Assessment of HIV vaccine requirements and effects of HIV vaccination in South Africa

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Synopsis

Background

South Africa has an alarmingly high incidence of HIV, in spite of the introduction of significant prevention programmes over the last decade. In the light of this, there is a desperate need for new interventions and technologies to limit the expansion of the epidemic. An HIV vaccine could reduce HIV incidence and AIDS mortality substantially, and the objective of this report is to assess the potential effect of such vaccines in South Africa. A further objective of this report is to determine which strategies for distributing an HIV vaccine would be most effective, both when vaccine supplies are limited and when there is sufficient vaccine stock to immunize a large proportion of the population. For each of these strategies, total vaccine requirements are also estimated.

Method

The ASSA2002 Vaccine model was developed by adapting a C++ version of the ASSA2002 AIDS and Demographic model, to allow for the effects of vaccines. This model of the South African HIV/AIDS epidemic was adapted by dividing the population into four classes of individuals:

- Unvaccinated individuals;
- Vaccinated individuals who are fully protected against HIV;
- Vaccinated individuals who are partially protected against HIV; and
- Vaccinated individuals who are currently not protected against HIV.

On being vaccinated, specified proportions of individuals enter each of the three vaccine classes, depending on the efficacy of the vaccine and the type of immunity it induces. The model allows for the possible loss of HIV protection over time, as the vaccine-induced immune response wanes. The vaccine is assumed to have no effect in individuals who are already HIV-infected at the time of vaccination. Individuals who become infected while partially protected against HIV are assumed to experience slower HIV disease progression and lower levels of HIV infectiousness during the early disease stages.

Due to the uncertainty regarding the likely characteristics of the first HIV vaccines, four hypothetical vaccines are considered:

- Vaccine A: a vaccine which does not prevent HIV infection, although it significantly reduces disease progression and HIV infectiousness;
- Vaccine B: a vaccine which reduces susceptibility to HIV by 30%, in addition to having the same effect as vaccine A on disease progression and HIV infectiousness;
- Vaccine C: as for vaccine B, but the duration of protection is greatest for individuals who are most frequently exposed to HIV;
- Vaccine D: a vaccine which reduces susceptibility to HIV by 95% but does not delay disease progression or reduce HIV infectiousness.

All four vaccines are assumed to consist of three doses, and the average duration of immune protection is assumed to be 10 years (except in the case of vaccine C, for which the duration of protection depends on the risk group of the vaccinated
individual). In individuals who do not complete the series of three doses, the vaccine is assumed to be less effective.

Several types of vaccine distribution are modelled. The model allows for rates of vaccine acceptance to depend on the age, sex and risk group of individuals offered HIV vaccination. The model also allows for the vaccine to be offered either without screening or with screening for HIV, for each vaccine distribution strategy. It is assumed that once vaccinated, some individuals revert to the levels of condom usage they would have practised in the absence of the HIV/AIDS epidemic. Vaccinated individuals are also assumed to be less likely to seek voluntary counselling and testing.

Uncertainty regarding the rates of vaccine acceptance, rates of series completion and change in risk reduction behaviour after vaccination is incorporated by sampling 500 combinations of parameters from distributions that represent plausible ranges of uncertainty for these parameters. These 500 parameter combinations are randomly paired with 500 combinations of other ASSA2002 parameters. The 95% prediction intervals around the model results thus reflect both uncertainty with respect to vaccine-related behaviour and uncertainty with respect to basic HIV epidemiology.

**Distribution strategies when vaccine supplies are limited**

Nine vaccine distribution strategies are considered, each involving a different sub-population:
- Strategy I: Commercial sex workers
- Strategy II: Women attending antenatal clinics
- Strategy III: Women attending family planning clinics
- Strategy IV: Adults attending STD clinics
- Strategy V: Adults seeking voluntary counselling and testing
- Strategy VI: Children born to HIV-positive mothers (vaccinated at 3 months)
- Strategy VII: Learners aged 12
- Strategy VIII: Learners aged 14
- Strategy IX: Learners aged 16

The number of vaccine doses consumed in 2015 is shown in the figure below for each distribution strategy. Estimates of vaccine consumption are shown both with and without screening for HIV, and in the case of strategies II to VI, the estimates represent only the amount of vaccine that would be consumed in public health facilities. Estimates do not include any allowance for wastage, but do take into account vaccine acceptance and series completion. For a vaccine consisting of three doses, the number of vaccine doses consumed in 2015 would be greatest if the vaccine was distributed through family planning clinics (2.8 million, 95% interval: 2.4-3.2 million) or STD clinics (2.3 million, 95% interval: 1.4-3.6 million), without screening. HIV screening would reduce substantially the amount of vaccine consumed in strategies I and IV.
A key factor to consider in choosing a vaccine distribution strategy, when vaccine supplies are limited, will be the relative efficiency of the different distribution strategies in terms of infections averted and AIDS deaths averted, per vaccine dose administered. Infections averted and AIDS deaths averted over the 2015-2025 period, per vaccination in 2015, were calculated. On the basis of these estimates, it would appear that the relative efficiency of the different strategies is highly dependent on (a) the properties of the vaccine, (b) whether screening is deemed appropriate, and (c) whether the objective is to avert HIV infections or avert AIDS deaths in the short term. The table below shows which vaccine distribution strategies are likely to be most efficient for different screening options and different policy objectives.

### Screening Policy objective (short-term)

<table>
<thead>
<tr>
<th>Screening</th>
<th>Avert HIV infections</th>
<th>Avert AIDS deaths</th>
</tr>
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<tbody>
<tr>
<td>No screening</td>
<td>Schools (age 16)</td>
<td>Infants born to HIV+ mothers, STD patients</td>
</tr>
<tr>
<td>With screening</td>
<td>STD patients, Sex workers</td>
<td>Sex workers, STD patients</td>
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### Large-scale vaccine distribution strategies

Four potential vaccine distribution strategies, distinct from the nine previously described strategies, are considered for the scenario in which there is sufficient vaccine stock to immunize a large proportion of the population:

- Strategy 1: Mass vaccination of 0 to 59 year olds in 2015, together with vaccination of infants at 3 months in each year from 2015 to 2025;
- Strategy 2: Mass vaccination of 15 to 49 year olds in 2015, together with vaccination of learners aged 15 in each year from 2015 to 2025;
- Strategy 3: As for strategy 2, but with the initial mass vaccination limited to 15 to 24 year olds;
- Strategy 4: Vaccination of infants at 3 months and learners aged 15 in each year from 2015 to 2025.

No allowance is made for HIV screening in these distribution strategies.
Assuming a vaccine consisting of three doses, the number of vaccine doses expected to be consumed between 2015 and 2025 is 115 million for strategy 1 (95% interval: 98-130 million), 68 million for strategy 2 (57-80 million), 40 million for strategy 3 (34-45 million) and 51 million for strategy 4 (47-55 million). Mass vaccination would require a heavy initial expenditure in 2015, but the amount of vaccine required for infant and learners in each subsequent year would be relatively small. Estimates of the amount of vaccine consumed over a six-year period are relatively insensitive to the year in which the vaccine is first introduced. As in the previous section, these estimates of vaccine consumption do not make allowance for vaccine wastage. Assuming a wastage rate of 35%, the total amount of vaccine required can be approximated by multiplying the above estimates by a factor of 1.35.

The figure below shows the percentage reduction in new HIV infections, over the 2015-2025 period, for each of the four distribution strategies and each of the hypothetical vaccines. Strategy 2 would probably be the most effective strategy, for all of the hypothetical vaccines, and the reductions in HIV incidence under strategy 2 are comparable to or greater than the reductions that have been achieved with other HIV prevention programmes in South Africa. Strategy 3 would be 10 to 20% less effective than strategy 2, but would require substantially less vaccine, and would therefore ensure a much more efficient use of the limited vaccine supply. Strategy 4 would not be as effective or as efficient as the other strategies considered, though it would require a substantially smaller initial expenditure in 2015.

The number of infections averted, per individual vaccinated, is likely to be strongly negatively correlated with the reversal of risk reduction behaviour in vaccinated individuals. The effect of this ‘behavioural disinhibition’ is particularly significant for disease-modifying vaccines, such as vaccine A. Hence, the lower the efficacy of the vaccine in reducing susceptibility to HIV, the greater will be the need for education programmes promoting continued risk reduction behaviour in vaccinated individuals. Reduction in utilization of VCT services could also significantly reduce the benefit of a disease-modifying HIV vaccine.

If male circumcision programmes were introduced in 2007, these would reduce the total number of new HIV infections over the next 10 years by 8.9% (95% interval: 5.1-13.6%). However, the impact of an HIV vaccine would not be mitigated to any
significant extent by male circumcision or other prevention programmes. The vaccine may have less impact on AIDS mortality in the short term if AIDS mortality has already been reduced to a significant extent by antiretroviral treatment.

**Strengths and limitations**

A key limitation of the ASSA2002 Vaccine model is that it does not allow for the effects of revaccination. This analysis considers the impact of HIV vaccination over a relatively short period (ten years), and it will probably be necessary to extend the model to allow for revaccination when evaluating longer-term vaccine distribution strategies.

The estimation of vaccine requirements is based on a number of simplifying assumptions. For example, it is assumed that if the vaccine is distributed through existing HIV prevention facilities, utilization of these facilities will remain unchanged, though there could be an increase in utilization if there is a substantial demand for the vaccine. It is also assumed that individuals who know they are HIV-positive are as likely to accept an HIV vaccine as individuals who are HIV-negative or unaware of their HIV status, though the vaccine is assumed to have no effect in individuals who are already HIV-positive. This analysis considers a vaccine which is made available free of charge, and ignores the potential private demand for an HIV vaccine.

The ASSA2002 Vaccine model includes a number of innovative features. Vaccine acceptance and series completion are modelled explicitly. Behavioural disinhibition is modelled as a reversal of behavioural inhibition rather than as an arbitrary increase in sexual risk behaviour. Results are presented with 95% prediction intervals, which reflect both uncertainty regarding basic HIV epidemiology and uncertainty regarding key vaccine parameters. Being a dynamic demographic and epidemiological model, the ASSA2002 Vaccine model is particularly useful in comparing different vaccine distribution strategies, both in terms of vaccine requirements and vaccine impacts.
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List of abbreviations

ANC  Antenatal clinic
ASSA  Actuarial Society of South Africa
BCG  Bacillus Calmette-Guerin
CSW  Commercial sex worker
CTL  Cytotoxic T-lymphocyte
DALY  Disability-adjusted life year
DHS  Demographic and Health Survey
DPT  Diptheria, pertussis and tetanus (vaccine)
FPC  Family planning clinic
HAART  Highly active antiretroviral treatment
HLA  Human leucocyte antigen
HPV  Human papillomavirus
IEC  Information and education campaigns
MC  Male circumcision
OPV  Oral polio vaccine
PCR  Polymerase chain reaction
PMTCT  Prevention of mother-to-child transmission
QALY  Quality-adjusted life year
SADC  Southern African Development Community
SHIV  HIV-SIV hybrid virus
SIV  Simian immunodeficiency virus
STD  Sexually transmitted disease
Th1  T-helper type 1
VCT  Voluntary counselling and testing
VEI  Vaccine efficacy in reducing infectiousness
VES  Vaccine efficacy in reducing susceptibility
VEP  Vaccine efficacy in reducing disease progression

The terms PRO, STD, RSK and NOT refer to the four risk groups in the ASSA2002 model (see explanation in section 4.1).
1. Introduction

South Africa is a country severely affected by HIV/AIDS, with one of the highest rates of HIV prevalence in the world (UNAIDS 2004). A distinguishing feature of the epidemic in South Africa, relative to that in other African countries, is the relatively late start to the epidemic coupled with the explosive growth in HIV prevalence since the first reported AIDS cases in the heterosexual population. Prevention programmes have had some success in curbing the spread of HIV, but the HIV incidence rate remains high, at roughly 1.3% in 2004 (Dorrington et al, 2004). In the light of the high rate at which new infections are occurring, there is a desperate 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 vaccine.

The objective of this report is to assess the potential impact of HIV vaccines in South Africa. In addition, the report attempts to determine which vaccine distribution strategies are likely to be most effective in distributing vaccine, both when vaccine supplies are limited and when there is sufficient vaccine stock to immunize a large proportion of the population. For each of the large-scale vaccine distribution strategies, it is also necessary to estimate the total amount of vaccine required, in order to inform vaccine production planning. These objectives are met by developing a mathematical model of the HIV/AIDS epidemic in South Africa which incorporates the effects of HIV vaccines. This model is developed by extending the existing ASSA2002 AIDS and Demographic model, as described in the sections that follow.

To inform the choice of model features and model parameters, a review is conducted of the literature concerning vaccine development prospects, potential vaccine characteristics, vaccine distribution strategies and individual-level responses to vaccines. This review is presented in section 2. Following this, in section 3, a review is presented of the mathematical modelling work that has been conducted to date to assess the potential impact of HIV vaccines. Section 4 then describes the ASSA2002 Vaccine model and the key assumptions made in the model, as well as the various scenarios that are considered. The results of the model are presented in section 5. The final section contains recommendations regarding vaccine distribution strategies, as well as a discussion of the strengths and limitations of the ASSA2002 Vaccine model.
2. Review: prospects for HIV vaccine development and impact

To date, no candidate HIV vaccine has been proven effective in a phase III trial. However, much research has been conducted to address key questions around HIV vaccines. This research is briefly reviewed in this section, and the results of this review are used to motivate the structure and parameters chosen for the ASSA2002 Vaccine model in section 4.

2.1 Expected time to vaccine distribution

There is currently much uncertainty as to when the first effective HIV vaccine is likely to be ready for distribution. At present there is only one phase III HIV vaccine trial in progress, with results expected in 2008/9 (Rodriguez-Chavez et al, 2006). This vaccine is a combination of an rgp120 vaccine and a canarypox vector vaccine, neither of which by itself is highly effective. An adenovirus 5 vector vaccine is currently being tested in a phase IIB trial, with results expected in 2007/8. There are approximately 30 phase I and phase II trials under way, and those which progress to phase III in future will usually require a further three years until completion of the phase III trials. Discounting the possible success of the current phase III trial, it therefore seems unlikely that any HIV vaccine candidate would be proven effective before 2010.

Even if an HIV 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 which 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 HIV vaccine efficacy may depend on local HIV strains, local host genetic profiles and local modes of HIV transmission. It may also be necessary to conduct separate trials in adolescents, as there is some controversy as to whether adolescents should be included in initial trials conducted in adults (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, investing hundreds of millions of dollars in setting up this production capacity is a significant gamble (Collins 2005). Realistically, the creation of production capacity would only begin once provisional results suggested a high level of efficacy. This could significantly delay distribution of the vaccine, given the five-year lead time typically required for setting up production capacity (International AIDS Vaccine Initiative 2005).

Realistically, therefore, it is improbable that an HIV vaccine would be ready for distribution in South Africa much before 2015. Earlier estimates have tended to be more optimistic. For example, when the AIDS Vaccine Advocacy Coalition was established in 1995, it promoted the target of an effective and inexpensive vaccine by 2007 (AIDS Vaccine Advocacy Coalition 2005). Clements et al (2004) estimate that an effective vaccine would be ready for distribution some time between 2009 and 2014, while Makgoba et al (2002) suggest that an effective vaccine is “within reach” between 2009 and 2012. The AIDS Vaccine Advocacy Coalition emphasizes that time
frames are often not met due to the many unforeseen complexities associated with vaccine development, and a degree of conservatism is therefore appropriate in forecasting the likely time to vaccine distribution.

2.2 Expected vaccine efficacy

A vaccine may be preventive (of benefit only to individuals who are HIV-negative) or therapeutic (of benefit to individuals who are HIV-positive at the time of vaccination). For preventive vaccines, which are the focus of this report, efficacy has several dimensions. Firstly, the level of protection induced by the vaccine is important: whether the vaccine is sterilizing (blocking infection) or disease-modifying (reducing viral load and delaying disease progression). Secondly, effectiveness will depend on the cross-reactivity of the immune response: whether the vaccine affords protection only against a single subtype or against multiple subtypes. A third dimension of efficacy is durability, the extent to which the vaccine provides lasting protection. These dimensions of efficacy, as well as the factors affecting them, are discussed below in relation to preventive HIV vaccine research.

2.2.1 Types of immunity

Over thirty preventive HIV vaccine candidates are currently in clinical trials. These can be broadly divided into those which aim to elicit a humoral (neutralizing antibody) response, those which aim to elicit a cellular (cytotoxic T-lymphocyte or CTL) response and those which 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.

It is generally held that a vaccine which induces an HIV-specific CTL response would probably not prevent HIV infection (Lemckert et al, 2004; Morris et al, 2001), though studies in non-human primates suggest it might alter HIV viral load and disease progression (Graham 2002). HIV-specific CTL responses have been shown to be important both in controlling initial HIV viraemia (Borrow et al, 1994) and in providing protection in long-term non-progressors (Cao et al, 1995). This suggests that a CTL vaccine would be disease-modifying. It is possible that a CTL vaccine may also be sterilizing to some degree, as HIV-specific CTL responses have often been detected in individuals who have been highly exposed to HIV but not infected (Rowland-Jones et al, 1998; Pinto et al, 1995; Promadej et al, 2003; Lo Caputo et al, 2003). However, the observed associations between HIV-specific CTL responses and HIV resistance do not necessarily imply that CTLs play a protective role, and current consensus is that the determinants of HIV protection are still poorly understood (Peeters et al, 2003; Lemckert et al, 2004).

Because HIV antibodies could clear free HIV virions before they enter CD4 cells, it is believed that a vaccine inducing a humoral immune response is more likely to prevent HIV infection. HIV-specific antibodies have been observed in individuals who are highly exposed to HIV yet uninfected (Lo Caputo et al, 2003; Mazzoli et al, 1999), and this suggests that the humoral immune response might indeed protect against HIV
infection. Studies conducted in macaques have also shown that when monoclonal antibodies are administered, they can block SHIV infection when animals are challenged intravaginally (Veazey et al, 2003; Parren et al, 2001). There is some evidence to suggest that a vaccine inducing a humoral immune response could also be disease-modifying. For example, studies in macaques have shown that even when monoclonal antibodies do not prevent SHIV infection, they are associated with delayed and reduced peak SHIV viraemia (Parren et al, 2001; Veazey et al, 2003). A recent study has also shown that individuals who are administered monoclonal antibodies may experience a delay in HIV viral rebound after discontinuing antiretroviral treatment (Trkola et al, 2005). The viral load reductions and delays in viral load increase observed in these studies are likely to be associated with reduced infectiousness and delayed disease progression.

2.2.2 Cross-reactivity

Studies suggest that antibody responses in HIV-infected individuals are not subtype-specific (Hu et al, 1999), though some monoclonal antibodies have been shown to neutralize certain subtypes more frequently than other subtypes (Binley et al, 2004). To date, no HIV vaccine candidate has managed to elicit a neutralizing antibody response that is broadly cross-reactive. However, attempts are being made to find HIV antibodies that are broadly cross-reactive and to identify the precise sections of the HIV envelope that these antibodies target, for use in future HIV vaccine candidates (Kahn 2005). These vaccine candidates should be more broadly cross-reactive than the previous envelope-based vaccines.

CTL responses also appear not to be subtype-specific, though the response to virus of a different subtype is usually not as strong as the response to virus of the same subtype (Peeters et al, 2003). Most of the vaccines that aim to elicit a cellular response make use of the highly conserved regions of the HIV genome, i.e. those regions of the genome which 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. It is therefore likely that a vaccine targeting cellular immunity would protect against multiple HIV subtypes.

