 0.5$). This allows the very different patterns of partner change by age observed empirically (Carael, 1995) for the two sexes, to be reflected in the parameters used.

One problem of internal consistency in such a model is the maintenance of a balance between the sexual partnerships formed in the population. To achieve this the rate of sexual

partner change also depends upon the partners age and activity group, (c_{klmij}^*) in a manner described by Garnett and Anderson (1994). Following this method, if there is a discrepancy between the rate of sexual partner formation of one sex, age and activity group and the other sexes age and activity group, then the rate of sexual partner change of both sexes is adjusted so that the rates match.

Say the discrepancy is given by the equation:

$$B_{lmij} = \frac{c_{k'mj} \rho_{k'mlji} N_{k'mj}}{c_{kli} \rho_{klmij} N_{kli}}$$

In order to make the necessary adjustments, the mean rate of sexual partner change of people of sex k' , age j , and activity group m with each group of the opposite sex of age i and activity group l becomes:

$$c_{k'mlji}^* = c_{k'mj} B_{lmij}^{-(1-\theta_1)},$$

And the partner change rate in the reverse direction becomes

$$c_{klmij}^* = c_{kli} B_{lmij}^{\theta_1},$$

For the simulation here, it is assumed that men and women alter their behaviour equally (i.e. θ_1 is assumed to equal 0.5). As an HIV epidemic progresses, incidence declines, because many of those exposed to infection have already been infected. Those with the highest rates of sexual partner change are at greatest risk of infection and they are consequently those most likely to die of AIDS, thus average levels of sexual activity within the population decline and incidence rates tend to fall. The same rule for balancing rates of sexual partner change is used at each step in numerical solutions to adjust for this differential mortality. In the simulation illustrated the differential loss to mortality of those with high activity and the subsequent adjustments to activity leads to reductions in the prevalence of infection.

Parameter Values

(1) Behaviour and Transmission Risk

The model parameter values were based on reported behaviours for a population based survey of sexual behaviour in 12 communities in rural Zimbabwe carried out by Dr S. Gregson (Pers Comm) and the prevalence of HIV in rural Zimbabwe. The men and women were asked to report on both their own sexual behaviour generally and also on behaviour during the last two sex partnerships. Because of potential recall and social desirability biases in reporting risk behaviours it is likely that risks are under-reported, particularly amongst women. Additionally, the simplified patterns of behaviour in the model are not necessarily directly estimated in reports of risk behaviour:

Transmission probabilities and partnerships:

The transmission probability per partnership was based upon the reported number of sex acts within a sexual partnership as a function of the number of partners reported using a binomial model for the transmission process: $\beta_p = 1 - (1 - \beta_a)^n$

where β_p represents the transmission probability per partnership, β_a the transmission probability per sex act and n the number of sex acts within the partnership. The transmission probability per sex act of 0.005 is similar to that estimated for rural Uganda by Gray and colleagues (2001).

	Number of reported sex partners over last year				
	1	2	3 to 4	6 to 10	10+
Mean number of reported acts over 2 weeks with last partner	3.72	1.37	0.72	0.25	0.29
Number of acts over 52 weeks with a partner	96.8	35.7	18.7	6.5	7.5
Transmission probability per partnership	0.384	0.164	0.089	0.032	0.037

From these reported behaviours the following transmission probabilities for a partnerships involving particular individuals were used:

- With a partner from the lowest activity group = 0.4
- Within second lowest activity group and between partners from higher activity groups and the second lowest = 0.2
- Within second highest activity group and between partners from the highest and second highest activity groups = 0.09
- Within highest activity group = 0.035

Within the rural Zimbabwean population the following proportions of the population by age fell into 4 activity groups with 0, 1, 2-5 and 6+ reported new partners in a year:

	Age Group (years)						
	15-19	20-24	25-29	30-34	35-39	40-44	45-49
New partners in 12 months	Men						
0	0.375746	0.371579	0.480926	0.574766	0.659218	0.689922	0.704301
1	0.361829	0.354737	0.276567	0.228972	0.189944	0.189922	0.172043
2-5	0.242545	0.235789	0.205722	0.154206	0.125698	0.100775	0.102151
6+	0.019881	0.037895	0.036785	0.042056	0.02514	0.01938	0.021505
	Women						
0	0.635036	0.724832	0.793727	0.811617	0.892697	0.91691	0.875
1	0.316302	0.233781	0.159228	0.160126	0.087928	0.068513	0.113095
2-5	0.046229	0.036913	0.039807	0.025118	0.014903	0.014577	0.011905
6+	0.002433	0.004474	0.007238	0.00314	0.004471	0	0

However, the current version of the model assumes that individuals remain in the same sexual activity class and that the rates of partner change in the activity classes varies with age. A mean rate of sex partner acquisition per year per year was assigned (in this case 2.15 partners on average per sexually active person per year) and the proportion of each sex entering each activity group at age 15 was assigned along with ratios for rates of sexual activity between activity classes and age groups.

Hence the following proportions of the population were assigned rates of sexual partner change:

	Activity Group			
Men	1	2	3	4
Proportion	0.03	0.19	0.27	0.51
Ratio of partner change rates by activity	100	35	5	1
Women				
Proportion	0.005	0.028	0.16	0.807
Rate of partner change	100	35	5	1

	Ratio of activity by age group						
Age group:	15-19	20-24	25-29	30-34	35-39	40-44	45-49
Men	2	4	6	8	5	3	1
Women	2	8	8	6	5	3	1

(2) Vaccine Related Parameters

We assume that a reasonable level of vaccine uptake of 65% can be achieved after 5 years. Vaccination uptake can be achieved in a number of different ways. In the case of *cohort vaccination* 65% of the population aged 15 years old are vaccinated each year. As this vaccinated cohort ages through time then the vaccination coverage increases towards 65%. In fact, the proportion of the adult population vaccinated will eventually exceed 65% because of the lower mortality rate in those protected by vaccination from HIV/AIDS. However, this strategy includes a long delay before coverage reaches 65% or is sufficient to have a marked impact on the epidemiology of HIV. An alternative strategy would be a *catch up* programme in those sexually active (i.e. over the age of 15 years in the model) prior to the vaccine's introduction, along side cohort vaccination in those entering the population. If this is used for 5 years a coverage of 65% can be achieved if the rate of vaccination satisfies the equation:

$$65 = (1 - e^{-V_b 5}) / 100$$

thus

$$V_b = -\ln(0.45) / 5$$

After 5 years the *catch up vaccination* programme could be stopped and *cohort vaccination* continued. This achieves a 65% coverage after 5 years and maintains coverage at 65%. However, if vaccine protection wanes over time it is likely that an alternative strategy will be required. This could be continual revaccination throughout the population (in the following simulations we use a rate of 0.21, which achieves 65% coverage after 5 years – it is assumed that

those in whom vaccine wanes are not ‘eligible’ for vaccination for an average of 6 months after the waning of protection and those in whom the vaccine fails are not eligible for revaccination for a period of 2 years), which is continued in a **blanket vaccination**. Alternatively, regular **vaccination campaigns** where a high fraction of the population could be used.

