THE POTENTIAL EFFECT OF AN HIV/AIDS VACCINE IN SOUTH AFRICA

By LF Johnson and RE Dorrington

ABSTRACT

This paper presents a model for assessing the potential effect of an HIV/AIDS vaccine in South Africa, and for calculating the amount of vaccine that would be required. A number of different hypothetical vaccine profiles and vaccine distribution strategies are considered. Results suggest that a sterilising vaccine could reduce the HIV incidence between 2015 and 2025 by up to 50%, while a disease-modifying vaccine would be unlikely to reduce HIV incidence by more than a third. The effect on AIDS mortality over the same period would be substantially smaller, and it is unlikely that any preventive vaccine would reduce AIDS mortality by more than 10% between 2015 and 2025.

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1.   INTRODUCTION

1.1   South Africa is a country severely affected by HIV/AIDS, with one of the highest rates of HIV prevalence in the world. In spite of the significant HIV prevention programmes that have been introduced in South Africa, HIV incidence remains high, with around 1400 new HIV infections every day (Dorrington et al., unpublished). There is thus a great need for new, more effective interventions and technologies to limit the spread of HIV. Much hope has been pinned on the potential development of an HIV/AIDS vaccine.

1.2   Mathematical models have been used extensively to demonstrate the potential benefits from an HIV/AIDS vaccine and to determine which strategies would be most appropriate for distributing such a vaccine. However, in a recent review of these models, Rowley (unpublished) has noted that none of the models examines the question of how differences in vaccine acceptance between sub-populations might influence the effect of an HIV/AIDS vaccine, and most studies have not adequately considered the range of possible characteristics the first vaccines may have. With a few exceptions (Garnett, 1998; Stover et al., unpublished; Davenport et al., 2004), most vaccine models are not age-structured, and thus cannot be used to predict the effect of limiting vaccination to particular age groups. It has been suggested that actuaries may have an important role to play in bridging the divide between epidemiological models of vaccine effects, which make limited allowance for population dynamics, and age-structured demographic models, which make little allowance for the effects of disease (Cornall, Chan & Sparks unpublished).

1.3   The objective of this paper is thus to explore the potential effects of an HIV/AIDS vaccine in South Africa, using an integrated demographic and epidemiological model of the HIV/AIDS epidemic, developed by the Actuarial Society of South Africa. In addition to addressing the needs of actuaries for estimates of the future effect of HIV/AIDS vaccines on levels of mortality and morbidity in South Africa, this paper addresses an important need for estimates of the amounts of vaccine stock that would be required, which will be critical in determining the level of vaccine production capacity required and the level of funding that will be needed in order to support an HIV/AIDS vaccination programme (Hecht & Suraratdecha, 2006). It also assesses which strategies for vaccine distribution are likely to be most appropriate in the South African context. Although it is likely to be several years before an HIV/AIDS vaccine is available for distribution, it is important that these questions be researched and debated well before a vaccine enters the mass-production phase.

2.   FACTORS AFFECTING THE IMPACT OF AN HIV/AIDS VACCINE

2.1   TIME TO VACCINE DISTRIBUTION

2.1.1   There is currently much uncertainty as to when the first effective HIV/AIDS vaccine is likely to be ready for distribution. Candidate vaccines have to be tested in phase I and II trials (safety and immunogenicity trials) and in a phase III (efficacy) trial before they can be licensed. At present there is only one phase III HIV/AIDS vaccine trial in progress world-wide, with results expected in 2008/9 (Rodriguez-Chavez et al., 2006). There are approximately 30 phase I and phase II trials under way, and those that progress to phase III in future will usually require a further three years until completion of these trials. Discounting the possible success of the current phase III trial, it therefore seems unlikely that any HIV/AIDS vaccine candidate would be proven effective before 2010.

2.1.2   Even if a vaccine were proven effective in 2010, several further hurdles would need to be cleared before the vaccine would be ready for distribution. The vaccine

would need to be licensed, both by the authorities that monitored the phase III trial and by the authorities in the country wishing to use the vaccine. It may be necessary to conduct local efficacy trials, as vaccine efficacy may depend on local HIV strains, local host genetic profiles and local modes of HIV transmission. For ethical and legal reasons, it may also be necessary to conduct separate trials in adolescents (WHO-UNAIDS Expert Group, 2005). It would also be necessary to establish the manufacturing capacity required to produce the vaccine. Ideally this should start when phase III trials are in progress, but because of the uncertainty as to whether the vaccines will prove successful, the investment of hundreds of millions of dollars in setting up this productive capacity is a significant gamble (Collins, 2005). Realistically, the creation of productive capacity would begin only once provisional results suggest a high level of efficacy. This could significantly delay distribution of the vaccine, given the five-year lead time typically required for the setting up of such capacity (International AIDS Vaccine Initiative, unpublished).

2.1.3   Realistically, therefore, it is improbable that an HIV/AIDS vaccine would be ready for distribution in South Africa much before 2015. The AIDS Vaccine Advocacy Coalition (2005) emphasises that, because of the many unforeseen complexities associated with vaccine development, time frames are often not met, and a degree of conservatism is therefore appropriate in forecasting the likely time to vaccine distribution.

2.2   VACCINE CHARACTERISTICS

2.2.1   A vaccine may be preventive (of benefit only to individuals who are HIV-negative at the time of vaccination) or therapeutic (of benefit to individuals who are HIV-positive at the time of vaccination). For preventive vaccines, which are the focus of this paper, efficacy has several dimensions. Firstly, the type of protection can be sterilising (blocking infection) or disease-modifying (reducing viral load and delaying progression to AIDS in individuals who become infected with HIV after vaccination). Secondly, efficacy will depend on the cross-reactivity of the immune response, i.e. whether the vaccine affords protection only against a single HIV subtype or against multiple subtypes. A third dimension of efficacy is durability, the extent to which the vaccine provides lasting protection.

2.2.2   The candidate HIV/AIDS vaccines currently being tested can be broadly divided into those that aim to induce a humoral (neutralising antibody) response, those that aim to induce a cellular (cytotoxic T-lymphocyte or CTL) response and those that follow a hybrid approach. Although HIV vaccine research initially focused mainly on humoral immunity, this approach was not successful, and almost all recent candidates aim to induce a CTL response (Global HIV/AIDS Vaccine Enterprise, 2005). It therefore seems probable that the first vaccines distributed will induce cellular rather than humoral immunity to HIV.

2.2.3   In order to understand the likely characteristics of the first HIV/AIDS vaccines, it is important to understand the distinction between cellular and humoral immunity to HIV. It is generally held that a vaccine that induces an HIV-specific CTL response would probably not prevent HIV infection (Lemckert, Goudsmit & Barouch,

2004; Morris, Williamson & Vardas, 2001), though studies in non-human primates suggest it might be disease-modifying (Graham, 2002). A vaccine that induces a humoral immune response, on the other hand, is more likely to prevent HIV infection, as HIV antibodies could clear free HIV virions before they enter CD4 cells and replicate.

2.2.4   To date, no HIV/AIDS vaccine candidate has managed to induce a neutralising antibody response that is broadly cross-reactive. However, a vaccine that targets a cellular immune response is more likely to protect against multiple subtypes, since most of these vaccines make use of the highly conserved regions of the HIV genome, i.e. those regions of the genome that are similar across HIV subtypes. CTL responses to these highly conserved regions have been shown to occur across a number of subtypes (Yu et al., 2005). In addition, many of the vaccines that aim to induce a cellular immune response use genes from more than one subtype.