2.2.3 Durability

It is currently not clear whether a vaccine inducing an HIV-specific humoral immune response would provide long-term or only temporary protection. Several studies have shown that HIV-specific IgA antibodies are present in individuals who are exposed to HIV but not infected, but many of these studies have shown that these IgA antibodies become less frequent the longer the time since last exposure (Lo Caputo et al, 2003; Mazzoli et al, 1999). The rgp120 vaccines that have targeted humoral immunity have only been able to induce short-lived antibody responses (Graham 2002). The evidence to date therefore does not suggest that an HIV vaccine eliciting HIV antibodies would provide lasting protection in uninfected individuals.

Studies of individuals who are highly exposed to HIV but not infected suggest that the HIV-specific cellular response that develops in these individuals also wanes over time (Kaul et al, 2001; Promadej et al, 2003; Pinto et al, 1995). This suggests that the
protective benefit from a vaccine eliciting a cellular immune response may also be short-lived in uninfected individuals. Certain live vector vaccines, however, may induce a more durable immune response, as some viral vectors are able to persist in the host for long periods of time.

Even if the CTL response induced by the vaccine is durable, protection against disease progression may be limited. Individuals who are infected with HIV after being vaccinated with a non-sterilizing vaccine may be able to control initial viraemia well, but there remains the risk that the virus with which they are infected may mutate and ‘escape’ the CTL response. Davenport et al (2004) suggest that because of this CTL escape, the duration of protection afforded by a disease-modifying vaccine is likely to be less than five years. It is possible that these ‘escape mutant viruses’ would be transmitted sexually, and the effect of the vaccine at a population level may be diminished as a result of the accumulation of these circulating escape mutants over time (Goulder et al, 2001). However, the escape mutant virus may also revert to wild type virus (Leslie et al, 2004; Smith and Kent 2005), and model simulations by Davenport et al (2004) suggest that when reversion to wild type is taken into account, the rate of CTL escape may have little impact on HIV incidence at a population level.

2.2.4 Factors affecting efficacy

A number of factors are likely to influence the efficacy of an HIV vaccine, both at an individual level and at a population level. These factors need to be considered when determining which sections of the population are most likely to benefit from the vaccine and when assessing the generalizability of efficacy estimates from phase III trials in other countries. Certain factors may also form the basis for interventions to improve efficacy (for example, programmes to reduce the prevalence of helminths prior to vaccination in helminth-endemic areas).

Factors affecting vaccine efficacy at the individual level

A number of factors, such as sex, age and frequency of exposure to HIV, may influence the degree of protection provided by an HIV vaccine. In the phase III trial of the rgp120 vaccine, for example, efficacy was found to be higher in women than in men and higher in trial participants categorized as engaging in ‘high risk behaviours’, though neither difference was statistically significant (rgp120 HIV Vaccine Study Group 2005). The authors suggest that the greater protection in those engaging in high risk behaviours may have been due to a natural priming of the vaccine-induced immune response through regular exposure to HIV, similar to that observed in highly exposed sex workers. It is therefore possible that an HIV vaccine may provide greater and longer-lasting protection in individuals who are regularly exposed to HIV than in individuals at a low risk of infection. This implies that an HIV vaccine may be more effective in a ‘high HIV prevalence’ setting than in a low prevalence setting.

The explanation for the greater efficacy of the rgp120 vaccine in females is not clear. Similar sex differences have been found in a vaccine against genital herpes, which is only effective in women (Stanberry et al, 2002). It has been suggested that women develop stronger cellular immune responses than men do, and this may partly explain the greater efficacy of the genital herpes vaccine in women (Jones and Cunningham
2004; Stanberry et al, 2002). It is possible that an HIV vaccine targeting a cellular response may also differ in efficacy between men and women.

*Factors affecting vaccine efficacy at the population level*

Various vaccines, such as BCG for tuberculosis, have been found to be less effective in developing countries than in developed countries (Markus 2003). The factors that compromise the effectiveness of these vaccines may also compromise the effectiveness of an HIV vaccine, and it is therefore critical that research be conducted into these factors.

It would appear that some vaccines are less effective in developing countries because immune systems in these settings are skewed towards Th2 immunity, and the Th1 immune response is often defective¹. Studies have identified important differences between study populations in Africa and Europe in terms of the production of cytokines that direct Th1 and Th2 responses (Wilfing et al, 2001; Rizzardini et al, 1996). The bias towards Th2 immunity is thought to lead to the suppression of Th1 immunity induced by vaccines that target cellular (Th1) immunity, and this is thought to explain the low efficacy of these vaccines (Fincham et al, 2003).

A number of possible explanations for this Th2 bias have been given. Firstly, the high prevalence of chronic infection with helminths in developing countries is a significant factor leading to Th2 polarization (Fincham et al, 2003). The role of helminths in compromising vaccine efficacy has been demonstrated in studies that have shown substantial improvements in the efficacy of tuberculosis and cholera vaccines following deworming programmes (Markus 2003). As the prevalence of helminths is extremely high in parts of South Africa (Appleton et al, 1999; Wolmarans et al, 2001; Gunders et al, 1993) and elsewhere in southern Africa (Bundy et al, 2000), the efficacy of HIV vaccines in SADC countries may be compromised if steps are not taken to combat helminth infection. Other factors have also been implicated in the predominance of Th2 immunity, such as genetic factors and zinc deficiency (Markus 2003).

The bias towards Th2 immunity in southern Africa has significant implications for the potential impact of an HIV vaccine. HIV vaccines that aim to induce CTL responses are likely to be less effective if a Th2 bias, induced by environmental and/or genetic factors, leads to suppression of cellular immunity. The prevalence of helminthic infection is usually highest in early adolescence, and this may have significant consequences if HIV vaccination is targeted at individuals in this age group. Much research still needs to be conducted into the causes and consequences of Th1/Th2 imbalance.

Infections other than helminths can also influence the efficacy of a vaccine. It has been suggested, for example, that an HIV vaccine may act synergistically with GB virus C (rgp120 HIV Vaccine Study Group 2005), a virus which has been shown to inhibit HIV replication in vitro (Xiang et al, 2001). It has also been suggested that genetic factors may result in some populations being more protected by a vaccine than

¹ T-helper type 1 (Th1) cells direct the cellular immune response, while T-helper type 2 (Th2) cells direct the humoral immune response.
others (Smith and Kent 2005). For example, the HLA-B*27 allele, which has been found to be associated with better CTL responses to an HIV vaccine candidate, is relatively rare in African populations (Kaslow et al, 2005). The efficacy of a vaccine may also depend on the main mode of transmission in the local population, as the mucosal immune response induced by the vaccine would be relevant in sexual transmission of HIV but irrelevant in transmission through injection with contaminated needles. There are thus several reasons why vaccine efficacy may differ between populations, even if the vaccine is effective against multiple subtypes.

2.3 Vaccine distribution strategies

Chang et al (2003) identify a number of potential strategies for distributing HIV vaccine. A distinction can be drawn between short-term distribution strategies and medium-term distribution strategies. The short-term strategies identified include:

- Phase IV effectiveness trials, which would assess the generalizability of the results obtained from the phase III trials
- Formal phased introduction
- Targeting high-risk groups (e.g. sex workers, truck drivers, military personnel)

Medium-term strategies identified by Chang et al (2003) and Clements et al (2004) include:

- Integration of HIV vaccination into existing HIV prevention facilities (i.e. providing vaccines through antenatal clinics, family planning clinics, STD clinics and VCT services)
- Integration of HIV vaccination into existing immunization programmes (childhood vaccination and school-based vaccination)
- Mass vaccination or ‘catch up’ vaccination (i.e. aiming to vaccinate all individuals in a particular age group)

The relative merits of the vaccine distribution strategies considered in section 4 are discussed below.

2.3.1 Targeting commercial sex workers

HIV prevalence rates measured to date in South African commercial sex workers have been between 45% and 68% (Rees et al, 2000; Ramjee et al, 1998; Williams et al, 2000). This is therefore a group that would benefit particularly from HIV vaccination, and several cost-effectiveness studies have suggested that it would be highly cost-effective to target HIV vaccination at these women (Desmond and Greener 2003; Novaes et al, 2002). However, this strategy would present several practical difficulties. Partly because of the criminalization of sex work, commercial sex workers do not exist as a clearly defined group and are not easily located, except possibly through NGOs working with sex workers. It is also likely that targeting HIV vaccination at sex workers would be highly controversial, and sex workers themselves may find the strategy to be stigmatizing. In addition, the term ‘sex worker’ would need to be clearly defined in order to make such a strategy practicable, and there could be further controversy regarding the forms of transactional sex that are targeted.
2.3.2 Antenatal clinics

Several studies have examined the potential effect of administering an HIV vaccine to pregnant women (Desmond and Greener 2003; Novaes et al, 2002; Tangcharoensathien et al, 2001). Such a strategy would have the advantage of protecting women when they are particularly susceptible to HIV (Gray et al, 2005) and would also be simple to integrate with existing prevention of mother-to-child transmission (PMTCT) programmes.

2.3.3 Family planning clinics

Although family planning clinics (FPCs) have been suggested as facilities through which HIV vaccination could be provided (Clements et al, 2004), cost-effectiveness analyses to date have not considered this strategy. It is difficult to estimate the potential demand for an HIV vaccine if it is administered through FPCs, due to uncertainty regarding future changes in utilization of these facilities if they are used to distribute vaccine. In the 1998 DHS it was found that 20% of women who used modern contraceptive methods reported obtaining these from FPCs, and the balance obtained contraception mostly from public hospitals, day clinics, mobile clinics, private hospitals or private doctors (Department of Health 1999). The proportion using FPCs may increase well beyond 20% if vaccination were offered only through these services.

2.3.4 STD treatment clinics

Many cost-effectiveness assessments have considered the effects of providing an HIV vaccine through STD clinics (Desmond and Greener 2003; Novaes et al, 2002; Tangcharoensathien et al, 2001). In practice, it would be difficult to limit the vaccine provision to people with STDs, as current STD treatment protocols in South Africa are based on patient-reported symptoms rather than laboratory tests or signs observed by clinicians. Individuals attending an STD clinic would therefore be eligible to receive HIV immunization even if they did not have an STD, provided they reported appropriate symptoms.

2.3.5 Voluntary counselling and testing (VCT) services

It has been suggested that HIV vaccination might be offered to individuals seeking voluntary counselling and testing (Clements et al, 2004). This would be a particularly appropriate strategy if the vaccine was considered potentially harmful to HIV-positive individuals and it was necessary to establish that individuals were HIV-negative before vaccinating them. It could also be an efficient strategy, if adults seeking HIV generally have a higher risk of HIV infection than other adults. However, it is a strategy for which it is difficult to estimate demand reliably, and no cost-effectiveness studies to date have considered the potential impact of offering HIV vaccination through VCT services.

2.3.6 Childhood vaccination

Childhood vaccination is currently the most common form of vaccination for a range of diseases, both locally and internationally. Most vaccine-preventable diseases are
childhood diseases, and it is debatable whether childhood vaccination would be as appropriate for a disease that occurs mostly in adults. The short-term benefit of vaccinating children against HIV soon after birth would be a reduction in the proportion of the HIV infections occurring as a result of breastfeeding by HIV-positive mothers. It has also been suggested that child vaccination might be coupled with adolescent vaccination, so that children are primed against HIV in infancy and then receive a booster dose of vaccine in early adolescence (WHO-UNAIDS Expert Group 2005).

The proportion of HIV infections prevented by an HIV vaccine administered in infancy will depend on the exact age at which the vaccine is administered. Currently in South Africa, most vaccines are administered up to 18 months after birth (Trusler et al, 1994). Vaccinating against HIV as soon after birth as possible would not necessarily be the most appropriate strategy, as the efficacy of the vaccine may depend on the age at which it is administered.

2.3.7 School-based vaccination

School-based vaccination has been recommended as a strategy for distributing an HIV vaccine for a number of reasons. Firstly, model simulations indicate that an increasingly high proportion of new HIV infections are occurring in youth (Johnson and Dorrington 2006), and vaccinating individuals just before the onset of sexual activity would therefore have a significant impact on HIV incidence. Secondly, learners in schools can be easily accessed, and a high proportion of all children between the ages of 7 and 15 are in school. Thirdly, individuals are more willing to be vaccinated at young ages (see section 2.4.1). The only difficulty associated with this strategy is that there is no currently accepted means of administering vaccines to adolescents (Chang et al, 2003).

If a cohort vaccination strategy is to be adopted, several issues need to be considered when deciding on which ages or grades to vaccinate. Ideally, the vaccine should be administered at an age at which most youth are not yet sexually active. However, those who are not sexually experienced may be less likely to regard themselves as being at risk of infection and therefore less likely to accept the vaccine (Zimet et al, 2005). Vaccinating at a young age also presents a risk if immunity wanes over time; in this instance, the majority of individuals may lose their immunity by the time they become sexually active. In South Africa, estimates of the proportion of youth who are sexually experienced by age 14 range from 8% to 26%, and estimates of the proportion sexually experienced by age 17 range from 37% to 56% (Shisana et al, 2005; Reproductive Health Research Unit 2004; LoveLife 2002; Reddy et al, 2003). School-based vaccination initiated in later adolescence may miss a significant proportion of youth, as school enrolment rates drop below 90% after age 16 (Statistics South Africa 2005).

2.3.8 Mass vaccination

Mass vaccination requires the identification of a particular age range in which vaccines are to be administered. Mass vaccination is usually once-off, though ‘pulsed campaigns’ or ‘follow up campaigns’ can involve mass vaccination on a periodic basis. For example, measles vaccination in South Africa is conducted once every four
years in all children between the ages of 9 and 59 months (Durrheim et al, 2001). Mass vaccination is a particularly expensive vaccine distribution strategy, per individual vaccinated, because it is vertically implemented and there is no integration with routine services (Hall et al, 1990; Wigton et al, 1996). Typically, special national or regional immunization days are held, on which individuals are encouraged to come to a particular vaccination point to be vaccinated. There is thus a significant need for information, education and promotion of the vaccine prior to the national immunization day.

2.4 Factors affecting the amount of HIV vaccine required

Several factors need to be considered in estimating the number of doses required for a particular vaccine distribution strategy. These include rates of vaccine acceptance, rates of series completion (if the vaccine consists of more than one dose) and rates of vaccine wastage. The number of doses required also depends on whether individuals are screened for HIV prior to vaccination. These factors are discussed below.

2.4.1 Probability of vaccine acceptance

A number of studies have attempted to estimate the proportion of individuals willing to be vaccinated with a hypothetical HIV vaccine, and have explored the potential determinants of vaccine acceptability. The results of these studies are summarized in Table 2.1 below. Results are presented only for those vaccines which were described to study participants as being free. The hypothetical vaccines were also described to study participants as having a particular level of efficacy, shown in the table.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population</th>
<th>n</th>
<th>Vaccine efficacy</th>
<th>Acceptance rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hom et al (1997)</td>
<td>Uganda</td>
<td>Male military recruits</td>
<td>192</td>
<td>-</td>
<td>88%</td>
</tr>
<tr>
<td>Bishai et al (2004)</td>
<td>Uganda</td>
<td>Households (ages 18-60)</td>
<td>1677</td>
<td>50-95%</td>
<td>94%</td>
</tr>
<tr>
<td>Forsythe (2001)</td>
<td>Kenya</td>
<td>Households (ages 18-55)</td>
<td>890</td>
<td>50%</td>
<td>64%</td>
</tr>
<tr>
<td>Jackson et al (1995)</td>
<td>Kenya</td>
<td>Male truck drivers</td>
<td>201</td>
<td>‘High’</td>
<td>93%</td>
</tr>
<tr>
<td>Jackson et al (2005)</td>
<td>Kenya</td>
<td>Sex workers</td>
<td>206</td>
<td>‘High’</td>
<td>94%</td>
</tr>
<tr>
<td>Suraratdecha et al (2002)</td>
<td>Thailand</td>
<td>Households (ages 18-60)</td>
<td>2524</td>
<td>50-95%</td>
<td>78%</td>
</tr>
<tr>
<td>Suraratdecha et al (2001)</td>
<td>Thailand</td>
<td>Sex workers</td>
<td>600</td>
<td>50-95%</td>
<td>96%</td>
</tr>
<tr>
<td>Liau and Zimet (2001)</td>
<td>US</td>
<td>Intravenous drug users</td>
<td>200</td>
<td>50-95%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>University students</td>
<td></td>
<td>549</td>
<td>50%</td>
<td>54%*</td>
</tr>
</tbody>
</table>

Table 2.1: Levels of uptake for a hypothetical free HIV vaccine

* Represents the mean self-rated probability of accepting the vaccine, not the proportion willing to be vaccinated
For developing countries with generalized 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. This is consistent with the findings of Bishai et al (2004) and Suraratdecha et al (2005), which show that there is a 7 to 14% difference (in absolute terms) between the rates of vaccine acceptance in those who regard themselves as being at risk of HIV infection and those in individuals who do not regard themselves as being at risk.

The level of efficacy of the hypothetical vaccine generally appears not to have a significant impact on its acceptability. Bishai et al (2004), Suraratdecha et al (2005) and Forsythe (2001) all found that rates of vaccine acceptance were less than 5% higher in individuals offered a hypothetical vaccine of 95% efficacy than in individuals offered a hypothetical vaccine of 50% efficacy, if the vaccine was free. Studies conducted among university students in the US, however, have shown that vaccine efficacy does significantly affect vaccine acceptance (Liau and Zimet 2001; Liau et al, 1998). This may be due to differences in study design; students in these two studies were asked to rate their probability of accepting several hypothetical vaccines, not simply to state whether they would accept a single hypothetical HIV vaccine. The difference may also be due to differences in HIV epidemic context. The studies of Bishai et al, Suraratdecha et al and Forsythe were all conducted in countries with generalized HIV/AIDS epidemics, and individuals in these contexts may be more likely to recognize the benefits of an HIV vaccine, even if its efficacy is limited.

Although the studies conducted in developing countries suggest that vaccine demand is not strongly influenced by vaccine efficacy, these studies have all considered vaccines that protect against HIV infection to some degree. If the vaccine did not protect against HIV infection but rather delayed disease progression in those who acquired HIV after vaccination, individuals may view the vaccine less favourably and may be less inclined to get vaccinated.

Age appears to be a significant determinant of vaccine acceptance. Both Bishai et al (2004) and Suraratdecha et al (2005) found that acceptance of a free HIV vaccine was highest below the age of 25, and 24-30% lower in individuals aged between 50 and 60. Whittington et al (2002) also found that the price individuals were willing to pay for an HIV vaccine was highest at young ages. All three studies controlled for measures of self-perceived risk of HIV infection, and the effect of age on vaccine acceptance therefore seems to be independent of sexual behaviour. Liau and Zimet (2001) also found that younger respondents were likely to rate hypothetical vaccines more highly than older respondents.

Although the focus of this discussion is limited to hypothetical vaccines that are available free of charge, it is worth noting that price and ability to pay are significant determinants of vaccine acceptability if the vaccine is not free. Studies have shown that levels of education and income affect vaccine acceptability if the vaccine is not free, with the wealthier and more educated more likely to accept the vaccine (Bishai et al, 2004; Suraratdecha et al, 2005). Men also appear to have slightly higher rates of vaccine acceptance than women if the vaccine is not free (Bishai et al, 2004; Suraratdecha et al, 2005; Liau and Zimet 2001; Whittington et al, 2002), though Suraratdecha et al found that women had a 2% higher acceptance rate than men if the
vaccine was free. It is therefore not clear whether gender and socioeconomic factors would significantly influence demand for a vaccine if it were available at no cost.

