SAND97-8209 • UC–407
Unlimited Release
Printed November 1996

A dynamic model of HIV transmission for evaluation of the costs and benefits of vaccine programs

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Prepared by
Sandia National Laboratories
Albuquerque, New Mexico 87185 and Livermore, California 94551
for the United States Department of Energy
under Contract DE-AC04-94AL85000

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A DYNAMIC MODEL OF HIV TRANSMISSION FOR EVALUATION OF THE COSTS AND BENEFITS OF VACCINE PROGRAMS

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ABSTRACT

We developed a dynamic model of HIV transmission to evaluate the costs and benefits of HIV vaccine programs in a population of homosexual men. We examined how changes in high-risk sexual behavior and the growth pattern of the epidemic influence the cost effectiveness of preventive vaccines, which prevent infection in uninfected people, and of therapeutic vaccines, which delay the onset of symptoms in HIV-infected people. We found that the effect of reductions in condom use are more important for therapeutic vaccines than for preventive vaccines, even if the preventive vaccines are imperfect. Therapeutic vaccines may increase HIV seroprevalence in the population, unless the vaccine program is accompanied by increased condom use. Epidemic growth patterns also influence the cost effectiveness of both preventive and therapeutic vaccines, but the effects are more pronounced for preventive vaccines. Preventive vaccines that are cost effective in a late-stage epidemic are even more cost effective—or even cost saving—in an early-stage epidemic.

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A DYNAMIC MODEL OF HIV TRANSMISSION FOR EVALUATION OF THE COSTS AND BENEFITS OF VACCINE PROGRAMS

1. INTRODUCTION

Estimates indicate that, worldwide, approximately 30 million people are infected with the human immunodeficiency virus (HIV), the virus that causes AIDS (WHO/UNAIDS 1996). In the United States, estimated 1995 health-care expenditures for HIV were projected to be approximately $15 billion (Hellinger 1992). Research on HIV vaccines costs an additional $136 million per year (Cohen 1994).

Although no HIV vaccines are yet available (Haynes 1993; Haynes, Pantaleo et al. 1996), many candidates have undergone phase I and II clinical trials (Dolin, Graham et al. 1991; Redfield, Birx et al. 1991; Wintsch, Chaignat et al. 1991; Graham and Wright 1995; World Health Organization 1995; Graham, Keefer et al. 1996). Both **preventive vaccines**, which prevent infection of uninfected people, and **therapeutic vaccines**, which delay or prevent the onset of symptoms or disease in infected individuals, are currently under development. Because therapeutic vaccines are likely to delay progression of HIV disease by reducing viral replication, they may also reduce the amount of virus in blood and other body fluids, and thereby reduce the probability that a vaccinated person will transmit HIV.

We analyzed the total health benefits and costs of a wide range of vaccine programs to determine the combinations of factors that would make such programs cost effective. We considered the type of the candidate vaccine (preventive or therapeutic), the characteristics of the vaccine (efficacy, duration of protection, cost), the change in infectivity induced by therapeutic vaccines, and the characteristics of the HIV epidemic. Our analysis simulates the effect of vaccine programs in a population of homosexual men using a dynamic compartmental model fitted to by data from San Francisco, CA. The HIV epidemic is growing at different rates in different risk groups, and researchers have shown that the timing of intervention programs can affect their cost effectiveness (Paltiel 1994); thus, we evaluated HIV vaccines in early-stage, rapidly growing epidemics, and in late-stage, slowly growing epidemics. Furthermore, researchers have suggested that vaccinated individuals may alter their risk behavior (Blower and McLean 1994; Brandeau and Owens 1994); thus, we considered the effect of those changes as well.

2. METHODS

We developed a dynamic compartmental model (Edwards 1995; Edwards, Shachter et al. 1995; Edwards, Shachter et al. 1995; Owens, Edwards et al. 1996) to simulate HIV transmission and progression in an adult population of homosexual men in San Francisco under different types of vaccine programs. We examined the vaccine programs in a late-stage epidemic with a high initial HIV seroprevalence and a low rate of new sexual contacts, and in an early-stage epidemic with a low initial HIV seroprevalence and a higher rate of new sexual contacts.

We examined both types of vaccines over a wide range of potential vaccine parameters. For preventive vaccines, we varied **efficacy** (how well the vaccine prevents the transmission of HIV in a partnership) between 10% and 90%, and **duration** (how long the protective effects of the vaccine persist) between 5 and 50 years. We assumed that at the end of the duration of the

vaccine, vaccinated individuals return to the unvaccinated population and thus become candidates for re-vaccination. We chose an upper end of 50 years to include vaccines that provide lifetime protection for members of the population that live that long. We modeled the effect of therapeutic vaccines as an increase in the **duration of the asymptomatic period** of HIV infection; we varied this increase from 1 to 10 years. We also evaluated therapeutic-vaccine–induced reductions in **infectivity** (the probability of transmission of the virus in a sexual partnership) from 0% (no reduction) to 90%. We define a sexual partnership to mean the entire duration of the relationship between the two individuals, not each particular act of sexual contact. Our analysis included a wide range of possible HIV vaccines. Because the purpose of the model is to compare the costs and benefits of different types of vaccines, we modeled vaccine programs as if these vaccines were available today.

We measured two outcomes of vaccine programs (Weinstein and Stason 1977):

1. The total discounted economic costs of the vaccination program (including direct costs of vaccination and indirect costs of medical care for all members of the population)
2. Total discounted quality-adjusted life-years (QALYs) lived by the members of the population. A **QALY** reflects the valuation that a year of life with HIV infection is less desirable than a year of life without HIV infection, and a year of life with asymptomatic HIV infection is more desirable than a year of life with symptomatic HIV infection. We quantify the relative desirability of these states of disease based on the results of a survey of physicians. (Owens and Sox Jr. 1990; Owens, Cardinalli et al. 1996)

We present the results for a 20-year period and for a longer (150-year) horizon. As other researchers have discussed as well (Paltiel and Kaplan 1993), some of the effects of vaccine programs persist well beyond a 20-year period and contribute significantly to the results for approximately 100 years, even though the effects are attenuated by the 5% discount rate. We realize that there are many uncertainties in such a long time frame, but present the results as an indication of the potential long-term effects of the vaccine programs.