2.2.5   The evidence to date does not suggest that an HIV/AIDS vaccine would provide lasting protection. Naturally-occurring HIV-specific immune responses, whether humoral or cellular, appear to wane in the absence of regular exposure to HIV (Mazzoli et al., 1999; Kaul et al., 2001), and the same may be true for vaccine-induced HIV-specific immune responses. It also seems likely that it will be necessary to administer multiple vaccine doses in order to establish an initial immune response (Suraratdecha & Hecht, unpublished), and many of the vaccine candidates currently being developed are based on a 'prime-boost' approach, which involves the administration of different vaccines at intervals of a few weeks or months. The only candidate that has thus far completed phase III-trial testing consisted of six doses, but this candidate was found not to be effective (rgp120 HIV Vaccine Study Group, 2005).

2.3   VACCINE DISTRIBUTION STRATEGY

2.3.1   Two types of vaccine distribution strategies are commonly modelled: 'cohort vaccination', in which individuals are vaccinated on reaching a certain age, and 'blanket vaccination', in which all unvaccinated individuals are vaccinated at a constant rate (Garnett, 1998). In reality, the strategy that would achieve the most rapid and extensive vaccine coverage would be 'mass vaccination'. This is usually once-off, although 'pulsed campaigns' or 'follow up campaigns' can involve mass vaccination every few years. Typically, a special national or regional immunisation day is held, on which individuals are encouraged to come to a particular vaccination point to be vaccinated. Following a mass vaccination campaign, vaccine coverage could be maintained through cohort vaccination.

2.3.2   The focus of this paper is limited to vaccine distribution strategies that would be appropriate when large amounts of vaccine stock are available. It should be noted, however, that when the first HIV/AIDS vaccines become commercially available, they are likely to be expensive and limited in supply. Alternative strategies for distributing HIV/AIDS vaccine would need to be considered under these circumstances (Chang, Vitek & Esparza, 2003).

2.4   RATES OF VACCINE ACCEPTANCE AND SERIES COMPLETION

2.4.1   A number of studies have examined individual willingness to receive a hypothetical HIV/AIDS vaccine. In developing countries with generalised HIV/AIDS epidemics, estimates of the proportions of individuals willing to be vaccinated against HIV lie between 64% and 96%. Rates of acceptance are particularly high in those groups with high HIV risk profiles: sex workers, truck drivers and military recruits (Jackson et al., 1995; Hom et al., 1997; Suraratdecha, Ainsworth & Tangcharoensathien, 2002). Rates of acceptance also appear to be higher at young ages than at old ages, even after controlling for the individual's perceived risk of HIV infection (Bishai et al., 2004; Suraratdecha et al., 2005). The acceptability of HIV/AIDS vaccination does not appear to be significantly influenced by the efficacy of the vaccine (Forsythe, unpublished; Bishai et al., 2004; Suraratdecha et al., 2005).

2.4.2   If the HIV/AIDS vaccine consists of more than one dose, not all individuals will return to complete the vaccine series. Although South African studies suggest that more than 80% of vaccine series in children are completed (Durrheim et al., 2001)[1], American studies of hepatitis B vaccination in adults suggest much lower series completion (Zimet et al., 2001; Sellors et al., 1997). As it is highly likely that the first HIV/AIDS vaccines will be multi-dose, and the vaccines will be less effective if the series is not completed, the low rate of series completion typical in adults is a significant cause for concern.

2.5   CHANGE IN BEHAVIOUR AFTER VACCINATION

2.5.1   It is possible that, because of reduced fear of HIV infection or its consequences, individuals who receive an HIV/AIDS vaccine may increase their level of sexual risk behaviour after vaccination. In studies that have asked individuals whether they would increase the amount of unprotected sex they have after HIV/AIDS vaccination, between 5% and one third report they would (Jackson et al., 1995; Suraratdecha et al., 2005; Hom et al., 1997). This change in behaviour appears to be more likely if the vaccine is highly effective than if the vaccine is only partially effective (Suraratdecha et al., 2005). However, these reports can provide an indication only of individuals' intended sexual behaviour after vaccination, and it remains uncertain what the actual extent of behaviour change would be.

2.5.2   Another possible change in behaviour after HIV/AIDS vaccination is reduced seeking of voluntary counselling and testing (VCT). Individuals may feel less need to seek VCT if they regard themselves as being protected against HIV. It is also likely that if the HIV/AIDS vaccine is highly immunogenic, it will induce HIV-specific antibodies, which will make standard antibody tests unreliable as measures of true HIV status. Vaccinated individuals seeking VCT would therefore have to be tested using polymerase chain reaction (PCR) or other tests, which are more expensive and time-consuming. This too could act as a disincentive for vaccinated individuals to seek VCT.

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1   cf. also Department of Health (1999) South Africa Demographic and Health Survey 1998: Full Report.

3. METHOD: THE ASSA2002 VACCINE MODEL

To assess the potential effect of HIV/AIDS vaccines in South Africa, a model was developed by adapting a C++ version of the ASSA2002 AIDS and Demographic model (Johnson, Dorrington & Matthews, unpublished). The more recent ASSA2003 version has not been used for this paper, as it was still being developed at the time that work started on the ASSA2002 Vaccine model. However, the ASSA2003 version produces similar results to the ASSA2002 version, and the two versions are structurally identical. The use of the ASSA2003 model as the basis for the vaccine model would therefore not substantially change the results presented in this paper. The ASSA2002 Vaccine model has been programmed both in C++ and in Excel/VBA, and the C++ and Excel/VBA versions produce identical results. The sections that follow describe the model structure, the choice of parameters and the scenarios considered in section 4.

3.1 BACKGROUND: THE ASSA2002 MODEL

3.1.1   The ASSA2002 AIDS and Demographic model is a model of the South African HIV/AIDS epidemic, developed under the auspices of the Actuarial Society of South Africa (ASSA). The sexual transmission of HIV is modelled by splitting the population aged 14 to 59 into four 'risk groups', which have different risks of HIV infection. The 'PRO' group represents sex workers and their frequent clients, while the 'STD' group represents individuals who are regularly infected with sexually transmitted diseases (STDs). The 'RSK' group represents individuals who are at risk of infection, although not falling into either of the previous two categories. Finally, the 'NOT' group represents individuals whose risk of infection is negligible, either because they are not sexually active or because they are in long-term, mutually monogamous relationships. All individuals over the age of 59 are assumed not to be at risk of acquiring HIV. Children under the age of 14 are also assumed not to be at risk of acquiring HIV, except through mother-to-child transmission (which is assumed to occur at or before birth, or through breastfeeding in the 12 months after birth).

3.1.2   After acquiring HIV, adults are assumed to progress through four stages of infection before either dying from AIDS or starting antiretroviral treatment. These four stages correspond to the four stages of the WHO Clinical Staging System. In addition to allowing for the effects of antiretroviral treatment, the model allows for the effect of four types of prevention strategy: improved treatment of STDs, social marketing (information and education campaigns), VCT and prevention of mother-to-child transmission (PMTCT).

