Modeling the potential impact of a partially effective HIV vaccine in a generalized African HIV-1 epidemic: Evaluating strategies for HIV vaccine use

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Abstract:

In anticipation of an effective HIV vaccine, it is important that vaccination strategies be developed to assure that vaccine resources are used effectively and efficiently. Because the worldwide demand for vaccine can be anticipated to exceed initial production capacities, it is essential that countries develop strategies for achieving optimal HIV control with limited vaccine supplies. This investigation employs a user-friendly computer simulation based on a deterministic mathematical model to analyze vaccine distribution strategies for a hypothetical generalized African HIV epidemic. Data from the Kenyan HIV epidemic was used to support the selection of model parameters. Vaccination strategies with a fixed supply of a partially effective HIV vaccine were investigated. The findings demonstrate that the population level impact of a vaccination program can vary dramatically as a result of the HIV vaccination policies enacted. In the scenarios presented, vaccination targeted to high-risk females is superior to the other strategies evaluated by the criterion of HIV infections prevented per person vaccinated. Exclusive vaccination of pre-adolescents, in particular, is shown to perform poorly for the near-term future. Modeling efforts of this sort could be used to help public health policy-makers evaluate HIV vaccination strategies.

Keywords: Compartmental model, vaccination policy, computer simulation, vaccine effects, uncertainty analysis.
INTRODUCTION

Since the start of the HIV pandemic, an estimated 60 million persons have been infected with HIV, of which 20 million persons have died of HIV/AIDS (1-2). Consequently, AIDS is now the fourth leading cause of death in the world and the leading cause of death in Sub-Saharan Africa (3). Such statistics highlight the vital importance that an effective prophylactic HIV vaccine could have in achieving control over this pandemic. Once an effective HIV vaccine has been developed, worldwide demand for vaccine will very likely exceed initial production capacities. Under such conditions it will be important that policy-makers and public health planners utilize appropriate strategies to ensure that scarce HIV vaccine resources are optimally employed against the HIV pandemic. These issues are likely to be particularly important in Sub-Saharan Africa, where an estimated 71 percent (28.5 million) of the persons living with HIV/AIDS reside, and where generalized HIV epidemics result from heterosexual transmission in the general populations of sexually active adults (1, 4).

The development and planning of disease control interventions and evaluation of associated public health strategies can be greatly facilitated by the use of mathematical and computer simulation models (5). Such modeling methods play a particularly important role in the evaluation of efforts to control infectious diseases because of the inherently nonlinear transmission dynamics that produce indirect protective effects for persons not receiving the intervention (6-10). Because mathematical and computer simulation models can be used to estimate these indirect effects, such models provide public health planners and policy-makers with an important means of estimating the total impact of public health interventions such as vaccination (11). The success of these
methods in providing both general insights and specific direction for implementing intervention programs has resulted in a steady increase in their use for vaccination policy analysis (12-16). When infectious disease transmission models are combined with optimization methods, it becomes possible to investigate optimal vaccine distribution policies with limited vaccine resources, as was done for influenza control by Longini et al. (17).

This paper describes the use of a deterministic mathematical model to analyze vaccine distribution strategies for a generalized HIV epidemic in Africa. The model described was implemented as part of a Joint United Nations Programme on HIV/AIDS (UNAIDS) and U.S. Centers for Disease Control and Prevention (CDC) project to develop a user-friendly computer simulation package to help public health officials evaluate potential HIV vaccination strategies in several countries experiencing different HIV epidemic stages and epidemiology. We first discuss the mathematical model for HIV transmission, vaccine effects, and vaccine distribution which was developed for this project. We then present some initial results on model validation, and comparative analyses of several vaccination strategies which demonstrate the robust nature of the results in spite of uncertainty in the computer simulation input parameters.

METHODS

Mathematical Model

The mathematical model consists of a nonlinear system of differential equations that are used to model the HIV epidemic. The model builds upon an extensive literature of epidemic modeling using differential equation compartmental models (5, 18-19). The
model represents the number of individuals within a population and their conditions (or states) at a particular point in time using variables in the differential equations. Individuals in each state (infected versus susceptible, vaccinated versus unvaccinated, etc.) are represented by a variable corresponding to a homogenous compartment. Their transitions between compartments are governed by terms in the differential equations that describe the instantaneous rate of change in the number of individuals in each state.

In epidemic modeling terminology, the model is a multi-infection stage, multi-mixing group, Susceptible-Infectious (SI) model with vital dynamics. Multi-infection stage refers to the use of multiple compartments to model different stages of HIV infection (20-23). Multi-mixing group refers to the representation of multiple groups or strata that make contact with each other in the HIV transmission process (20,24). SI refers to the two immune states possible in the HIV transmission process, and the term vital dynamics refers to the fact that new individuals can both enter and leave the population over time. A prototype of the model has been described previously (25). The mathematical model presented here is specifically designed to represent a generalized African HIV epidemic and is a subset of the more general model developed to represent HIV epidemics in other countries and scenarios. A brief overview of the model is presented here, with the model details described in the technical appendix.

Figure 1 illustrates the possible states in the vaccination model and the possible transitions that individuals can make between these states. Descriptions of each state represented in the model and the notation used in the equations describing the model are included in Table 1. The arrows in the illustration indicate the possible instantaneous transitions between states.
Figure 1. Compartmental representation of the mathematical model for HIV transmission and HIV vaccine effects indicating the possible states for individuals in the population. The compartments represent risk activity life-stages, immune, and disease states; while the arrows between compartments indicate the possible transitions between states. Overlapped compartments indicate that multiple mixing group strata exist for the compartment.
Table 1. Variable names and notation for mathematical model with input parameter values and distributions for uncertainty analyses.