A schematic of the model is shown in Figure 1. We modeled the adult male homosexual and bisexual population in San Francisco, which in 1987 consisted of an estimated 55,816 members and with an estimated HIV seroprevalence of 49.3% (Lemp, Payne et al. 1990). We considered only HIV transmission through sexual contact among the members of this population. The population is divided according to disease stage, screening status, and vaccination status into eight mutually exclusive, collectively exhaustive states. The unvaccinated states are: uninfected, unidentified infected asymptomatic, identified infected asymptomatic, infected symptomatic without AIDS, and AIDS. Uninfected men become infected based on interactions with infected men, and infected men progress through the stages of disease until death. Some infected asymptomatic men become identified through screening programs, and are modeled as a separate compartment because their behavior may be different from that of unidentified infected asymptomatic men. Men in each disease stage may have different degrees of infectiousness and different partnering and condom-use behavior.

The model for preventive-vaccine programs has two additional compartments: vaccinated uninfected and vaccinated unidentified infected asymptomatic. Vaccinated uninfected men have a lower probability of becoming infected and may have condom-use behavior different from that of uninfected men who have not received the vaccine. The compartment of vaccinated unidentified infected asymptomatic men is required because we assume that the preventive

vaccine is administered without an additional screening program; unidentified infected asymptomatic men appear uninfected, and thus may receive a preventive vaccine. The preventive vaccine will have no effect on these men, but may induce a behavior change, just as it may in uninfected men.

The model for therapeutic-vaccine programs also contains a compartment for vaccinated identified infected asymptomatic men. Men in this compartment may live longer, may be less likely to transmit the virus, and may have condom-use behavior different from that of identified infected asymptomatic men who have not received the vaccine. In sections 2.1 through 2.3, we describe the model in more detail, the outcome measures, and the implementation.

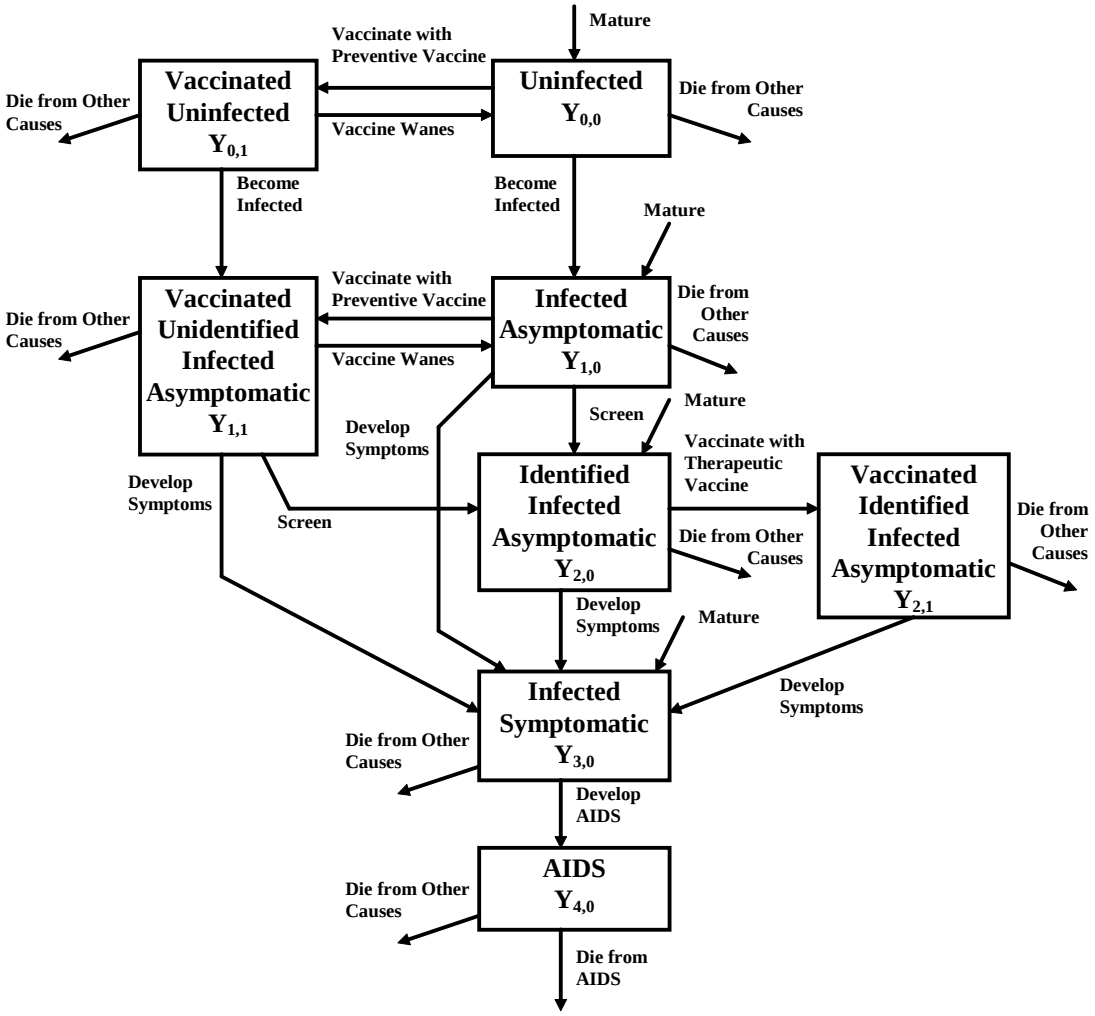

Figure 1. Model of the transmission and progression of HIV in a population of homosexual men under a vaccine program.

The population is divided into eight compartments according to disease stage and vaccination status. The arrows represent transitions into and out of the population and between compartments. The variables Yi,j represent the number of people in the (i,j)th compartment at time t. The text in section 2 contains an explanation, and Table 2 contains the model equations.

2.1 Model Description

The model variables are defined in Table 1. The model, shown in Table 2, consists of a set of deterministic differential equations that describe the flows of individuals between each of the health states: men entering and exiting the adult homosexual-male population; men becoming infected, screened, or vaccinated; and infected men progressing through the stages of disease.

Equation 1 represents the change in time in the number of uninfected men ($dY_{0,0}(t)/dt$). The number of uninfected individuals at time *t* equals the new arrivals, minus the people who receive the preventive vaccine and it takes, minus the people who die of non-AIDS-related causes, minus the people who become infected, plus the vaccinated uninfected people in whom the protective effects of the vaccine have waned. Young uninfected homosexual men enter the uninfected state when they mature into adulthood (reach 18 years of age) at the constant rate of I_0. Men leave the uninfected population by one of three means:

(1) By receiving a preventive vaccine that "takes" and moving to the vaccinated uninfected state (0,1). The number of uninfected people who receive the preventive vaccine and in whom it actually takes is represented by the second term in Equation 1, $\psi p_p Y_{0,0}(t)$, where ψ is the vaccine take and $p_p(t)$ is the time-dependent percentage of people who receive the preventive vaccine. (We set $p_p(t)$ equal to a constant percentage for 20 years and then equal to zero afterward.)