Targeting of vaccination could provide a more cost-effective intervention. Such targeting could take two forms: (1) where high activity groups are targeted to increase the impact of the vaccine in recipients. (2) Experience with Hepatitis B vaccine suggests the high activity population may be difficult to reach with the vaccine so we also explore the situation where only the lower risk populations can be reached using the vaccine.

(3) Alternative Interventions

In the current model it is possible to alter rates of sexual partner change or to adjust transmission probabilities, which represents the impact of condoms reducing the number of unprotected sex acts. This can be used to directly compare the impact of interventions which manage to change patterns of risk behaviour with vaccination.

As the model does not describe the concomitant epidemiology of STDs an alternative model of STDs, HIV and vaccination was used to explore this comparison. This model has previously been described by Desai and Colleagues (1999) and the following assumptions were made:

In all cases, HIV vaccine assumed to have 50% efficacy (i.e. 75% take x 67% reduction in susceptibility). In all cases, STD treatment is assumed to decrease STD prevalence to 1/3 of equilibrium levels in absence of HIV. For example, if STD prevalence in the general population is 8%, then after treatment intervention this is 2.6%, in absence of HIV, when treating high-risk individuals only. The duration of STD intervention is 5 years rather than continual. HIV vaccination and STD treatment was performed in 80% of high-risk men and women, who make up 15% of population. e.g. if population size is 500,000, we treated 60,000 individuals who are the high risk men and women (e.g. commercial sex workers and male clients of std clinics). Interventions begin when HIV incidence reaches 20% in high risk men and women. At this point, all individuals are included immediately in the intervention.

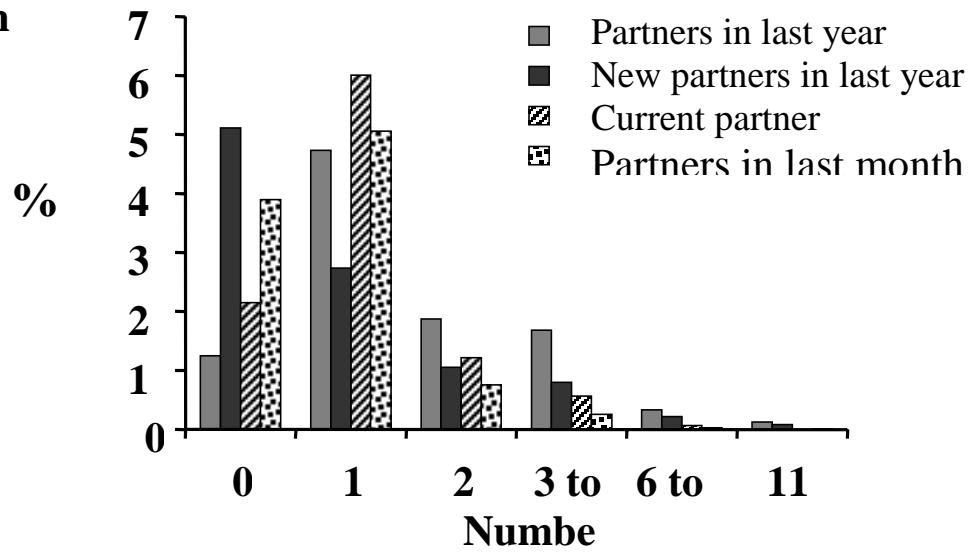
Four scenarios were considered based on two levels of HIV-STD interaction, high versus low, in combination with two levels of STD prevalence, high versus low:

Scenario	Increased HIV susceptibility due to STD	Increases HIV transmissibility due to STD	Increased STD Susceptibility due to HIV	Increased STD transmissibility due to HIV	STD prevalence before intervention	STD prevalence after intervention
1	4	3	1.5	1.5	1.8	0.5
2	2	2	1.5	1	1.5	0.5
3	4	3	1.5	1.5	8.0	2.8
4	2	2	1.5	1	8.5	2.8

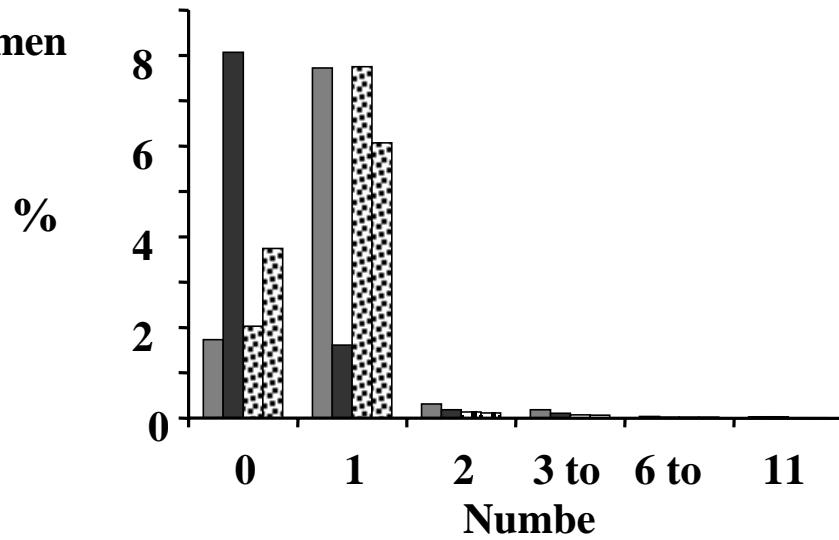
The HIV epidemic simulated in the model is indicative of that observed in rural Zimbabwe based on patterns of risk behaviour observed in population based surveys (Gregson Pers Comm.) and the observed percent prevalence over time in a number of sentinel antenatal clinics(Each symbol in graph c represents a different clinic):