2.4.2 Parental consent

Currently, South African children below the age of 14 require the consent of their parent or guardian before they can receive a vaccine, while children aged 14 and older do not require their parent’s consent. The draft Children’s Bill, which is likely to replace the current Child Care Act, will change this so that children aged 12 and older will be able to consent to vaccination independently of their parents or guardians (A. Strode (Ethics, Law and Human Rights Working Group of the African AIDS Vaccine Programme), personal communication). By the time an HIV vaccine is available, it is therefore likely that parental consent will only be required for children younger than 12.

Studies suggest that the vast majority of parents would consent to HIV vaccination of their children. In two US studies, the proportions of parents indicating that they would consent were 93% (Zimet et al, 2005) and 91% (Mays et al, 2004). In a pooled analysis, Hutchins et al (1993) found that the median proportion of unvaccinated children who had not been vaccinated due to parental refusal was only 3%. The authors noted that parental refusal was generally more common in industrialized countries than in developing countries.

2.4.3 Screening prior to vaccination

A controversial question is whether or not individuals should undergo HIV screening prior to vaccination. Some of the candidate HIV vaccines, such as the recombinant BCG vaccine, may be harmful in individuals who are immunosuppressed, and screening would be appropriate in such cases. Screening may also be appropriate if vaccine supplies are very limited and it is felt that vaccines should only be given to individuals who would benefit from them (i.e. individuals who are HIV-negative). If the vaccine is highly immunogenic, screening would also prevent those who have already been vaccinated from being revaccinated, if they have developed HIV antibodies.

However, screening would also introduce several problems (Chang et al, 2003). Firstly, it is unlikely that it would be possible to conduct HIV screening without also providing counselling for those who test positive. The cost of screening would be significant, particularly if coupled with counselling. Screening would also add significantly to the time taken to vaccinate each individual, and the additional time required may discourage individuals from agreeing to vaccination.

2.4.4 Rates of series completion

The rate of series completion is an important parameter to consider, as it appears increasingly likely that the first vaccines to be distributed will consist of more than one dose (Suraratdecha and Hecht 2005). Series completion appears to be highly dependent on the way in which the vaccine is distributed and the age at which it is administered. The 1998 DHS shows that about 82% of South African mothers who bring their child for its first DPT dose subsequently bring the child for both its second
and third doses (Department of Health 1999). Of South African children who received their first dose of polio vaccine, approximately 90% received the second dose when the vaccine was administered as part of a pulsed campaign (Durrheim et al, 2001). These rates of series completion are high when compared with the rates of series completion that are typically observed in adults. Rates of return for the second dose of a hepatitis B vaccine, among American patients attending STD clinics, have been estimated at 9% (Zimet et al, 2001) and 60% (Sellors et al, 1997). One might expect higher rates of return if the vaccine is effective against HIV, which is perceived as more of a health threat. Rates of series completion may also be higher if the vaccine is provided through antenatal clinics or FPCs, where attendance is more regular. Women attending antenatal clinics, for example, make four visits on average during the course of their pregnancy (Day and Gray 2005), whereas attendance at STD and VCT clinics is likely to be once-off.

2.4.5 Wastage

In estimating vaccine requirements, allowance needs to be made for vaccine wastage. In South Africa’s 1996 mass vaccination campaign for measles, the vaccine wastage rate was 30%, and in the 1997 campaign, wastage was 40% (Uzicanin et al, 2004). Rates of wastage may be even higher for routine vaccination services, with wastage rates ranging between 40% and 60% for OPV and DPT (multi-dose vaccines) and between 80% and 90% for BCG, a single-dose vaccine (Hutchins et al, 1993). Wastage is often the result of opened vials being discarded at the end of a vaccination session, when not all of the vaccine in the vial has been used. It has therefore been suggested that wastage could be reduced by reducing the number of vaccine doses in each vial (Hutchins et al, 1993).

2.5 Behavioural effects

It is possible that HIV vaccination may to some extent reverse the positive changes in HIV risk behaviour introduced by other HIV/AIDS interventions, such as social marketing, voluntary counselling and testing, and prevention of mother-to-child transmission. In the sections that follow, evidence of such behaviour changes is discussed.

2.5.1 Effect of vaccination on sexual behaviour

It is likely that some individuals would change their sexual behaviour after being vaccinated against HIV, due to reduced fear of HIV infection or its consequences. Table 2.2 summarizes the findings of four surveys in which individuals were asked whether they would increase sexual risk behaviour if they were vaccinated against HIV. In most surveys, more than 80% of respondents answered that they would not increase sexual risk behaviour. Suraratdecha et al (2005) found that increases in sexual risk behaviour were related to the effectiveness of the vaccine, with individuals being less likely to answer that they would increase unsafe sex if the vaccine was of limited efficacy. Responses to such questions must be treated with caution, however, as these questions are likely to be subject to significant social desirability bias, and even if subjects report honestly on their intended behaviour, this will not necessarily correspond to their actual behaviour.
Table 2.2: Proportions of individuals who report that they would increase sexual risk behaviour if they received an HIV vaccine

Studies of individuals recruited into HIV vaccine trials also suggest that HIV vaccination does not lead to significant changes in sexual behaviour. In a study of gay men enrolled in phase I and II HIV vaccine trials, Chesney et al (1997) found that the proportion of men practising unprotected insertive anal intercourse increased from 9% at enrollment to 20% one year later, while the proportion of men practising unprotected receptive anal intercourse did not change. In a phase III trial conducted in the US, Canada and the Netherlands, the frequency of unprotected anal intercourse did not increase over the course of the trial (rgp120 HIV Vaccine Study Group 2005), even in subjects who thought they had received the vaccine rather than the placebo (Bartholow et al, 2005). Although these studies suggest that vaccination has little effect on sexual risk behaviour, it should be stressed that these studies were randomized control trials in which subjects were not told whether they had received the vaccine or a placebo. Changes in sexual behaviour may well have been different if individuals knew they were receiving a vaccine of proven efficacy.

2.5.2 Effect of vaccination on utilization of VCT

It is likely that individuals who are vaccinated against HIV will be less likely to seek VCT independently. 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 vaccine is highly immunogenic, vaccinated individuals will produce HIV-specific antibodies, which will make standard serological tests unreliable as measures of true HIV status. Vaccinated individuals seeking VCT would therefore have to be tested using PCR or other tests, which are considerably more expensive and time-consuming. This too could act as a disincentive for vaccinated individuals to seek VCT.

2.5.3 Effect of vaccination on PMTCT

It is possible that women may be less likely to accept offers for HIV screening during pregnancy if they have previously been vaccinated against HIV. It is also possible that HIV-positive mothers may be less concerned about breastfeeding their children if their children have been vaccinated against HIV.
3. Review: mathematical modelling of HIV vaccines

Many models have been developed to explore the possible effects of an HIV vaccine on the evolution of the AIDS epidemic, and to identify the optimal strategies for distributing HIV vaccines. The characteristics and results of these models are discussed in the following sections.

Sixteen papers on modelling HIV vaccine effects were identified. A number of other studies were identified that assessed vaccine requirements and cost-effectiveness of different vaccine distribution strategies, although they were not based on epidemiological or demographic modelling. The latter group of studies is discussed briefly in section 3.5 below.

3.1 Population modelling in vaccine models

Models of HIV vaccines differ in terms of the level of detail with which demographic processes and risk behaviours are modelled. Table 3.1 below summarizes the types of populations modelled, the degree of demographic detail and the extent of allowance for heterogeneity in risk behaviours. Some studies used multiple models to examine vaccine effects in different epidemic conditions, and this is indicated where relevant.

Table 3.1 shows that three epidemic patterns have been modelled in assessing vaccine impacts: the homosexual epidemic in Western cities, the heterosexual epidemic in African countries, and the epidemic in Southeast Asia, which is driven by both intravenous drug use and heterosexual sex. The type of epidemic pattern needs to be considered when comparing different models of vaccine effects, as it has been shown that the cost-effectiveness of vaccination and the relative effectiveness of different vaccination strategies vary substantially according to the type of epidemic being modelled (Stover et al, 2002).

Most models do not divide the sexually active population according to age, or model demographic processes in any detail, and thus cannot be used to estimate accurately the numbers of individuals requiring vaccination, particularly with the size and age profile of the population changing over time. They also cannot be used to assess the effect of targeting vaccination at particular age groups. Age-structured models are important in the modelling of vaccines that result in delayed HIV disease progression, as the delay of the period of high infectiousness in late HIV disease, to an older age at which the individual is less sexually active, is likely to result in a substantially greater reduction in HIV incidence than would be expected in a population in which sexual behaviour is assumed to be the same at all ages (Davenport et al, 2004).

With the exception of the models of homosexual populations, most of the models allow for some degree of heterogeneity in risk behaviour. In almost all cases, this is achieved by dividing the population of individuals at risk of infection into different ‘risk groups’, representing different levels of sexual behaviour or intravenous drug use. These risk groups are allowed to interact with each other, and this interaction determines the simulated spread of the epidemic. In some cases, individuals are assumed to migrate between risk groups (Nagelkerke and De Vlas 2003; Bogard and Kuntz 2002). The only model of behavioural heterogeneity which does not work with
risk groups is the iwgAIDS model (applied by Stover et al (2002)), which models three types of relationships and allows rates of partnership formation and dissolution to vary according to age (Bernstein et al, 1998).

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Structured by age?</th>
<th>Number of behavioural groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owens et al (1998)</td>
<td>Homosexuals in SF</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Porco and Blower (1998)</td>
<td>Homosexuals in SF</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Garnett (1998)</td>
<td>African population*</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>Anderson and Garnett (1996)</td>
<td>African population*</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>Anderson et al (1991)</td>
<td>Homosexuals</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Anderson et al (1995)</td>
<td>Not stated</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>African population*</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>Stover et al (2002)</td>
<td>Manicaland (Zimbabwe)*</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Kampala (Uganda)†</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Thailand†</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Barth-Jones &amp; Longini (2002)</td>
<td>Southeast Asia (IDUs and heterosexuals)</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>McLean and Blower (1993)</td>
<td>Homosexuals in SF</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Blower and McLean (1994)</td>
<td>Homosexuals in SF</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Davenport et al (2004)</td>
<td>Multiple heterosexual epidemic scenarios</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Gray et al (2003)</td>
<td>Rakai (Uganda)</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Bogard and Kuntz (2002)</td>
<td>IDUs in Bangkok</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Van Ballegooijen et al (2003)</td>
<td>Homosexuals in Amsterdam</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Nagelkerke and De Vlas (2003)</td>
<td>Southern India</td>
<td>No</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3.1: Population modelling in vaccine models

* Based on variations of the Imperial College model, as described by Garnett & Anderson (1993).
† Based on a variation of the iwgAIDS model (described by Bernstein et al (1998)). In the simulation for Thailand, both heterosexual and IDU epidemics are modelled.
SF = San Francisco, IDU = intravenous drug user

Models that incorporate a degree of heterogeneity in sexual behaviour have the advantage of being more realistic, and are more likely to match observed trends in HIV prevalence. They are also useful in assessing the effects of targeting vaccination programmes at specific high-risk groups, as will be shown in section 3.5. Garnett (1998) shows that models which do not include allowance for heterogeneity in risk behaviours are likely to underestimate the extent to which the marginal returns from vaccination diminish as vaccine coverage increases. The results of such models therefore need to be interpreted with caution.
3.2 Modelling HIV in the absence of vaccines and other interventions

The modelling of HIV infectiousness and HIV disease progression is important in the modelling of vaccine effects, as these are the parameters that are most likely to be affected by a vaccine. Models differ substantially in terms of the modelling of disease progression. Almost all divide the time from infection to death into a series of disease stages. In some cases, a simple two-stage system is used to distinguish between AIDS and HIV infection pre-AIDS (Porco and Blower 1998; McLean and Blower 1993; Blower and McLean 1994). In other cases, three-stage systems are used to further divide the pre-AIDS phase (van Ballegooijen et al, 2003; Nagelkerke and De Vlas 2003). Four-stage systems can be used to further distinguish between asymptomatic cases aware of their HIV status and asymptomatic cases not aware of their HIV status (Edwards et al, 1998; Owens et al, 1998; Bogard and Kuntz 2002), or to further distinguish between the different disease phases within the pre-AIDS stage (Garnett 1998; Barth-Jones and Longini 2002). Other models assume a uniform rate of AIDS mortality, and do not allow for any progression through different HIV stages (Anderson et al, 1991).

Some models also incorporate viral load markers into the model of disease progression. For example, in the disease progression model of van Ballegooijen et al (2003), the second disease stage (between seroconversion and AIDS) is divided into three different stages representing different levels of viral load. In the model of Davenport et al (2004), the viral load is modelled as a function of the time from HIV infection, and the individual’s probability of dying from AIDS is assumed to depend on their viral load.

Most of the models that allow for a non-uniform rate of AIDS mortality also assume that HIV infectiousness varies over the course of HIV disease. In almost all of the models, it is assumed that individuals cease to be sexually active once they enter the AIDS phase. It is also often assumed that HIV infectiousness is increased during the initial period of high viraemia around seroconversion (Garnett 1998; van Ballegooijen et al, 2003; Stover et al, 2002; Barth-Jones and Longini 2002) and during the symptomatic period prior to AIDS (Garnett 1998; Barth-Jones and Longini 2002). Other models allow HIV transmission probabilities to be determined by viral load (Gray et al, 2003; Davenport et al, 2004; van Ballegooijen et al, 2003). The effects of vaccines on these levels of infectiousness are discussed in section 3.4 below.

3.3 Vaccines that reduce susceptibility to HIV infection

Most of the current models of vaccine effects consider the effects of vaccines that reduce vaccinated individuals’ susceptibility to HIV infection (sterilizing vaccines). If such a vaccine is developed in future, it is unlikely that it will be fully effective in preventing HIV transmission. McLean and Blower (1993) define three different ways in which vaccines may fail to be fully effective:

- **Take**: Some of the vaccinated individuals do not receive any benefit from the vaccine. The ‘take’ parameter is the proportion of vaccinated individuals who receive some benefit from the vaccine.
• **Duration**: The protection provided by the vaccine might not be lifelong. The ‘duration’ parameter is defined to be the rate at which successfully vaccinated individuals lose their vaccine-acquired protection.

• **Degree**: Even when individuals are receiving a benefit from vaccination, the protection is not necessarily complete. The ‘degree’ parameter is defined as the proportional reduction in the risk of acquiring HIV infection from an infected partner, as a result of vaccination, among those in whom the vaccine has ‘taken’ and has not yet worn off.

These three forms of imperfection are commonly referred to in the vaccine modelling literature. Barth-Jones and Longini (2002) further refine this model by distinguishing between individuals who are completely protected by vaccination (100% degree) and those who are only partially protected by vaccination (degree of less than 100%).

The relative disadvantages of the various forms of imperfection have been assessed in some detail. McLean and Blower (1993) show that within the first ten years of a vaccination programme, a vaccine that has 100% take and 100% degree, but which confers less than lifelong protection, is likely to be more effective in reducing HIV incidence than vaccines with other forms of imperfection. The same may not be true over the longer term, as more individuals lose their acquired immunity. McLean and Blower also demonstrate that a 100% degree is preferable to a 100% take – a conclusion that is also drawn by Stover *et al* (2002) and Nagelkerke and De Vlas (2003).

As might be expected, vaccines that do not confer lifelong protection produce results that are sensitive to the assumptions about the rates at which protection wanes. The extent of this sensitivity depends, however, on how long the average period of risk behaviour lasts. For example, in the iwgAIDS model, which assumes risk behaviour is concentrated in the relatively short interval between onset of sexual behaviour and marriage, vaccine impacts are relatively insensitive to the assumed duration of vaccine protection. In the Imperial College model, however, sexual risk behaviour is spread over a longer age interval, and the model results are consequently more sensitive to the assumed duration of the protection provided by the vaccine (Stover *et al*, 2002). The sensitivity of the model results to the duration parameter also depends on whether allowance is made for revaccination in those in whom vaccine protection has waned. Models that allow for revaccination (Davenport *et al*, 2004; Edwards *et al*, 1998; Nagelkerke and De Vlas 2003) are likely to be less sensitive to the duration parameter than those that do not (McLean and Blower 1993; Bogard and Kuntz 2002).

Some models – particularly those in which there is assumed to be uniformity in sexual risk behaviour – measure vaccine impacts in terms of the basic reproductive number. The basic reproductive number (often denoted \(R_0\)) is the average number of secondary infections generated by one primary infection if all of the contacts of the primary infection are initially uninfected. It can be shown that if the basic reproductive parameter is less than one, the epidemic will ‘die out’. Several studies have therefore attempted to assess how effective a vaccine needs to be in order for it to reduce \(R_0\) below one.

In general, the vaccine requirements necessary to meet this condition are substantial. Anderson and Garnett (1996) show that for a vaccine with 100% degree, it would not be possible to eradicate the epidemic if the vaccine ‘takes’ in less than 50% of
individuals or the average duration of protection is less than ten years – even if 100% vaccine coverage were achieved. Similarly, Gray et al (2003) demonstrate that for a vaccine with 100% take, 75% degree and lifelong duration of protection, a vaccine coverage rate of roughly 50% would be required in order to reduce $R_0$ below one. Vaccines that only affect disease progression and HIV infectiousness are even less likely to have the desired effect (Anderson et al, 1995). It must be stressed, however, that the assumption of uniform risk behaviour, implicit in the calculation of $R_0$, is unrealistic. In reality, it is extremely unlikely that any vaccine would completely eradicate the HIV epidemic, as infection would probably persist in those groups with high levels of risk behaviours unless the vaccine was close to perfect in all respects and coverage was close to 100%. Imperfect vaccines can nevertheless have substantial impacts on the course of the AIDS epidemic (Anderson et al, 1995).

Models of vaccines that reduce susceptibility to HIV infection have also explored the effectiveness of vaccination programmes when introduced at different stages in an AIDS epidemic. It has been shown that such vaccines are likely to be more effective in reducing HIV incidence and in saving quality-adjusted life years (QALYs) the earlier in the AIDS epidemic that they are introduced (Edwards et al, 1998; Owens et al, 1998). This adds further urgency to the search for an HIV vaccine.

### 3.4 Vaccines that reduce HIV infectiousness and delay disease progression

Vaccines are usually described as ‘disease-modifying’ if they alter the nature of the disease in those individuals becoming infected after vaccination, and ‘therapeutic’ if the vaccine can alter the course of disease when administered after the initial infection has occurred. Several models of such disease-modifying and therapeutic vaccines have been developed. The features of the vaccines modelled are summarized in Table 3.2 below. All of the studies assume that vaccines have some impact on the rate of HIV disease progression. Only two studies assume the vaccine has no effect on HIV infectiousness, and only two studies consider the effects of therapeutic vaccines.

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapeutic/disease-modifying</th>
<th>Effect on HIV disease progression</th>
<th>Effect on HIV infectiousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards et al (1998)</td>
<td>Therapeutic</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Owens et al (1998)</td>
<td>Therapeutic</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anderson &amp; Garnett (1996)</td>
<td>Disease-modifying</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anderson et al (1991)</td>
<td>Disease-modifying</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Barth-Jones &amp; Longini (2002)</td>
<td>Disease-modifying</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Davenport et al (2004)</td>
<td>Disease-modifying</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Van Ballegooijen et al (2003)</td>
<td>Disease-modifying</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 3.2: Types of vaccine effects modelled
In modelling vaccines that both delay disease progression and reduce HIV infectiousness, an important question is whether the vaccine is likely to reduce or increase HIV incidence. Van Ballegooijen et al (2003) provide probably the most realistic model to address this question, incorporating the interaction between viral load, HIV infectiousness and disease progression. In this model, it is predicted that a vaccine which reduces the viral set point below 1000 RNA copies/ml (thus reducing initial HIV infectiousness and delaying disease progression) is unlikely to have a significant impact on cumulative HIV incidence in the longer term – though it may reduce HIV incidence substantially in the short term. Similarly, Davenport et al (2004) predict that a vaccine is likely to have little impact on HIV incidence if it reduces disease progression rates by 20% or more, and reduces log viral load by less than 0.5. If it is assumed, however, that the vaccine reduces log viral load by between 0.5 and 1.5, and has little impact on disease progression, a substantial reduction in HIV incidence is likely to occur.