(2) By dying from non-AIDS–related causes. The number of uninfected people who die of non-AIDS-related causes is represented by the third term in Equation 1, $\mu Y_{0,0}(t)$, where μ is the non-AIDS-related death rate.

(3) By becoming infected with HIV and moving to the infected asymptomatic state (1,0). The annual number of uninfected people who become infected is represented by the fourth term in Equation 1, $p_0\lambda(t)Y_{0,0}(t)$, where p_0 is the average annual number of partnerships and $\lambda(t)$ is the probability of acquiring the infection from any one partner.

Previously vaccinated uninfected men (state 0,1) may return to the uninfected (unvaccinated) state (0,0) when the effects wear off from a vaccine that does not provide lifetime protection. The number of vaccinated uninfected people in whom the preventive effects of the vaccine wane is represented by the final term of Equation 1, $\omega Y_{0,1}(t)$, where ω is the reciprocal of the vaccine duration.

Equation 2 represents the change in time in the number of vaccinated uninfected men (state 0,1). Uninfected men (state 0,0) enter the vaccinated uninfected state when they receive a preventive vaccine that takes. Men leave the vaccinated uninfected state (1) by dying from non-AIDS–related causes, (2) by returning to the uninfected (unvaccinated) state (0,0) when the effects of the vaccine wear off, or (3) by becoming infected despite receiving the vaccine and moving to the vaccinated infected asymptomatic state (1,1).

The remaining state equations (3-8) have some common terms, which we explain here. Each equation for an unvaccinated state ($Y_{i,0}(t)$) has a maturation term (I_i) that represents the number of young homosexual men that enter state (i,0) when they reach the age of 18 years. Every equation has a term that represents the number of deaths due to non-AIDS–related causes

Table 1. Definition of Model Variables

Symbol	Definition
Disease Stage (i)	
$i=0$	Uninfected (HIV-)
$i=1$	Infected (HIV+) asymptomatic (unidentified)
$i=2$	Identified infected (HIV+) asymptomatic
$i=3$	Infected (HIV+) symptomatic
$i=4$	AIDS
Vaccination Status (j)	
$j=0$	Unvaccinated
$j=1$	Vaccinated
Disease-Stage Specific Variables	
$Yi,j(t)$	Number of people in disease stage i with vaccination status j
$\lambda(t)$	Probability of acquiring the infection at time t from any one partner
$\lambda_V(t)$	Probability of acquiring the infection at time t from any one partner, under behavior modifications due to vaccination
$\beta_{i,j}$	Infectivity
p_i	Contact rate
$1/\mu_{i,j}$	Duration of disease stage (in years)
q_i	Quality-adjustment for a year of life
c_i	Annual cost of medical treatment
$I_{i,j}$	Annual immigration
Outcome Variables	
C	Total discounted economic costs of the vaccination program (including both the direct costs of vaccination and the indirect costs of medical care for all members of the population)
Q	Total discounted quality-adjusted life-years (QALYs) lived by the members of the population(Weinstein and Stason 1977)
Preventive-Vaccine Variables	
$v_p(t)$	% of uninfecteds to vaccinate each year with preventive vaccine
κ_p	Per-person cost of the preventive vaccine
ψ	Vaccine take (% in whom vaccine has any effect)
ε	Vaccine efficacy (% of partnerships protected from infection)
$1/\omega$	Vaccine duration (years)
Δ_p	Change in condom use after preventive vaccine (1.25 = 25% increase, 0.75 = 25% decrease)
Therapeutic-Vaccine Variables	
$v_t(t)$	% of identified asymptomatic infecteds to vaccinate each year with therapeutic vaccine
κ_t	Per-person cost of the therapeutic vaccine
ψ	Vaccine take (% in whom vaccine has any effect)
$1/\mu_V$	Additional years asymptomatic under vaccine therapy
β_V	Change in infectivity of asymptomatics due to vaccine (1 = no change, 0.75 = 25% decrease)
Δ_t	Change in condom use after therapeutic vaccine (1.25 = 25% increase, 0.75 = 25% decrease)

Table 2. Model Equations[*]

State Equations

$$\frac{dY_{0,0}(t)}{dt} = I_0 - \psi\nu_p(t)Y_{0,0}(t) - \mu Y_{0,0}(t) - p_0\lambda(t)Y_{0,0}(t) + \omega Y_{0,1}(t) \quad (1)$$

$$\frac{dY_{0,1}(t)}{dt} = \psi\nu_p(t)Y_{0,0}(t) - \mu Y_{0,1}(t) - \omega Y_{0,1}(t) - p_0(1-\varepsilon)\lambda_v(t)Y_{0,1}(t) \quad (2)$$

$$\frac{dY_{1,0}(t)}{dt} = I_1 + p_0\lambda(t)Y_{0,0}(t) - \sigma\xi Y_{1,0}(t) - \nu_p(t)Y_{1,0}(t) + \omega Y_{1,1}(t) - \mu_{1,0}Y_{1,0}(t) - \mu Y_{1,0}(t) \quad (3)$$

$$\frac{dY_{1,1}(t)}{dt} = p_0(1-\varepsilon)\lambda_v(t)Y_{0,1}(t) + \nu_p(t)Y_{1,0}(t) - \omega Y_{1,1}(t) - \sigma\xi Y_{1,1}(t) - \mu_{1,1}Y_{1,1}(t) - \mu Y_{1,1}(t) \quad (4)$$

$$\frac{dY_{2,0}(t)}{dt} = I_2 + \sigma\xi\left(Y_{1,0}(t) + Y_{1,1}(t)\right) - \nu_t(t)\psi Y_{2,0}(t) - \mu_{2,0}Y_{2,0}(t) - \mu Y_{2,0}(t) \quad (5)$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t(t)\psi Y_{2,0}(t) - \mu_{2,1}Y_{2,1}(t) - \mu Y_{2,1}(t) \quad (6)$$

$$\frac{dY_{3,0}(t)}{dt} = I_3 + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1}\mu_{i,j}Y_{i,j}(t) - \mu_{3,0}Y_{3,0}(t) - \mu Y_{3,0}(t) \quad (7)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - \mu_{4,0}Y_{4,0}(t) - \mu Y_{4,0}(t) \quad (8)$$

Outcome Equations

$$C = \int_0^T \left[\kappa_p\nu_p\left(Y_{0,0}(t) + Y_{1,0}(t)\right) + \kappa_t\nu_{t_i}Y_{2,0}(t)\right]e^{-rt}dt + \int_0^T \sum_{j=0}^{j=1}\sum_{i=0}^{i=4} c_i Y_{i,j}(t)e^{-rt}dt \quad (9)$$

$$Q = \int_0^T \sum_{j=0}^{j=1}\sum_{i=0}^{i=4} q_i Y_{i,j}(t)e^{-rt}dt \quad (10)$$

($-\mu Y_{i,j}(t)$) and a term that represents the number of men whose disease progresses to the next stage ($-\mu_{i,j}Y_{i,j}(t)$). The following paragraphs explain the remaining terms in equations 3-8.