<table>
<thead>
<tr>
<th>Variable Names and Model Parameters</th>
<th>Notation</th>
<th>Best Fit Model Parameters</th>
<th>Uncertainty Analysis Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>State Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children younger than HIV vaccination age</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preadolescents of vaccination age, not yet engaged in sexual activity</td>
<td>B</td>
<td></td>
<td></td>
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<tr>
<td>Susceptible individuals</td>
<td>S</td>
<td></td>
<td></td>
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<tr>
<td>HIV infected individuals</td>
<td>H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals receiving sterilizing immunity from vaccination</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative deaths from AIDS</td>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals past period of significant partner change activity</td>
<td>Z</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants with pediatric AIDS</td>
<td>I</td>
<td></td>
<td></td>
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<tr>
<td>Cumulative deaths from pediatric AIDS</td>
<td>P</td>
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<tr>
<td><strong>Vaccination Status Superscripts</strong></td>
<td></td>
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<tr>
<td>Unvaccinated</td>
<td>U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td>V</td>
<td></td>
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<tr>
<td><strong>Mixing Group Indices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male heterosexuals, Low sexual partner-change level {M,L}</td>
<td>i = 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male heterosexuals, High sexual partner-change level {M,H}</td>
<td>i = 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female heterosexuals, Low sexual partner-change level {F,L}</td>
<td>i = 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female heterosexuals, High sexual partner-change level {F,H}</td>
<td>i = 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV Infection Stage Indices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary HIV infection</td>
<td>r = 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic HIV infection</td>
<td>r = 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-AIDS stage HIV infection</td>
<td>r = 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS Stage HIV infection</td>
<td>r = 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial Population Strata Size and Composition Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial size of children strata</td>
<td>C(t₀)</td>
<td>63000</td>
<td></td>
</tr>
<tr>
<td>Initial size of pre-sexually active preadolescents/adolescents</td>
<td>B(t₀)</td>
<td>8400</td>
<td></td>
</tr>
<tr>
<td>Initial size of the sexually active population</td>
<td>A(t₀)</td>
<td>91600</td>
<td></td>
</tr>
<tr>
<td>Initial size of post-sexually active population</td>
<td>Z(t₀)</td>
<td>35400</td>
<td></td>
</tr>
<tr>
<td>Proportion of females in the sexually active population</td>
<td>F</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>High sexual partner-change proportion in {Males}</td>
<td>hₘ</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>High sexual partner-change proportion in {Females}</td>
<td>hᵢ</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td><strong>Initial HIV Infection Seeding Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial HIV infection proportion for {M,L} mixing strata</td>
<td>γ₁</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Initial HIV infection proportion for {M,H} mixing strata</td>
<td>γ₂</td>
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<td></td>
</tr>
<tr>
<td>Initial HIV infection proportion for {F,L} mixing strata</td>
<td>γ₃</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Initial HIV infection proportions for {F,H} mixing strata</td>
<td>γ₄</td>
<td>0.03</td>
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</tr>
<tr>
<td><strong>State-Space Durations and Vital Dynamics Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood time span</td>
<td>δₜ</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>Post-vaccination, pre-sexually active time span</td>
<td>δₜ₀</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Sexual activity time span {M,L}</td>
<td>δ₁</td>
<td>440</td>
<td>437.78</td>
</tr>
<tr>
<td>Sexual activity time span {M,H}</td>
<td>δ₂</td>
<td>460</td>
<td>454.42</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Sexual activity time span {F,L}</td>
<td>$\delta_1$</td>
<td>392</td>
<td>387.29</td>
</tr>
<tr>
<td>Sexual activity time span {F,H}</td>
<td>$\delta_4$</td>
<td>115</td>
<td>114.64</td>
</tr>
<tr>
<td>Post partner-change time span</td>
<td>$\delta_2$</td>
<td>120</td>
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</tr>
<tr>
<td>Fertility Rate</td>
<td>$F$</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Average duration of the Primary infection stage of HIV</td>
<td>$\delta_{H1}$</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td>Average duration of the Asymptomatic infection stage of HIV</td>
<td>$\delta_{H2}$</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Average duration of the Pre-AIDS infection stage of HIV</td>
<td>$\delta_{H3}$</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Average duration of the AIDS infection stage of HIV</td>
<td>$\delta_{H4}$</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Average lifespan of a perinatally HIV infected infant</td>
<td>$\delta_p$</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Sexual Partner-Change Contact Rate Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average monthly sexual partner-change contact rate {M,H}</td>
<td>$C_1$</td>
<td>0.19</td>
<td>0.198</td>
</tr>
<tr>
<td>Average monthly sexual partner-change contact rate {M,L}</td>
<td>$C_2$</td>
<td>0.050</td>
<td>0.050</td>
</tr>
<tr>
<td>Average monthly sexual partner-change contact rate {F,L}</td>
<td>$C_3$</td>
<td>0.043</td>
<td>0.0440</td>
</tr>
</tbody>
</table>

**Transmission Probability Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline per partnership transmission probability</td>
<td>$\beta_0$</td>
<td>0.171</td>
<td>0.172</td>
</tr>
<tr>
<td>Perinatal transmission probability</td>
<td>$\beta_p$</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Initial reduction of transmission probability to and from {F,H} mixing group</td>
<td>$\pi_0$</td>
<td>0.333</td>
<td>0.334</td>
</tr>
<tr>
<td>Gender transmission effect {Males}</td>
<td>$g_M$</td>
<td>1.11</td>
<td>1.137</td>
</tr>
<tr>
<td>Gender transmission effect {Females}</td>
<td>$g_F$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HIV infection stage transmission effect {Primary infection}</td>
<td>$S_1$</td>
<td>8.2</td>
<td>8.306</td>
</tr>
<tr>
<td>HIV infection stage transmission effect {Asymptomatic infection}</td>
<td>$S_2$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HIV infection stage transmission effect {Pre-AIDS infection}</td>
<td>$S_3$</td>
<td>1.4</td>
<td>1.395</td>
</tr>
<tr>
<td>HIV infection stage transmission effect {AIDS infection}</td>
<td>$S_4$</td>
<td>3.34</td>
<td>3.365</td>
</tr>
<tr>
<td>Minimum reduction for {F,H} group transmission probability due to behavioral change</td>
<td>$\pi_m$</td>
<td>0.019</td>
<td>0.019</td>
</tr>
<tr>
<td>Time (in months) when the {F,H} transmission probability change began</td>
<td>$\tau_c$</td>
<td>42.5</td>
<td>39.87</td>
</tr>
<tr>
<td>Time (in months) before minimum reduction for {F,H} transmission probability is achieved</td>
<td>$\tau_{ac}$</td>
<td>135</td>
<td>132.07</td>
</tr>
</tbody>
</table>

**Vaccine Effect Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>$\alpha$</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>One minus Theta</td>
<td>$1-\theta$</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Vaccine Effect on Infectiousness</td>
<td>$VE_I$</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Vaccine Effect on Progression</td>
<td>$VE_P$</td>
<td>0.60</td>
<td></td>
</tr>
</tbody>
</table>