In contrast, vaccines that only delay disease progression are expected to have the effect of increasing HIV incidence (Edwards et al, 1998; Anderson et al, 1991). It is unlikely, however, that a vaccine would impact only on disease progression and not on infectiousness, as both parameters are dependent largely on the individual’s viral load. It is also clear that even when vaccines have a negative or negligible impact on HIV incidence, they can have a positive net benefit in terms of QALYs saved and in terms of deaths averted (Owens et al, 1998; Anderson et al, 1991; Davenport et al, 2004).

Unlike vaccines that reduce susceptibility to HIV infection, the impact of therapeutic vaccines is less likely to depend on the stage in the AIDS epidemic at which the vaccination programme is introduced. Owens et al (1998) show that the gain in QALYs saved from a therapeutic vaccine is likely to be marginally greater if the vaccine is introduced later in the epidemic than it is when introduced early in the epidemic.

### 3.5 Vaccination strategies

Models show that the extent of vaccine coverage is one of the most critical determinants of the success of a vaccination programme. Two types of vaccination are commonly modelled: ‘cohort’ vaccination and ‘blanket’ vaccination (Garnett 1998). Under cohort vaccination, individuals are vaccinated on reaching a certain age or on entry into a particular sub-population, and they cannot be revaccinated at a later date. Under blanket vaccination, unvaccinated individuals are vaccinated at a constant rate. For individuals in whom the vaccine has not ‘taken’ or the vaccine protection has worn off, revaccination is generally assumed to occur at the same constant rate. Some modellers assume a combination of cohort and blanket vaccination. The term ‘catch up’ vaccination is sometimes also used to describe blanket vaccination at a high initial rate, with the objective of achieving a high vaccine coverage in the short term. The vaccination rate decreases in subsequent periods to a level sufficient to maintain vaccine coverage at the same stable rate (Stover et al, 2002).

Little research has been conducted into the relative benefits of ‘cohort’, ‘blanket’ and ‘catch up’ vaccination. Research has focussed instead on the relative benefits of
different targeting strategies. It is recognized that the first vaccines developed are likely to be expensive and limited in supply, and that it might therefore not be cost-effective to administer the vaccine to everyone.

Several models have explored the effect of targeting the vaccination at those risk groups with the highest levels of risk behaviours. This strategy has been shown to be substantially more cost-effective, in preventing HIV infections, than vaccinating all adults (Barth-Jones and Longini 2002; Stover et al., 2002). However, in epidemics in which the ‘high risk’ groups targeted make up less than 5% of the adult population, and the HIV prevalence is already high, this strategy is unlikely to have a significant impact on the overall HIV incidence (Anderson et al., 1995; Stover et al., 2002). This is partly because most of those in the ‘high risk’ groups would already have been infected (and would therefore be unlikely to benefit from vaccination), and partly because a high level of HIV prevalence would already have been established in the unvaccinated groups. If the vaccine is administered to other ‘high risk’ groups, overall HIV incidence would be further reduced. Expansion of vaccination beyond the 40% of the adult population with the highest level of risk behaviour, however, is likely to be subject to rapidly diminishing marginal returns (Anderson et al., 1995).

Alternative targeting strategies have also been considered, such as targeting adolescents and targeting pregnant women. Targeting women of reproductive age is likely to be more cost-effective than targeting all adults – except in epidemics such as that in Thailand, where most of those infected are male (Stover et al., 2002). The effect of targeting adolescents, through a cohort vaccination programme, depends on the duration of protection provided by the vaccine and on the age profile of the population. If the duration of the protection is short, and most of the adolescents vaccinated are not yet sexually active, the programme may in fact be less cost-effective than vaccinating all adults (Stover et al., 2002). The effectiveness of different targeting strategies therefore depends very much on the local demographic and epidemiological conditions.

A series of studies have explored the potential demand and strategic use of HIV vaccines in southern Africa, Brazil, southern India and Thailand (Desmond and Greener (2003), Novaes et al (2002), Seshadri et al (2003) and Tangcharoensathien et al (2001) respectively). While not based on epidemiological and demographic modelling, these analyses do assess the costs and benefits of different vaccination strategies, and are therefore worth considering here. The analyses of Desmond and Greener (2003), Novaes et al (2002) and Tangcharoensathien et al (2001) follow a similar format. All three consider the costs and benefits of targeting vaccination at different groups, as well as the ease with which the different groups can be accessed. All three studies show that the number of HIV infections averted per vaccination is likely to be greatest if the vaccine is targeted at commercial sex workers. Other groups in which vaccination is likely to be particularly effective are girls in high school (Desmond and Greener 2003), intravenous drug users (Novaes et al, 2002; Tangcharoensathien et al, 2001), male transport workers and men attending STD clinics (Desmond and Greener 2003; Tangcharoensathien et al, 2001). Although these three analyses are valuable, there are a number of associated limitations which should be noted:

• The analyses only consider primary and secondary infections prevented during the period of vaccine protection. Simulation models, such as those described
above, are needed in order to estimate the reductions in new infections more accurately.

- The analyses are based on a vaccine that is assumed to be 100% effective in reducing susceptibility to HIV infection, and no allowance is made for the more probable reductions in infectiousness and delays in disease progression.
- The analyses are based on current demographic conditions and current levels of HIV incidence and prevalence in southern Africa, Brazil and Thailand, which are likely to change substantially by the time a vaccine is available for distribution.

The analysis of Seshadri et al (2003) differs from the previous three analyses in that it estimates only the cost and demand for a single vaccination strategy: all 11 to 14 year olds in schools, plus ‘high risk’ groups that make up 1% of the adult population. All analyses present both the costs of ‘catch up’ vaccination and the annual cost of maintaining vaccine coverage at the same level in subsequent years.

### 3.6 The impact of behaviour change

Many modellers have noted that vaccinated individuals may engage in more high-risk behaviour if they perceive themselves to be at a lower risk of infection or disease progression (‘behavioural disinhibition’). However, it has also been suggested that if vaccination is accompanied by intensive counselling, vaccination may lead to a reduction in risk behaviours (Bogard and Kuntz 2002). Several models have therefore explored the potential effects of behaviour change in response to the development of a vaccine.

The forms of behaviour change modelled are summarized in Table 3.3 below. All of the models of behaviour change consider the possibility of an increase in risk behaviour, and four models consider also the possibility of decreases in risk behaviours. In models of heterosexual transmission, these behaviour changes are usually assumed to take the form of changes in condom usage or changes in the rate at which individuals acquire new sexual partners.

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect of vaccine on risk behaviours</th>
<th>Type of risk behaviour change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards et al (1998)</td>
<td>Increase or decrease</td>
<td>Condom usage</td>
</tr>
<tr>
<td>Owens et al (1998)</td>
<td>Increase or decrease</td>
<td>Condom usage</td>
</tr>
<tr>
<td>Stover et al (2002)</td>
<td>Increase</td>
<td>Not stated</td>
</tr>
<tr>
<td>Blower &amp; McLean (1994)</td>
<td>Increase or decrease</td>
<td>Not stated</td>
</tr>
<tr>
<td>Gray et al (2003)</td>
<td>Increase</td>
<td>Partner change</td>
</tr>
<tr>
<td>Bogard and Kuntz (2002)</td>
<td>Increase or decrease</td>
<td>Frequency of needle use and needle sharing</td>
</tr>
<tr>
<td>Nagelkerke and De Vlas (2003)</td>
<td>Increase</td>
<td>Condom usage</td>
</tr>
</tbody>
</table>

Table 3.3: Forms of behaviour change modelled

Not surprisingly, the effect of increases in risk behaviour is to negate some of the gains that would otherwise be expected from vaccination (Gray et al, 2003;
Davenport et al., 2004). Some modellers have suggested that the net effect of the vaccination may even be negative, with increases in risk behaviours being sufficient to increase HIV incidence (Stover et al., 2002; Blower and McLean 1994). However, other modellers have shown that increases in risk behaviours are only likely to pose a serious threat if the vaccine has low efficacy, and that for a near-perfect vaccine, the vaccine impact is likely to be relatively insensitive to the degree of behaviour change (Bogard and Kuntz 2002; Nagelkerke and De Vlas 2003). This suggests that more intensive educational programmes will need to accompany vaccination if the vaccine has low efficacy.

Although all of the studies discussed here have considered the potential for ‘behavioural disinhibition’, none have modelled the ‘behavioural inhibition’ that would presumably have resulted from AIDS in the earlier stages of the epidemic, before the advent of highly active antiretroviral therapy and vaccines. Effectively, it is assumed that individuals do not reduce their risk behaviour in response to the threat of AIDS, yet they do increase their risk behaviour when the threat of AIDS is mitigated. These assumptions are clearly inconsistent. Unless risk behaviour levels in the pre-AIDS era are treated as a natural upper limit to risk behaviour levels in the post-vaccine era, the potential threats associated with ‘behavioural disinhibition’ are likely to be greatly exaggerated.

Behaviour change is usually assumed to be restricted to those individuals who are receiving a degree of protection from the vaccine. Individuals in whom the vaccine protection has waned and in whom the vaccine has not produced any benefit are generally assumed to follow the same pattern of risk behaviours as unvaccinated individuals – even though many would not, in reality, be aware of the vaccine protection having waned. Stover et al. (2002) suggest that behaviour change may also occur in unvaccinated individuals if it is widely believed that the vaccine will result in ‘herd immunity’2. Stover et al. demonstrate that if ‘behavioural disinhibition’ occurs in both the unvaccinated and vaccinated groups, the benefit from the vaccination programme is likely to be much smaller than would be expected if the behavioural change was limited only to those who were successfully vaccinated. Education programmes may therefore need to be targeted not only at those individuals receiving the vaccine, but also at unvaccinated individuals.

3.7 Other HIV/AIDS interventions

A few studies have explored the effects of prevention programmes, such as information and education campaigns to promote condom use, and improved treatment for sexually transmitted diseases (Garnett 1998; Anderson and Garnett 1996; Stover et al., 2002; Nagelkerke and De Vlas 2003). In some cases, the purpose of this modelling is to compare the relative effectiveness and cost-effectiveness of vaccines and other interventions. Stover et al. (2002), for example, demonstrate that although vaccination might have a greater impact on HIV incidence than other prevention programmes, it would not necessarily be more cost-effective. Other studies

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2 The term ‘herd immunity’ refers to a situation in which the individual’s risk of infection is reduced even if he/she has not been vaccinated. This arises if the effect of the vaccination is to reduce the prevalence or infectiousness of the pathogen in the rest of the community.
have attempted to assess whether vaccination and other prevention programmes would be ‘synergistic’ or ‘antagonistic’ (i.e. whether the HIV infections averted through vaccination and other interventions together would be more or less than the sum of the infections averted from each programme when implemented on its own). Garnett (1998) shows that vaccination and condom promotion are likely to be neither antagonistic nor synergistic when targeted at ‘high risk’ groups, but that they are likely to become antagonistic when introduced into the general population. Programmes that promote reduced rates of partner change, however, are likely to be synergistic when combined with vaccination, except at very high rates of programme coverage (Anderson and Garnett 1996). Condom usage and vaccination affect the same model parameter (the transmission probability), while partner change and vaccination affect different model parameters. This may account for the differences in the degree of antagonism.

Relatively few studies have examined the effect of interactions with highly active antiretroviral treatment (HAART) programmes. Although Anderson et al (1991) develop a model that is capable of assessing the impacts of both antiretroviral treatment and a disease-modifying vaccine, they do not use it to compare the relative impacts of the two interventions, or the effects of the two interventions combined. Only Gray et al (2003) have conducted such an analysis. Their results suggest that HAART to HIV-positive individuals with a log viral load above 4.7 is likely to be less effective in reducing HIV incidence than a vaccine that reduces susceptibility to HIV infection by 50%. When the programmes are combined, the reduction in HIV incidence appears to be only marginally greater than would be expected if the vaccine alone were introduced. No analysis has been done, however, of the life years gained under the different scenarios.

3.8 Differences between HIV-1 strains and subtypes

There is much uncertainty as to whether the first vaccines developed will be uniformly effective against all HIV-1 subtypes. It is also unclear to what extent it will be possible for vaccine-resistant strains to develop. Two models have been developed to investigate these questions, and their results are briefly summarized here.

The first model, developed by Porco & Blower (1998), considers an epidemic into which a new ‘invading’ subtype is introduced. If the invading subtype is more readily transmitted than the endemic subtype, the endemic subtype will eventually be eradicated (this conclusion is based on the simplifying assumption that infection with one subtype prevents super-infection with another subtype). When a vaccine is introduced five years after the invading subtype enters the population, the equilibrium conditions change, and the probability of the one subtype surviving while the other is eradicated depends on the relative effectiveness of the vaccine in reducing susceptibility to the two subtypes, as well as the rate of vaccine coverage. It is unlikely that both subtypes would be eradicated, unless vaccine coverage rates of over 85% are achieved and the vaccine is highly effective in reducing susceptibility to both subtypes.

The second model, developed by Davenport et al (2004), allows for the development of resistance to disease-modifying vaccines. Two HIV-1 strains are modelled: wild-
type virus and escape mutant virus. It is assumed that the escape mutant virus develops, on average, between six months and five years after infection in vaccinated individuals. Individuals who develop escape mutants then experience rates of AIDS mortality similar to those in unvaccinated individuals with the same viral load. They can also transmit escape mutant viruses sexually, though it is assumed that transmission to vaccinated individuals is not as likely as transmission to unvaccinated individuals. The model shows that although the escape mutants would ultimately account for about half of all HIV-1 infections, the rates of HIV incidence and AIDS mortality are relatively insensitive to the assumptions about rates of viral escape. This suggests that the allowance for viral escape does not substantially improve the predictive value of the model.

### 3.9 Conclusions

Much work has already been done to model the potential effects of HIV vaccines. Areas that have been studied extensively are the effects of different forms of vaccine imperfection, and the likely dangers associated with ‘behavioural disinhibition’. However, most of the studies to date have assumed that the vaccines developed will only reduce susceptibility to HIV infection. While this may have seemed like a reasonable assumption in the early days of HIV vaccine research, the shift in focus towards CTL responses suggests that it is no longer reasonable to ignore the effects vaccines are likely to have on infectiousness and disease progression. A further shortcoming in models of ‘behavioural disinhibition’ is that they fail to link behavioural responses to AIDS and behavioural responses to vaccines. As a result, these models have the potential to exaggerate the dangers associated with behaviour change. Very little work has been done to explore the effects of vaccines when there is heterogeneity between strains or subtypes in terms of their susceptibility to vaccine-induced immune responses. Assessments of the impact of targeting vaccination at particular sub-populations have been limited to the consideration of different theoretical ‘risk groups’, age and gender groups. Further work is required to assess the impact of targeting vaccination at more readily identifiable groups, but this requires the use of models that are age-structured, together with detailed demographic analysis.
4. Description of the ASSA2002 Vaccine model

The ASSA2002 Vaccine model is an adaptation of a C++ version of the ASSA2002 model, described elsewhere (Johnson et al, 2006). Section 4.1 briefly summarizes the key features of the ASSA2002 model relevant to this analysis. The adaptations made to the ASSA2002 model for the purpose of modelling vaccines can be divided into four classes:

- Adaptations for modelling vaccine efficacy and vaccine characteristics
- Adaptations for modelling vaccine timing and vaccine distribution
- Adaptations for modelling vaccine acceptance and series completion
- Adaptations for modelling behavioural effects of vaccination

These adaptations are described in sections 4.2 to 4.5.

For each of the four classes of parameters introduced, there is considerable uncertainty regarding the true parameter values, and it is necessary to reflect this uncertainty when presenting the results of the model. Uncertainty regarding vaccine efficacy is allowed for by considering four different hypothetical vaccines, described in section 4.2. Uncertainty regarding vaccine distribution strategies is allowed for by considering a range of hypothetical distribution scenarios: nine appropriate to a situation in which vaccine supplies are very limited, and four appropriate to a situation in which there is sufficient vaccine to immunize a large proportion of the population. These scenarios are described in section 4.3.

Uncertainty regarding rates of vaccine acceptance, series completion and behavioural effects of vaccination is allowed for using Monte Carlo simulation, as described in section 4.6. This section also describes the process by which uncertainty regarding vaccine parameters is integrated with uncertainty regarding other ASSA2002 model parameters. This makes it possible to produce 95% prediction intervals around the model outputs.

4.1 The ASSA2002 model

The ASSA2002 AIDS and Demographic model is a combined cohort component projection model and AIDS model, developed under the auspices of the Actuarial Society of South Africa (ASSA) to represent the HIV/AIDS epidemic in South Africa and its impact on the country’s demographic profile. The assumed modes of transmission are heterosexual intercourse and mother-to-child transmission. The model is calibrated to HIV prevalence data and reported death data, collected up to 2002, and the demographic assumptions in the model are derived from the 1970, 1996 and 2001 censuses as well as other data sources.

The spread of HIV in the adult population is simulated by dividing the 14 to 59 age group 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 STDs (although not regularly engaging in commercial sex). 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. Assumptions about rates of partner change, frequency of sex, condom usage and partner preferences are made separately for each of these risk groups.

In the absence of antiretroviral treatment, adults infected with HIV are assumed to progress through four stages of infection before dying from AIDS. These four stages correspond to the four stages of the WHO Clinical Staging System, the first two corresponding to relatively asymptomatic infection, the third corresponding to pre-AIDS symptoms and the fourth corresponding to clinical AIDS. If antiretroviral treatment is available, individuals starting treatment are assumed to enter a fifth disease stage, representing individuals receiving treatment. From this stage, individuals either die or enter a sixth disease stage when they discontinue treatment.

Children are assumed to be infected by HIV-positive mothers, either before/during birth or during breastfeeding. Children infected with HIV are assumed to progress through two stages of disease in the absence of treatment: pre-AIDS and AIDS. As with adults, the effect of antiretroviral treatment is represented by two additional stages. Children infected at or before birth are assumed to progress to AIDS much more rapidly than children infected through breastfeeding.

The ASSA2002 model allows for the effects of prevention and treatment programmes which have been implemented or are in the process of being implemented in South Africa. These include syndromic management of STDs, social marketing, VCT, PMTCT and HAART. The model of sexual transmission allows for changes in the frequency of sex in response to HIV-related symptoms and in response to knowledge of HIV status resulting from VCT. The model also allows for changes in HIV transmission probabilities over the course of HIV infection, including reductions in HIV infectiousness after starting HAART. In addition, the model of sexual transmission allows for changes in rates of condom usage over time, as a result of social marketing programmes.

A more detailed description of the ASSA2002 model is given elsewhere (Johnson and Dorrington 2006). Several changes were made to the ASSA2002 model in developing a C++ version of the model that was used for the purposes of the uncertainty analysis (Johnson et al, 2006). These changes were made in order to simplify the uncertainty analysis and to test hypotheses about certain parameters, but the changes do not significantly alter the results of the model. The C++ version is used for the purpose of developing the ASSA2002 Vaccine model, as the uncertainty analysis is critical to the assessment of the range of possible impacts an HIV vaccine may have. An Excel version of the ASSA2002 Vaccine model was also developed, and produces identical results.
4.2 Modelling vaccine efficacy and vaccine characteristics

4.2.1 Model structure

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

- 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 against HIV.