3.1.3   The ASSA2002 model, user guide and supporting documentation are freely available from www.assa.org.za/aids.

### 3.2 MODELLING VACCINE CHARACTERISTICS

3.2.1   In order to model vaccine characteristics, the ASSA2002 Vaccine model splits the population into four classes:

– class 1: unvaccinated individuals;
– class 2: vaccinated individuals who are fully protected against HIV;

– class 3: vaccinated individuals who are partially protected against HIV; and
– class 4: individuals who have been vaccinated but are currently not protected.

3.2.2   The potential movements between the classes are illustrated in Figure 3.1. On being vaccinated, specified proportions of vaccinated individuals are moved into classes 2 to 4, depending on the efficacy of the vaccine and the type of immunity it induces. Individuals who are vaccinated after HIV infection are assumed to derive no benefit from the vaccine. Individuals who are initially protected by the vaccine can lose protection over time, and individuals are assumed to progress from fully protected to partially protected, and from partially protected to unprotected. No allowance is made for revaccination, either before or after the protection has waned.

Figure 3.1. Possible movements between vaccination classes
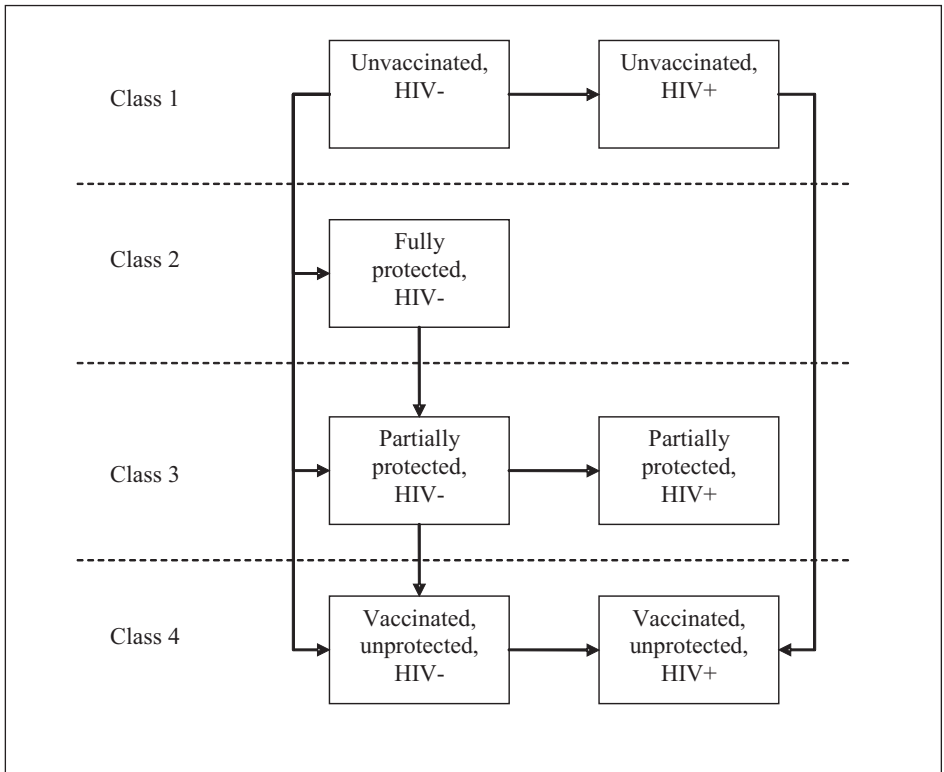
3.2.3   Individuals who are in the 'fully protected' class are by definition not at risk of HIV infection. Individuals in the 'partially protected' class may be at a reduced risk of infection, and may also be at a reduced risk of progression to AIDS if they become infected with HIV after vaccination. Individuals in the 'unprotected' class, however, are protected neither against infection nor against progression to AIDS.

3.2.4   Because of the uncertainty regarding the likely characteristics of the first HIV/AIDS vaccine, four different hypothetical vaccines are considered in section 4. The characteristics of these four hypothetical vaccines are summarised in Table 3.1. These vaccine parameters were selected to represent a range of plausible vaccine characteristics, and do not necessarily represent actual vaccines being developed. The efficacy rates of the different vaccines are expressed in terms of:
– the reduction in susceptibility to infection, VE_S;
– the reduction in the level of HIV infectiousness during stages 1 and 2 of disease, VE_I;
– the reduction in the rate of progression to AIDS, VE_P; and
– the mean duration of protection, μ.
It is assumed that all four vaccines consist of a series of three doses. (Although it is not clear how many doses will comprise the first HIV/AIDS vaccine, a three-dose vaccine is considered more likely than the conventionally assumed single-dose vaccine—cf. ¶2.2.5.) All individuals who receive the full series of doses are moved into the 'partially protected' class. Of individuals who do not receive the full series of doses, half are moved into the 'partially protected' class and the remaining half are moved into the 'unprotected' class. The efficacy parameters in Table 3.1 relate only to adults in the partially protected class (zero efficacy is assumed for the unprotected class).

Table 3.1. Characteristics of four hypothetical vaccines

Vaccine	VE_S (reduction in susceptibility)	VE_I (reduction in infectiousness)	VE_P (reduction in progression to AIDS)	Mean duration of protection (years)
A	0,00	0,83*	0,84	10
B	0,30	0,83*	0,84	10
C	0,30	0,83*	0,84	∞
D	0,95	0,00	0,00	10

*The value shown is an average; the VE_I parameter depends on the assumed exponential increase in infectiousness per unit increase in the logarithm of the viral load, which varies in the uncertainty analysis.

3.2.5   For vaccines A, B and C, which are disease-modifying, the VE_I and VE_P parameters are consistent with what one would expect for an HIV vaccine that reduces the logarithm of the HIV viral load by two units, a reduction that would appear to be achievable on the basis of candidate vaccines tested in non-human primates (Shiver et al., 2002; Barouch et al., 2000; Egan et al., 2000). These VE_I and VE_P parameters are derived from estimates of the increase in HIV infectiousness per unit increase in the logarithm of the HIV viral load, θ_I, and the increase in the rate of progression to AIDS per unit increase in the logarithm of the HIV viral load, θ_P. Uncertainty analysis of the ASSA2002 model suggests that the distribution of plausible θ_I values has a mean of 152%, and a 95% range of 76 to 270% (Johnson, Dorrington & Matthews, op. cit.). In the uncertainty analysis of

the ASSA2002 Vaccine model, this distribution is used to simulate the distribution of possible VE_I parameters, by calculating VE_I as:

$$VE_I = 1 - (1+\theta_I)^{-\log 100}.$$

3.2.6   This reduction in infectiousness is assumed to apply only when the infected individual is in WHO clinical stages 1 and 2, after which the protection provided by the vaccine is assumed to be lost. Similarly, the VE_P parameter is calculated as:

$$VE_P = 1 - (1+\theta_P)^{-\log 100}.$$

3.2.7 θ_P is assumed to be 150% (O'Brien et al., 1998; Lyles et al., 1999; Hubert et al., 2000), which gives the VE_P value of 0,84 in Table 3.1. On the assumption that the effect of the vaccine is limited to WHO stages 1 and 2, the median terms spent in stages 1 and 2 are set to be 191% greater in vaccinated individuals than in unvaccinated individuals, which is consistent with the VE_P value of 0,84. (For a more detailed explanation, see Johnson & Dorrington (unpublished, p.73).)