**Vaccination Program Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (in months) when vaccination program begins</td>
<td>$\tau_v$</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Target proportion for vaccination of pre-adolescent strata</td>
<td>$P_B$</td>
<td>1.00 or 0</td>
<td></td>
</tr>
<tr>
<td>Target proportion for vaccination of {M,L} mixing strata</td>
<td>$P_I$</td>
<td>1.00 or 0</td>
<td></td>
</tr>
<tr>
<td>Target proportion for vaccination of {M,H} mixing strata</td>
<td>$P_2$</td>
<td>1.00 or 0</td>
<td></td>
</tr>
<tr>
<td>Target proportion for vaccination of {F,L} mixing strata</td>
<td>$P_3$</td>
<td>1.00 or 0</td>
<td></td>
</tr>
<tr>
<td>Target proportion for vaccination of {F,H} mixing strata</td>
<td>$P_4$</td>
<td>1.00 or 0</td>
<td></td>
</tr>
<tr>
<td>Annual Vaccine Allocation (i.e., potential persons vaccinated)</td>
<td>$V$</td>
<td>500 or 7500</td>
<td></td>
</tr>
<tr>
<td>Priority indicator for vaccination of pre-adolescent strata</td>
<td>$I_B$</td>
<td>1 or 0</td>
<td></td>
</tr>
<tr>
<td>Priority indicator for vaccination of {M,L} mixing strata</td>
<td>$I_1$</td>
<td>1 or 0</td>
<td></td>
</tr>
<tr>
<td>Priority indicator for vaccination of {M,H} mixing strata</td>
<td>$I_2$</td>
<td>1 or 0</td>
<td></td>
</tr>
<tr>
<td>Priority indicator for vaccination of {F,L} mixing strata</td>
<td>$I_3$</td>
<td>1 or 0</td>
<td></td>
</tr>
<tr>
<td>Priority indicator for vaccination of {F,H} mixing strata</td>
<td>$I_4$</td>
<td>1 or 0</td>
<td></td>
</tr>
</tbody>
</table>
An important aspect of this model is the representation of vaccine effects. As a result of their vaccination, individuals in the model are subject to a mixed model of vaccine action and will develop either complete immunity to HIV infection or a homogenous partial reduction in their susceptibility (denoted as $\theta$) (26-30). A proportion $\alpha$ of the vaccinated individuals can experience fully effective vaccination making a transition from the unvaccinated susceptible compartment ($S^U$) to fully resistant vaccinated compartment ($R^V$). These individuals cannot be infected with HIV. The remaining proportion ($1-\alpha$) will experience partially effective vaccination and develop only a partial reduction in their susceptibility to infection, transitioning into the vaccinated susceptible state ($S^V$). The vaccine effect on susceptibility ($VE_S$) can, therefore, be defined as $1-((1-\alpha)\theta)$, representing the average relative decrease in susceptibility in all vaccinees as compared with the unvaccinated individuals (27).

Although these partially protected individuals ($S^V$) are not totally resistant to HIV infection, if they become infected, their infectiousness to others can be reduced through vaccine effects on infectiousness ($VE_I$ effects) (31-32) and their progression to the onset of AIDS can be delayed through vaccine effects on progression ($VE_P$ effects) (26).

Several recent publications discuss vaccine effects beyond the standard susceptibility effects, including $VE_I$ and $VE_P$ (33-37).

The compartments in Figure 1 that are represented with overlapped compartments are separated into distinct mixing group strata. For this generalized African model, heterosexual contact is the predominant mode of HIV transmission, and thus, male and female heterosexuals $\{M, F\}$ are the only mixing groups represented in this particular model version. These groups are further subdivided into one of two sexual partner-
change (or HIV infection risk activity) strata \{\text{High denoted as H, and Low denoted as L}\}. The partner change rates for these strata indicate the number of new sexual partners acquired per month and determine the HIV risk activity levels. A proportional sexual mixing formulation is used in model version presented (20,38). Pre-adolescent or adolescent individuals who are not yet involved in sexual activity may be immunized with HIV vaccine in the model depending on the HIV vaccination policies being considered. Two additional state space variables (not shown in Figure 1) are used to represent infants with pediatric AIDS (I) and the resultant cumulative deaths due to pediatric AIDS (P).

**Objective Functions**

This investigation focuses on two main objectives: 1) the number of HIV infections prevented, and 2) the number of HIV infections prevented per person vaccinated. The first objective function is appropriate when a fixed amount of vaccine will be distributed and the outcome of interest is simply the potential impact of this fixed amount of vaccine. The second objective function in the form of infections prevented per person vaccinated places an emphasis on achieving a maximal impact of vaccination with a minimal use of vaccine resources. This makes the second objective function valuable for evaluating the maximal global impact on the HIV pandemic during the initial period of limited vaccine availability that will exist while manufacturing capacity is constrained and competition for vaccine resources between nations might be anticipated. These objective functions are defined in a manner that combines both the direct effects (i.e., HIV infections directly prevented in persons who were vaccinated) and indirect effects (i.e., HIV infections
indirectly prevented by changes in the HIV transmission dynamics due to the vaccination program) (9,26,39-41).

Calculation of these overall effects is accomplished by simultaneously running two identical simulation models that differ only by the fact that in one of the models no vaccination program exists, while in the other the vaccination program is implemented as specified by the model parameters. This second simulation without the vaccination program can be described as the *counterfactual* simulation population (42). By comparing the two simulated populations: the actual population (i.e., the simulation with the vaccination program) and counterfactual population, the number of HIV infections prevented by the vaccination program can be determined.

**Computer Simulation Implementation**

The model is implemented as a user-friendly computer simulation in the ordinary differential/difference equation simulation package, Stella Version 7.01 (43). The HIV vaccine package has an easy to use graphical interface that allows the user to easily modify simulation parameters, and produce graphs and data files with simulation results. The interface was designed to be suitable for use by public health planners for developing an understanding of the potential impact of vaccination programs on the various program objectives.

**Comparative Strategy Analyses**

Comparative analyses were performed examining the impact of several potential vaccination strategies over time using the best-fit model parameters listed in Table 1. For
all of the analyses presented in this report, the vaccine modeled provides low efficacy for protection to infection ($V_{ES}=0.3$), but moderate protection against infection of sexual partners ($V_{EI}=0.6$) and disease progression ($V_{EP}=0.6$) in those persons infected despite vaccination. The hypothetical vaccination program considered in these analyses begins five years after the initiation of the HIV epidemic. Nine different strategies were investigated involving vaccination of: 1) high-risk females only, 2) low-risk females only, 3) high-risk males only, 4) low-risk males only, 5) pre-adolescents only, 6) high and low-risk females, 7) high-risk males and females, 8) pre-adolescents and high-risk males and females and 9) pre-adolescents, high and low-risk females and high-risk males. These comparative analyses were conducted for two levels of vaccine availability: 1) highly constrained (with enough vaccine to vaccinate only about 0.5% of the population per year), and 2) moderate constraint (with sufficient vaccine to vaccinate about 7.5% of the population per year). The analyses were conducted for both of the two objective functions mentioned previously, and these objective functions are plotted and ranked over the course of the simulation time (i.e., 40 years following the start of the epidemic).