Equation 3 represents the change in time in the number of unidentified infected asymptomatic men (state 1,0). Men enter state (1,0) through infection ($p_0\lambda(t)Y_{0,0}(t)$), or because they believe that the protective effects of a vaccine have waned ($\omega Y_{1,1}(t)$). (Note that because these men were already HIV+, the only effect of the preventive vaccine was that the men may have altered their risk behavior. When they believe the protective effects of a vaccine have waned, these men revert to their unvaccinated risk behavior.) Men leave state (1,0) because they have been

[*] The Appendix contains equations for λ(t) in Table A2 and defines the initial conditions for the equations in Table A3.

correctly identified as HIV+ through a screening program ($-\sigma\xi Y_{1,0}(t)$), or because they receive the preventive vaccine and believe that it "took" ($-\nu_p(t)Y_{1,0}(t)$).

Equation 4 represents the change in time in the number of vaccinated unidentified infected asymptomatic men (state 1,1). Men enter state (1,1) through infection despite the vaccine ($p_0(1-\varepsilon)\lambda_v(t)Y_{0,1}(t)$), or because they receive the preventive vaccine and believe that it "took" ($\nu_p(t)Y_{1,0}(t)$). Men leave state (1,1) because they believe that the protective effects of a vaccine have waned ($-\omega Y_{1,1}(t)$), or because they have been correctly identified as HIV+ through a screening program ($-\sigma\xi Y_{1,1}(t)$).

Equation 5 represents the change in time in the number of identified infected asymptomatic men (state 2,0). Men enter state (2,0) because they have been correctly identified as HIV+ through a screening program ($\sigma\xi\left(Y_{1,0}(t)+Y_{1,1}(t)\right)$) and leave state (2,0) because they receive a therapeutic vaccine that "takes" ($-\nu_t(t)\psi Y_{2,0}(t)$).

Equation 6 represents the change in time in the number of vaccinated identified infected asymptomatic men (state 2,1). Men enter state (2,1) because they receive a therapeutic vaccine that "takes" ($\nu_t(t)\psi Y_{2,0}(t)$).

Equation 7 represents the change in time in the number of infected symptomatic men (state 3,0). Men enter state (3,0) when they develop symptoms in either the vaccinated (1,1) or unvaccinated (1,0) unidentified asymptomatic stages, or in the vaccinated (2,1) or unvaccinated (2,0) identified asymptomatic phases ($\sum_{i=1}^{i=2}\sum_{j=0}^{j=1}\mu_{i,j}Y_{i,j}(t)$).

Equation 8 represents the change in time in the number of men with AIDS (state 4,0). Men enter state (4,0) when they develop AIDS ($\mu_{3,0}Y_{3,0}(t)$).

The model allows for two additional states (3,1) and (4,1), representing the vaccinated infected symptomatic state and the vaccinated AIDS state, respectively, but we do not use these states in this analysis, because we consider therapeutic vaccines that affect only the asymptomatic period.

2.2 Outcome Measures

The equations that calculate the outcomes total discounted economic costs and total discounted QALYs gained are Equations 9 and 10, respectively, in Table 2. We determine the total discounted costs and QALYs accrued in the population without a vaccine program, and use that as a reference point for our analyses. Thus we consider the *difference* in the total discounted costs and QALYs accrued in the population with a vaccine program and the total discounted costs and QALYs accrued in the same population without a vaccine program.

We present the total net discounted costs and QALYs of each vaccine program as a point on a cost-effectiveness graph of the form shown in Figure 2 (originally developed by Shepard and Thompson, 1979). Because we record the *difference* in the total discounted costs and QALYs between the vaccine program compared to the reference case of no vaccine program, the origin of the graph (the point 0,0) represents the zero incremental costs and zero incremental QALYs accrued by the population without a vaccine program. **Cost-saving programs**—those that save