3.3   MODELLING VACCINE TIMING AND DISTRIBUTION

3.3.1   For the purpose of the analysis that follows, we consider the relatively optimistic scenario in which the first HIV/AIDS vaccine is introduced in 2015, and there is sufficient vaccine stock available to immunise a significant proportion of the South African population. Four potential strategies for distributing the vaccine are considered, and these are described in Table 3.2. All four strategies are combinations of mass vaccination, childhood vaccination and school-based vaccination. The first represents the most extensive vaccination that could be achieved. Strategies 2 and 3 target those sections of the population with higher levels of sexual activity. Strategy 4 is similar to the distribution strategy suggested at a recent WHO consultation (WHO-UNAIDS Expert Group, 2005). The periods over which these distribution strategies are implemented are shown in the last column.

Table 3.2. Vaccine distribution strategies

Strategy number	Type of distribution strategy	Ages	Distribution period
1	Mass vaccination	0–59	2015
	Childhood vaccination	3 months	2015–2025
2	Mass vaccination	15–49	2015
	School-based vaccination	15	2015–2025
3	Mass vaccination	15–24	2015
	School-based vaccination	15	2015–2025
4	School-based vaccination	15	2015–2025
	Childhood vaccination	3 months	2015–2025

3.3.2   Vaccine distributed by mass vaccination and childhood vaccination is assumed to be offered to all individuals in the population in the relevant age groups.

Vaccine distributed by school-based vaccination is assumed to be offered only to the 95% of 15-year olds who are in school.[2]

3.4 MODELLING VACCINE ACCEPTANCE AND SERIES COMPLETION

3.4.1 On the basis of the studies reviewed in ¶2.4.1, vaccine acceptance in the 14-to-59 age range is assumed to depend on both age and risk group, but not on vaccine efficacy. For each combination of age band and risk group, the probability of acceptance is simulated using a beta distribution. The means and standard deviations of these distributions are shown in Table 3.3. To ensure that for each model simulation, the rates of acceptance in different age and risk groups are consistent with one another, the same uniform (0, 1) random variable, U_1, is used to sample from each inverted cumulative beta distribution. The sensitivity analysis therefore examines the relationship between model outputs and the U_1 random variable.

Table 3.3. Means (and standard deviations) of the beta distributions
used to simulate the probability of vaccine acceptance

Age group	Risk group			
	PRO	STD	RSK	NOT
14 to 24	0,98 (0,01)	0,95 (0,02)	0,90 (0,03)	0,80 (0,05)
25 to 34	0,95 (0,02)	0,90 (0,03)	0,85 (0,04)	0,75 (0,06)
35 to 44	0,85 (0,04)	0,80 (0,05)	0,75 (0,06)	0,65 (0,08)
45 to 59	0,75 (0,06)	0,70 (0,07)	0,65 (0,08)	0,55 (0,09)

3.4.2 Vaccine acceptance below age 12 would require parental consent, which is assumed to be given in 98% of cases (Hutchins et al., 1993). (Current South African legislation requires that all children under the age of 14 receive parental consent prior to any medical treatment, but this age of consent is likely to be lowered to 12 in the near future.[3]) Since rates of vaccine series completion tend to be high in childhood, and since high rates of follow-up are possible if vaccines are distributed through schools, both childhood vaccination and school-based vaccination are assumed to be associated with high rates of series completion. In both cases, the probability of completing the series of three doses after receiving the first is simulated using a beta distribution with mean 0,85 and standard deviation 0,05. The probability of series completion under mass vaccination is simulated to be lower, using a beta distribution with mean 0,60 and standard deviation 0,10. For each simulation, the same uniform (0, 1) random variable, U_2, is used to simulate both completion probabilities.

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2 Statistics South Africa (2005) *General household survey, July 2004.* Available:
   http://www.statssa.gov.za/Publications/P0318/P0318July2004.pdf
3 Ann Strode, University of KwaZulu-Natal, personal communication

3.5   MODELLING EFFECTS OF VACCINE ON BEHAVIOUR

3.5.1   In the ASSA2002 Vaccine model, change in sexual behaviour in the HIV-negative population ('behavioural inhibition') is assumed to be the result of social marketing programmes. HIV-negative individuals who are regularly exposed to social marketing programmes and have easy access to condoms are assumed to increase condom usage. In response to HIV vaccines, however, a proportion of these individuals revert to their former sexual practices, using condoms to the same extent as in the absence of social marketing programmes. This proportion is simulated using a beta distribution, with mean 0,25 and standard deviation 0,08 in the case of vaccines A to C, and with mean 0,5 and standard deviation 0,15 in the case of vaccine D. It is thus assumed that a vaccine that is highly effective in preventing HIV would be associated with greater reductions in condom usage. A more detailed mathematical explanation of the modelling of the change in sexual behaviour and HIV transmissibility after vaccination is given in Johnson & Dorrington (op. cit.).

3.5.2   Allowance is also made for reductions in utilisation of VCT services by individuals who have been vaccinated. The reduction in the annual probability of seeking VCT is simulated using a beta distribution, with mean 40% and standard deviation 20% in the case of vaccines A to C, and with mean 80% and standard deviation 10% in the case of vaccine D.

3.6   UNCERTAINTY ANALYSIS AND SENSITIVITY ANALYSIS

3.6.1   Uncertainty regarding vaccine parameters is modelled using Monte Carlo simulation, parameter values being sampled from the beta distributions described above. 500 combinations of these vaccine parameters are randomly generated. These parameter combinations are then randomly paired with 500 combinations of other ASSA2002 parameters, generated in an earlier uncertainty analysis (Johnson, Dorrington & Matthews, op. cit.). These other parameters determine HIV survival in the absence of treatment, and sexual behaviour and probabilities of HIV transmission in the absence of prevention programmes. Allowance has also been made for uncertainty regarding the future availability of antiretroviral treatment and the effectiveness of PMTCT programmes. The uncertainty analysis presented here therefore reflects both uncertainty with respect to HIV/AIDS vaccine parameters and uncertainty with respect to basic HIV epidemiology.

3.6.2   For each of the vaccine-distribution scenarios and hypothetical vaccines, results of the uncertainty analysis are presented in terms of means (of the results generated using the 500 different parameter combinations) and 95% prediction intervals (2,5 and 97,5 percentiles of the 500 result sets). Sensitivity analysis is conducted by scatterplot and by calculation of correlation coefficients.

4. RESULTS

4.1 AMOUNT OF VACCINE REQUIRED

4.1.1   The projected numbers of individuals vaccinated between 2015 and 2025 are shown in Figure 4.1(a). Strategy 1 (vaccinating the population under the age of 60 in 2015 and infants born in each subsequent year) would require the most vaccine. Of the 46,5 million individuals who would be vaccinated under this strategy (95% interval: 42,8–49,9 million), it is expected that roughly 36,9 million (95% interval: 33,2–40,2 million) would be vaccinated in 2015 and the balance would be infants vaccinated in subsequent years. Strategies 2 and 3 would also require very large initial amounts of vaccine stock, as shown in Figure 4.1(c). Mass vaccination of 15- to 49-year olds in 2015 (strategy 2) would result in 20,3 million vaccinations (95% interval: 17,4–22,7 million) in 2015, while mass vaccination of 15- to 24-year olds in 2015 (strategy 2) would require 8,2 million vaccinations (95% interval: 7,4–8,9 million) in that year. Although strategy 4 would also require a large total investment (18,5 million vaccinated individuals, 95% interval: 17,4–19,6 million), this would be more evenly spread over the 2015–2025 period. Only 1,7 individuals would be vaccinated in 2015 (95% interval: 1,6–1,8 million) and similar numbers would be vaccinated in each subsequent year (Figure 4.1(e)).