To simplify this comparison of vaccination strategies, the following approach was used for the results shown here: 1) vaccine was allocated only to groups designated as high-priority (i.e., if excess vaccine beyond what was required for the priority vaccinations was available, it was stockpiled rather than being administered to the low-priority groups) and 2) vaccine acceptance was assumed to be 100 percent for all of the vaccine-eligible groups selected as a high-priority group for vaccination. The vaccine allocation strategies used in actual vaccination programs will be more complex, with varying levels of vaccine acceptance in different risk subpopulations, but restricting the
results in this fashion makes the comparison of the vaccination strategies targeting the
different groups easier to interpret.

**Validation and Uncertainty Methods**
Validation and uncertainty analyses for the model were conducted in an integrated
fashion which accommodated uncertainty in both the input parameters and the HIV
prevalence results used to validate the model. Validation analyses use surveillance data
from the HIV epidemic in the scenario country to assure that the simulation parameters
and model configurations selected can reproduce the antecedent HIV/AIDS epidemic
(44). Such analyses should take into consideration the quality of the reporting
information, potential biases associated with the surveillance methods and the precision
of the estimates. Because of this, we defined ranges of plausible simulation outcomes
rather than considering only those parameter sets that would exactly reproduce the
observed prevalence curves for each modeled subpopulation. This approach is further
supported by the fact that this simulation model is intended to support vaccination policy
analyses for generalized African HIV epidemics. We used sentinel surveillance data from
the National AIDS and STD Control Programme (NASCOP) of the Kenyan Ministry of
Health to estimate the HIV prevalence for females with high and low partnership-change
rates (mixing groups \{F,L\} and \{F,H\}) and for males with high partner-change rates
(mixing group \{M,H\}) (45). Females in the high partner-change rate mixing group
(\{F,H\}) included both commercial sex workers and women engaged in significant
partner-change behavior, but who were not involved in commercial sex work. The HIV
prevalence for this \{F, H\} mixing group was estimated by weighting data from
commercial sex workers and women attending antenatal clinic surveillance sites proportionally. Antenatal clinic data was used exclusively to estimate HIV prevalence for the females with low partner-change rates (45). HIV prevalence data from STD treatment sites was used to represent the male high partner-change mixing group (\{M,H\}). The prevalence data for each group was smoothed by running averages taken over time in order to adjust for random variation or possible variations caused by changes in survey sampling methods over time.

We assessed the validity of each set of simulation parameters by generating a lack-of-fit statistic that compared the closeness of each simulation run with the observed prevalence data. Sets of simulation parameters which perfectly reproduced the observed prevalence curves, thus minimizing the absolute deviation of the simulation data from the prevalence data over time for each mixing group, would receive a lack-of-fit score of zero. Ranges of lack-of-fit statistics that were considered consistent with plausible epidemic outcomes for a generalized African HIV epidemic were retained as “near-fit” simulations.

Uncertainty analyses were also conducted because many of the input parameters for the simulation model are imprecisely known and many combinations of these parameters could be capable of reproducing the antecedent HIV/AIDS epidemics. These analyses repeatedly sampled sets of input parameters from probability density functions to determine whether the results would be affected by the uncertainty in the input simulation parameters (46). Plausible values for the input parameters were obtained either from the available published literature (with parameters estimates coming from Kenyan studies, then other African sources, and, finally, non-African sources, in order of preference), or
they were estimated using unpublished data from NASCOP when possible. Such uncertainty analysis methods are used frequently for policy evaluations employing epidemiologic models, providing some assurance regarding the generalizability of the policy recommendations in spite of the uncertainty in the model parameters (47-51).

Input parameters were sampled from normal distributions centered on initial estimates with standard deviations set to include plausible ranges for the input parameters. Only those parameter sets that produced prevalence results consistent with a “near-fit” to the Kenyan epidemic were retained as validated parameter sets, and simulations were repeatedly run with sampled parameters until 200 near-fit simulations were obtained. The column labeled “Best-Fit” in Table 1 provides the parameter estimates associated with the best fit to the Kenyan prevalence data for the {M,H}, {F,L} and {F,H} mixing groups for a hypothetical population of 100,000 individuals. For 16 of the parameters, a mean and standard deviation are listed; these parameter values were allowed to vary for each simulation run and the parameter values were sampled as described. The sampled parameters are related to sexual activity time spans, sexual partner-change contact rates, and transmission probability parameters. For those simulations where the fit to the Kenyan prevalence curves was considered a near-fit validation, the means and standard deviations are provided in Table 1. Where only the best-fit parameter is listed, the parameters were the best-fit parameter was fixed for the 200 near-fit validated simulation runs.

The uncertainty analyses were conducted with time horizons of five and ten years after the vaccination program was initiated because it was considered likely that
manufacturing capacity can be developed sufficiently to meet worldwide vaccine demand within these approximate time frames.

RESULTS

Model Validation

The fits between the Kenyan prevalence data and the simulation run results for the period from January, 1980 to June, 2001 are provided in Figure 2 for the 200 near-fit simulations. Figure 2A illustrates the fits for females with high partner-change contact rates (mixing group \{F,H\}); Figure 2B illustrates the fits for females with low partner-change contact rates (mixing group \{F,L\}); and Figure 2C illustrates the fits for males with high partner-change contact rates (mixing group \{M,H\}). As can be seen in the figure, a range of input parameters and associated results were retained as being consistent with a generalized African HIV epidemic in order to accommodate uncertainty in both the input parameters and prevalence results.

Comparative Strategy Analyses

The results from the comparative strategy analyses performed using the best-fit model parameters are illustrated in Figure 3. Figure 3A provides the results for the objective function of total HIV infections prevented when the annual vaccine allocation is sufficient to vaccinate 500 persons. Figure 3B provides the results for the contrasting objective function of HIV infections prevented per 100 persons when 500 persons are vaccinated annually. Figure 3C provides the results for the objective function of total HIV infections prevented when the annual vaccine allocation is sufficient to vaccinate
Figure 2A. Females with high partner-change contact rates \{F,H\}

Figure 2B. Females with low partner-change contact rates \{F,L\}
Figure 2C. Males with high partner-change contact rates \{M,H\}

Figure 2. Model validation and uncertainty results. The smoothed Kenyan prevalence data from January, 1980 to June, 2001 and the best fitting simulation run from 200 “near-fit” runs are shown. Sets of input parameters were randomly sampled using multivariate uncertainty analysis methods and 200 input parameter sets producing “near-fits” to the prevalence data were retained. The distribution of 200 prevalence curves from these near-fit simulation runs are illustrated by shaded data clouds for the non-parametric kernel probability density estimates.
Figure 3A. Total HIV infections prevented with annual vaccine allocation for 500 persons
VES=0.3, VEI=0.6