Reported partner numbers

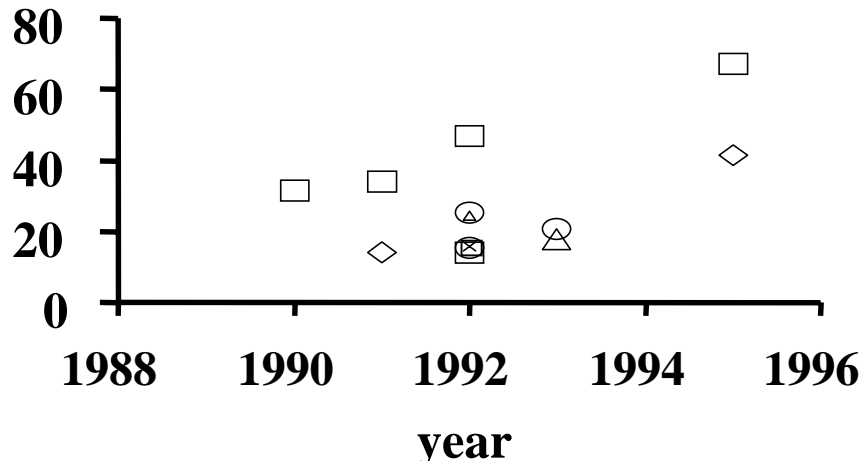
- Men



Women



Pregnant Women in Manicaland, Zimbabwe



Results

The impact of vaccination is a product of how and when it is used and its properties. Outcome can best be illustrated through a comparison of HIV incidence or prevalence, with and without vaccination. Because the majority of estimates of the scale of the epidemic are based on the prevalence of infections we chose in the majority of results to illustrate the prevalence in all adults aged 15-49 years old. This can be seen in Fig. 5a where the prevalence of infection with and without a vaccine with lifelong protection is illustrated. In this case the most likely vaccination campaign of a catch up programme followed by cohort vaccination such that 65% of the population is vaccinated after 5 years (which is 10 years into the epidemic) which is then maintained through cohort vaccination. Three efficacies, 95%, 75% or 50%, which are assumed to provide complete protection when successful (i.e. take) are illustrated showing that as long as protection is long lasting a vaccine with 50% efficacy can have a major impact.

The impact of such a vaccine would be seen as a change in prevalence over the long term. However, its immediate impact will be on the incidence of HIV infection as illustrated in the cases with and without a vaccine with 50% efficacy in Fig 5b. In this case the reduction in incidence in men is more dramatic than in women. This impact would not though be seen, rather the impact on AIDS incidence and disease in the community would be detected (Fig 5c), which takes longer to emerge. An earlier impact will be detectable amongst young women ie 15-19 year olds attending antenatal clinics (Fig. 5d).

The timing of introduction of the vaccine has obvious effects, but only with catch up programmes can the early introduction of vaccine prevent the peak in the epidemic. This is illustrated in Figure 6 where the vaccine is introduced in year 5 or year 15 with a blanket programme which achieves 65% coverage after 5 years or a cohort programme where 65% of the population are vaccinated. In both cases the eventual prevalence falls to the same level, but this fall is rapid with general coverage.

The importance of the duration of protection is illustrated in Fig.7 where the impact of a vaccine with 50% take is explored for three durations. If protection is lifelong then catch up and cohort vaccination are adequate. However, if protection wanes with time, some kind of continual vaccination providing boosters is required. Even with continued blanket vaccination waning protection substantially undermines the impact of this moderate efficacy vaccine. This is illustrated further in Figure 8 where different campaigns are illustrated for a vaccine with low efficacy (50% take) and a short duration of protection (5 years). Cohort alone has least impact because individuals rapidly move back into the susceptible class and remain at risk for the remainder of their sexually active life with no further chance of revaccination. It is important to note that we define the mean duration of vaccine derived protection as the average period that a cohort of vaccinated individuals remain protected assuming an exponential decay in vaccine derived protection. This is equivalent to a vaccine with a shorter median duration of protection (i.e. half-life) :

$$\frac{-\ln(0.5)}{1/D} = T$$

is the relationship between the mean duration of protection as we define it, D , and the half life of the vaccine T . Thus, a vaccine with a mean duration of protection of 5 years has a median duration of protection of 3.47 years and a vaccine with a mean duration of protection of 10 years has a median duration of protection of 6.93 years. A major assumption made within our modelling exercise is that, although the average sexual activity of those within a particular activity group alters with age individual remain within their original activity class and high activity is maintained. This exaggerates the requirement for a long duration of protection covering the bulk of the assumed sexually active ages 15 to 49 years. If individuals rapidly progress through experimental phases of their life, or enter short periods of drug use or commercial sexual activity, then a vaccine covering this period would have a substantial impact.

Targeting is explored assuming a longer protection from the vaccine (i.e. lifelong) in Figure 9. Here a vaccine supplied throughout the population is compared with one used in the highest activity group (3% of men and 0.5% of women), the two highest activity groups (21% of men and 3.33% of women), the lowest activity group (51% of men and 80.7% of women) and the two lowest activity groups (78% of men and 96.7% of women). It can be seen that high activity targeting can be potentially cost effective (although not the most effective strategy) but that a large fraction of those at risk (i.e. the two higher activity groups need to be included. Interestingly though, if these high-risk groups are excluded, then the impact on HIV can still be substantial because of the direct protection afforded by the vaccine. The number of doses of vaccination used cumulatively for each of the vaccine strategies has also been derived and allows for the cost-benefit calculations in the overview report.

The action of the vaccine has obvious implications for this direct protection. If a degree vaccine is used it is less likely to protect those with many exposures so will provide less useful vaccine for targeting. The difference in the widespread use of a vaccine with take and degree protection is illustrated in Figure 10. It is noticeable that the difference in efficacy is more important than the difference in mechanism of vaccine action in this example. The difference between the two types of action becomes more influential as vaccine efficacy falls. An additional point of note identified in our introduction is that a degree type protection is more susceptible to behavioural reversals than a take type protection. The danger of behavioural recidivism undermining the impact of the vaccine is a serious concern. However, the consequences depend upon the scale of behaviour change and who it occurs in. As illustrated in the simple model solutions if the vaccine provides protection from a fraction of challenges then there is an equivalence to reductions in risk caused by vaccination and increases in risk through behaviour change. Whereas if the protection is absolute in those vaccinated it is much harder for increases in patterns of risk to overturn the benefits gained from the vaccine.

Behavioural recidivism is illustrated in Figure 11 a and b. We illustrate the importance of which group of individuals is assumed to change behaviour. The case is much worse if all change behaviour rather than just those who are vaccinated. We also show that changing the transmission probability a given percentage is equivalent to a similar percentage change in the partner change rates. (NB The decrease in condom use across all groups was reversed n year 35)

Comparison with reductions in risk behaviour – condom use and partner change rates are made in Fig 11c. The major problem is understanding what behaviour changes are possible. Here we assume reductions of a third.

In comparing STD interventions with vaccination (Fig. 12) the assumptions made about the importance of the STD are crucial. Under the assumptions of our simulations, aggressive treatment of STDs (i.e. reducing prevalence by two-thirds) makes little or no impact when baseline prevalence of STD is low (1.5%). This is the case irrespective of strength of HIV-STD interaction. Thus, the benefit of HIV vaccination is observed to be the same whether STDs treated or not. When baseline prevalence is high (8.0%) the benefit of STD treatment is observable. In terms of reducing prevalence, HIV vaccination alone is better than STD treatment alone. The marginal benefit of adding STD treatment to HIV vaccination is less than the marginal benefit of adding HIV vaccination to STD treatment. Thus STD prevalence needs to be high for STD treatments to have an impact on HIV prevalence. In the context of a widespread HIV epidemic when there is a reasonable enhancing impact then the prevalence of HIV is moderately insensitive to its magnitude.