This four-class categorization is the same as that used in other HIV vaccine models (Barth-Jones and Longini 2002; Stover et al., 2002). The potential movements between the classes are illustrated in Figure 4.1. On being vaccinated, specified proportions of vaccinated individuals are moved into each of the three vaccine classes, 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, i.e. the vaccine is assumed to have no therapeutic effect. 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 4.1: Possible movements between vaccination classes](#)
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 HIV disease progression if they become infected with HIV after vaccination. Individuals in the ‘unprotected’ class, however, are protected neither against infection nor against disease progression. Using this model structure, it is possible to model both ‘take’ and ‘degree’ vaccine effects. A vaccine with a 60% ‘take’, for example, could be modelled by moving 60% of vaccinated individuals into the ‘fully protected’ class and the balance into the ‘unprotected’ class. A vaccine with a 60% ‘degree’, on the other hand, could be modelled by moving all vaccinated individuals into the ‘partially protected’ class and assuming a 60% reduction in the transmission probabilities in this class.

If the vaccine is disease-modifying in adults, it is assumed that it will increase the median time spent in each of WHO stages 1 and 2 and reduce infectiousness in WHO stages 1 and 2. After adults progress to WHO stage 3, they are assumed to no longer receive any benefit from the vaccine, and the rates of mortality and levels of infectiousness are the same as they would have been if they had not received the vaccine. This loss of vaccine benefit represents the effect of viral escape rather than a waning of the immune response induced by the vaccine. Individuals who are classified as ‘partially protected’ at the time of HIV infection remain classified as such until death, though the modelling of their infection and behaviour is the same as that in the ‘unprotected’ class after entry into HIV stage 3.

A similar approach is taken to modelling the effects of disease-modifying vaccines in children under the age of 14. The vaccine is assumed to increase the median time in the ‘pre-AIDS’ phase. On reaching age 14, HIV-infected children who are partially protected are assumed to experience the same rates of AIDS mortality and same levels of HIV infectiousness as partially protected adults who have been infected for 14 years.

As discussed in section 2.2.4, the effects of an HIV vaccine may depend on sex and on frequency of exposure to HIV. The model therefore allows for the following parameters to be set separately for each risk group and each sex:

- % of vaccinated individuals fully protected
- % of vaccinated individuals partially protected
- Mean duration of full protection
- Mean duration of partial protection

These parameters can also be set separately for men and women below the age of 14 and over the age of 59. When individuals move between age groups or risk groups, they remain in the same vaccination class, and experience the reduction in susceptibility and rate of loss of protection specific to the new age or risk group. Both the duration of full protection and the duration of partial protection are assumed to follow exponential distributions, so that the rate at which protection is lost is independent of the length of time spent in the ‘protected’ state in the previous age or risk group.

In addition to allowing the vaccine effects to depend on sex, age group and risk group, the ASSA2002 Vaccine model allows for vaccine effects to depend on whether the vaccinated individual has received the full series of doses. The specified proportions
of vaccinated individuals moving into the fully and partially protected groups can be altered for individuals who do not receive the full series of doses.

### 4.2.2 Parameters for four hypothetical vaccines

In the analysis that follows, four hypothetical HIV vaccines are considered:

- **Vaccine A**: a vaccine which does not prevent HIV infection, although it significantly reduces disease progression and HIV infectiousness;
- **Vaccine B**: a vaccine which slightly reduces the risk of HIV infection and significantly reduces disease progression and HIV infectiousness in those who become infected;
- **Vaccine C**: as for vaccine B, but the duration of protection is greatest in individuals who are most frequently exposed to HIV;
- **Vaccine D**: a vaccine which significantly reduces the risk of HIV infection but does not delay disease progression or reduce infectiousness in those who become infected.

Vaccines B and C most closely resemble the profile expected for the first HIV vaccines.

In all four cases, it is assumed that the vaccine consists of a series of three doses. 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 characteristics of the four hypothetical vaccines are summarized in Table 4.1. The efficacy rates of the different vaccines are expressed in terms of $VE_S$, the reduction in susceptibility to infection; $VE_P$, the reduction in the rate of progression to AIDS; $VE_I$, the reduction in the level of HIV infectiousness during stages 1 and 2 of disease; and $\mu$, the mean duration of protection. For vaccines A, B and C, the $VE_P$ and $VE_I$ parameters are consistent with what one would expect for an HIV vaccine that reduces viral set point 100-fold, a reduction that would appear to be achievable based on candidate vaccines tested in non-human primates. For vaccines A, B and C, the median time spent by vaccinated adults in each of WHO stages 1 and 2 is increased by 191%, and the median time spent by vaccinated children in the pre-AIDS stage is increased by 40%. A more detailed explanation of how these parameters were set is given in Appendix A.

For vaccine C, the duration of protection is assumed to depend on the risk group of the susceptible individual, consistent with the ‘natural priming’ explained in section 2.2.4. The average rate at which vaccine protection wanes is similar for vaccines B and C, but because the duration of protection is less uniform in the case of vaccine C, the effects of vaccines B and C can differ when introduced in particular sub-populations.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>$V_{ES}$ (reduction in susceptibility)</th>
<th>$V_{EP}$ (reduction in disease progression)</th>
<th>$V_{EI}$ (reduction in infectiousness)</th>
<th>$\mu$ (mean duration of protection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>84%*</td>
<td>84%†</td>
<td>10</td>
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<tr>
<td>B</td>
<td>30%</td>
<td>84%*</td>
<td>84%†</td>
<td>10</td>
</tr>
<tr>
<td>C</td>
<td>30%</td>
<td>84%*</td>
<td>84%†</td>
<td>PRO 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>STD 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RSK 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NOT 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Young 10</td>
</tr>
<tr>
<td>D</td>
<td>95%</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 4.1: Characteristics of four hypothetical vaccines (in partially protected individuals)
* Approximate (see Appendix A). † Reduction in infectiousness only applies during HIV stages 1 and 2. The $V_{EI}$ parameter varies depending on the assumed increase in infectiousness per log increase in viral load; 0.84 is obtained when the average increase in infectiousness per log is used (see Appendix A).

4.3 Modelling vaccine timing and distribution

4.3.1 Model structure

The ASSA2002 Vaccine model allows for eight types of vaccine distribution, corresponding to those distribution strategies described in sections 2.3.1 to 2.3.8.

Two of the vaccine distribution strategies are limited to particular risk groups. Distribution of vaccine to sex workers is assumed to be restricted to women in the PRO group, while vaccination through STD clinics is assumed to be restricted to men and women in the PRO and STD groups. It is assumed that individuals in the STD and PRO groups have an annual probability of 0.65 of attending an STD clinic, based on reported numbers of STD cases treated in 2002 (Human Sciences Research Council 2002) and ASSA2002 estimates of the size of the STD and PRO groups at this time.

Distribution through antenatal clinics and distribution through family planning clinics (FPCs) are assumed to reach only women in the reproductive age range. A woman’s annual probability of attending an antenatal clinic is assumed to be equal to her probability of giving birth in that year, which depends on her age and risk group. These fertility rates are estimated for each age and risk group by the ASSA2002 model. A woman’s annual probability of attending a public FPC is calculated as the probability that a woman of her age uses modern contraception, multiplied by the proportion of female contraceptive users who obtain their contraception from public FPCs (20%). Both quantities are estimated from the 1998 DHS (Department of Health 1999), and the resulting estimates of FPC utilization are shown in Table 4.2 below.
Table 4.2: Annual probabilities of using family planning clinics

In modelling the effects of vaccine distribution through VCT services, it is assumed that the probability that an unvaccinated individual seeks VCT in a given year is the same as the probability assumed in the ASSA2002 model in the absence of vaccination. It is further assumed that the vaccination is only offered through independent VCT services and not through VCT services offered as part of PMTCT programmes or ARV screening programmes. The assumptions in the ASSA2002 model have been set so that when VCT is provided in all health facilities, 6% of individuals at risk of infection seek VCT per annum and 5% of individuals not at risk of infection seek VCT per annum.

In the case of both school-based vaccination and childhood vaccination, it is assumed that only individuals at a specified age are offered the vaccine. In modelling school-based vaccination, it is assumed that the vaccine is offered only to children currently attending school. The proportions of children in school at each age are assumed to be the same as those measured in the 2004 General Household Survey (Statistics South Africa 2005). These proportions are shown in Table 4.3 below. Mass vaccination, unlike childhood vaccination and school-based vaccination, is assumed to be introduced over a specified age range, rather than at a specified age.

Table 4.3: School enrolment rates by age in 2004
Source: Statistics South Africa (2005)

In Appendix B, a mathematical description is given of the approach to determining numbers of individuals receiving HIV vaccines in each year.

4.3.2 Hypothetical vaccine distribution strategies

In the analysis that follows, two possible dates of vaccine introduction are considered: 2015 and 2020. In section 5, results are presented for the 2015 scenario only. In Appendix D, selected results for the two scenarios are compared.

Thirteen vaccine distribution strategies are considered in total: nine appropriate to the situation in which HIV vaccine supplies are limited, and four appropriate to a situation in which there is sufficient vaccine stock to immunize a large proportion of the population. The characteristics of the first nine vaccine distribution strategies are summarized in Table 4.4 below.
Table 4.4: Distribution strategies when vaccine supplies are limited

<table>
<thead>
<tr>
<th>Strategy number</th>
<th>Type of distribution strategy</th>
<th>Risk groups targeted</th>
<th>Ages targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Sex workers</td>
<td>Female PRO</td>
<td>14-59</td>
</tr>
<tr>
<td>II</td>
<td>Antenatal clinics</td>
<td>All females</td>
<td>15-49</td>
</tr>
<tr>
<td>III</td>
<td>Family planning clinics</td>
<td>All females</td>
<td>15-49</td>
</tr>
<tr>
<td>IV</td>
<td>STD treatment clinics</td>
<td>STD, PRO</td>
<td>14-59</td>
</tr>
<tr>
<td>V</td>
<td>VCT services</td>
<td>All</td>
<td>14-59</td>
</tr>
<tr>
<td>VI</td>
<td>Children born to HIV-positive mothers</td>
<td>All</td>
<td>3 months</td>
</tr>
<tr>
<td>VII</td>
<td>School-based</td>
<td>All</td>
<td>12</td>
</tr>
<tr>
<td>VIII</td>
<td>School-based</td>
<td>All</td>
<td>14</td>
</tr>
<tr>
<td>IX</td>
<td>School-based</td>
<td>All</td>
<td>16</td>
</tr>
</tbody>
</table>

As the purpose of this analysis is to assess which of these short-term strategies are optimal in the public health sector, distribution strategies that are implemented through health facilities (strategies II to VI) are assumed to apply only to users of public health facilities. The assumed proportions of health facility users using public health facilities that offer HIV vaccines are shown in Table 4.5 below. School-based strategies (strategies VII to IX) are assumed to be implemented at all schools, both public and private. Distribution to sex workers (strategy I) is assumed to reach only 50% of women in the PRO group, due to the difficulties associated with reaching this marginalized group.

Table 4.5: Assumed proportions of health facility users who attend public clinics that offer HIV vaccines

<table>
<thead>
<tr>
<th>Strategy number</th>
<th>Type of distribution strategy</th>
<th>%</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Antenatal clinics</td>
<td>82%</td>
<td>1998 DHS (Department of Health 1999)</td>
</tr>
<tr>
<td>III</td>
<td>Family planning clinics</td>
<td>20%</td>
<td>See 4.3.1</td>
</tr>
<tr>
<td>IV</td>
<td>STD treatment clinics</td>
<td>40%</td>
<td>Schneider et al (2001)</td>
</tr>
<tr>
<td>V</td>
<td>VCT services</td>
<td>56%</td>
<td>Public VCT consultations in 2002 from Ramkissoon et al (2004), divided by total VCT consultations in 2002 from ASSA2002 (592272/1054490)</td>
</tr>
<tr>
<td>VI</td>
<td>Children born to HIV-positive mothers</td>
<td>82%</td>
<td>As for strategy II</td>
</tr>
</tbody>
</table>

The characteristics of the remaining four distribution strategies are summarized in Table 4.6 below. All four strategies are combinations of distribution strategies. 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 represents the distribution strategy suggested at a recent WHO consultation (WHO-
UNAIDS Expert Group 2005). The periods over which these distribution strategies are implemented, in the 2015 scenario, are shown in the table.

<table>
<thead>
<tr>
<th>Strategy number</th>
<th>Type of distribution strategy</th>
<th>Ages</th>
<th>Distribution period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mass vaccination</td>
<td>0-59</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>Childhood vaccination</td>
<td>3 months</td>
<td>2015-2025</td>
</tr>
<tr>
<td>2</td>
<td>Mass vaccination</td>
<td>15-49</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>School-based vaccination</td>
<td>15</td>
<td>2015-2025</td>
</tr>
<tr>
<td>3</td>
<td>Mass vaccination</td>
<td>15-24</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>School-based vaccination</td>
<td>15</td>
<td>2015-2025</td>
</tr>
<tr>
<td>4</td>
<td>School-based vaccination</td>
<td>15</td>
<td>2015-2025</td>
</tr>
<tr>
<td></td>
<td>Childhood vaccination</td>
<td>3 months</td>
<td>2015-2025</td>
</tr>
</tbody>
</table>

Table 4.6: Large-scale vaccine distribution strategies

For all four strategies, mass vaccination and childhood vaccination are assumed to be offered to all individuals in the population in the relevant age groups, regardless of whether they are users of private or public health facilities. School-based vaccination is assumed to be offered to all children who are in school at the relevant age.

For the nine vaccine distribution scenarios described in Table 4.4, estimates of vaccine requirements are presented both with and without allowance for HIV screening prior to vaccination. For the remaining four scenarios, which involve vaccination of a large proportion of the population, it is assumed that it would not be practical to conduct screening prior to vaccination, and estimated numbers of vaccinations are therefore presented on the assumption of no screening.

4.4 Modelling vaccine acceptance and series completion

Assumptions regarding vaccine acceptance and series completion rates are set at levels appropriate to a vaccine that is made freely available. It is assumed that vaccine acceptance is not influenced by the efficacy of the vaccine or the means by which the vaccine is distributed. Based on the studies reviewed in section 2.4.1, vaccine acceptance in the 14 to 59 age range is assumed to depend on both age and risk group, as shown in Table 4.7 below. Individuals who are HIV-positive and are aware of their HIV status are assumed to have the same probability of vaccine acceptance as individuals who are not aware they are HIV-positive, though they derive no benefit from the vaccine.
### Table 4.7: Assumed probabilities of vaccine acceptance

Vaccine acceptance below age 12 is dependent only on parental consent, which is assumed to be given in 98% of cases. Children aged 12 and 13 are assumed to have acceptance rates of 80% (the same as the rate assumed for other adolescents who are not yet sexually experienced).

Rates of series completion depend on the manner in which the vaccine is distributed, as shown in Table 4.8. For those distribution strategies in which it is likely that a high rate of follow-up will be achieved, 85% of those receiving the first vaccine dose are assumed to receive their third dose. For other distribution strategies, a lower rate of series completion is assumed. For the purpose of calculating the total number of vaccine doses required, the proportion of individuals who receive two doses is calculated as the square root of the relevant probability of receiving all three doses.

### Table 4.8: Probability of completing a series of three doses after receiving a first dose of vaccine

Due to the uncertainties regarding rates of vaccine acceptance and series completion, the parameters listed in Table 4.7 and Table 4.8 are considered in an uncertainty analysis (see section 4.6).

### 4.5 Modelling effects of vaccine on behaviour

In the ASSA2002 Vaccine model, behavioural inhibition in the HIV-negative population is assumed to be the result of social marketing programmes. HIV-negative individuals who are exposed to social marketing programmes on a regular basis and have easy access to condoms are assumed to increase condom usage. In response to HIV vaccines and antiretroviral treatment, however, a proportion of these individuals...
revert to their former sexual practices, engaging in the same risk behaviours they would have practised in the absence of social marketing programmes. This proportion is assumed to be 50% for vaccines which induce a high level of sterilizing immunity (vaccine D) and 25% for vaccines which are mainly disease-modifying (vaccines A, B and C). This analysis allows for reductions in condom usage in partnerships in which one or both partners have been vaccinated, and the mathematical approach to modelling this is explained in Appendix C.

Allowance is also made for reductions in utilization of VCT services, in individuals who have been vaccinated. It is assumed that individuals receiving vaccine D are 80% less likely to seek VCT independently than unvaccinated individuals. Individuals receiving vaccine A, B or C are assumed to be 40% less likely to seek VCT independently than unvaccinated individuals. These parameters, as well as the parameters determining the reversion to former sexual practices, are considered in the uncertainty analysis (section 4.6).

4.6 Uncertainty analysis and sensitivity analysis

Uncertainty regarding selected vaccine parameters is incorporated using Monte Carlo simulation, with parameter values being sampled from distributions that represent plausible ranges of uncertainty. These parameters and the distributions from which their values are sampled are shown in Table 4.9. The table also shows the means and standard deviations of these distributions, the means being the values specified for the relevant parameters in sections 4.2 to 4.5. Beta distributions are used in all cases, as all parameters lie on the interval [0, 1]. 500 combinations of these parameters are randomly generated, as explained below.

Values are simulated from these beta distributions by inverting the cumulative beta distributions and evaluating these inverted cumulative beta distribution for large numbers of random uniform (0, 1) variates. For each parameter combination, rates of vaccine acceptance in different age groups and risk groups are simulated using the same uniform variate, to ensure that for a given randomly generated parameter combination the rates of vaccine acceptance are consistent. This uniform variate is used in the sensitivity analysis when considering the relationship between rates of vaccine acceptance and total vaccine requirements. Similarly, for each parameter combination, rates of series completion for different distribution strategies are simulated using the same uniform variate. This ensures that in a scenario in which multiple vaccine distribution strategies are being introduced, rates of series completion are consistent across distribution strategies.