4.1.2   Figures 4.1(b), (d) and (f) show the total doses consumed for each of the four strategies, on the assumption of a vaccine consisting of three doses. The numbers of vaccine doses consumed are between two and three times the total numbers of individuals vaccinated.

4.2 POTENTIAL EFFECTS OF AN HIV/AIDS VACCINE

4.2.1   The percentage reduction in new HIV infections between 2015 and 2025 is shown in Figure 4.2(a), for all hypothetical vaccines and all vaccine distribution strategies. As might be expected, the reduction in new infections is greatest for vaccine D and smallest for vaccine A. Strategy 2 is marginally more effective than strategy 1, as there are more short-term benefits to vaccinating individuals in early adolescence than there are to vaccinating children, whose vaccine-induced immune responses may wane by the time they become sexually active (the exception is vaccine C, which is assumed to provide lifelong protection). Strategy 4 is likely to be the least effective of the four strategies considered, as it results in protection of only a small proportion of the sexually active population. Strategy 3 can be expected to be 10% to 20% less effective than strategy 2 in preventing HIV, though this strategy requires considerably less vaccine.

4.2.2   Figure 4.2(b) shows the reduction in AIDS deaths between 2015 and 2025, as a result of vaccination. Reductions in AIDS mortality are significantly smaller than reductions in new HIV infections. Although there are significant differences between the vaccines in terms of the extent to which they reduce HIV incidence, differences in terms of reduced AIDS mortality are less substantial. Vaccines A, B and C are less effective than vaccine D in preventing HIV, but are nevertheless effective in delaying disease progression, and thus there is relatively little difference between the vaccines in terms of reduced AIDS mortality.

Figure 4.1. Numbers of vaccinated individuals and vaccine doses, 2015–2025
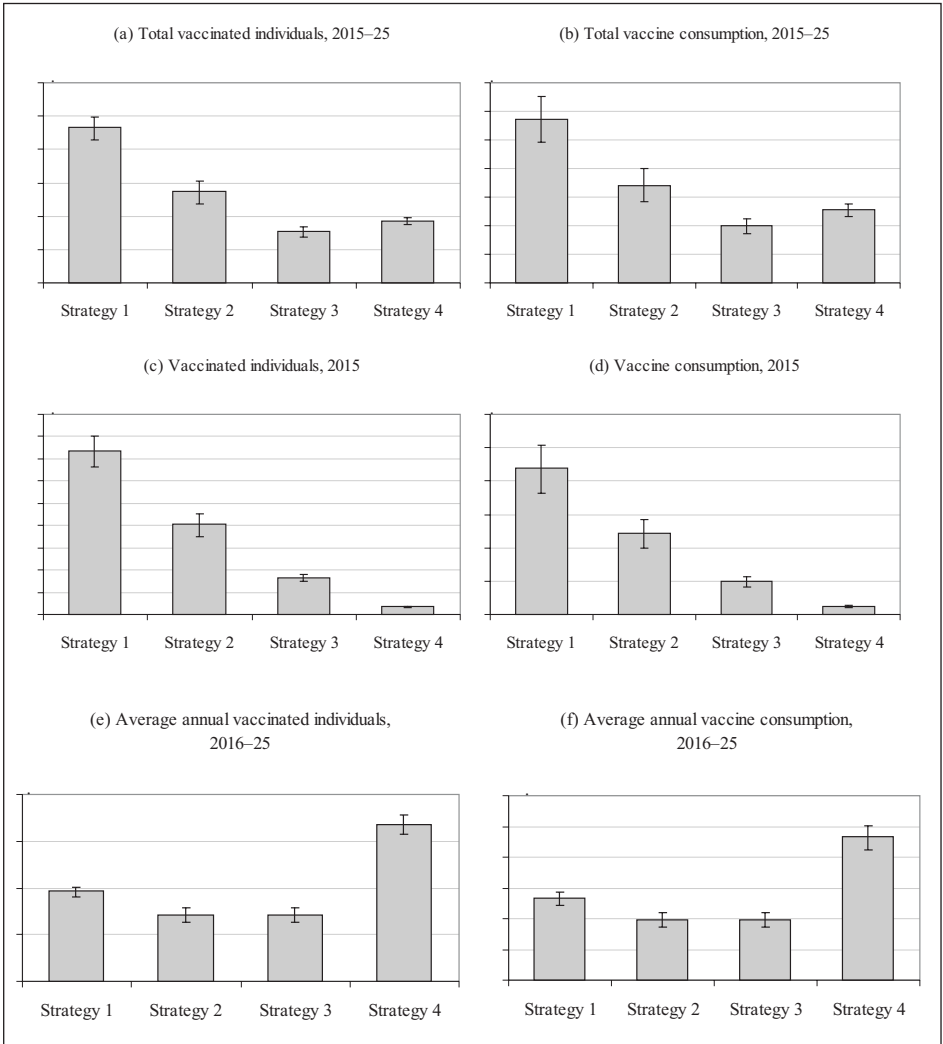
4.2.3   Trends in the annual number of new HIV infections are shown in Figure 4.3[4] for three scenarios: a 'no vaccine' scenario (a), a scenario in which vaccine B is distributed in accordance with strategy 2 (b), and a scenario in which vaccine D is distributed in accordance with strategy 2 (c). Vaccine B would reduce HIV incidence

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4   The Excel files used to generate this figure and other figures are available from the authors on request.