Discussion

The diversity of potential properties of HIV vaccines generates a great number of combinations to be explored in anticipation of an actual vaccine with properties defined in a trial. This along with the range of methods of using the vaccine creates a bewildering level of complexity that defies easily communicated prescriptions about when and how a vaccine should be used. However, some general rules emerge. First a low efficacy vaccine which provides protection in approximately 50% of recipients could have a major impact on the HIV pandemic, reducing the prevalence of HIV by 65% in an epidemic like that seen in Zimbabwe. However, this assumes that the vaccine provides lifelong protection. With a low mean duration, for example on average 5 years the impact is substantially undermined in situations where high risk behaviour is of long duration. To some extent this can be overcome by using booster vaccination (e.g. regular vaccination campaigns), but this will substantially increase costs.

The vaccination strategy required is influenced in part by the duration of protection, but also by the need to rapidly establish a high coverage if the dramatic epidemics of HIV being observed in developing countries are to be stalled. Additionally targeting is an option. Whether it would be appropriate will depend upon practical concerns. Targeting high activity groups is the most cost effective strategy, if these groups can be easily reached and there is the political will to protect them. Our results illustrate how the protection provided by vaccinating those with high-risk behaviours extends through the population providing some indirect protection to those with a lower risk. However, a vaccine used throughout the population would be the most effective. Such widespread use may not be socially accepted but would be desirable. An alternative problem may be the inaccessibility of 'high risk groups'. Our results illustrate that vaccinating those with a lower risk alone can still be valuable.

The comparison of vaccine with other interventions is somewhat spurious. Once a vaccine becomes available, issues will surround its administration, but it will have a biomedical impact with a straightforward pattern of causation. Other interventions aimed at reducing numbers of sex partners, increasing condom use and improving STD services are more dependent upon how well the work is carried, how strong the link is between the output of the intervention and its outcome in the shape of changing patterns of risk. If successful other interventions can have a major impact as witnessed in Thailand with the 100% condom use program (Rojanapithayakorn and Hanenberg, 1996). The generalization and maintenance of such

interventions is not as straightforward as effort to improve coverage with a vaccine has proved to be in controlling vaccine preventable infections of childhood. It should be noted that in some areas vaccine coverage has been inadequate, but because the risk of acquiring an infection like measles or rubella is fairly homogeneous and the reproductive number is extremely high achieving very high levels of coverage has been necessary for these vaccines, which would not be as true for an HIV vaccine.

Furthermore, in comparing interventions it is important to recognize that they are not mutually exclusive. 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. Generally, a vaccine that entirely protects a fraction immunized acts independently of other behavioural changes so would produce an additive impact, whereas a vaccine that protects from a fraction of challenges works in the same way as interventions reducing the transmission probabilities or partner change rates. If the combination of interventions reduces the reproductive number to near one they will have a better than additive impact. However, beyond this effort is duplicated. A general intervention, which takes in those with a low risk is likely to reduce their reproductive number below one and further widespread interventions be mainly redundant, a problem which is avoided in the case of targeted interventions. However, combining interventions will be necessary to prevent the potential recidivism in risk behaviour. Such an increase in risk would be more serious if it were throughout the entire population rather than being restricted to those vaccinated.

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Fig. 5. The impact of a vaccination on the prevalence of HIV simulated for Zimbabwe. (a) The baseline prevalence over 50 years in the absence of vaccination compared with prevalence for a vaccine introduced in year 5 which takes 5 years to achieve 65% coverage through a catch up programme followed by cohort vaccination. Vaccines with 95%, 75% and 50% 'take' are illustrated. (b) The incidence of HIV infection amongst men and women is illustrated with and without a vaccine with 50% take and lifelong protection, with a catch up followed by cohort vaccination policy. (c) The incidence of AIDS for the HIV epidemics illustrated in graph b. (d) The prevalence of HIV in 15-19 year old for the HIV epidemic illustrated in graph b.