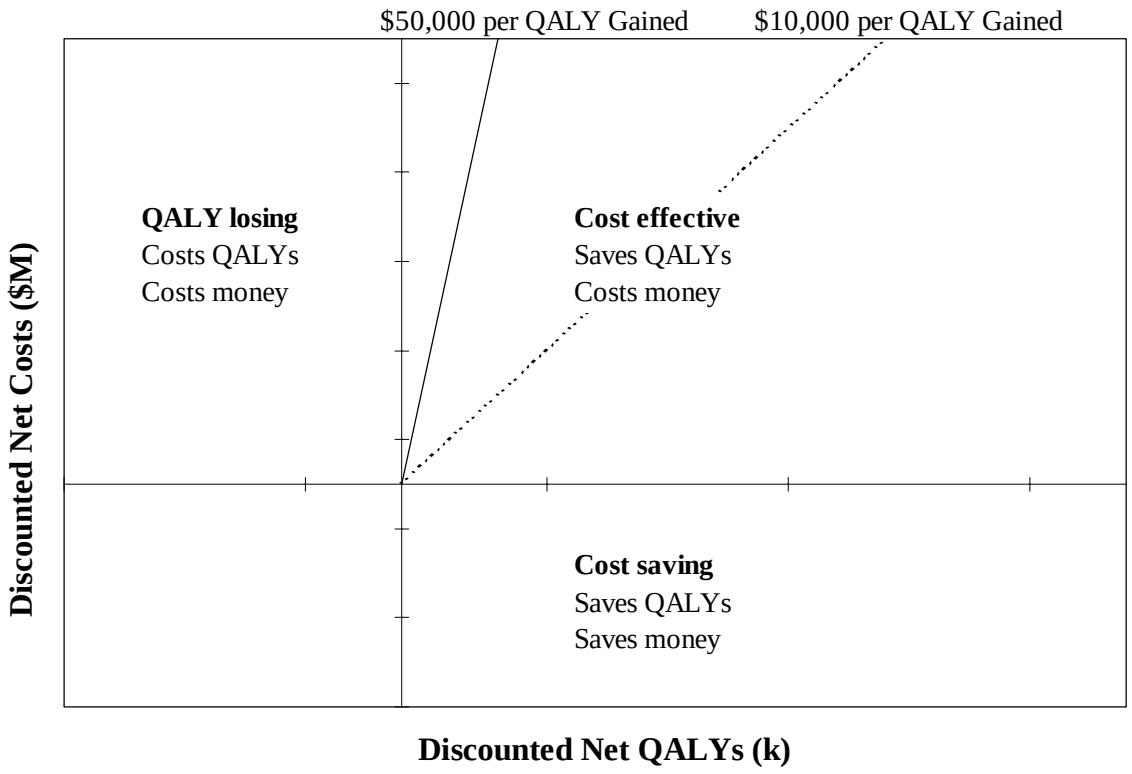

Figure 2. Cost-effectiveness graph for evaluation of vaccine programs.
The total net discounted costs and quality-adjusted life-years (QALYs) of a vaccine program would be represented by a point on the graph. Programs that fall in the lower right region are cost saving. Programs that fall in the upper right region are cost effective. Programs that fall in the upper left region are QALY losing. No HIV vaccine program falls in the lower left region.

both money and QALYs—appear in the lower right quadrant. Programs that save QALYs but cost less than a specified threshold are labeled **cost-effective programs**, and appear in the upper right quadrant. The slope of the line connecting the program outcomes to the origin is equal to the cost effectiveness of the program: Programs with flatter slopes are more cost effective. We compared the programs to a reference cost-effectiveness line of $50,000 per QALY, but recognize that other cost-effectiveness lines are valid as well. Programs that result in a loss of QALYs *and* cost money appear in the upper left quadrant. Programs that lose QALYs but save money would appear in the lower left quadrant, but no HIV vaccine programs fall into this category.

For each type of vaccine program (preventive or therapeutic), we examined a wide range of possible vaccine characteristics by varying two key vaccine parameters together. We plotted the resulting net discounted total costs and QALYs for each pair of parameter values as a point on the cost-effectiveness graph, and joined the extreme points in a polygon. To test the sensitivity of the results to a third parameter, we plotted the original polygon of results and superimposed a new polygon of results that shows the effect of the change in the third parameter.

2.3 Model Implementation

We developed the model and performed the initial analyses using the software package STELLA II® (High Performance Systems 1994). To perform sensitivity analyses and to achieve faster performance, we translated the model into the MATLAB® software (The MathWorks Inc. 1992) in a UNIX™ environment. Both software packages project compartment sizes using Runge–Kutta algorithms.

2.4 Input Data and Sources

Tables 3 and 4 show the input data and sources for our parameters. The epidemiologic parameters were based on survey and prospective study data (Communication Technologies in association with The San Francisco AIDS Foundation 1990; Lemp, Payne et al. 1990; Brandeau, Owens et al. 1993; Samuel, Mohr et al. 1994).

The model of the natural history of HIV is consistent with epidemiological cohort studies (Longini, Clark et al. 1989; Owens and Nease 1994; Owens, Harris et al. 1995). The QALY adjustments are based on a survey of physicians (Owens, Cardinalli et al. 1996). The costs of medical treatment are based on estimates from the AIDS Cost and Service Utilization Survey (Hellinger 1992; Hellinger 1993; Owens, Harris et al. 1995).

We assumed a per person vaccine cost of $1,000 for all analyses. We further assumed that this cost incorporated all related expenditures for vaccine administration. We chose a high vaccine cost because HIV vaccines may be based on recombinant DNA products, and thus may be more expensive than other types of vaccines. Because the cost of the vaccine is unknown, we examined vaccine costs for $100 to $2,000. Sensitivity analysis indicated that our conclusions were unchanged by variation in vaccine cost, and thus we present results only for vaccines that cost $1,000.

Table 3. Input values for population variables

Variable	Value	Source
Initial size of total population (*Y0*)	55,816	(Lemp, Payne et al. 1990)
Initial prevalence of HIV ($\phi 0$)	49.3%	(Lemp, Payne et al. 1990)
Non-AIDS–related annual death rate (μ)	0.0222	(California Department of Health Services 1993)
Fraction of population that is screened annually for HIV (σ)	0.15	(Communication Technologies in association with The San Francisco AIDS Foundation 1990)
True-positive rate of screening process (ξ)	0.983	(Brandeau, Owens et al. 1993)

Table 4. Input values for disease-stage specific variables[*]

Disease Stage and Vaccination Status (i, j)	Infectivity $(\beta_{i,j})$ [1,2]	Contact Rate (p_i) [2,3]	Duration of Disease Stage $(1/\mu_{i,j}$, *in years*$)$ [4]	Quality-Adjustment for a Year of Life (q_i) [5]	Annual Cost of Medical Treatment (c_i) [6]	Annual Immigration $(I_{i,j})$ [7]
0, 0	---	2	---	1	$3,307	$\mu \cdot Y0 \cdot 0.90$
1, 0	0.066	2	7.1	1	$5,467	$\mu \cdot Y0 \cdot 0.04$
2, 0	0.066	2	8.1	0.83	$5,467	$\mu \cdot Y0 \cdot 0.04$
3, 0	0.147	2	2.7	0.42	$12,586	$\mu \cdot Y0 \cdot 0.02$
4, 0	0.147	0.667	2.1	0.17	$35,394	0
0, 1	---	2	---	1	$3,307	0
1, 1	0.066	2	7.1	1	$5,467	0
2, 1	0.066 * β_V	2	8.1 + $1/\mu_V$	0.83	$5,467	0
3, 1	0.147	2	2.7	0.42	$12,586	0
4, 1	0.147	0.667	2.1	0.17	$35,394	0

Sources for Parameter Values:
1 (Brandeau, Owens et al. 1993)
2 (Samuel, Mohr et al. 1994)
3 (Communication Technologies in association with The San Francisco AIDS Foundation 1990)
4 Estimated from a Markov model (Beck and Pauker 1983; Sonnenberg and Beck 1993) fitted to epidemiologic cohort data (Longini, Clark et al. 1989; Owens and Nease 1994; Owens, Harris et al. 1995)
5 (Owens, Cardinalli et al. 1996)
6 (Hellinger 1992; Hellinger 1993; Owens, Harris et al. 1995)
7 We assume that the total rate of immigration into the population equals the death rate from all states due to non-AIDS–related causes; thus the size of the population would be constant if HIV-disease were not present. We assume that 90% of maturations are to the uninfected state.

[*] Table A1 in the Appendix contains the condom-use parameters.