Figure 4.2. Percentage reduction in new HIV infections and AIDS deaths

(a) % reduction in new HIV infections, 2015–25

(b) % reduction in AIDS deaths, 2015–25
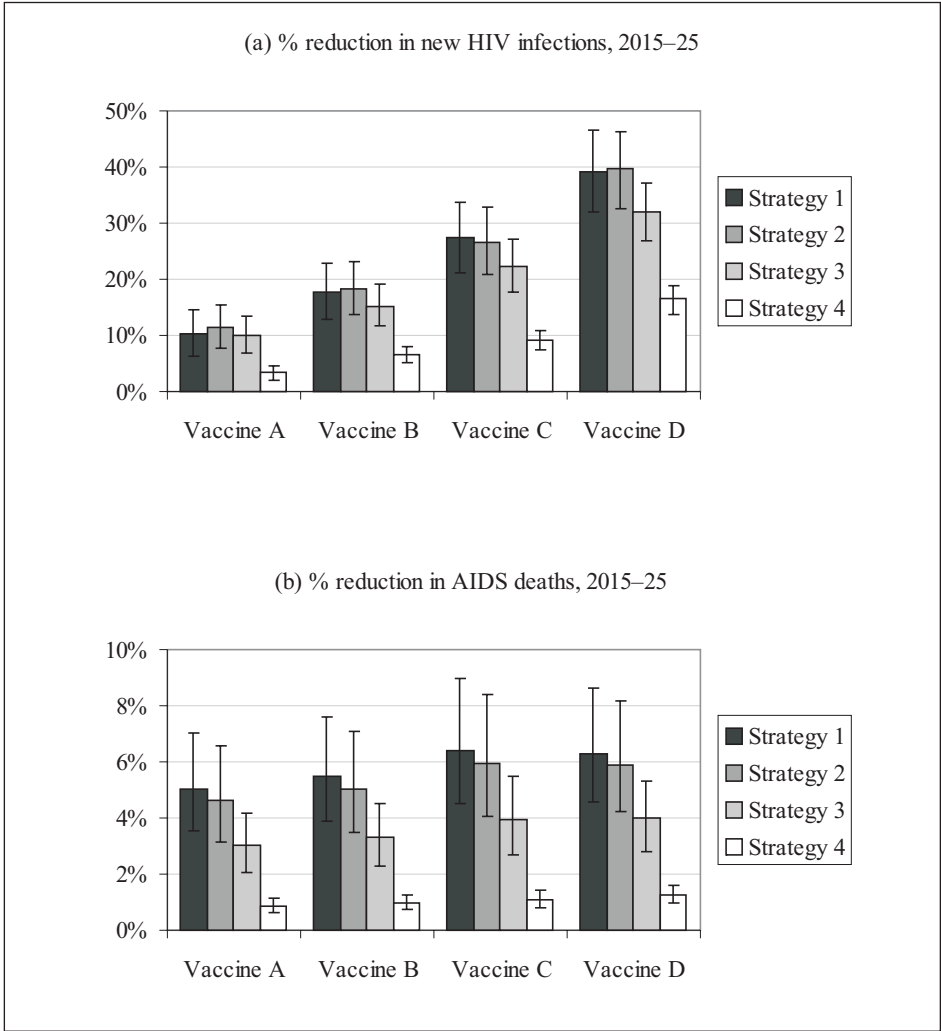
modestly at first (fewer primary infections), but would have a more significant effect on HIV incidence over the longer term (fewer secondary infections, due to reduced infectiousness of individuals infected after vaccination). In contrast, vaccine D would reduce HIV incidence very significantly in 2015, but the preventive benefit of the vaccine (relative to the 'no vaccine' scenario) would wane over time, as vaccinated individuals lose their immunity.

4.2.4   For the same three scenarios, trends in total HIV infections are shown in Figures 4.3(d)–(f). While vaccine D would lead to a significant drop in HIV prevalence

after 2015, the reduction in prevalence would be considerably smaller for vaccine B. Reductions in AIDS mortality would be less noticeable over the short term. Figures 4.3(g)–(i) show that for both vaccine B and vaccine D there would be slight reductions in annual numbers of AIDS deaths after 2015.

Figure 4.3. Trends in HIV incidence, HIV prevalence and AIDS mortality, with and without vaccine*
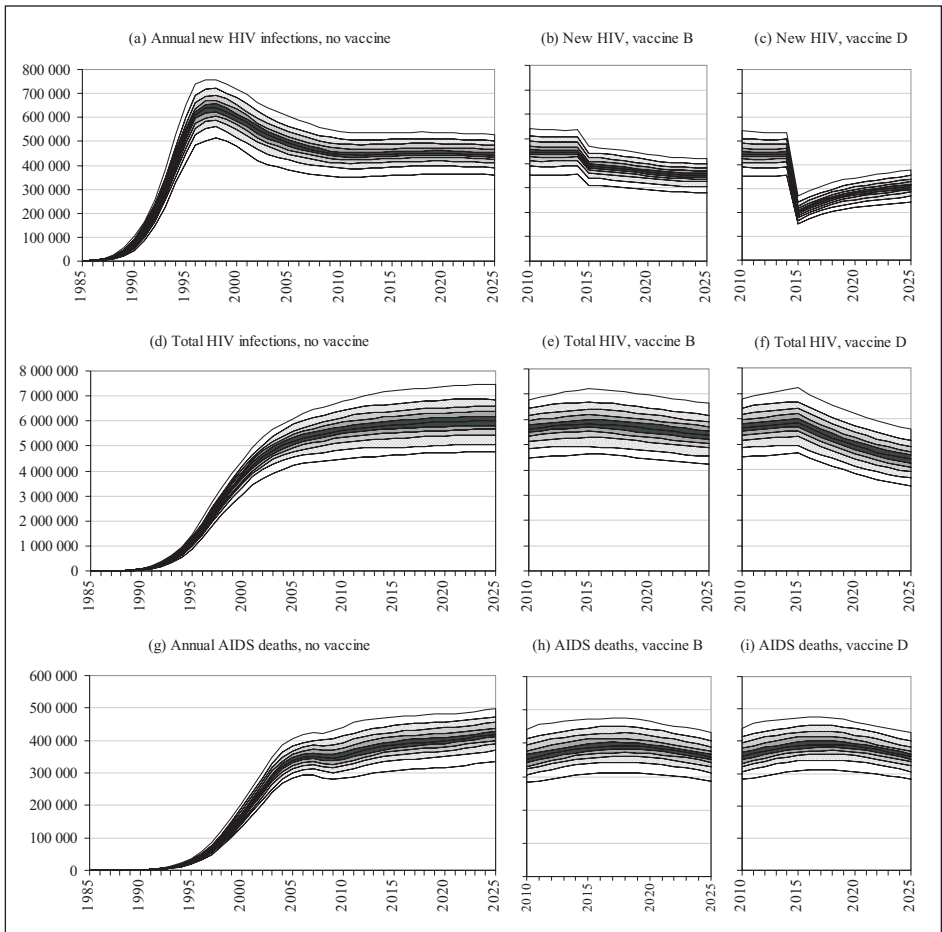
*Vaccine is assumed to be distributed in accordance with strategy 2. Solid outer lines represent 95% prediction intervals (2,5 and 97,5 percentiles of model outputs). ■ Interval between 40 and 60 percentiles. ■ Intervals between 30–40 and 60–70 percentiles. ■ Intervals between 20–30 and 70–80 percentiles. ▫ Intervals between 10–20 and 80–90 percentiles.

4.3   EFFICIENCY OF VACCINE DISTRIBUTION STRATEGIES

Figure 4.4 compares the various vaccines and vaccine distribution strategies in terms of HIV infections averted per vaccinated individual, over the 2015–2025 period. Strategy 3 is likely to be the most efficient strategy, in terms of preventing HIV, as it is the strategy that targets the group with the highest incidence of HIV (15- to 24-year-olds).