Figure 3B. HIV infections prevented per 100 persons with annual vaccine allocation for 500 persons
VES=0.3, VEI=0.6
Figure 3C. Total HIV infections prevented with annual vaccine allocation for 7,500 persons
VEF=0.3, VEI=0.6

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

Figure 3. Comparative analyses of targeted vaccination strategies using the best fitting input parameters.
7,500 persons, and Figure 3D provides the results for the contrasting objective function of HIV infections prevented per 100 persons when 7,500 persons are vaccinated annually. Under the conditions used in Figure 3A, vaccinating high-risk females consistently prevents the greatest number of HIV infections during the time horizon examined. Other strategies, such as vaccinating: 1) high-risk males; 2) high-risk males and females; or 3) pre-adolescents plus high-risk males and females all perform similarly to each other, but prevent comparatively fewer HIV infections than vaccinating only high-risk females. Also notable is the particularly poor performance of the strategy of vaccinating pre-adolescents only under these conditions. When the objective of HIV infections prevented per person vaccinated is considered as shown in Figure 3B, the results change somewhat. Vaccinating high-risk females continues to be the top-ranked strategy for the entire time horizon examined, although the relative advantage of this strategy diminishes somewhat over time. It should also be noted that the strategy of vaccinating high-risk females exceeds the level of 100 HIV infections prevented per 100 persons vaccinated at the point 15 years after the vaccination program was initiated and remains above this level thereafter. Additionally, it should be noted that the strategy of vaccinating only pre-adolescents, which ranked eighth out of the nine strategies for the entire time horizon with regard to HIV infections prevented in Figure 3A, now increases in relative efficiency over the time horizon in Figure 3B.

Figures 3C and 3D illustrate the results when only a moderate vaccine availability constraint exists allowing vaccination of about 7.5% of the vaccine eligible population per year. As can be seen in Figure 3C, where the objective is to limit the total number of HIV infections in the population and additional vaccine availability exists, the strategy of
vaccinating only high-risk females no longer performs as well as other strategies involving the vaccination of multiple risk groups. The strategies of vaccinating high-risk males and females; high-risk males and females, and pre-adolescents; or all females, high-risk males, and pre-adolescents are all superior and closely competitive strategies for preventing total numbers of HIV infections. However, when efficient use of vaccine resources is considered as the primary objective as shown in Figure 3D, vaccination of only high-risk females remains the top-ranked strategy with no closely competitive strategies. A number of cross-overs in the relative rankings of these strategies over time can also be seen in figure 3D, emphasizing the importance of considering a particular time horizon for any decision criterion in comparing strategies.

Uncertainty Analyses

The uncertainty analyses are provided in Figures 4 and 5 which present box-plots for the distributions of the two objective functions five years after the initiation of the vaccination program for the 200 near-fit simulations with annual vaccine allocations of 500 persons and 7,500 persons, respectively.

The results for the objective functions of 1) total HIV infections prevented, and 2) the number of HIV infections prevented per one hundred persons vaccinated, are presented in Figures 4A and 4B, respectively. Under the conditions of extreme vaccine constraint where only 500 person can be vaccinated per year, the strategy of vaccinating high-risk females only stands out as superior in preventing total number of HIV infections in spite of the uncertainty in the values of the 16 sampled input parameters,
while the strategies of vaccinating only pre-adolescents, or low-risk males or females, are notably inferior in these analyses. The same general patterns are observed in Figure 4B.

For the moderate vaccine availability constraint conditions (i.e., enough vaccine to vaccinate 7,500 persons per year), Figures 5A and 5B present the results for total HIV infections prevented and HIV infections prevented per 100 persons vaccinated, respectively. In Figure 5A, several other vaccination strategies overlap considerably with the high-risk female vaccination strategy due to uncertainty in the 16 sampled model parameters. The strategies of vaccinating only low-risk males, low risk females or pre-adolescents, however, continue to appear clearly inferior to the other vaccination strategies considered in these analyses. In contrast, in Figure 5B reveals that the superiority of the high-risk female strategy to any of the other vaccination strategies considered is even more pronounced than it was under the conditions of extreme vaccine constraint.

DISCUSSION

Initial supplies of the first HIV vaccines are likely to be greatly constrained relative to the potential demand due to the lead times required to develop full-scale manufacturing capacities. This investigation examined potential vaccine distribution strategies for a generalized African HIV epidemic with moderate or severe limitations on vaccine availability as part of a larger project to examine these issues for several different epidemic scenarios in developing countries. Input parameter ranges were selected to be consistent with the Kenyan HIV epidemic and results were validated by the ability of sampled sets of input parameters to broadly produce near-fits to Kenyan HIV prevalence
Figure 4A. Total HIV infections prevented

<table>
<thead>
<tr>
<th>fe = Females, High &amp; Low</th>
<th>mh = Male High</th>
</tr>
</thead>
<tbody>
<tr>
<td>fh = Female High</td>
<td>p = Pre-Adolesc. only</td>
</tr>
<tr>
<td>fl = Female Low</td>
<td>ph = Pre-Adol., Male &amp; Female High</td>
</tr>
<tr>
<td>hi = Male &amp; Female High</td>
<td>px = Pre-Adol., Male High, Females</td>
</tr>
</tbody>
</table>

Figure 4B. HIV infections prevented per one hundred persons vaccinated

Figure 4. Uncertainty Analyses for the 200 near-fit simulations under extreme vaccine constraint (annual vaccine allocation for 500 persons). Results presented for period five years after the initiation of the vaccination program.
Figure 5. Uncertainty Analyses for moderate vaccine constraint (annual vaccine allocation for 7,500 persons). Results presented for period five years after the initiation of the vaccination program.
data. The simulation experiment scenarios reveal several results important for policy-makers and planners seeking to develop sound HIV vaccination strategies that will most significantly impact the epidemic despite constrained vaccine resources.