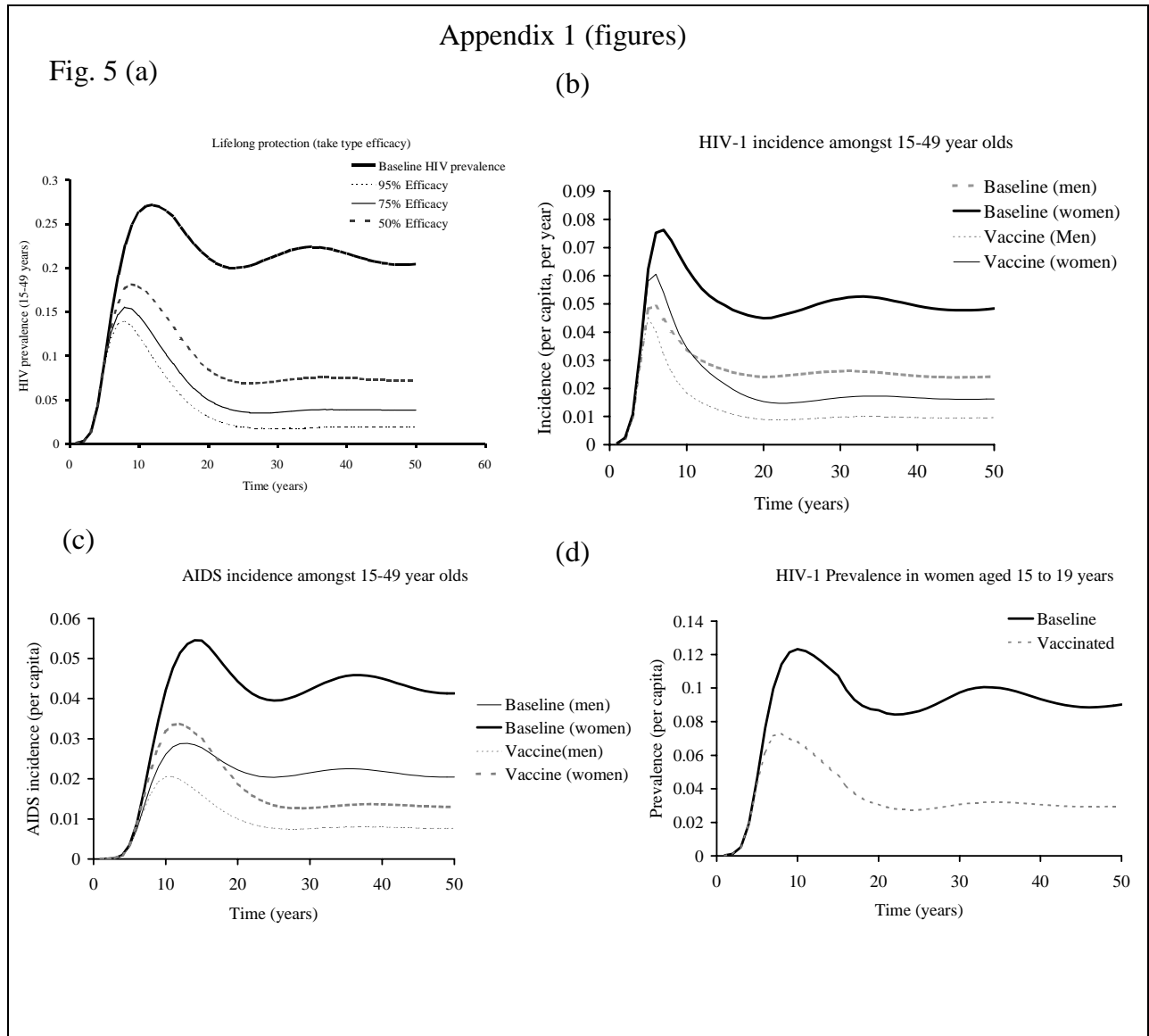


Fig. 6. The timing of HIV vaccines introduction is illustrated by comparing the prevalence of infection with and without vaccination when the vaccine is introduced in year 5 and year 15. Cohort (65% coverage) and blanket (21% vaccinated per year with a two year mean gap before eligible for revaccination). The vaccine is assumed to provide a 50% take with a lifelong protection thereafter.

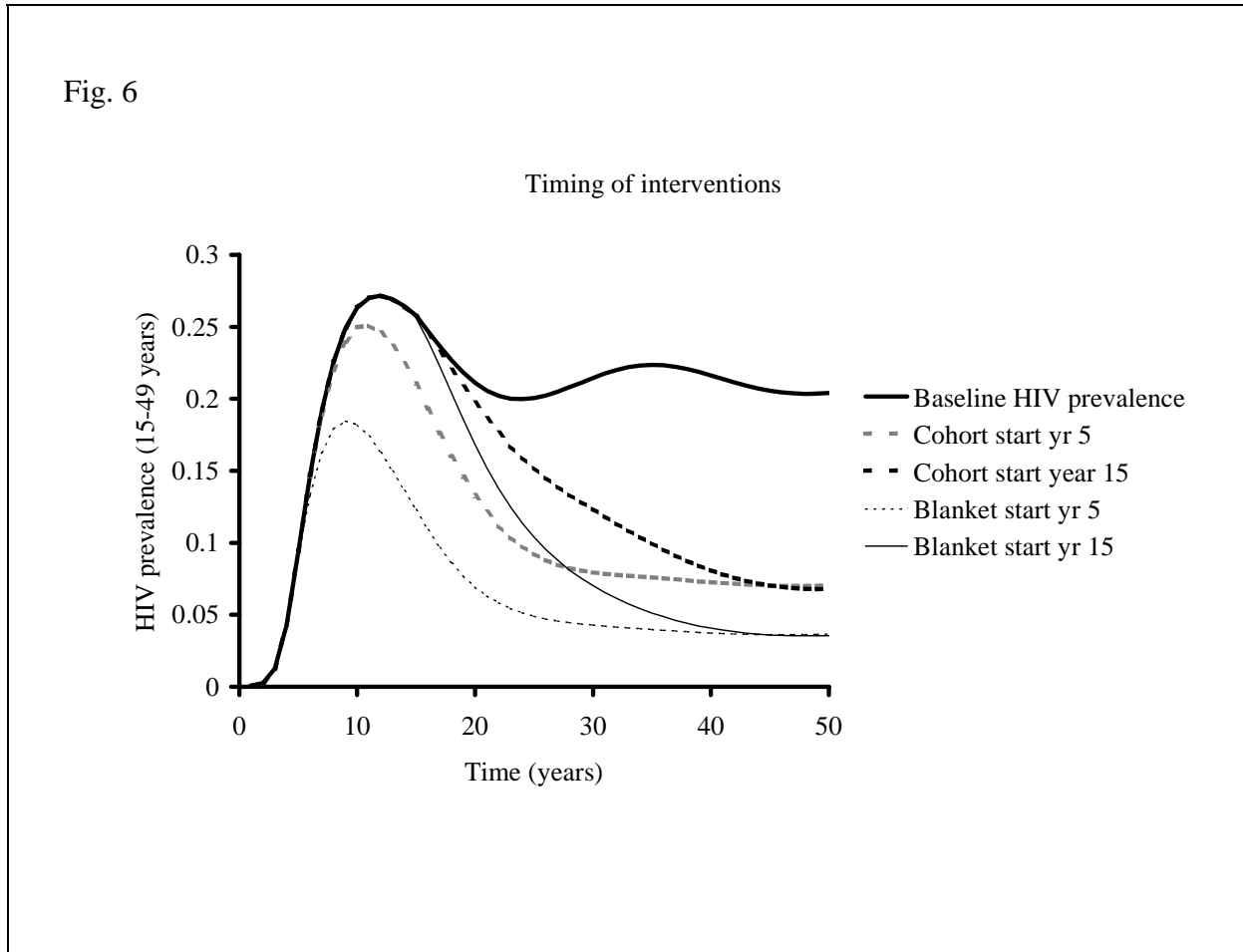


Fig.7. The impact of the mean duration of protection provided by a vaccine with a 50% take. No vaccine is compared with vaccines of lifelong, 10 year and 5 year durations of protection. Graph a – cohort vaccination – 65% of 15 year olds vaccinated each year. Graph b - blanket vaccination (21% vaccinated per year with a two year mean gap before eligible for revaccination).