4.4   CORRELATES OF VACCINE CONSUMPTION AND EFFICIENCY

4.4.1   Correlations between total doses consumed under strategy 2 and measures of vaccine acceptance and series completion are shown in Figure 4.5. As explained in section 3.4, the measures of vaccine acceptance (U_1) and series completion (U_2) are the uniform (0, 1) random variables used to simulate the vaccine acceptance and

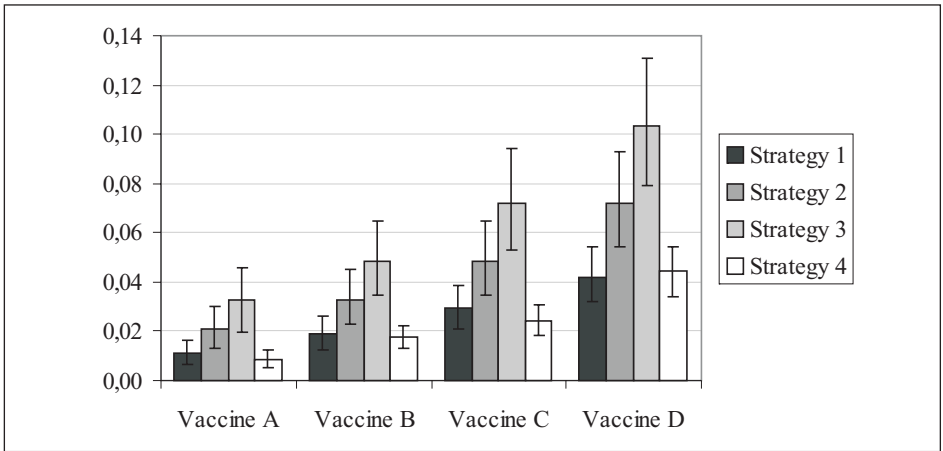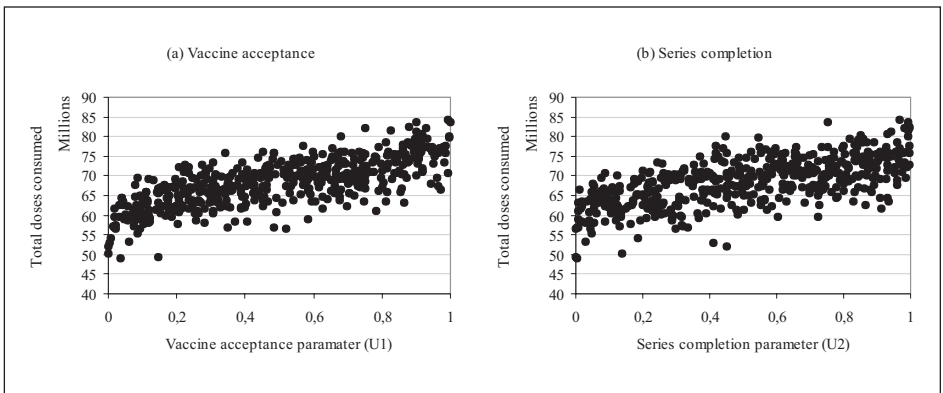Figure 4.4. HIV infections averted, per individual vaccinated (2015–2025)

Figure 4.5. Correlates of vaccine consumption (distribution strategy 2)

completion rates. Vaccine consumption is strongly positively related to the measure of vaccine acceptance (r = 0,73, p < 0,001), and is also strongly correlated with the measure of series completion (r = 0,65, p < 0,001).

4.4.2 A number of factors influence the efficiency of the vaccine distribution strategy. Figure 4.6 shows the correlation between the numbers of infections averted per vaccination and various parameters, for vaccine B when distributed in accordance with strategy 2. The parameter with which the number of infections averted per vaccination is most strongly correlated is the proportion of the initial sexually active population in the RSK group (r = 0,55, p < 0,001). This is because the incidence of HIV is dependent mainly on the size of the RSK group in the late stages of the epidemic, when there are few HIV-susceptible individuals remaining in the PRO and STD groups. The number of infections averted per individual vaccinated is also strongly associated with the increase in HIV infectiousness per unit increase in the logarithm of the viral load (VL) (r = 0,18, p < 0,001). This is partly due to the strong positive correlation between the effect of viral load on HIV infectiousness and HIV incidence in the later stages of the HIV/AIDS epidemic, when average viral-load levels are higher. It is also partly due to the fact that VE_I increases as θ_I increases.

4.4.3 Figure 4.6 also shows that the number of infections averted per vaccinated individual is likely to be significantly negatively related to the reversal of improvements in condom usage after vaccination (r = –0,26, p < 0,001). If a straight line is fitted through the scatterplot in Figure 4.6(c), the predicted number of infections averted when there is a 50% reversal of behavioural inhibition is 23% less than the predicted number of infections averted if there is no reversal of behavioural inhibition. The extent to which vaccinated individuals reduce their utilisation of VCT services is also significantly correlated with the efficiency of the vaccine in preventing HIV, though not as significantly as the reversal of behavioural inhibition (r = –0,15, p < 0,001). Although not shown in Figure 4.6, there is also significant negative correlation between the number of infections averted per vaccinated individual and the vaccine acceptance parameter U_1 (r = –0,22, p < 0,001), which indicates that there are likely to be diminishing marginal returns associated with HIV/AIDS vaccination programmes. The series-completion parameter U_2 is strongly positively associated with the number of infections averted per vaccinated individual (r = 0,40, p < 0,001).

4.4.4 The potential negative effect of reductions in condom usage on the preventive benefit of a vaccine is a cause for concern. Table 4.1 shows the correlation coefficients between the infections averted per vaccination and the reversal of behavioural inhibition, for each of the hypothetical vaccines and vaccine distribution strategies. From this it is clear that reversals of behavioural inhibition have the most effect when the vaccine reduces susceptibility to HIV by only a small degree and the duration of protection provided by the vaccine is short (vaccines A and B). The effect of reversal of behavioural inhibition appears to be similar for each of the vaccine distribution strategies.

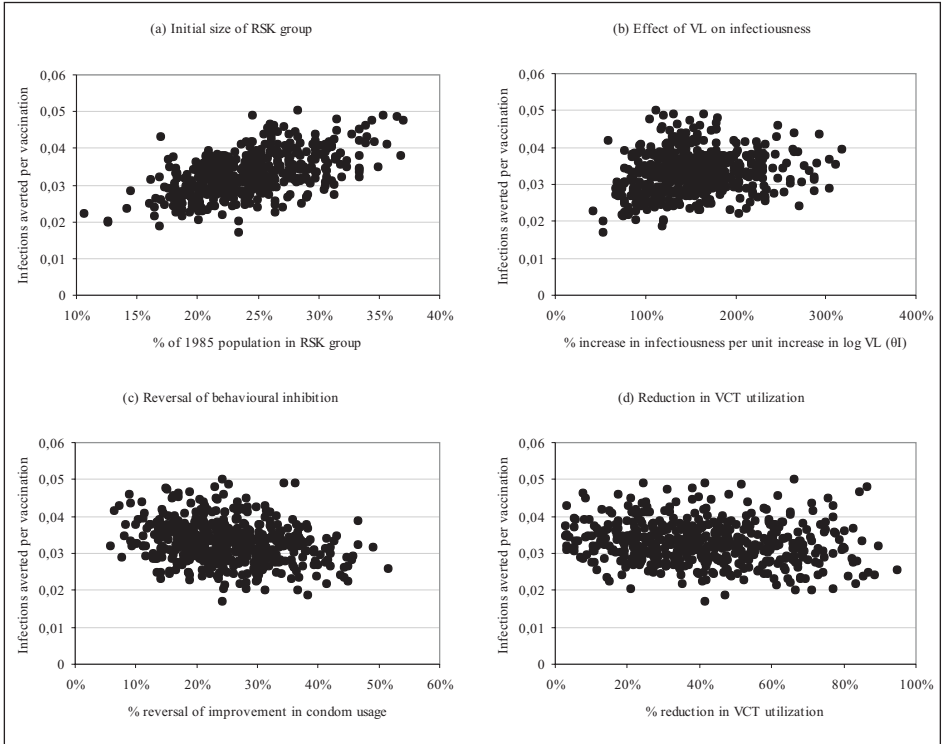Figure 4.6. Correlates of infections averted per vaccination (vaccine B, strategy 2)