For the purpose of the uncertainty and sensitivity analysis, 500 combinations of the parameters listed in Table 4.9 are randomly generated. These 500 parameter combinations are then randomly paired with 500 combinations of other ASSA2002 parameters, generated in a separate uncertainty analysis. 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. A more detailed description of this uncertainty analysis is given elsewhere (Johnson et al, 2006). The uncertainty analysis presented here therefore reflects both uncertainty with
respect to HIV vaccine parameters and uncertainty with respect to basic HIV epidemiology.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution</th>
<th>Mean</th>
<th>Std dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual probability of seeking STD treatment (PRO/STD group)</td>
<td>Beta (14.1, 7.6)</td>
<td>0.65</td>
<td>0.10</td>
</tr>
<tr>
<td>Rate of vaccine acceptance in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO 14-24</td>
<td>Beta (191.1, 3.9)</td>
<td>0.98</td>
<td>0.01</td>
</tr>
<tr>
<td>PRO 25-34, STD 14-24</td>
<td>Beta (111.9, 5.9)</td>
<td>0.95</td>
<td>0.02</td>
</tr>
<tr>
<td>STD 25-34, RSK 14-24</td>
<td>Beta (89.1, 9.9)</td>
<td>0.90</td>
<td>0.03</td>
</tr>
<tr>
<td>PRO 35-44, RSK 25-34</td>
<td>Beta (66.9, 11.8)</td>
<td>0.85</td>
<td>0.04</td>
</tr>
<tr>
<td>STD 35-44, NOT 14-24</td>
<td>Beta (50.4, 12.6)</td>
<td>0.80</td>
<td>0.05</td>
</tr>
<tr>
<td>PRO 45-59, RSK 35-44, NOT 25-34</td>
<td>Beta (38.3, 12.8)</td>
<td>0.75</td>
<td>0.06</td>
</tr>
<tr>
<td>STD 45-59</td>
<td>Beta (29.3, 12.6)</td>
<td>0.70</td>
<td>0.07</td>
</tr>
<tr>
<td>RSK 45-59, NOT 35-44</td>
<td>Beta (22.5, 12.1)</td>
<td>0.65</td>
<td>0.08</td>
</tr>
<tr>
<td>NOT 45-59</td>
<td>Beta (16.3, 13.3)</td>
<td>0.55</td>
<td>0.09</td>
</tr>
<tr>
<td>Rate of series completion in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSWs, VCT/STD services, mass imm.</td>
<td>Beta (13.8, 9.2)</td>
<td>0.60</td>
<td>0.10</td>
</tr>
<tr>
<td>ANC, FPCs, childhood/school-based imm.</td>
<td>Beta (42.5, 7.5)</td>
<td>0.85</td>
<td>0.05</td>
</tr>
<tr>
<td>% reversal of behavioural inhibition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccines A, B and C</td>
<td>Beta (7.07, 21.2)</td>
<td>25%</td>
<td>8%</td>
</tr>
<tr>
<td>Vaccine D</td>
<td>Beta (5.06, 5.06)</td>
<td>50%</td>
<td>15%</td>
</tr>
<tr>
<td>% reduction in utilization of VCT services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccines A, B and C</td>
<td>Beta (2.0, 3.0)</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Vaccine D</td>
<td>Beta (12.0, 3.0)</td>
<td>80%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 4.9: Distributions for vaccine parameters
ANC = antenatal clinic, CSW = commercial sex worker, FPC = family planning clinic, imm. = immunization, Std dev. = standard deviation

An additional source of uncertainty is that relating to the effectiveness and rollout of other HIV prevention and treatment programmes. As there is a large number of these parameters, and it is not practical to evaluate all of them here, only a limited set of the most significant intervention parameters are considered. These parameters and the distributions from which their values are sampled are listed in Table 4.10.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution</th>
<th>Mean</th>
<th>Std dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultimate rate of HAART rollout</td>
<td>Beta (8.9, 7.3)</td>
<td>55%</td>
<td>12%</td>
</tr>
<tr>
<td>Reduction in intrauterine/intrapartum transmission in women on PMTCT programme</td>
<td>Beta (4.7, 5.3)</td>
<td>47%</td>
<td>15%</td>
</tr>
<tr>
<td>Reduction in breast-milk transmission in women on PMTCT programme</td>
<td>Beta (5.1, 5.1)</td>
<td>50%</td>
<td>15%</td>
</tr>
<tr>
<td>Reduction in susceptibility to HIV in circumcised men</td>
<td>Beta (13.8, 9.2)</td>
<td>60%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 4.10: Distributions for intervention parameters
Except in the case of the reduction in HIV susceptibility in circumcised men, these parameters have been explained and motivated elsewhere (Johnson and Dorrington 2006). The effect of male circumcision, as an intervention, is modelled by reducing the probability of female-to-male transmission by a factor of

\[
\frac{(1 - \gamma)(1 - \Omega \pi) + (1 - (1 - \gamma)(1 - \Omega \pi))(1 - \delta)}{(1 - \gamma) + \gamma(1 - \delta)},
\]

where \(\gamma\) is the prevalence of male circumcision in the absence of intervention, \(\Omega\) is the proportion of men who have been offered free circumcision, \(\pi\) is the proportion of men agreeing to be circumcised, and \(\delta\) is the reduction in susceptibility to HIV in circumcised men. The prevalence of circumcision in adult South African males is estimated at 35% (Human Sciences Research Council 2002), and the rate of circumcision acceptance in uncircumcised men is estimated at 60% (Lagarde et al, 2003; Scott et al, 2005; Rain-Taljaard et al, 2003). The distribution chosen for the reduction in susceptibility in circumcised males is based on the results of a recent randomized control trial (Auvert et al, 2005). Although male circumcision is not included as an intervention in the ASSA2002 model, a separate analysis is conducted here to assess the effect of male circumcision if it is introduced as an intervention between 2007 and 2009, with 90% of adult men having been offered circumcision by 2009.

500 values of each parameter in Table 4.10 are generated randomly and these are then randomly paired with the 500 parameter combinations previously described.

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 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.
5. Results of the ASSA2002 Vaccine model

5.1 Distribution strategies when vaccine supplies are limited

5.1.1 Amount of vaccine required

For each of the nine distribution strategies defined in Table 4.4, the expected number of vaccinated individuals in 2015 are shown in Figure 5.1(a). The results are shown both for the ‘screening’ and ‘no screening’ scenarios, i.e. with and without HIV testing prior to vaccination. The number of vaccine doses that are expected to be consumed are shown in Figure 5.1(b). The expected numbers of vaccinated individuals and vaccine doses are the same for all four hypothetical vaccines described in 4.2.2.

Figure 5.1(b) shows that the number of vaccine doses required in the absence of screening would be greatest if the vaccine were distributed through family planning clinics (2.8 million, 95% interval: 2.4-3.2 million) or through STD clinics (2.3 million, 95% interval: 1.4-3.6 million). Vaccine consumption would be relatively low if the vaccine were distributed only to commercial sex workers (89 000, 95% interval: 74 000-104 000) or children born to HIV-positive mothers (570 000, 95% interval: 430 000-720 000). In target groups such as school children, in which HIV prevalence is low, there is little difference in the number of vaccine doses required between the ‘screening’ and ‘no screening’ scenarios. However, in those target groups in which there is a high prevalence of HIV (sex workers and STD patients), vaccine requirements are reduced substantially if the vaccine is distributed only to individuals who test HIV-negative. The numbers of vaccine doses consumed are typically two to three times the expected number of vaccinated individuals, assuming a vaccine consisting of three doses and allowing for failure to complete the series. The prediction intervals are particularly wide for the STD patient distribution strategy, due to uncertainty regarding the size of the STD group in the ASSA2002 model, as well as uncertainty regarding the annual probability of seeking STD treatment in this group.

5.1.2 Vaccine impact in the absence of screening

Figure 5.2 shows the numbers of HIV infections averted and AIDS deaths averted, per individual vaccinated in 2015, over the 2015-2025 period. Results are presented for each of the nine distribution strategies, assuming no screening prior to vaccination (although the VCT distribution strategy involves screening, it is included here for comparison purposes). While the 95% prediction intervals in Figure 5.2 indicate the uncertainty around the effects of the distribution strategies in absolute terms, Figure 5.3 shows how the different distribution strategies rank relative to one another, across the 500 parameter combinations sampled. Figure 5.3 thus shows which distribution strategies are most efficient and least efficient, from the point of view of averting HIV infections and AIDS deaths, in the absence of screening.

As might be expected, both the numbers on infections averted and the numbers of AIDS deaths averted, per vaccinated individual, are greatest for vaccine D and lowest for vaccine A. There is little difference between vaccines B and C in terms of deaths averted and infections averted.
In the absence of screening, the strategies which are likely to be most efficient in preventing HIV are vaccinating 16 year olds in school and vaccinating STD patients. Vaccination of STD patients is relatively more efficient, compared to vaccination of 16 year olds, the less effective the vaccine is in inducing sterilizing immunity. The efficiency of targeting adolescents in schools is highly dependent on the age at which vaccination occurs. Vaccine B, for example, would be expected to avert 0.029 infections per vaccinated individual (95% interval: 0.019-0.040) if administered to 12-year olds, and 0.074 infections per vaccinated individual (95% interval: 0.050-0.101) if administered to 16-year olds. Except in the case of vaccine A, the least efficient strategy, in terms of infections averted per vaccination, is vaccination of sex workers (Figure 5.3). Figure 5.2(g) shows that for vaccine D, this strategy has significant potential to increase the rate at which HIV infections occur, due to behavioural disinhibition in vaccinated HIV-positive women.
Figure 5.2: HIV infections averted and AIDS deaths averted (2015-2025), per individual vaccinated in 2015, no screening

Figure 5.2 shows that for most vaccine distribution strategies, the number of HIV infections averted per vaccinated individual exceeds the number of AIDS deaths averted per vaccinated individual, over the 2015-2025 period. Exceptions, in the case
of the disease-modifying vaccines (A, B and C), are distribution to sex workers and
distribution to children born to HIV-positive mothers. AIDS deaths averted per
vaccinated sex worker exceed infections averted because the disease-modifying
vaccines provide little protection against HIV infection in these highly exposed
women, but do protect against disease progression. In children born to HIV-positive
mothers, disease-modifying vaccines have relatively little effect on HIV incidence,
since there are no secondary infections that can be averted (i.e. HIV-infected children
are assumed not to transmit the virus to other children). However, disease-modifying
vaccines have a relatively large effect on AIDS mortality in children, as all of the
children infected after vaccination are infected in 2015 or 2016 (after which they are
no longer breastfed) and the effect of the vaccine on AIDS mortality is thus evaluated
over a longer period than would be the case if infections occurred throughout the
2015-25 period. For all hypothetical vaccines, vaccination of children born to HIV-
positive mothers is likely to be the most efficient strategy, in terms of AIDS deaths
averted over the short term, in the absence of screening (Figure 5.3). Vaccination of
STD patients is also likely to be a relatively efficient strategy in terms of reduced
AIDS mortality in the short term.

Certain distribution strategies change efficiency, relative to other strategies, as
vaccine characteristics change. Figure 5.3 shows, for example, that distribution of
vaccine to women attending family planning clinics becomes less efficient in averting
HIV infections, relative to other distribution strategies, the higher the degree of
sterilizing immunity induced by the vaccine.

5.1.3 Vaccine impact when screening is conducted

Figure 5.4 shows the numbers of HIV infections averted and AIDS deaths averted, per
vaccinated individual, when screening is included in each of the nine vaccine
distribution strategies. In most cases, the inclusion of screening makes little difference
to the efficiency of the distribution strategies in absolute terms. The efficiency of the
sex worker and STD patient distribution strategies, however, are substantially
improved if screening is included. Figure 5.5, which shows the rankings of the
distribution strategies when screening is included, illustrates that distribution
strategies targeting sex workers and STD patients are likely to be the most efficient
strategies in terms of HIV infections averted. The sex worker distribution strategy
becomes more efficient in preventing HIV, relative to the STD distribution strategy,
the lower the effectiveness of the vaccine in preventing HIV. Regardless of the
vaccine characteristics, the sex worker distribution strategy is most efficient in terms
of averting AIDS deaths, and the STD distribution strategy is second most efficient. It
is shown in Appendix D that the efficiency of each distribution strategy is virtually
unchanged if the vaccine is introduced in 2020 instead of 2015.
Figure 5.3: Rankings of distribution strategies, in terms of HIV infections averted and AIDS deaths averted per vaccinated individual, no screening
Figure 5.4: HIV infections averted and AIDS deaths averted (2015-2025), per individual vaccinated in 2015, with screening
Figure 5.5: Rankings of distribution strategies, in terms of HIV infections averted and AIDS deaths averted per vaccinated individual, with screening

5.2 Large-scale vaccine distribution strategies

5.2.1 Amount of vaccine required

Anticipated numbers of individuals vaccinated between 2015 and 2025 are shown in Figure 5.6(a), for each of the vaccine distribution strategies described in Table 4.6.
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 expenditure on vaccine stock, as shown in Figure 5.6(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 million individuals would be vaccinated in 2015 (95% interval: 1.6-1.8 million) and similar numbers would be vaccinated in each subsequent year (Figure 5.6(e)).

Figures 5.6(b), (d) and (f) show the total doses consumed for each of the four strategies, assuming a vaccine consisting of three doses. As in section 5.1, the numbers of vaccine doses consumed are between two and three times the total numbers of individuals vaccinated.

5.2.2 Impact of HIV vaccine

The percentage reduction in new HIV infections between 2015 and 2025 is shown in Figure 5.7(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. Strategy 4 is likely to be the least effective of the four strategies considered, as it results in protection for 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. Appendix D shows that similar reductions in HIV incidence would be achieved if vaccine distribution only started in 2020.

Figure 5.7(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 this accounts for the relatively small differences between the vaccines in terms of reduced AIDS mortality.
Figure 5.6: Expected numbers of vaccinated individuals and vaccine doses, 2015-2025
Trends in the annual number of new HIV infections are shown in Figure 5.8 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 modestly at first (fewer primary infections), but would have a more significant impact 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.
Figure 5.8: 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 lines represent average levels from 500 simulations. Dashed lines represent 95% prediction intervals (2.5 and 97.5 percentiles of model outputs).

For the same three scenarios, trends in total HIV infections are shown in Figures 5.8(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 5.8(g)-(i) show that for both vaccine B and vaccine D there would be slight reductions in annual numbers of AIDS deaths after 2015.

5.2.3 Efficiency of vaccine distribution strategies

Figure 5.9 compares the various vaccines and vaccine distribution strategies in terms of HIV infections averted per vaccinated individual and in terms of AIDS deaths 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 which
targets the group with the highest incidence of HIV (15 to 24 year olds). Its efficiency is comparable to that of the most efficient short-term strategies in the absence of screening (Figure 5.2), for all four hypothetical vaccines. This strategy is also likely to be most efficient in terms of reducing AIDS mortality over the short term.

Figure 5.9: HIV infections averted and AIDS deaths averted (2015-2025), per individual vaccinated

5.2.4 Correlates of vaccine consumption and vaccine efficiency

Correlation between total doses consumed under strategy 2 and measures of vaccine acceptance and series completion are shown in Figure 5.10. As explained in section 4.6, the measures of vaccine acceptance and series completion are the uniform (0,1) variates used to sample from the distributions specified in Table 4.9. 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 ($r = 0.65$, $p < 0.001$).
A number of factors influence the efficiency of the vaccine distribution strategy. Figure 5.11 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 preventive benefit of the vaccine is not strongly correlated with the percentage reduction in the annual number of partners due to social marketing ($r = 0.05$, $p = 0.24$). This suggests that the relationship between HIV vaccination programmes and social marketing programmes is neither antagonistic nor synergistic. The number of infections averted per individual vaccinated is strongly associated with the increase in HIV infectiousness per log increase in viral load ($r = 0.18$, $p < 0.001$). 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 (Johnson et al., 2006). It is also partly due to the effect of vaccine B on HIV infectiousness being more significant the greater the influence of viral load on HIV infectiousness, since the model assumes that vaccine B would reduce viral set point by 2 log RNA copies/ml.

Figure 5.11 also shows that the number of infections averted per vaccinated individual is likely to be significantly negatively related to the degree of behavioural disinhibition ($r = -0.26$, $p < 0.001$). If a straight line is fit through the scatterplot in Figure 5.11(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 utilization of VCT services is also significantly correlated with the efficiency of the vaccine in preventing HIV, though not as significantly as the degree of behavioural disinhibition ($r = -0.15$, $p < 0.001$).
Figure 5.11: Correlates of infections averted per vaccination (vaccine B, strategy 2)

The potentially negative effect of behavioural disinhibition on the preventive benefit of a vaccine is a cause for concern. Table 5.1 shows the correlation coefficients between the infections averted per vaccination and the degree of behavioural disinhibition, for each of the hypothetical vaccines and vaccine distribution strategies. From this it is clear that reversals of behavioural inhibition have the most impact when the vaccine reduces susceptibility to HIV by only a small degree. The effect of behavioural disinhibition appears to be similar for each of the vaccine distribution strategies.

<table>
<thead>
<tr>
<th>Vaccine distribution strategy</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine A</td>
<td>-0.38</td>
<td>-0.35</td>
<td>-0.37</td>
<td>-0.44</td>
</tr>
<tr>
<td>Vaccine B</td>
<td>-0.27</td>
<td>-0.26</td>
<td>-0.29</td>
<td>-0.32</td>
</tr>
<tr>
<td>Vaccine C</td>
<td>-0.25</td>
<td>-0.23</td>
<td>-0.27</td>
<td>-0.30</td>
</tr>
<tr>
<td>Vaccine D</td>
<td>-0.22</td>
<td>-0.20</td>
<td>-0.24</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

Table 5.1: Correlation coefficients between infections averted per vaccinated individual and degree of behavioural disinhibition

Similarly, Table 5.2 shows that the reduction in VCT utilization significantly affects the number of infections averted per vaccinated individual if the vaccine does not induce a high level of sterilizing immunity. However, if the vaccine is highly effective in reducing susceptibility to HIV, the impact of the vaccine would not be significantly affected by the extent of the reduction in VCT utilization. The impact of the vaccine
would also not be significantly affected by the VCT utilization rate if the vaccine were distributed only to infants and 15 year olds (strategy 4), as VCT is assumed to affect sexual behaviour only in individuals who test HIV-positive, and the proportion of vaccinated individuals who are HIV-positive is likely to be very low if strategy 4 is adopted.

<table>
<thead>
<tr>
<th>Vaccine distribution strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>Vaccine A</td>
</tr>
<tr>
<td>Vaccine B</td>
</tr>
<tr>
<td>Vaccine C</td>
</tr>
<tr>
<td>Vaccine D</td>
</tr>
</tbody>
</table>

Table 5.2: Correlation coefficients between infections averted per vaccinated individual and reduction in VCT utilization

Figure 5.12 shows the relationship between the number of infections averted per vaccinated individual and the reduction in susceptibility to HIV in men who have been circumcised, in a scenario in which a male circumcision (MC) programme is introduced in 2007. The correlation is negative ($r = -0.10$, $p = 0.015$), which indicates that the impact of an HIV vaccination programme is likely to be smaller the more effective MC is in reducing male susceptibility to HIV infection. Although this relationship is statistically significant, the difference between the average numbers of infections averted per vaccination in the ‘with MC’ scenario (0.032, 95% interval: 0.22-0.43) and the ‘without MC’ scenario (0.33, 95% interval: 0.23-0.45) is small.

Figure 5.12: Correlation between reduction in HIV susceptibility after MC and HIV infections averted per vaccination (vaccine B, strategy 2)

Figure 5.13 shows the correlation between the AIDS deaths averted per vaccination and the ultimate rate of HAART rollout (the percentage of people progressing to AIDS who are able to access antiretroviral treatment). There is a significant negative correlation between the extent of antiretroviral rollout and the short-term reduction in AIDS mortality due to the vaccine ($r = -0.50$, $p < 0.001$). This negative correlation exists because antiretroviral treatment extends HIV survival, with the result that there are fewer deaths averted over the short term (2015-2025) and relatively more deaths averted over the longer term.

Figure 5.13: Correlation between reduction in HIV susceptibility after MC and AIDS deaths averted per vaccination (vaccine B, strategy 2)
5.2.5 Comparison with other prevention programmes

Vaccine distribution strategy 2 is compared with other prevention programmes in Figure 5.14, for each of the hypothetical vaccines. The figure shows the percentage reduction in total new HIV infections over the first 10 years after the introduction of each prevention programme. Different prevention programmes have been introduced at different dates and have been phased in at different rates in South Africa, and this analysis does not standardize for these differences. Nevertheless, Figure 5.14 suggests that even disease-modifying vaccines (vaccines A, B and C) could have an impact on HIV incidence comparable to or greater than that achieved by other HIV prevention programmes. Male circumcision is a form of prevention that has not yet been introduced in South Africa. If introduced in 2007, however, it would reduce new HIV infections between 2007 and 2016 by 8.9% (95% interval: 5.1-13.6%).
Figure 5.14: Percentage reduction in new HIV infections over the first 10 years after the introduction of prevention programmes
IEC = information and education campaigns, MC = male circumcision, PMTCT = prevention of mother-to-child transmission, STD = sexually transmitted disease, VCT = voluntary counselling and testing
6. Discussion

6.1 Distribution strategies when vaccine supplies are limited

When vaccine supplies are limited, the key question to consider in selecting a vaccine distribution strategy should be which strategies are likely to be most efficient in averting HIV infections and AIDS deaths. The analysis in section 5.1 shows that this is likely to depend on (a) the properties of the vaccine, (b) whether screening is deemed appropriate, and (c) whether the objective is to avert HIV infections or avert AIDS deaths in the short term. Table 6.1 summarizes the results presented in section 5.1, showing which vaccine distribution strategies are likely to be optimal for different screening options and different policy objectives.