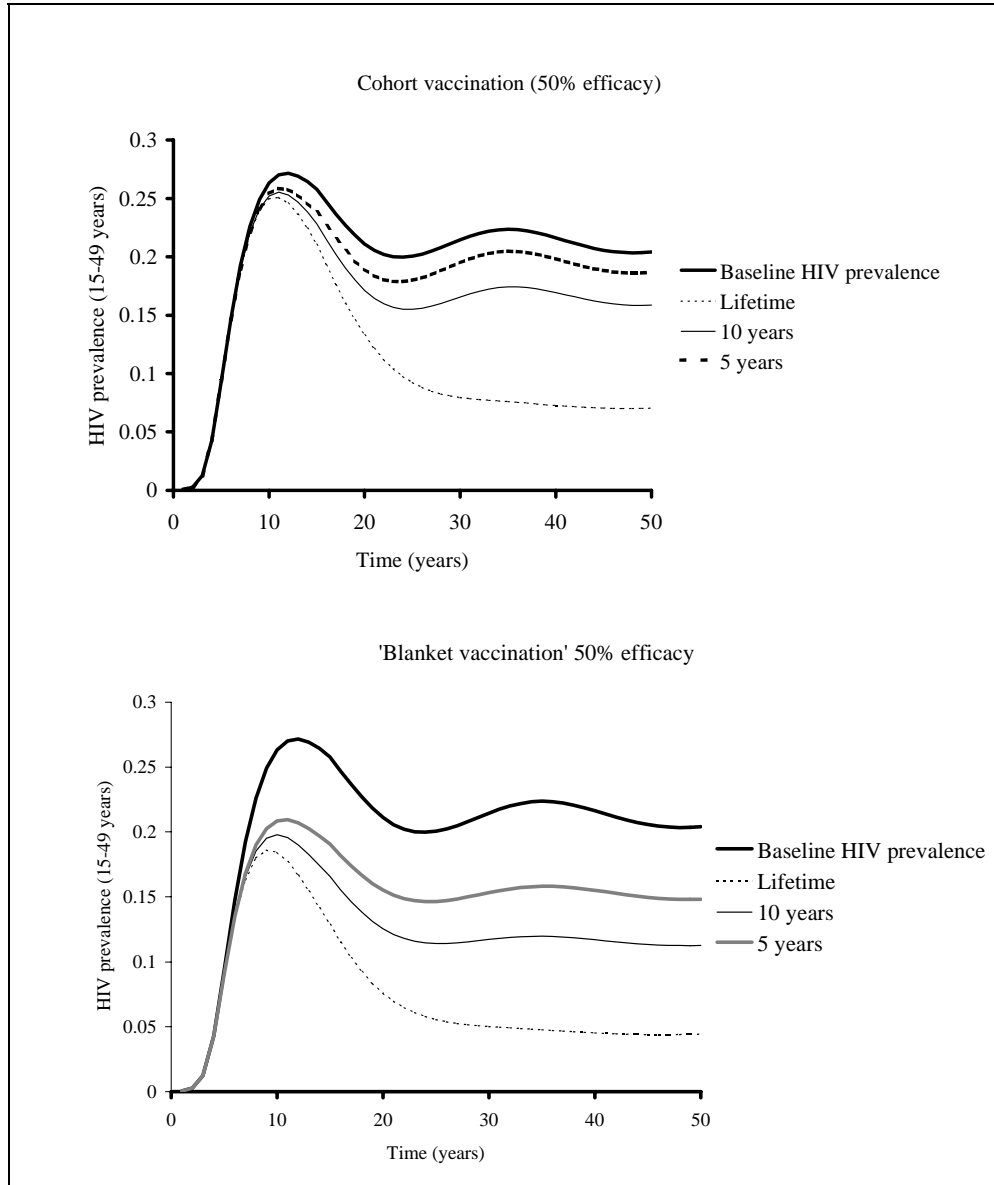


Fig. 8. Alternative vaccination strategies assuming a vaccine with a 50% take and 5 years mean duration of protection. Graph a – cohort vaccination – 65% of 15 year olds vaccinated each year. Graph b – a catch-up programme to achieve 65% coverage after 5 years followed by cohort vaccination with 65% of 15 year olds vaccinated each year. Graph c- blanket vaccination (21% vaccinated per year with a two year mean gap before eligible for revaccination). Graph d – campaigns following a catch-up programme to achieve 65% coverage after 5 years, with cohort vaccination with 65% of 15 year olds vaccinated each year. In addition every five years a general campaign where 21% of the sexually active population are vaccinated over a year.

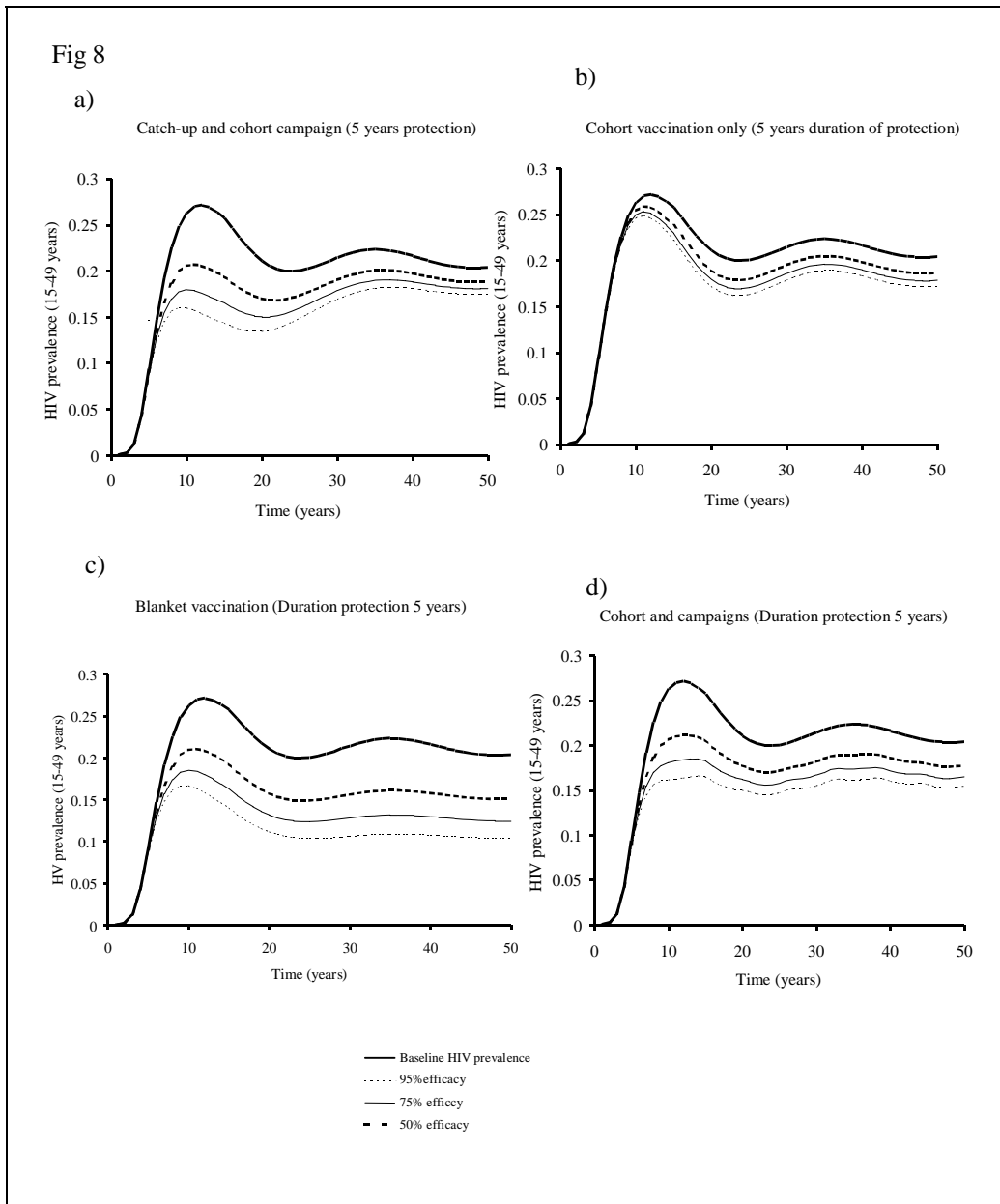


Fig. 9. The targeting of a vaccine with 50% take and lifelong protection. Graph a the prevalence of HIV with different distributions of vaccine.