2.5 Model Validation

We validated the model in the late-stage epidemic. We initialized the model in the year 1987 with a population size of 55,816 and an HIV seroprevalence of 49.3%, and compared the model results to published and unpublished data for the years 1990 through 1994. The number of AIDS cases matches published data within 15% (San Francisco Department of Public Health 1994), except in the year 1992, where the difference is 25%. The HIV seroprevalence predicted by the model for the year 1992 (41%) compares favorably to the published estimate of 43% (San Francisco Department of Public Health 1992).

2.6 Analyses

For each type of vaccine program (preventive or therapeutic) we first performed a base-case analysis, then examined a wide range of possible vaccines. For these analyses, we assumed, as a conservative estimate, that men decrease their condom use by 25% after vaccination because of the additional protection provided by the vaccine. We performed these analyses for a **late-stage epidemic**, in which the initial HIV seroprevalence is 43% and men have decreased their annual number of partners to an average of two. We examined the sensitivity of the results to changes in condom-use behavior by comparing the results for the 25% decrease in condom use to results for a 25% increase in condom use. Finally, we examined the sensitivity of the results to the stage of epidemic by considering an **early-stage epidemic**, in which the initial HIV seroprevalence is 10% and the average annual number of partners is four.

3. RESULTS

3.1 Preventive-Vaccine Programs

Table 5 shows the results of our analysis of a preventive vaccine administered to 75% of the asymptomatic (both uninfected and unidentified infected asymptomatic) population during a 20-year period from 1995 to 2015. We assumed an efficacy of 75%, a take of 100%, a duration of 10 years, a known duration of vaccine efficacy, and that vaccinated men decrease their condom

Table 5. Health and economic outcomes of vaccine programs

	Infections prevented	QALYs gained	Total cost ($M)	Cost-effectiveness ($/QALY)
Preventive vaccine				
20-year outcomes	2,520	8,010	-9.4	–*
150-year outcomes	2,960	25,870	-18.8	–*
Therapeutic vaccine				
20-year outcomes	-1,040	2,410	9.2	3,810
150-year outcomes	-1,480	-5,290	45.8	dominated†

* Saves QALYs and saves money.

† Loses QALYs and costs money.

use by 25%. Over a 20-year horizon, this vaccine program results in 2520 infections prevented, 8010 QALYs gained, and a savings of $9.4 million. Extending the time horizon of the analysis to 150 years indicated that the vaccine may prevent an additional 440 infections, save an additional 17,860 QALYs and an additional $9.4 million.

To evaluate a spectrum of potential preventive HIV vaccines, we varied vaccine efficacy from 10% to 90%, and duration of protection from 5 to 50 years (Figure 3a). All preventive

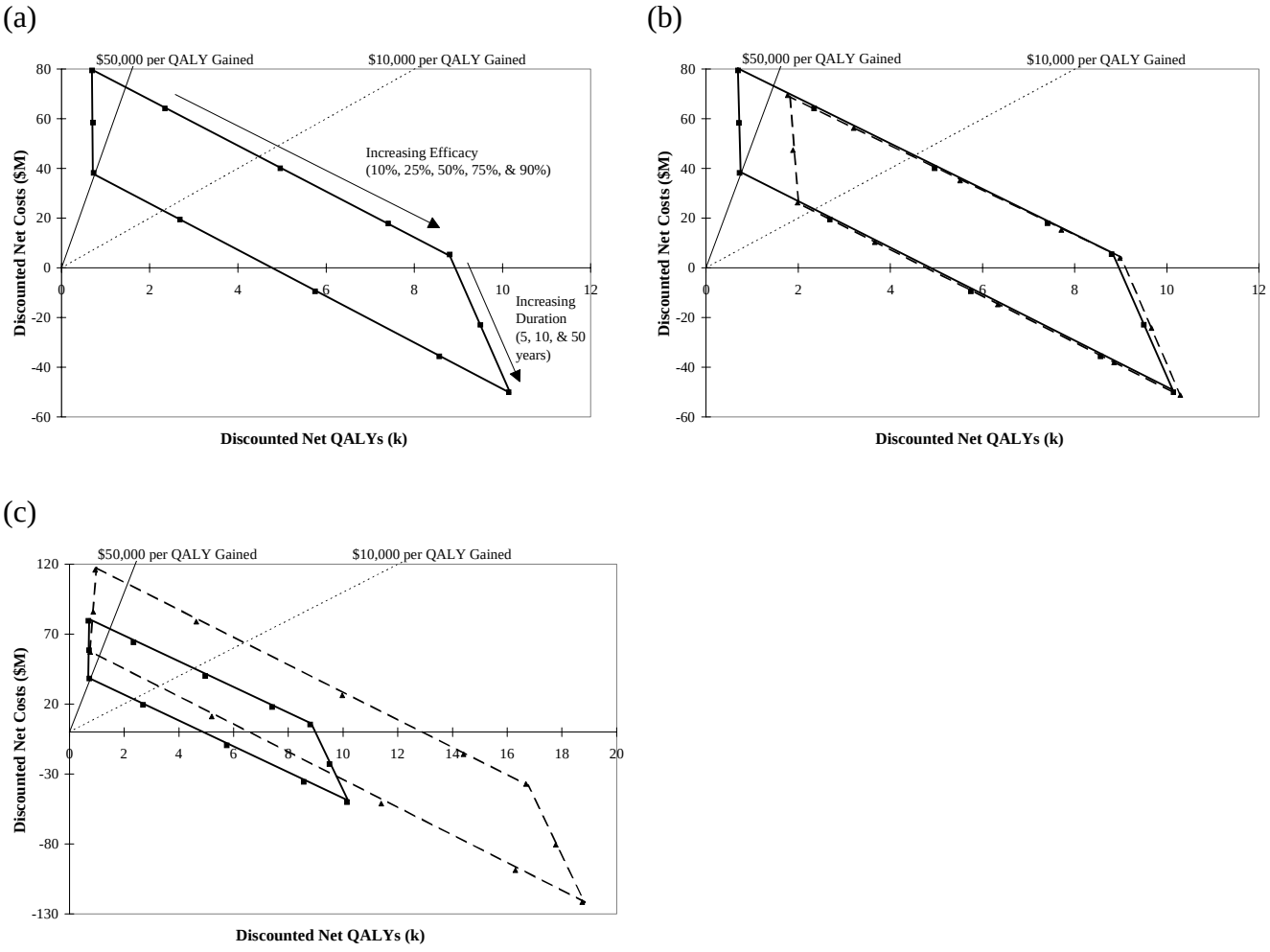

Figure 3. Preventive-vaccine outcomes.