Even a small quantity of a “low-efficacy” (e.g., VE_S=0.3, VE_I=0.6) HIV vaccine could have a dramatic impact on preventing HIV infections, if optimally distributed in a scenario population. In the analyses shown in Figure 3B, where only about one half of a percent of the total population could be vaccinated per year, the vaccination strategy focused on high-risk females projected more than one infection prevented per person vaccinated. Such indirect effects, whereby persons who are not vaccinated are protected from infection, can have profound impacts on the overall population impact of a vaccination program (11,52,53). Strategies that maximize these indirect effects will be much more successful at the population level, especially if vaccination brings the basic reproduction number below one, thus halting epidemic transmission (5,54). In contrast, the comparative results demonstrated that sub-optimal vaccine allocation strategies would be relatively ineffectual in reducing the epidemic. These findings further support the results of previous HIV vaccine modeling endeavors which have indicated that the impact of low VE_S HIV vaccines could be quite substantial (55-56) and emphasize the importance of also measuring potential VE_I and VE_P effects (or their surrogates) in assessments of the potential population impact of HIV vaccines (31-33,35,37,57-59).

The strategy of vaccinating high-risk females appears to be superior when judged by the criteria of number of infections prevented per person vaccinated, both when vaccine resources are quite limited and when they are more plentiful. Allocating vaccine to other groups that do not play such critical roles in the transmission of HIV slows the
rate of vaccine penetration in the high-risk females when vaccine resources are constrained. As a result, these strategies, which split the available vaccine with less epidemiologically influential groups, result in fewer total infections prevented. When the criterion of total infections prevented is used, however, the strategy of vaccinating high-risk females is only superior when vaccine resources are scarce.

Other strategies are seen to consistently perform poorly under the conditions examined by this model. While it is easily anticipated that vaccinating low-risk males and females would be less viable strategies, the poor short-term performance of targeting HIV vaccination only to pre-adolescents is an important finding.

In addition to the specific results for the vaccine strategy scenarios analyzed here, this modeling can contribute to an understanding of several important issues for deciding a vaccine strategy. First, the criteria used to evaluate the vaccine strategies influences their rankings, so policy makers must be clear about their objectives. The number of HIV infections prevented per persons vaccinated is an appropriate objective when maximal impact utilizing a minimal amount of vaccine is sought. Alternatively, the total number of HIV infections prevented would be more appropriate when the concern is the maximal number of HIV infections with a fixed amount of vaccine. The former objective (maximal impact for minimal vaccine) might be particularly advantageous during the initial stages of vaccine availability when vaccine resources will likely be highly constrained. However, as vaccine resources become more widely available, the primary objective would likely evolve to minimizing the total number of HIV infections in each population.
Time horizons for measuring effect of strategies can also influence the outcomes, as demonstrated by the occurrence of points at which different strategy outcomes cross over each other as time advances in Figures 3B and 3D. These “cross-overs” in the optimal vaccination strategy at different points in time typically involve policies that set pre-adolescent children as a high priority, since the benefits of vaccinating these preadolescents are not realized until much later in the epidemic. If new HIV vaccine candidates were to become available within the decade after first vaccine introduction, then it would most likely be inappropriate to make policy decisions based on a 30-year time horizon.

Although not illustrated by the analyses presented here, optimal distribution of limited vaccine supplies among the risk groups in a population will also be dependent on the stage of the HIV epidemic when vaccination is initiated, the sexual mixing behavior between and among the risk groups, the specific VE$_S$, VE$_I$ and VE$_P$ values for the vaccine in question, the levels of vaccine acceptance within the risk groups, and the feasibility of vaccine distribution to the risk groups. Research on vaccine acceptance levels and the feasibility of vaccine distribution among various risk groups will be of particular importance. Previous experience with Hepatitis B vaccine acceptance among risk groups such as men who have sex with men or sexually transmitted disease patients has demonstrated that achieving high vaccination proportions can be difficult to accomplish in some risk groups (60-61). A growing literature regarding factors influencing HIV vaccine demand and acceptance is developing (62-69), which will be critical to the formulation of sound vaccination policies. While several studies have suggested that vaccine effects on susceptibility to HIV infection may influence the level of acceptance
of hypothetical vaccines, it will be important to assess the relative value associated with vaccine effects reducing infectiousness or progression of disease, and how these vaccine effects influence vaccine acceptance among potential recipients.

Furthermore, while it is useful for policy-makers to be made aware of those risk groups in which vaccination would have the greatest public health benefits, implementing targeted vaccination to particular risk groups is likely to be much more complicated, both logistically and ethically. Identifying individuals with high partnership-change rates would be difficult in practice, particularly for adolescents whose future risk behavior is not highly predictable. Also, attention must be given to the issues of whether targeted vaccination for high risk groups may result in the stigmatization of members of these groups, placing them at risk for unattended adverse outcomes and limiting vaccine acceptance in an attempt to avoid stigma (70). Because of these issues, the targeting of risk groups for vaccination will most likely be best achieved by social marketing of vaccination to high risk groups (71-72), public subsidies for vaccination costs for these groups, and by policies assuring vaccine access for epidemiologically significant risk groups if it is threatened by demand from non-targeted groups. If targeted vaccination programs are pursued, it may be important for governments to implement legal reforms and communications campaigns that combat stigma against high risk groups and community involvement of risk groups in vaccination program implementation to ensure successful and equitable vaccine distribution.

This paper adds to a growing body of literature modeling the potential impact of HIV vaccines in at-risk populations (66, 73-76). As in all such modeling endeavors, it is not possible, or even desirable, to abstract all aspects of reality that might be important
for an examination of potential HIV vaccine impact. Limitations of the model include a limited age structure, the assumption of random mixing between sexual contacts, limited levels of risk heterogeneity, and life-long risk group assignment. These modeling limitations could effect the degree to which these results would reflect actual vaccination program impacts. For example, it is well appreciated that differential equation models representing sexual contacts with randomly mixing partnerships will over-represent the speed and intensity of an epidemic (77-80). Also, the scale-up of prevention strategies that increase knowledge of serostatus in populations may affect both risk behavior and sexual mixing. Fortunately, concerns about the impact of such issues are mitigated somewhat by our comparison of otherwise identical simulations with and without vaccination programs, so that the vaccination strategies being evaluated are being compared on similar “playing fields” using equivalent models.

Despite the use of uncertainty methods for some of the variables, the results obtained in these scenarios are dependent on the specific parameters used for these simulations. For example, when applying this model to locations where effective mother to child transmission programs exist, the parameter for the perinatal transmission probability would quite likely need to be reduced and this would most likely alter the relative superiority of vaccination strategies targeting high-risk females. Therefore, a thorough examination of potential vaccination strategies for any particular country or location is likely to be computationally intensive and time-consuming in order to assure that results are robust and any strategy recommendations can be expected to perform well despite uncertainty in specific model parameters. Sensitivity analyses identifying input parameters that have significant effects on the optimal vaccination strategies (46) and
sophisticated Bayesian melding methods for validating and reconciling input parameters with epidemic prevalence data could be useful in future applications of this model (81).