<table>
<thead>
<tr>
<th>Screening</th>
<th>Policy objective (short-term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avert HIV infections</td>
<td>Avert AIDS deaths</td>
</tr>
<tr>
<td>No screening</td>
<td>Schools (age 16), STD patients</td>
</tr>
<tr>
<td>With screening</td>
<td>STD patients, Sex workers</td>
</tr>
</tbody>
</table>

Table 6.1: Optimal vaccine distribution strategies under different conditions

These findings may present a dilemma to decision makers if forced to adopt a strategy which does not allow for screening prior to vaccination. While vaccinating infants born to HIV-positive mothers would be the most efficient strategy in terms of reducing AIDS mortality in the short term, it would be one of the least efficient strategies in terms of averting HIV infections. Similarly, vaccinating 16-year old learners would be the most efficient strategy in terms of reducing HIV incidence, but it would be considerably less efficient (relative to other strategies) in terms of averting AIDS deaths in the short term. Over the longer term, it might be expected that the strategies which are most efficient in reducing HIV incidence would also be most efficient in reducing AIDS mortality. The question of whether it is preferable to prevent AIDS deaths or HIV infections over a ten-year horizon is thus to some extent a question of timing. Extending this analysis to allow for the calculation of disability-adjusted life years (DALYs) saved per vaccination would provide an alternative perspective on which distribution strategies are optimal.

Other studies have suggested that if a vaccine induces a high degree of sterilizing immunity, vaccination of sex workers would be the most efficient strategy (in terms of infections averted per vaccine dose) for distributing the vaccine if screening is conducted (Desmond and Greener 2003; Novaes et al, 2002; Tangcharoensathien et al, 2001). The present analysis suggests that although vaccinating sex workers would be highly efficient under these circumstances, vaccinating STD patients is likely to be more efficient. This may be due to the partners of sex workers having a higher HIV prevalence than the partners of STD patients, which would lead to fewer secondary infections averted per sex worker vaccinated than would be averted per STD patient vaccinated. Desmond and Greener estimate that even without screening, vaccination
of sex workers would still be the most efficient strategy for distributing a vaccine which induces a high degree of sterilizing immunity. They acknowledge, however, that their model does not allow for behaviour change in vaccinated individuals, and that this could lead to the benefits of vaccinating sex workers being overstated. The present analysis suggests that after taking into account this behaviour change, vaccination of sex workers is in fact likely to be the least efficient of the distribution strategies considered, in the absence of screening.

The analyses of Novaes et al (2002) and Tangcharoensathien et al (2001) both suggest that vaccine distribution strategies which target high school learners or university students would be among the least efficient strategies. The present analysis shows that while vaccination of 12 year olds is likely to be a relatively inefficient strategy, vaccination of 16 year olds is likely to be the third most efficient strategy for preventing HIV if screening is conducted. The discrepancy between these findings and the findings of Novaes et al and Tangcharoensathien et al can be attributed to the assumption in both analyses that the lifetime risk of infection in a cohort is equivalent to the current HIV prevalence in the cohort. This assumption is clearly not plausible in a cohort of adolescents.

This analysis determines which vaccine distribution strategies are likely to make the best use of a limited vaccine supply. The choice of distribution strategy will ultimately depend on this as well as other criteria, such as the cost of implementing the strategy, the ease with which the strategy can be integrated with the longer term vaccine distribution strategy, and the social acceptability of limiting vaccine distribution to the particular sub-population. It may be necessary to adopt more than one distribution strategy, depending on the amount of vaccine available in the short term. It may also be appropriate to adopt different strategies for males and females, e.g. vaccination of female learners at age 12 and male learners at age 16.

### 6.2 Large-scale vaccine distribution strategies

Of the four strategies considered, the most effective strategy would 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 were 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.

The strategy suggested at a recent WHO consultation, which is to vaccinate all newborn infants as well as all children entering adolescence (WHO-UNAIDS Expert Group 2005), 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.
Other model-based evaluations have suggested that a vaccine which reduces susceptibility to HIV by more than 90% could eradicate the HIV/AIDS epidemic (Anderson and Garnett 1996; Blower and 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. In spite of these detracting factors, HIV vaccines can be expected to have an impact on HIV incidence similar to or greater than that of other HIV prevention programmes that have been introduced to date in South Africa.

Reversal of behavioural inhibition in vaccinated individuals has the potential to reduce significantly the impact of a vaccine which is primarily disease-modifying. If, however, the vaccine induces a high level of sterilizing immunity, the impact of the vaccine is significantly less sensitive to the extent of the behavioural disinhibition, as other studies have shown (Bogard and Kuntz 2002; Nagelkerke and De Vlas 2003). This suggests that the poorer the ability of the vaccine to induce sterilizing immunity, the greater will be the need for education promoting continued risk reduction behaviour in vaccinated individuals. The extent to which VCT utilization changes after vaccination could also significantly affect the preventive benefit of the vaccine. This is a parameter which has not been explored in previous research on the potential impact of HIV vaccines. It is possible that reductions in VCT utilization may prove to be even more significant over the longer term (post-2025), as VCT utilization in vaccinated individuals would influence secondary infections averted rather than primary infections averted.

This analysis does not suggest that other HIV prevention programmes would mitigate the impact of HIV vaccination to any significant extent. The number of HIV infections averted per vaccination was found to be uncorrelated with the reduction in numbers of partners following social marketing programmes. Although there was a significant negative correlation between the number of infections averted per vaccination and the effectiveness of male circumcision in reducing susceptibility to HIV, the average number of infections averted per vaccination was very similar, whether male circumcision interventions were included or excluded. The number of infections averted per vaccination was also not sensitive to the effectiveness of PMTCT programmes (results not shown). However, the numbers of AIDS deaths averted per vaccination were significantly negatively correlated with levels of access to HAART. This relationship was observed over a short time interval, and it is expected that it would not persist over a longer time period.

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 about 35% for a multi-dose HIV vaccine, the total number of vaccine doses required can be estimated by multiplying the estimates in Figures 5.6(b), (d) and (f) by a factor of 1.35. The resulting 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). Estimates of vaccine requirements are relatively insensitive to the time at which the vaccine is introduced, as shown in Appendix D.

6.3 Strengths and limitations of the ASSA2002 Vaccine model

A key limitation of the ASSA2002 Vaccine model is that it does not allow for the potential effects of revaccination. In South Africa, mass immunization against measles is conducted at regular intervals, regardless of whether or not children have been vaccinated against measles previously, as the effect of the vaccine is fairly short-lived (Uzicanin et al, 2002). It may be necessary to adopt a similar distribution strategy for HIV vaccination in adults if HIV vaccine protection wanes rapidly. The effects of this would need to be explored by extending the ASSA2002 Vaccine model.

The purpose of this analysis has been to assess the demand for an HIV vaccine and the potential impact of an HIV vaccine if it is provided free of charge as part of a programme coordinated by the public health sector. It is likely, however, that many individuals would be willing to pay for HIV vaccination through the private health sector if vaccine stocks in the public health sector were very limited (Suraratdecha et al, 2005; Whittington et al, 2002). It is also likely that medical schemes would provide cover for HIV vaccination. These factors need to be considered when assessing vaccine requirements for the country as a whole.

Vaccine requirements are difficult to estimate reliably for several of the constrained distribution strategies, for a number of reasons. Firstly, if vaccine is distributed exclusively through existing HIV prevention services, it is probable that utilization of the services will increase. The ASSA2002 Vaccine model assumes, however, that utilization of VCT, STD treatment and family planning services would not be affected by the availability of HIV vaccine at these service points. The model may therefore under-estimate the actual need for vaccine in strategies III, IV and V. Secondly, strategies II to VI are considered from the point of view of the public health sector, and are therefore assumed to be implemented only through public health services. If, however, the private health sector were not to offer HIV vaccine to the same extent as the public health sector, utilization of public health facilities may well increase. This too could result in under-estimation of vaccine requirements. Thirdly, the proportion of individuals using public health facilities is difficult to estimate reliably, and may well have changed by the time an HIV vaccine is available for distribution. The likely introduction of social health insurance and a state medical scheme, for example, will probably decrease the proportion of the population using public health facilities. Fourthly, assumptions regarding school enrolment rates are based on the 2004 General Household Survey, which does not include in the sampling frame children living outside of households, who are less likely to be in school. The model may therefore over-estimate slightly the need for vaccine in strategies VII to IX.
The likely effects of vaccination are also difficult to estimate reliably for certain of the constrained distribution strategies, due to the structure of the ASSA2002 model. For example, in the ASSA2002 model it is assumed that roughly 1% of women start sex work on becoming sexually active and continue to engage in sex work until their late fifties. Evidence suggests that most women engage in sex work over short periods of time, out of economic necessity, and do not remain sex workers for long periods (Rees et al, 2000; Morison et al, 2001). As a result of the assumption that sex workers have been cumulatively exposed to HIV for long periods of time, the ASSA2002 model tends to overestimate HIV prevalence in sex workers, and thus the ASSA2002 Vaccine model may slightly under-estimate the effectiveness of distribution strategy I. The effectiveness of distribution strategy IV is also difficult to estimate reliably, due to the ASSA2002 assumption that only individuals with high rates of partner change (individuals in the PRO and STD groups) experience STD symptoms. In reality, a substantial proportion of women not experiencing STDs attend STD clinics, seeking treatment for bacterial vaginosis, candidiasis or other vaginitis not due to sexually transmitted infection (Johnson et al, 2005).

The ASSA2002 Vaccine model estimates HIV vaccine requirements both with and without HIV screening. This is an important feature of the model, since it is necessary to consider the possibility of introducing screening prior to vaccination when vaccine supplies are limited. A limitation of the model, however, is that it does not allow for the effect of screening on behaviour in those who test positive, except in the case of distribution strategy V (implemented through VCT services). If HIV screening is coupled with pre- and post-test counselling, it is likely that those testing positive would reduce their sexual risk behaviours (Weinhardt et al, 1999). The model therefore probably under-estimates the infections averted when screening precedes vaccination.

In the absence of screening, it is assumed that HIV-positive individuals aware of their HIV status are as likely to accept HIV vaccination as HIV-positive individuals unaware of their HIV status. However, if public education programmes emphasize that the vaccine provides no benefit in individuals who are already infected with HIV, individuals who know they are HIV-positive are less likely to seek vaccination. The model may therefore slightly overestimate vaccine requirements in the absence of screening. Since the model estimates the number of HIV-positive individuals knowing their HIV status, who get vaccinated in each year, the potential extent of this overstatement can be assessed. For example, under distribution strategy 2, 27.4 million individuals (95% interval: 23.7-30.5) are expected to be vaccinated between 2015 and 2025. Of these, 2.09 million (1.60-2.62 million) are estimated to know they are HIV-positive. The estimated vaccine requirements could thus be reduced by as much as 10% if it is assumed that individuals who know they are HIV-positive are less likely to accept vaccination.

A limitation of this analysis is that it presents the effects of HIV vaccination over a relatively short time period (ten years). The differences between vaccines B and C, in terms of the duration of the protection they afford, are less apparent over a short interval than over a longer period. In addition, certain strategies which appear to be inefficient over the short term may prove to be substantially more cost-effective over the longer term. Childhood vaccination, for example, is likely to become more
effective as vaccinated children enter adolescence and become sexually active. Conversely, certain strategies may be effective over the short term but relatively ineffective over the longer term. Van Ballegooijen et al (2003) have shown, for example, that non-sterilizing disease-modifying vaccines can reduce HIV incidence significantly in the short term, but these vaccines also have the potential to increase HIV incidence over the longer term.

The ASSA2002 Vaccine model suggests that adoption of riskier sexual behaviours in vaccinated individuals is unlikely to reduce the number of infections averted by vaccine B by more than 25%. This finding differs from the results of other mathematical models, which suggest a more substantial effect due to behaviour change (Blower and McLean 1994; Gray et al, 2003). This is partly due to the assumption that behaviour change would only be significant if vaccine efficacy were high, which is consistent with empirical evidence (Suraratdecha et al, 2005). It is also partly due to the assumption that levels of risk behaviour would not increase above the levels of risk behaviour that would be expected in the absence of an HIV/AIDS epidemic. In addition, the model does not allow for increases in rates of partner change in vaccinated individuals and also does not consider potential changes in behaviour in HIV-negative individuals who have not been vaccinated. The ASSA2002 Vaccine model could therefore understate the extent of behavioural disinhibition.

An advantage of the ASSA2002 Vaccine model is that it allows for the modelling of multiple vaccine distribution strategies being implemented concurrently, without double counting numbers of vaccinations. Suraratdecha and Hecht (2005) note that double counting is a limitation of many of the existing estimates of HIV vaccine demand. A further advantage of the ASSA2002 Vaccine model is that it allows 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.

Although previous studies have examined the effects of distributing HIV vaccine selectively in different sub-populations (Desmond and Greener 2003; Novaes et al, 2002; Tangcharoensathien et al, 2001), these analyses have been subject to a number of limitations, as described in section 3.5. As a dynamic demographic and epidemiological model, the ASSA2002 Vaccine model is capable of assessing the effect of AIDS and demographic change on vaccine requirements over the longer term. It is also capable of assessing the effect of future changes in HIV incidence and prevalence on the relative efficiency of different vaccine distribution strategies. Being a demographic model also makes the ASSA2002 Vaccine model particularly useful in assessing the effect of limiting vaccination to particular age groups. This analysis shows, for example, that the short-term benefits of school-based vaccination are highly dependent on the age at which the vaccine is administered.

With a few exceptions (Davenport et al, 2004; Barth-Jones et al, 2003; Blower et al, 2001), most model-based evaluations of vaccine impact 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 comparing vaccine distribution strategies, as it is seldom certain which strategy is likely to be optimal, and it is useful to indicate the likelihood of a particular strategy outperforming other strategies.

A source of uncertainty which has not been considered in this analysis is uncertainty regarding the timing of mother-to-child transmission of HIV and rates of survival in HIV-infected children. It has been assumed that the vaccines are as effective in preventing mother-to-child transmission of HIV as they are in preventing sexual transmission, though this is by no means certain. Investigation of vaccine efficacy in infants, as well as adults, will need to be conducted before conclusive statements can be made about the appropriateness of infant vaccination, relative to other vaccine distribution strategies. Estimates of the impact of immunization in infancy, presented in this report, should therefore be treated with caution.

### 6.4 Future work

A key message emerging from this analysis is that vaccine distribution policy will be contingent upon a wide range of factors, many of which are still highly uncertain. It will be necessary to repeat this analysis closer to the time that an HIV vaccine is available for distribution, once there is greater certainty regarding the properties of the vaccine and greater certainty regarding the dynamics of the South African HIV/AIDS epidemic. In the interim, it will be necessary to conduct studies that will assist in resolving some of the other uncertainties. For example, there is a need for studies of levels and correlates of HIV vaccine acceptability in South Africa, similar to those which have been conducted elsewhere in Africa (Bishai et al, 2004; Jackson et al, 1995). It is particularly important that these studies address the question of how acceptable disease-modifying vaccines might be relative to vaccines that induce sterilizing immunity. It will also be necessary to learn from the challenges associated with distributing the recently-developed human papillomavirus (HPV) vaccines (Villa et al, 2005). The epidemiology of HIV is in many respects similar to that of HPV, and the strategies favoured for distributing HIV and HPV vaccines should thus have much in common.

The ASSA2002 Vaccine model could be improved by allowing for revaccination. This would be particularly important in exploring the effect of introducing a high-efficacy vaccine a few years after the introduction of a relatively low-efficacy vaccine, a scenario which appears particularly likely (Streefland 2003). Revaccination is also likely to play an important part in longer-term vaccine distribution. There is a need to examine the potential effects of vaccine distribution strategies beyond the 2025 horizon, and hence it would be useful to adapt the model to allow for the effects of revaccination.

The ASSA2002 Vaccine model was developed for South Africa, and the conclusions drawn regarding the appropriateness of various vaccine distribution strategies will not necessarily be applicable to other settings. There is a need for similar modelling of vaccine requirements and vaccine impacts in other SADC countries, especially in the light of the enormous HIV/AIDS burden in these countries.
Acknowledgements

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Appendix A: Approach to setting VEP and VEi parameters

Rates of progression to AIDS and levels of HIV infectiousness have both been shown to be strongly related to HIV viral load. In setting assumptions about the likely effect of a disease-modifying HIV vaccine, it is therefore necessary to consider the likely reduction in viral set point that would be induced by the vaccine.

A.1 Reduction in viral set point due to disease-modifying vaccine

Studies have shown that the viral set point in rhesus macaques infected with simian immunodeficiency virus (SIV) or HIV-SIV hybrid virus (SHIV) is typically more than 2 log copies/ml lower in macaques which have received experimental HIV vaccines prior to infection than in those which have not (Shiver et al, 2002; Barouch et al, 2000; Egan et al, 2000). While it cannot be assumed that the same reductions in HIV viral load would be observed in humans, it would seem plausible that an HIV vaccine might reduce HIV viral set point by 2 log RNA copies/ml (i.e. a 100-fold reduction in HIV RNA). For vaccines A, B and C, it is therefore assumed that the levels of HIV viral load in WHO stages 1 and 2 are 2 log RNA copies/ml lower in individuals vaccinated prior to infection than in unvaccinated individuals. In WHO stages 3 and 4, HIV viral load is assumed to be the same in vaccinated and unvaccinated individuals, as individuals are assumed to have experienced CTL escape by the time they reach WHO stage 3. (It is possible that in reality these vaccinated individuals would still have a lower viral load, as escape mutants may have lower fitness (Leslie et al, 2004).)

A.2 Reduction in HIV disease progression due to disease-modifying vaccine

Suppose that in unvaccinated individuals, the time from HIV infection to AIDS follows a Weibull distribution with parameters \( \lambda \) and \( \phi \), i.e. the proportion of individuals surviving without having progressed to AIDS, \( t \) years after infection, is

\[
S(t) = \exp(-\lambda t^\phi).
\]  

(A1)

Further suppose that in individuals who are vaccinated prior to infection, the time from infection to AIDS follows a Weibull distribution with parameters \( \lambda^* \) and \( \phi \). The ‘shape’ parameter \( \phi \) is assumed to remain the same, as this makes it possible to determine the VEp parameter independently of \( t \). VEp, the reduction in the rate of progression to AIDS in vaccinated individuals, is

\[
VEp = 1 - \frac{\lambda^* \phi t^{\phi-1}}{\lambda \phi t^{\phi-1}} = 1 - \frac{\lambda^*}{\lambda},
\]  

(A2)

which is independent of \( t \). Studies have estimated the rate of progression to AIDS increases by a factor of between 2 and 3.5 per log increase in viral set point (Lyles et al, 1999; Hubert et al, 2000; O’Brien et al, 1998). If it is assumed that the rate of
progression to AIDS increases by a factor of 2.5 per log increase in viral set point, and
a vaccine is expected to reduce viral set point by 2 log RNA copies/ml, then

\[ \text{VE}_p = 1 - 2.5^{-2} = 0.84 . \]  \hspace{1cm} (A3)

The mean of the Weibull distribution is given by the formula

\[ \Gamma\left(1 + \frac{1}{\phi}\right) \lambda^{-1/\phi} . \]  \hspace{1cm} (A4)

Hence the factor by which the mean pre-AIDS survival increases, as a result of the
HIV vaccine, is

\[ \frac{\Gamma(1+1/\phi)\lambda^*^{-1/\phi}}{\Gamma(1+1/\phi)\lambda^{-1/\phi}} = \left(\frac{\lambda^*}{\lambda}\right)^{-1/\phi} . \]  \hspace{1cm} (A5)

If it is assumed that \( \phi \) is 2.5, as previous modelling of adult survival suggests
(Johnson et al, 2006), then by combining the results in equations (A2), (A3) and (A5),
the factor by which the mean pre-AIDS survival in adults increases is

\[ (1 - 0.84)^{-1/2.5} = 2.08 . \]  \hspace{1cm} (A6)

In children infected through breastfeeding, the pre-AIDS survival is assumed in the
ASSA2002 model to follow a Weibull distribution with \( \phi = 5.5 \). Using this in place of
2.5 in equation (A6), the factor by which pre-AIDS survival is increased in children
infected by breastfeeding, as a result of the vaccine, is 1.40. It can be shown that the
factor by which the mean pre-AIDS survival increases, due to the vaccine, is the same
as the factor by which the median pre-AIDS survival increases, if the shape parameter
remains constant. Hence, assuming that median pre-AIDS survival in vaccinated
children is 40% greater than that in unvaccinated children is equivalent to assuming a
\( \text{VE}_p \) parameter of 0.84, if the shape parameter remains constant at 5.5.