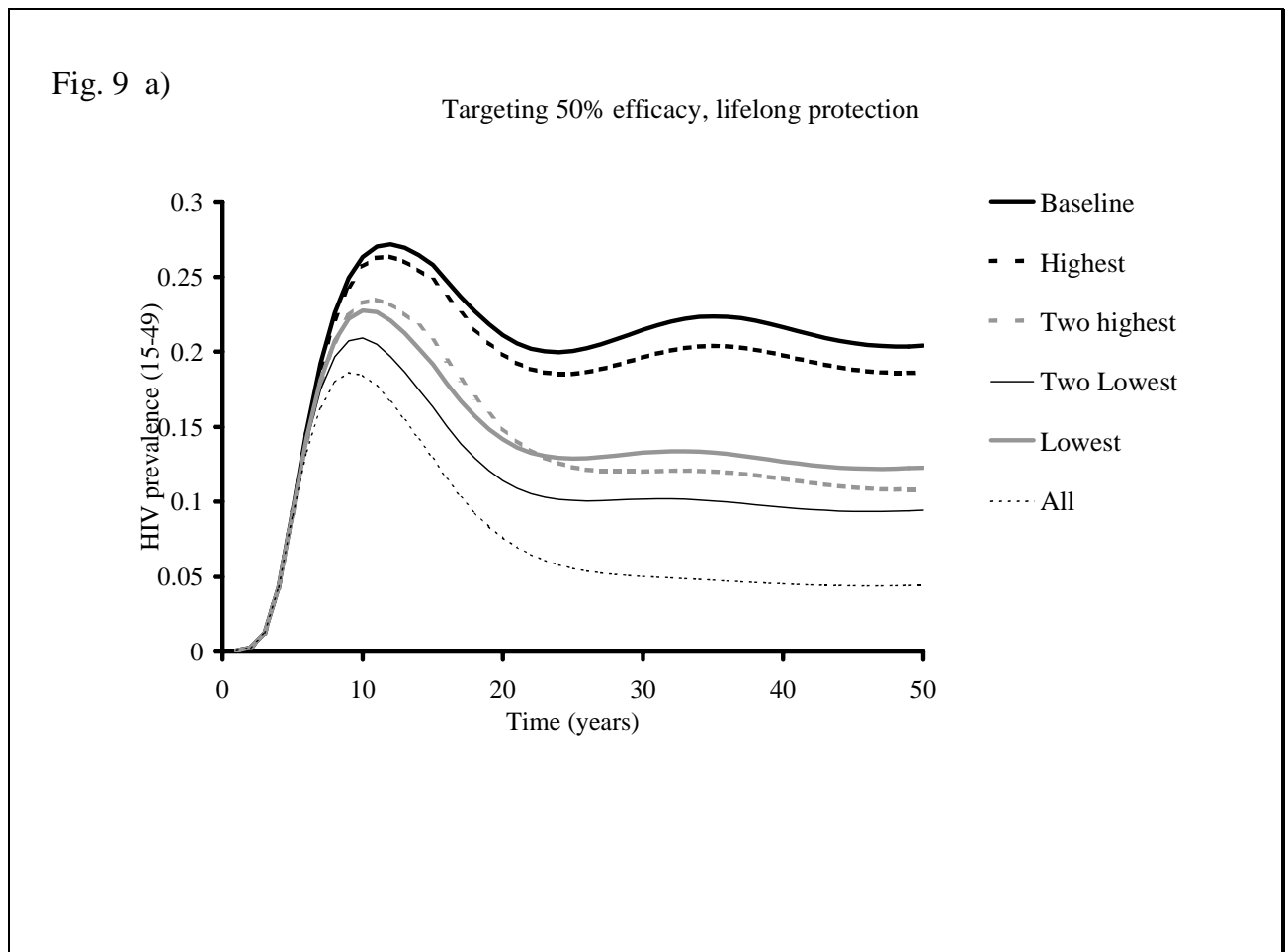


Fig. 10. The impact of a vaccine with 5 years duration of protection and an efficacy of 95% is compared with that of a vaccine with efficacy of 50%. For each efficacy is defined in two ways – in the case of take those responding to the vaccine are assumed to be protected from all challenges. In the case of degree everyone is assumed to respond to the vaccine but it only reduces the hazard of acquiring infection in each challenge (i.e. partnership with an infectious individual).