These graphs show the outcomes for a range of preventive-vaccine programs. (a) Base case preventive-vaccine programs. Each point represents the total discounted net costs and quality-adjusted life-years (QALYs) for a vaccine program using a vaccine with efficacy of 10%, 25%, 50%, 75%, or 90% and duration of 5, 10, or 50 years. (b) Sensitivity to changes in condom-use. The results for the full range of preventive-vaccine programs under two conditions: that vaccinated individuals increase their condom use by 25% (dashed polygon) and that vaccinated individuals decrease their condom use by 25% (solid polygon). (c) Sensitivity to stage of the epidemic. The results for the full range of preventive-vaccine programs under both an early-stage (dashed polygon) and a late-stage epidemic (solid polygon). The diagonal lines indicate thresholds for $10,000 and $50,000 per QALY gained.

vaccines with efficacy of 25% or greater cost less than $50,000 per QALY. The vaccine program is cost saving in two cases: (1) the efficacy is at least 75% and the duration is at least 10 years, or (2) the efficacy is 50% and the duration is 50 years. Extending the time horizon of the analysis enhances the benefits of the preventive-vaccine programs.

These analyses assumed that vaccinated men decrease their condom use by 25%. Counter to that assumption, men may increase their condom use in response to counseling that accompanies the administration of the vaccine. This response would enhance the benefits of the preventive vaccine. The results for both assumptions are shown in Figure 3b. We see that, for preventive vaccines with efficacy of 10%, the change in condom-use behavior determines whether the vaccine program will cost more or less than the reference cost-effectiveness value of $50,000. But programs with vaccines with efficacy of at least 25% cost less than $50,000, regardless of changes in condom-use behavior.

Figure 3c shows the results of a preventive-vaccine program in an early epidemic. In the early epidemic, preventive vaccines are even more cost effective than in the late epidemic, and are cost saving in more cases as well.

3.2 Therapeutic-Vaccine Programs

Table 5 shows the results of our analysis of a base-case therapeutic vaccine administered to 75% of the identified infected asymptomatic population during a 20-year period from 1995 to 2015. We assumed a take of 100%, a 5-year increase in the asymptomatic period, no change in infectivity, and that vaccinated men decrease their condom use by 25%. Over a 20-year period, the additional years of life allow additional transmission of the virus, so the net result of the program is an *additional* 1040 infections. The losses from these additional infections are offset by the gains in additional QALYs in the infected men. Thus, the program results in a net gain of 2410 QALYs at a cost of $9.2 million. Extending the time horizon of the analysis to 150 years indicated that the therapeutic vaccine could cause an additional 440 infections. These additional infections would erode the gains due to delayed progression of the disease, so the vaccine program would result in a net loss of 5290 QALYs at a cost of $45.8 million. Clearly, if we consider the long-term effects, this vaccine program loses QALYs and thus the population is better with no vaccine program than with this vaccine program, given that the program is accompanied by a 25% decrease in condom use.

To evaluate a spectrum of potential therapeutic HIV vaccines, we varied the increase in the length of the asymptomatic period between 1 and 10 years, and the reduction in infectivity from 0% to 90%. Figure 4a shows the results. Therapeutic vaccines are cost saving in the following cases: (1) they add at least 10 years of life, (2) they decrease infectivity by at least 50%, or (3) they add at least 5 years of life with at least a 25% decrease in infectivity. Therapeutic vaccines cost less than $50,000 per QALY in the following cases: (1) they add at least 5 years of life, (2) they decrease infectivity by at least 50%, or (3) they add at least 2 years of life with at least a 25% decrease in infectivity. In a longer time horizon of 150 years, the long-term effects of the additional infections erode some of the benefits of these vaccines; to cost less than $50,000 per QALY, the vaccines must either (1) decrease infectivity by 50%, or (2) add at least 5 years of life with at least a 25% decrease in infectivity.

These analyses assumed that vaccinated men decrease their condom use by 25%. As we mentioned, however, men may increase their condom use in response to counseling that accompanies the administration of the vaccine. This response would enhance the benefits of the

therapeutic vaccine to the extent that *any* therapeutic-vaccine program would save both QALYs and dollars (Figure 4b).

Figure 4c shows the results under the late-stage epidemic compared to an early-stage epidemic. Therapeutic vaccines that reduce infectivity by 25% or less are more cost effective in the late epidemic than in the early epidemic. Therapeutic vaccines that reduce infectivity by 75% to 90% and add less than two years of life are more cost saving in an early epidemic than in a