Table 4.1. Correlation coefficients between infections averted
per vaccinated individual and reversal of behavioural inhibition

	Vaccine distribution strategy			
	1	2	3	4
Vaccine A	–0,38	–0,35	–0,37	–0,44
Vaccine B	–0,27	–0,26	–0,29	–0,32
Vaccine C	–0,16	–0,17	–0,18	–0,18
Vaccine D	–0,22	–0,20	–0,24	–0,21

5.   DISCUSSION

5.1   PROSPECTS FOR REDUCTIONS IN HIV INCIDENCE AND AIDS MORTALITY

5.1.1   Although it is widely believed that the development of an effective HIV/AIDS vaccine would be a *deus ex machina*, the reality is likely to be different. It is likely that the first vaccine will be disease-modifying rather than sterilising, and this analysis has shown that such a vaccine would be unlikely to reduce HIV incidence by more than a third over the 2015–2025 period. Other model-based evaluations have suggested that a vaccine that reduces susceptibility to HIV by more than 90% could eradicate the HIV/AIDS epidemic (Anderson & Garnett, 1996; Blower & McLean, 1994). In this analysis, however, it has been shown that vaccine D (which reduces susceptibility to HIV by 95%) is unlikely to reduce the total number of new HIV infections by more than 50%, even with the most extensive vaccine distribution programmes. This is partly because the model assumes a proportion of individuals decline the offer to be vaccinated, even though they are at risk of acquiring HIV. It is also partly because of the assumption that a significant proportion of individuals receiving the vaccine through a mass vaccination programme would not return to complete the vaccine series, and the vaccine would be less effective in these individuals. In addition, it is assumed that the protection provided by the vaccine wanes over time, and that individuals who have been vaccinated will tend to revert to the level of sexual risk behaviour they would have engaged in during the pre-AIDS era. Allowing for these considerations, it seems highly unlikely that an HIV/AIDS vaccine would by itself lead to the eradication of the HIV/AIDS epidemic.

5.1.2   Reversal of behavioural inhibition in vaccinated individuals has the potential to reduce significantly the effect of a vaccine that is primarily disease-modifying. If, however, the vaccine induces a high level of sterilising immunity, the effect of the vaccine is significantly less sensitive to the reversal of behavioural inhibition, as other studies have shown (Bogard & Kuntz, 2002; Nagelkerke & De Vlas, unpublished). This suggests that the poorer the ability of the vaccine to induce sterilising immunity, the greater will be the need for education promoting continued risk-reduction behaviour in vaccinated individuals. The extent to which VCT utilisation changes after vaccination could also significantly affect the preventive benefit of the vaccine. This is a parameter that has not been explored in previous research on the potential effect of HIV/AIDS vaccines.

5.1.3   This analysis suggests that even the most effective vaccines would be unlikely to reduce AIDS mortality by more than 10% over the 2015–2025 period. This can be explained by the fact that most of the AIDS deaths that are expected to occur over that period are the result of HIV infections occurring prior to 2015, which would not be prevented by the first vaccines. More substantial reductions would be expected over the longer term, however. It is possible that a vaccine might achieve more immediate reductions in AIDS mortality if the vaccine is therapeutic, but it is not clear whether the first vaccines are likely to have therapeutic properties (Peters, 2002).

5.2   VACCINE DISTRIBUTION STRATEGIES AND VACCINE REQUIREMENTS

5.2.1   Of the four strategies considered, the most effective strategy would probably be to conduct mass vaccination of 15- to 49-year olds in 2015, together with vaccination of high-school learners aged 15, in 2015 and subsequent years. However, if there is not sufficient vaccine available in 2015 to vaccinate 20 million people, a suitable alternative may be to limit the initial mass vaccination to 15- to 24-year olds, which would require enough vaccine for only 8 million individuals in 2015. This strategy would avert 10 to 20% fewer infections than the first strategy, but would ensure a much more efficient use of the limited vaccine supply.

5.2.2   The strategy suggested at a recent WHO consultation, namely to vaccinate all newborn infants as well as all children entering adolescence (WHO-UNAIDS Expert Group, op. cit.), is likely to be neither effective nor efficient, relative to the other strategies considered. It may, however, prove to be more effective over the longer term, as protection may be boosted considerably when children who have been vaccinated in infancy are revaccinated in early adolescence. This strategy would also have the advantage of requiring a less substantial initial expenditure on vaccine in 2015, but would require more vaccine than the other strategies in each subsequent year.

5.2.3   When estimating the total number of vaccine doses required in South Africa, the estimates of total vaccine doses consumed should be increased to allow for wastage. Wastage rates of 30 to 40% have been measured in mass vaccination programmes for measles in South Africa (Uzicanin et al., 2004). Assuming a wastage rate of 35% for a three-dose HIV/AIDS vaccine, the numbers of vaccine doses required over the 2015–2025 period would be 155 million for strategy 1 (95% interval: 133–176 million), 92 million for strategy 2 (77–108 million), 54 million for strategy 3 (46–60 million) and 69 million for strategy 4 (63–74 million).

5.3   STRENGTHS AND LIMITATIONS OF THE ASSA2002 VACCINE MODEL

5.3.1   The ASSA2002 Vaccine model improves on earlier estimates of vaccine requirements (Hecht & Suraratdecha, 2006) by allowing explicitly for rates of vaccine acceptance and rates of series completion in calculating the number of vaccine doses required. With the exception of the study of Esparza et al. (2003), other estimates of vaccine requirements have not taken these factors into consideration explicitly. The model also improves on earlier estimates of vaccine requirements by using projections of the future population (taking into account changing population size and the effect of AIDS up to the time that the vaccine is distributed) rather than using a fixed population set at current estimates. Being a combined demographic and epidemiological model, the ASSA2002 Vaccine model is also particularly useful in assessing the effect of restricting vaccine distribution to particular age groups and risk groups.

5.3.2   With a few exceptions (Davenport et al., 2004; Barth-Jones et al., unpublished; Blower et al., 2001), most model-based evaluations of vaccine effect have not included prediction intervals or plausibility bounds around model estimates. The ASSA2002 Vaccine model integrates both uncertainty regarding basic HIV epidemiology and uncertainty regarding vaccine parameters, to produce 95% prediction

intervals around all model estimates. This is particularly important when making long-term projections, which are shown to be subject to extreme uncertainty.

     5.3.3   A key limitation of the ASSA2002 Vaccine model is that it does not allow for the potential effects of revaccination. If vaccine protection wanes, as is assumed in the cases of vaccines A, B and D, it may be necessary to revaccinate individuals every few years. Because revaccination is likely to become particularly important in assessing the effect of an HIV/AIDS vaccine over the longer term, the focus of this analysis has been deliberately restricted to the 2015–2025 period. There is a need to examine the potential effects of vaccine distribution strategies beyond the 2025 horizon, and it would therefore be useful to adapt the model to allow for the effects of revaccination.

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