In summary, a user-friendly computer simulation application has been constructed to allow policy-makers and planners to run simulation scenarios and investigate various vaccination strategies. The investigation presented here was conducted as part of a broader project conducting similar modeling investigations for Southeast Asia, and Latin America. Additional investigations including studies to evaluate the combined population effects of anti-retroviral therapy and vaccine strategies are also warranted (82-84) and a more sophisticated version of the software is planned to support the computer intensive modeling that will be required for in-depth planning by health departments and governmental agencies. It is hoped that the findings produced by this project will be used to help public health policy-makers and planners determine sound HIV vaccination practices for initially scarce vaccine resources in various epidemic scenarios.

APPENDIX

Model States and Transitions

The distinct mixing group strata in the model are represented subscripted with the letter \( i \); these indices are presented in Table 1. The second variable subscript \( r = 1,2,3,4 \) indicates the HIV infection stage for HIV infected individuals, corresponding to primary, asymptomatic, pre-AIDS, and AIDS stage. The model employs this multi-infection stage formulation because HIV transmission probabilities are related, at least in part, to viral
load levels, and vary significantly between the different stages of HIV infection (21,38,85-88).

The average durations spent in each HIV infection stage ($H_{i1},...,H_{i4}$) before transitioning into the subsequent infection stage are specified as parameters in the model (parameters $\delta_{H_{i1}},...,\delta_{H_{i4}}$). A single separate parameter ($\delta_P$) defines the average duration of pediatric AIDS in those infants who become HIV infected via perinatal transmission. For individuals with partially effective vaccination who become infected despite vaccination, their transition rate from the asymptomatic stage of HIV infection ($H_{i2}$) to the pre-AIDS stage ($H_{i3}$) is multiplied by a factor of $1-\text{VE}_P$, effectively delaying their transition into symptomatic HIV infection.

The vital dynamics of the model involve individuals entering the population as children who are not yet sexually active, and thus not at risk for HIV infection. We do not represent vertically infected children in the model vital dynamics because, in the absence of anti-retroviral therapy, very few of these children would survive to sexual maturity. Instead, vertical transmissions are counted separately in another part of the model. Births into the childhood state ($C$) are explicitly balanced with deaths due to non-AIDS related causes, although this can be easily modified via an additional parameter ($f$) in order to model populations which are undergoing significant population growth. Individuals remain in this childhood stage for a period of some years as specified by the duration parameter $\delta_C$. During the subsequent pre-adolescent/adolescent stage, individuals are still not involved in risk activity, but may be HIV vaccinated depending on the established HIV vaccination policies. The unvaccinated and vaccinated states are designated by $B^U$.
and $B^V$, respectively. The average length of time spent in these states is determined by the duration parameter $\delta_B$.

Following the onset of sexual activity, individuals are at risk for HIV infection and make the transition into one of three states in accordance with their vaccination status. Unvaccinated pre-adolescents/adolescents ($B^U$) move into the unvaccinated susceptible compartment ($S^U$) where subsequent state transitions can occur involving vaccination and/or HIV infection. Vaccinated pre-adolescents/adolescents ($B^V$) move into one of the two risk-active, vaccinated states ($S^V$ or $R^V$). Individuals in the $S^V$ state are only partially protected against HIV infection and are subject to possible subsequent state transitions involving HIV infection. Individuals in the $R^V$ state are fully protected against HIV infection and are not subject to possible subsequent state transitions involving HIV infection.

Individuals are also subject to removal from the sexual/IDU risk activity states by making a transition into the post-sexual/IDU activity state ($Z$) or, for those with AIDS, through AIDS related mortality into the absorbing states ($D^U$ and $D^V$). The durations of the sexual activity time spans for each of the $i$ mixing group substrata are given by the parameters $\delta_1, \ldots, \delta_6$. Individuals in the post-sexual/IDU activity state $Z$ remain in that state for an average duration of $\delta_Z$. Perinatal HIV infections (not illustrated in Figure 1), are modeled in the following fashion: HIV positive women are subject to a birth rate and a perinatal transmission probability for each birth, resulting in pediatric AIDS cases. The resultant pediatric AIDS cases ($I^V$ and $I^U$) are calculated separately for women who experienced partially effective vaccination or were unvaccinated, respectively. Both
groups of pediatric AIDS cases transition to their respective absorbing pediatric AIDS death states \((p^V, p^U)\) at a rate of \(1/\delta_P\).

**Sexual Mixing Behavior**

Sexual mixing behavior between and among the risk groups in the model is an essential determinant of epidemic dynamics. Accordingly, the differential equations for the HIV transmission process specify the contact patterns between the model substrata on the basis of the following characteristics: risk group \(\{M, F\}\), partner-change level \(\{L, H\}\), vaccination status \(\{Unvaccinated, Partially protected or something of the equivalent\}\) and HIV infection stage \(\{S, H_1, ..., H_4\}\). Only heterosexual contacts are represented in the model.

Because a proportional (random) mixing formulation is used in the model, members of each gender will select sexual partners from the opposite gender in proportion to the fraction of the total number of sexual contacts that are made by each opposite gender substrata. If \(c_j\) is used to denote the sexual activity contact rate for substrata \(j\) of size \(n_j\) in the opposite gender, then the proportion of contacts \(\rho_j\) made with members of substrata \(j\) is given by \(\rho_j = c_j n_j / \sum c_j n_j\) \((20, 38)\).

Because the sizes of each substrata will vary over time in reaction to recruitment into and migration from the state of sexual activity and due to AIDS-related mortality, a mechanism is required to balance the number of sexual acts between the two genders. This balancing mechanism is required to assure that the following logical condition is met: For every sexual contact made by a female with a male, there must also have been a sexual contact between a male and a female. For this model, gender-balancing was
enforced by allowing the contact rate in the high sexual activity females to vary in response to the sexual act demand created by the fixed contact rates and variable population sizes of the male substrata (89). Sexual contacts are modeled as sexual partnerships with all of the partnership’s sexual acts concentrated into a transmission probability for the sexual partnership (23,90). In order to allow for appropriate representation of both long-term partnerships which have multiple sexual contacts within the partnership and shorter-term sexual contacts occurring in more casual partnerships, the per-partnership transmission probabilities for more shorter-term partnerships are reduced from the base-line, per-partnership transmission probability ($\beta_0$) by a multiplicative model parameter ($\pi$). This allows the shorter-term sexual partnerships to have different per-partnership transmission probabilities than are used for the longer-term sexual partnerships. In those scenario populations for which data on the relationship between the average number of sexual contacts per partnership and the average number of partners per year is available, the values of $\beta_0$ and $\pi$ can be explicitly modeled as a function of the per sex-act transmission probability, the average number of sexual contacts in a partnership between members of the respective mixing groups and the partnership contact rates ($c_i$) of the mixing groups (23, 91).