In adults, the effect of the vaccine is assumed to be limited to stages 1 and 2 of
disease, though stage 3 is also considered ‘pre-AIDS’. In the absence of antiretroviral
treatment, unvaccinated adults are assumed to spend 47% of the time from HIV
infection to death in stages 1 and 2, 36% in stage 3 and 17% in stage 4 (AIDS)
(Johnson and Dorrington 2006). If the mean survival in stage 3 is unchanged in
vaccinated individuals, then it follows that the percentage increase in mean survival in
stages 1 and 2, \( \theta \), is related to the previously calculated increase in mean pre-AIDS
survival by the formula

\[ 2.08 = \frac{0.47 \times (1 + \theta) + 0.36}{0.47 + 0.36} . \]  \hspace{1cm} (A7)

From this it follows that the percentage increase in mean survival in stages 1 and 2, \( \theta \),
is 191%. Equivalently, if the shape parameter is unchanged, the median survival in
each of stages 1 and 2, due to the vaccine, is increased by 191% in vaccinated
individuals. The ASSA2002 Vaccine model therefore assumes that median survival in
stages 1 and 2 is increased by 191% in adults who are vaccinated, which is approximately equivalent to a VEₚ parameter of 0.84. The relation is only approximate because in the ASSA2002 model, the adult pre-AIDS survival time is modelled as the sum of three Weibull-distributed variables (one for each of WHO stages 1 to 3), not a single Weibull distribution. The sum of the three Weibull-distributed variables is similar in shape to a single Weibull distribution with a shape parameter of 2.5, but not identical.

A.3 Reduction in HIV infectiousness due to disease-modifying vaccine

In the uncertainty analysis, allowance is made for uncertainty regarding the effect of viral load on HIV infectiousness. In earlier uncertainty analysis work, used as the basis for the uncertainty analysis presented here, the posterior average increase in infectiousness per log increase in viral load was 152%, with a 95% credibility interval of 76% to 270% (Johnson et al, 2006). If a vaccine were to reduce HIV viral load in HIV stages 1 and 2 by 2 log RNA copies/ml, and HIV infectiousness were to increase by 152% for each log increase in HIV viral load, then the VE₁ parameter would be calculated as

\[
VE₁ = 1 - (1 + 1.52)^{-2} = 0.84 .
\]

(A8)

A different value of the VE₁ parameter is calculated for each different value sampled from the posterior distribution of the ‘increase in infectiousness per log viral load’ parameter.
Appendix B: Mathematical approach to estimating numbers receiving HIV vaccine

In the ASSA2002 Vaccine model, it is assumed that individuals get vaccinated at the start of each projection year, i.e. before any adjustments are made for deaths, migration, new HIV infections etc. Projection years run from 1 July to 30 June of successive years, and thus the model estimate of total vaccinations in 2015, for example, is based on the estimated population at mid-2015.

Suppose that $\Omega_{xisg}$ is the probability that an individual aged $x$, of risk group $i$ and sex $s$, is offered HIV vaccination in a particular year, through vaccine distribution strategy $g$. This is the product of the probability of using the relevant facility type/service/school and the rate of vaccine rollout (see section 4.3).

Suppose that further symbols are defined as follows:

- $\alpha_{xi}$ is the probability that an individual aged $x$, in risk group $i$, accepts an HIV vaccine if it is offered to him/her (see section 4.4);
- $\sigma_g$ is an indicator variable, indicating whether screening is applied under distribution strategy $g$ ($0 = \text{no screening}, 1 = \text{screening}$);
- $\lambda_g$ is the probability that the vaccination series is completed under distribution strategy $g$ (see section 4.4);
- $\Omega^-_{xis}$ is the probability that an HIV-negative individual aged $x$, of risk group $i$ and sex $s$, is offered HIV vaccination in a particular year; and
- $\Omega^+_{xis}$ is the probability that an HIV-positive individual aged $x$, of risk group $i$ and sex $s$, is offered HIV vaccination in a particular year.

$\Omega^-_{xis}$ is then calculated as

\[ 1 - \prod_{g=1}^{7} \left( 1 - \Omega_{xisg} \right), \quad (B1) \]

and $\Omega^+_{xis}$ is calculated as

\[ 1 - \prod_{g=1}^{7} \left( 1 - \Omega_{xisg} (1 - \sigma_g) \right). \quad (B2) \]

The proportion of HIV-negative individuals who receive vaccines is $\alpha_{xi} \Omega^-_{xis}$, and of those receiving vaccines, the proportion who complete the vaccine series is calculated as

\[ \frac{1 - \prod_{g=1}^{7} \left( 1 - \Omega_{xisg} \lambda_g \right)}{\Omega^-_{xis}}. \quad (B3) \]
Similar formulae are used to calculate the proportion of HIV-positive individuals accepting vaccines and completing the vaccine series.
Appendix C: Mathematical approach to modelling effect of vaccination on sexual behaviour and sexual transmission of HIV

The approach to modelling the sexual transmission of HIV in ASSA2002 is described in detail elsewhere (Johnson and Dorrington 2006). Briefly, \( T_{ij}(y) \) is defined as the probability that an HIV-positive \( y \)-year old woman, in stage \( t \) of disease and in risk group \( j \), transmits the virus to a partner in risk group \( i \) in a single act of sex. The parameter is calculated using the formula

\[
T_{ij}(y) = r_{ij} \cdot I_t \left( 1 - \left[ 1 - (1 - c_j(y))R_t \right]e \right)
\]  

(C1)

where

- \( r_{ij} \) is the average probability of transmission from an HIV-positive female in risk group \( j \) to an HIV-negative male in risk group \( i \), in a single act of unprotected sex;
- \( I_t \) is the factor by which \( r_{ij} \) is multiplied if the HIV-positive female is in stage \( t \) of disease;
- \( c_j(y) \) is the probability that a sero-discordant couple use a condom when the index partner is aged \( y \) and in risk group \( j \);
- \( R_t \) is the factor by which the proportion of sex acts that are unprotected is multiplied in stage \( t \) of disease (taking into account the effect of knowledge of HIV status); and
- \( e \) is the probability that a condom is effective in preventing HIV transmission in a single act of sex.

A similar formula is used to define the probability of male-to-female transmission, with male-specific parameters \( T_{ij}^*(y) \), \( r_{ij}^* \) and \( R_t^* \) replacing \( T_{ij}(y) \), \( r_{ij} \) and \( R_t \) respectively.

C.1 The effect of vaccination on knowledge of HIV status

In the ASSA2002 model, it is assumed that a proportion \( k_t \) of women in stage \( t \) of HIV infection know their HIV status (and similarly, a proportion \( k_t^* \) of men in stage \( t \) of infection know they are HIV-positive). These proportions are updated for each projection year, taking into account utilization of VCT services over each year. When modelling the effects of vaccination, it is necessary to take into account that HIV-infected individuals who have been vaccinated may be more or less likely to know their HIV status than unvaccinated infected individuals. The parameters \( k_t^v \) and \( k_t^{*v} \) are therefore introduced to represent knowledge of HIV status in vaccination class \( v \).

As stated in section 4.4, it is assumed that knowledge of HIV status has no effect on willingness to be vaccinated. However, vaccinated individuals are assumed to be less likely to seek VCT independently than unvaccinated individuals. In addition, if vaccinated individuals are partially protected but become infected, they survive for longer and there is thus a greater period of time in which they can learn their HIV
status. For these reasons, $k_{rv}$ and $k^{*}_{rv}$ values can be expected to differ between vaccination classes.

### C.2 The effect of vaccination on condom usage

From equation (C1) it is clear that the probability that a sero-discordant couple use a condom is

$$1 - (1 - c_j(y))R_v.$$  \hspace{1cm} (C2)

This can be re-expressed as

$$1 - \left[ k_v (1 - c_j(y)) \left( 1 - \frac{1 - R_v}{k_v} \right) + (1 - k_v)(1 - c_j(y)) \right],$$ \hspace{1cm} (C3)

where the first term in the square brackets represents the probability of knowing one’s HIV status multiplied by the probability of not using a condom, and the second term represents the probability of not knowing one’s HIV status multiplied by the probability of not using a condom.

In the ASSA2002 Vaccine model, equations (C2) and (C3) are modified to allow for the fact that a sero-discordant couple is less likely to use a condom if either (a) the index partner has been vaccinated and is unaware of his/her HIV status, or (b) the susceptible partner has been vaccinated. If neither partner has been vaccinated, the probability of condom use remains the same as in equation (C2). If the susceptible partner has been vaccinated, then – regardless of the index partner’s vaccination status – the probability of using a condom becomes

$$1 - \left( 1 - c_j^0(y) - (1 - \rho)(c_j(y) - c_j^0(y)) \right)R_v,$$ \hspace{1cm} (C4)

where $c_j^0(y)$ is the rate of condom usage that would have been expected in the absence of an HIV/AIDS epidemic, $\rho$ is the percentage reduction in the benefit of social marketing due to vaccination, and $R_v$ is the factor by which the proportion of sex acts that are unprotected is multiplied when the index partner is in stage $t$ of disease and in vaccination class $v$.

If the index partner has been vaccinated and the susceptible partner has not been vaccinated, the probability of using a condom becomes

$$1 - \left[ k_v (1 - c_j(y)) \left( 1 - (1 - R_v)/k_v \right) + (1 - k_v)(1 - c_j^0(y) - (1 - \rho)(c_j(y) - c_j^0(y))) \right].$$ \hspace{1cm} (C5)

It is thus assumed that if the index partner does not know that he/she is infected with HIV, he/she will use condoms less frequently as a result of being vaccinated. However, if the index partner knows he/she is HIV-positive and his/her partner has not been vaccinated, the probability of using a condom is assumed to be the same as it would have been if neither partner had been vaccinated.
C.3 The effect of vaccination on HIV infectiousness

As explained in section 4.2.1, it is assumed that individuals who become infected with HIV in spite of being partially protected by the vaccine have reduced HIV infectiousness in stages 1 and 2 of disease. The factor $I_t$ in equation (C1) is thus replaced by $I_{tv}$, where $v$ is the vaccination class of the infected individual and

$$I_{tv} = \begin{cases} I_t (1 - VE_t) & \text{if } v = 3 \text{ and } t = 1 \text{ or } t = 2 \\ I_t & \text{otherwise} \end{cases}$$  \hspace{1cm} (C6)

C.4 The effect of vaccination on HIV susceptibility

It is likely that a vaccine would protect individuals against some partners but not others (e.g. partners infected with subtypes different from those the vaccine is designed to protect against, vaccinated partners who have developed escape mutants, or partners who have an HLA profile similar to that of their susceptible partner). Continued intercourse with an infected partner is likely to prime the immune response induced by the vaccine, so that the probability of HIV transmission per act of intercourse reduces as the cumulative number of exposures to the infected partner increases. It would thus seem reasonable to assume vaccination leads to a constant reduction in the probability of HIV infection per partnership, rather than assume it leads to a constant reduction in the probability of HIV transmission per act of sex. However, when the probability of HIV infection per partnership is small, it makes little difference whether the vaccine is assumed to affect the probability of transmission per act of sex or the probability of transmission per partnership.

For the sake of consistency with the existing model structure, it is assumed that the risk of HIV transmission per act of sex is multiplied by a factor $B_u$ if the susceptible partner is in vaccine class $u$, where

$$B_u = \begin{cases} 1 & \text{if } u = 1 \text{ or } u = 4 \\ 0 & \text{if } u = 2 \\ 1 - VE_u & \text{if } u = 3 \end{cases}$$  \hspace{1cm} (C7)

To summarize the developments thus far, equation (C1) can be reformulated as follows in the ASSA2002 Vaccine model. Suppose $T_{ijuv}(y)$ is defined as the probability that an HIV-positive $y$-year old woman, in stage $t$ of disease, in risk group $j$, and in vaccine class $v$, transmits the virus to a partner in risk group $i$ and in vaccine class $u$ in a single act of sex. The parameter is calculated using the formula

$$T_{ijuv}(y) = r_{ij} I_{tv} B_u (1 - C_{ijuv}(y)) c$$  \hspace{1cm} (C8)

where $C_{ijuv}(y)$ is the probability that a sero-discordant couple use a condom, and is equal to equation (C2) when $u$ and $v$ are both 1 (i.e. both partners unvaccinated); equation (C4) when $u$ is 2, 3 or 4; and equation (C5) when $u$ is 1 and $v$ is 2, 3 or 4.
C.5 The effect of vaccination on the frequency of sex per partnership

In the ASSA2002 model, probabilities of HIV infection are calculated at annual intervals. The probability that a female aged \( x \), in risk group \( i \), becomes infected in a given year is calculated as

\[
1 - \left[1 - a(x) \sum_{j=1}^{4} w_j \sum_{y=14}^{59} f(y \mid x) \sum_{t=1}^{6} p_{yt}(y) \left[1 - \left(1 - T_{yt}(y)\right)_{p_{yD_t}}\right]\right]^{p_{Sx}} \quad (C9)
\]

where
- \( a(x) \) is the factor by which the per-partnership transmission probability is multiplied in women aged \( x \);
- \( w_j \) is the proportion of male partners who are in risk group \( j \);
- \( p_{yt}(y) \) is the proportion of male partners (aged \( y \) and in risk group \( j \)) who are HIV-positive and in stage \( t \) of disease;
- \( n_{yt} \) is the number of coital acts per partnership between a female in risk group \( i \) and a male in risk group \( j \);
- \( D_t \) is the factor by which the coital frequency is multiplied in stage \( t \) of disease (taking into account the effect of disease symptoms and knowledge of HIV status);
- \( P_i \) is the average annual number of partners for a woman in group \( i \).

A similar formula for the annual infection probability is used for males, with female-specific parameters being replaced by male-specific parameters.

The number of coital acts per partnership, \( n_{ij} \), is in equation (C9) multiplied by a factor \( D_t \), representing the effect of knowledge of HIV status and the severity of the symptoms occurring in stage \( t \). Since knowledge of HIV status differs between vaccination classes, it is necessary to replace \( D_t \) with \( D_{tv} \), where \( D_{tv} \) is the factor by which coital frequency is multiplied when the index partner is in vaccine class \( v \) and HIV stage \( t \).

C.6 The effect of vaccination on choice of partner

It is assumed that when choosing partners, individuals are indifferent to whether or not prospective partners have been vaccinated. This is possibly unrealistic, but the assumption is made in order to avoid a rebalancing of sexual activity between age, sex and risk groups, which would be complex.

In the ASSA2002 Vaccine model, equation (C9) is replaced with the following formula for the probability of HIV infection in a woman aged \( x \), in risk group \( i \) and vaccine class \( u \):

\[
1 - \left[1 - a(x) \sum_{j=1}^{4} w_j \sum_{y=14}^{59} f(y \mid x) \sum_{v=1}^{4} \phi_{jv}(y) \sum_{t=1}^{6} p_{yt}(y) \left[1 - \left(1 - T_{ijv}(y)\right)_{p_{yS_D}}\right]\right]^{p_{Sx}} \quad (C10)
\]
\( p_{jt} (y) \) is the proportion of male partners (aged \( y \), in vaccine class \( v \) and in risk group \( j \)) who are HIV-positive and in stage \( t \) of disease. \( \varphi_{jt} (y) \) is the proportion of all males (aged \( y \) and in risk group \( j \)) who are in vaccine class \( v \).

C.7 The effect of vaccination on annual numbers of partners

Vaccination is assumed to have no effect on the average annual number of partners. This is possibly unrealistic, as the model assumes that the average annual number of partners reduces as a result of behavioural inhibition, and it would therefore be logical to assume that rates of partner change increase in response to behavioural disinhibition. However, whereas behavioural inhibition affects all HIV-susceptible individuals, behavioural disinhibition in response to HIV vaccines would probably only affect those susceptible individuals who have been vaccinated. Allowing for increased rates of partner change in vaccinated individuals would therefore necessitate a rebalancing of sexual activity between age, sex and risk groups, which would be complex. It was therefore decided that this would not be modelled. Vaccinated individuals are assumed to use condoms less frequently and to seek VCT less frequently, but are not assumed to modify their rate of partner change as a result of being vaccinated. The ASSA2002 Vaccine model may therefore slightly understate the extent of behavioural disinhibition, as discussed in section 6.3.
Appendix D: Comparison of 2015 and 2020 scenarios

Figure D.1 below shows a comparison of the numbers of individuals who would be vaccinated under distribution strategies I to IX, assuming HIV screening is conducted. Results are shown for two scenarios: the scenario in which the vaccine is distributed in 2015 and the scenario in which the vaccine is distributed in 2020. In general, there is very little difference between the two scenarios in terms of numbers of vaccinated individuals. Numbers of adolescent learners vaccinated would be slightly lower in 2020 than in 2015, as declines in fertility rates over time will lead to smaller numbers of new school entrants each year.

![Figure D.1: Comparison of numbers of vaccinated individuals in the 2015 and 2020 scenarios, strategies I to IX, with screening](image)

It is also clear that the year in which the vaccine is introduced has little effect on the number of infections averted per vaccinated individual, over the first six years following the introduction of the vaccine. This is demonstrated in Figure D.2, which shows infections averted per individual receiving vaccine B, for the same scenarios as considered in Figure D.1.

![Figure D.2: Comparison of HIV infections averted per vaccinated individual in the 2015 and 2020 scenarios, strategies I to IX](image)

Infections averted are calculated over the 2015-20 period in the 2015 scenario and over the 2020-25 period in the 2020 scenario. Vaccine B is assumed to be distributed with screening in all scenarios.
HIV vaccine requirements for the population as a whole are also relatively insensitive to the time at which the vaccine is introduced. Figure D.3 shows that for each of vaccine distribution strategies 1 to 4, the number of vaccinated individuals over the 2015-20 period (in the 2015 scenario) is similar to the number of vaccinated individuals in the 2020-25 period (in the 2020 scenario). The effect of vaccine B in the two time periods is also similar, as Figure D.4 shows.

Figure D.3: Comparison of numbers of vaccinated individuals in 2015 and 2020 scenarios, strategies 1 to 4
Numbers of vaccinated individuals are calculated over the 2015-20 period in the 2015 scenario and over the 2020-25 period in the 2020 scenario.

Figure D.4: Comparison of % reduction in new HIV infections in the 2015 and 2020 scenarios, strategies 1 to 4
% reduction in new HIV infections, due to vaccine B, is calculated over the 2015-20 period in the 2015 scenario and over the 2020-25 period in the 2020 scenario.