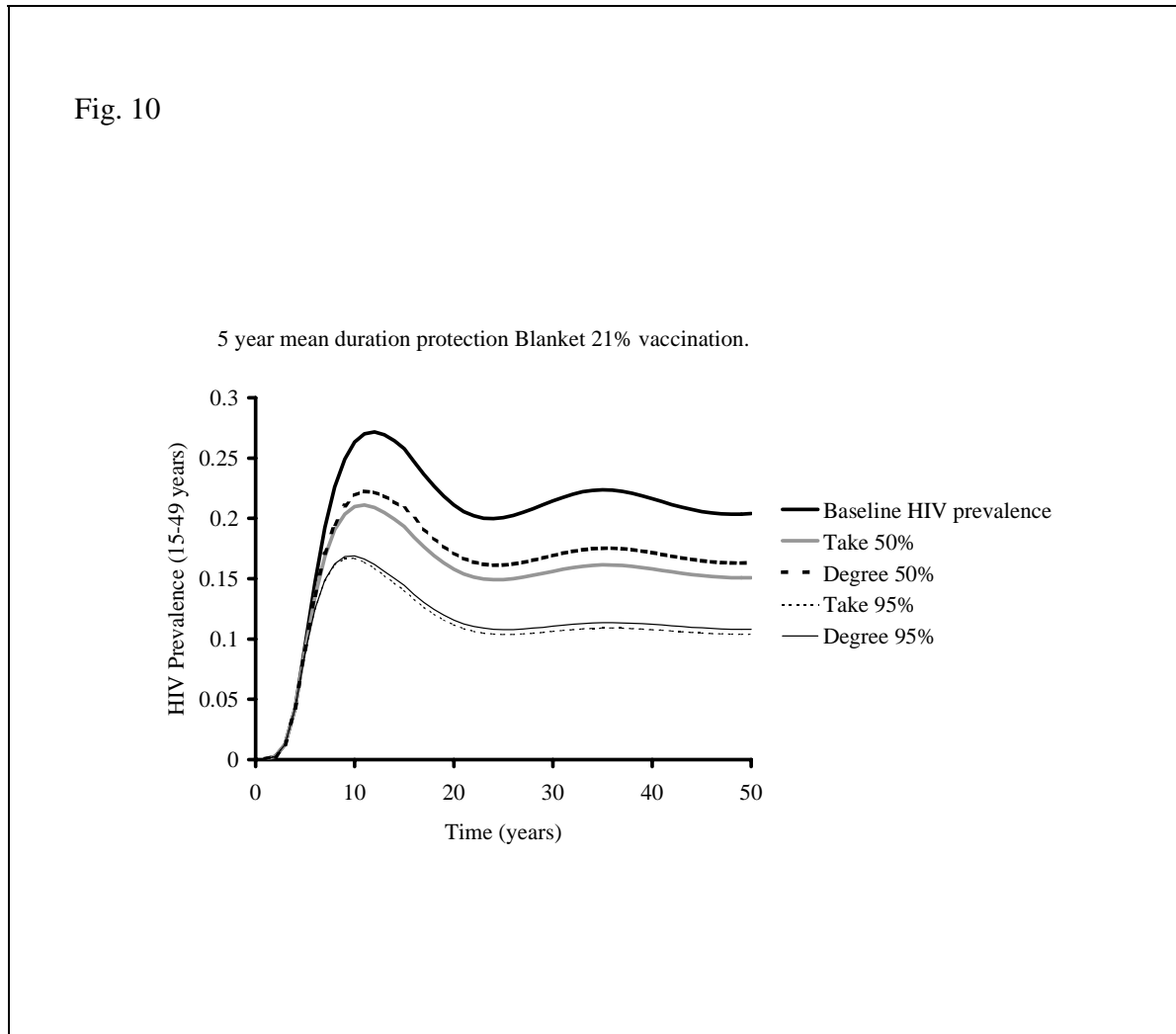


Fig. 11. The impact of behaviour changes Graph a) the impact of behavioural reversals when vaccine only provides 5 years protection in 50% of recipients. The behaviour change is assumed to be a 33% increase in the transmission probability resulting from a decrease in condom use and is applied to everyone, only those who receive the vaccine, only those in high risk groups. Graph b) a comparison of the increase in risk in everyone through an increase in the transmission probability by 33% with an increase in the rate of sexual partner change of 33%. Graph c) A vaccine which provides lifelong protection in 50% of recipients is compared with a 33% reduction in partner change rates or transmission probability per partnership.

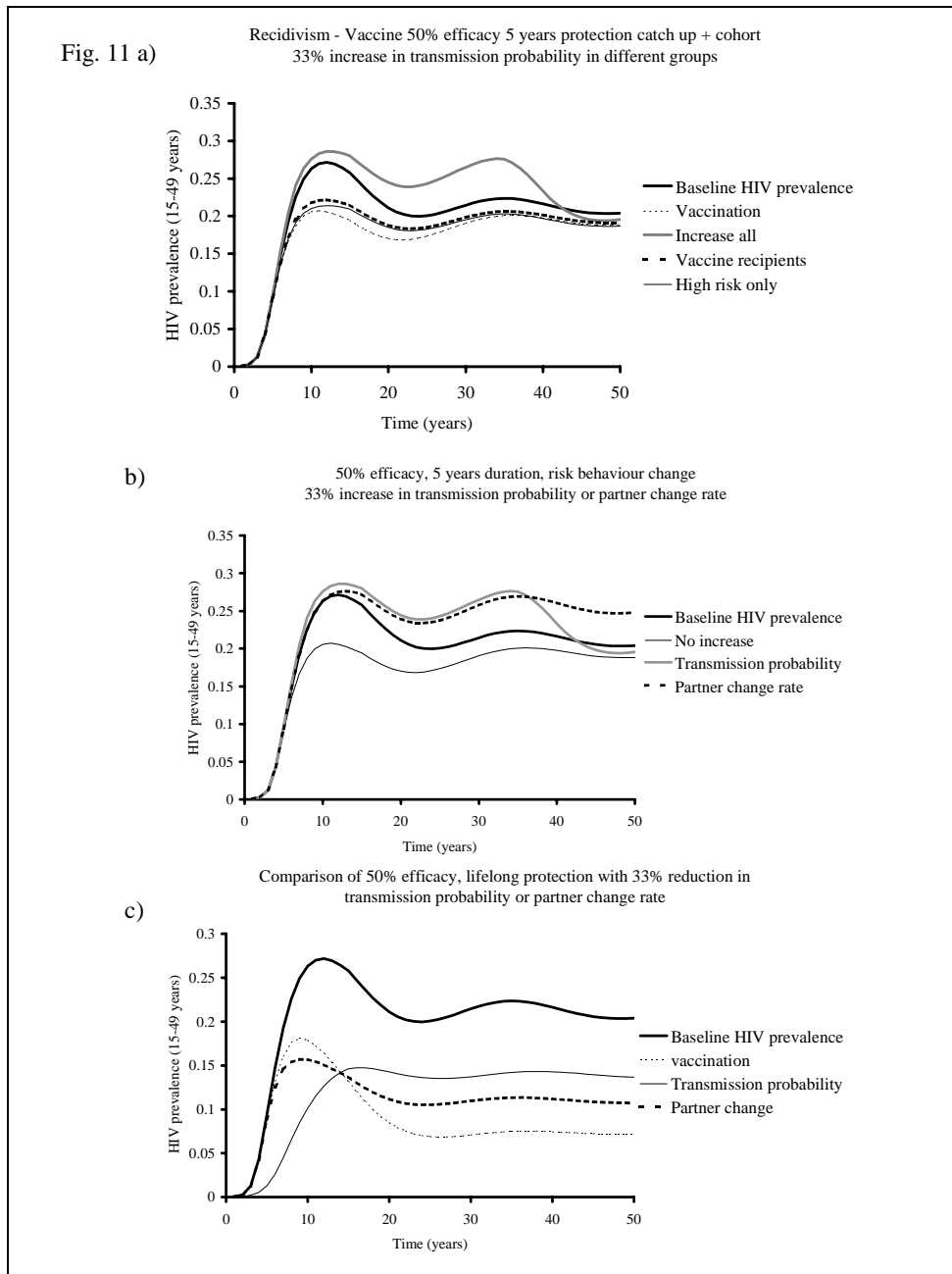


Fig. 12 A comparison of STD treatment and vaccination under four different assumptions about the prevalence of the STD and level of increase in transmissibility and susceptibility for HIV associated with the presence of the STD (see text for details).