**HIV Transmission Probabilities**

HIV transmission probabilities between infectious individuals and uninfected partners depend both on the infectiousness of the infected partners and on the susceptibility of the uninfected partners (92-93). Accordingly, the transmission probabilities in the model are specified dependent on the characteristics of both of the partners between whom HIV
transmission is possible. A multi-staged model of HIV infection was employed in order to allow HIV transmission probabilities to vary by HIV infection stage of the infective partner. HIV transmission studies and mathematical models of HIV epidemics provide evidence that the periods of greatest HIV transmissibility occur during primary and AIDS stage HIV infection, while the pre-AIDS stage is a period of intermediate infectivity and the asymptomatic HIV infection stage is the period of lowest transmissibility (22,37,85,94-96). The model employs a baseline per-sexual partnership transmission probability for infectives in the asymptomatic HIV infection stage ($\beta_0$) and three multiplicative parameters which modify the per-partnership transmission probabilities for infectives in the primary ($s_1$), pre-AIDS ($s_2$) and AIDS stages of infection ($s_3$).

HIV transmission studies have also sometimes observed higher male-to-female transmission probabilities than were observed for the converse female-to-male transmission probabilities (92-96). In order to allow for the possibility of differential infectivity by gender, an additional parameter ($g$) can be used to modify the base-line per-partnership transmission probability according to the gender of the infected sexual partner.

As previously mentioned, the per-partnership transmission probabilities for shorter-term partnerships are modified from the base-line per-partnership transmission probability ($\beta_0$) by a model parameter ($\pi$) which allows the short-term sexual partnerships to have different per-partnership transmission probabilities than are used for longer-term sexual partnerships. Additionally, in order to allow for behavior changes occurring in reaction to the HIV epidemic, the transmission probability for short-term partnerships with high-partner change females can be optionally parameterized so it will undergo a
logistically smoothed transition from its initial value to a new value at a specific point in time in the epidemic. The time required for this transition to occur can also be modified. This adaptive change in base-line transmission probabilities allows the model to represent changes in condom use over time in reaction to the AIDS epidemic in the population (97-98).

HIV transmission probabilities in the model are also modified by the HIV vaccination status of each of the partners. Individuals who experience fully effective vaccination and enter space state $R^V$ cannot be infected and thus play no role in the HIV transmission process. Individuals who experience partially effective vaccination, however, will experience a reduction in their susceptibility and infectiousness as specified by the vaccine effect parameters in the model. Let $\beta_{ij}$ denote the transmission probability between a susceptible individual in mixing group $i$ and an infective individual in mixing group $j$, based on their previously mentioned gender, infection stage and commercial sex worker traits. If the uninfected partner has experienced a partially effective vaccination, then the transmission probability $\beta_{ij}$ will be multiplied by a proportional reduction parameter ($\theta$). If the infected partner has experienced a partially effective vaccination, then the transmission probability $\beta_{ij}$ will be multiplied by a proportional reduction parameter $\phi$, where $\phi = 1-\text{VE}_1$. The transmission probability between a susceptible individual with partially effective vaccination and an infective individual who had been infected despite vaccination would thus be specified as $\theta\phi\beta_{ij}$ in the model. For perinatal HIV infections, partially effective vaccination reduces the perinatal transmission probability ($\beta_P$) from mother to infant by a factor of $\phi$, where $\phi = 1-\text{VE}_1$. 

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HIV Vaccination Process

There are five subpopulations in the model which are candidates for HIV vaccination: pre-adolescents who have reached the specified age for HIV vaccination, and risk-active susceptibles in the four mixing group strata ($S_i^U$). It should be recognized that the size of each of these subpopulations would continually change during the course of an epidemic simulation due to vital dynamics (birth and death processes) and epidemic dynamics. Accordingly, the HIV vaccination process in the model is formulated as a dynamic process that allows for the specification of fixed vaccination goals and adapts appropriately under circumstances where those goals are not achievable. The process allows for the specification of a target proportion of each of these groups to be vaccinated per time period. These are the maximal achievable proportions that policy-makers believe should/could be vaccinated in each risk group if sufficient vaccine was available to do so. Each group is also assigned a vaccination priority (High or Low) according to the specified vaccination policy.

When the simulation time has reached the specified vaccination time, the vaccination process begins. At the start of the vaccination program, an initial vaccine inventory becomes available and then continues to arrive at a specified rate ($\nu$) thereafter. Simultaneously, vaccine distribution commences with the specified target proportion of each subpopulation receiving the vaccine, if sufficient vaccine stock is available. The vaccine distribution method can be described as follows. Let $X(t)$ be the amount of available vaccine at time $t$. Additionally, let $V_T(t)$ be the amount of vaccine required to meet all of the target proportions, and $V_P(t)$ be the amount required to meet only the high
priority target proportions at time $t$. Then, if $X(t) > V_T(t)$ (i.e., if the available vaccine stock exceeds all of the target proportion requirements), then the excess vaccine is stockpiled for future distribution. Furthermore, when the available vaccine is only sufficient to meet the high priority targets (i.e., $V_T(t) > X(t) > V_P(t)$), then vaccine is allocated to the high priority groups preferentially, so that the high priority goals will be met and any additional vaccine is allocated to the low priority groups with their target proportions reduced proportionately by a factor $A_N$. Finally, if the available vaccine is insufficient to meet the high priority targets (i.e., $V_P(t) > X(t)$), then the low priority groups are not vaccinated and the high priority groups have their target proportions reduced by a factor $A_P$.

**Space State Initialization**

Initialization parameters in the model allow for the specification of the gender, and high sexual activity group proportions. In combination, these parameters determine the relative proportion of the sexually active population allocated to each of the four mixing groups at the start of the simulation and control the allocation of new members of these mixing groups as they arrive from the pre-sexually active state ($B$). Three additional parameters the determine sizes of the initial sexually active population ($C(t_0)$), the pre-sexually active population ($B(t_0)$) and the post-sexually active population $Z(t_0)$, respectively. Six infection initialization parameters ($\gamma_1, \ldots, \gamma_6$) indicate the proportion of each mixing group strata to be initialized as HIV infected when the simulation is started. Within each mixing group, the infected individuals are distributed between the four HIV infection states according to an initialization parameter which ranges between placing all
of the initial infectives in primary stage infection to allocating the initial infectives in
direct proportion to the relative durations of the HIV infection stages (i.e., \( \varepsilon_r = \frac{\delta_{H_r}}{\Sigma \delta_{H_r}} \))
(23).
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