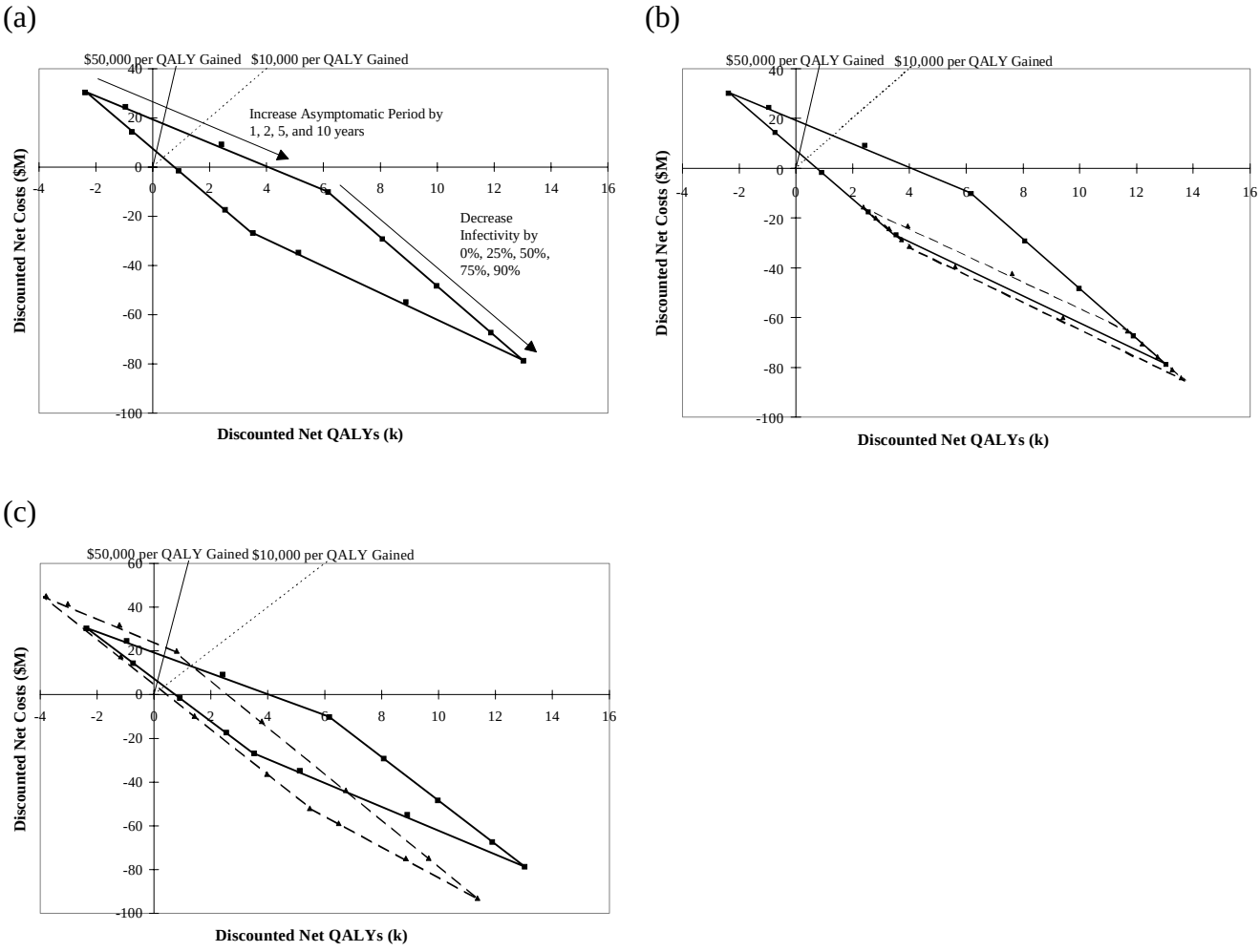

Figure 4. Therapeutic-vaccine outcomes.

These graphs show the outcomes for a range of therapeutic-vaccine programs. (a) Base case therapeutic-vaccine programs. Each point represents the total discounted net costs and quality-adjusted life-years (QALYs) for a vaccine program using a vaccine that increases the period of asymptomatic HIV infection by 1, 2, 5, or 10 years and decreases infectivity by 0%, 25%, 50%, 75%, or 90%. (b) Sensitivity to changes in condom-use. The results for the full range of therapeutic-vaccine programs under two conditions: that vaccinated individuals increase their condom use by 25% (dashed polygon) and that vaccinated individuals decrease their condom use by 25% (solid polygon). (c) Sensitivity to stage of the epidemic. The results for the full range of therapeutic-vaccine programs under both an early-stage (dashed polygon) and a late-stage epidemic (solid polygon).

late; this is because the primary mode of action for these vaccines is to prevent disease transmission, and thus their effect is similar to that of preventive vaccines. Therapeutic vaccines that reduce infectivity by 75% to 90% and add more than five years of life save more money but fewer QALYs in the early epidemic than in the late epidemic. In an early epidemic, the therapeutic vaccine costs less than $50,000 per QALY in the following cases: (1) the vaccine adds 10 years of life, (2) the vaccine reduces infectivity by at least 50%, or (3) the vaccine adds at least 5 years of life and reduces infectivity by at least 25%. In a 150-year time horizon, some these benefits erode; to cost less than $50,000 per QALY, the therapeutic vaccine must reduce infectivity by at least 50%.

4. CONCLUSIONS

We used an epidemic transmission model and an economic model of HIV vaccination and treatment costs to evaluate the costs and benefits of potential HIV vaccine programs in a population of homosexual men. In this analysis, we emphasized two questions: How do changes in high-risk behavior that may accompany a vaccine program affect the program's effectiveness and cost effectiveness?, and How does the rate of epidemic growth affect the outcomes of a vaccine program? We evaluated the first question because of the concern that HIV vaccine recipients may perceive themselves as immune from HIV and consequently increase their high-risk behavior. We investigated the second question because the growth rate of the HIV epidemic varies dramatically among populations at risk.

Our study has two main findings. First, the behavioral changes that accompany a vaccine program can substantially influence the desirability of the program, particularly for therapeutic vaccines. Second, the cost effectiveness of vaccine programs depends on the epidemic growth rate, a finding with implications for the design of vaccine programs.

Our analysis indicates that although vaccines are cost effective over a broad range of vaccine characteristics, increases in high-risk sexual behavior would attenuate the benefit of both preventive vaccines (Figure 3b) and therapeutic vaccines (Figure 4b); the effect is more troublesome for therapeutic-vaccine programs. Because a therapeutic-vaccine program would extend length of life of HIV-infected people, such a program could lead to increased transmission of HIV during the additional years that vaccine recipients live (Anderson, Gupta et al. 1991; Paltiel and Kaplan 1991). In our base-case analysis, we assumed that condom use among vaccine recipients would decrease by 25%. Given this assumption, therapeutic HIV vaccines that extend life by less than 5 years, and that do not substantially reduce infectivity of vaccine recipients, cause a net loss of QALYs in the population (and, of course, also increase health-care expenditures). In contrast, however, if counseling associated with a vaccine program produced a 25% increase in condom use, the benefit from vaccine programs increases substantially: all preventive vaccines cost less than $50,000 per QALY gained, and all therapeutic vaccines become cost saving. These findings underscore the profound effect that changes in risk behavior have on the course of the HIV epidemic.

Second, we found that the growth pattern of the HIV epidemic influences the cost effectiveness of preventive and therapeutic vaccines. In an early-stage epidemic (prevalence 10%) that is growing rapidly, preventive vaccines are cost effective at lower efficacies than they are in late-stage, slow growing epidemics (prevalence approximately 40%) (Figure 3c). This finding suggests that initiation of immunization early in an HIV epidemic with a preventive vaccine of lower efficacy, may be a superior strategy to immunization late in an epidemic, but

with a better vaccine. Therapeutic vaccines that reduce infectivity by less than 25% are more cost effective in the late epidemic than in the early epidemic (Figure 4c). Therapeutic vaccines that reduce infectivity by 75% or more are cost saving in both early- and late-stage epidemics.

We note several limitations of our analysis. The effect of a vaccine program depends on transmission patterns of HIV within the populations at risk. Both the frequency and type of sexual behavior varies among populations, and within the same population over time. In addition, data on sexual high-risk behavior depend on self reporting, and are therefore uncertain and difficult to verify. Because the mode of HIV transmission varies among risk groups, our findings cannot be generalized to other risk groups without further study.

Our findings have implications both for the development of HIV vaccines and for the design of HIV vaccine programs. Development of preventive vaccines should be a high priority, even if those vaccines are not likely to provide complete protection from HIV. Policy makers should consider coupling vaccine programs with state-of-the-art behavioral interventions (DiClemente and Wingood 1995); such interventions could enhance substantially a programs' effectiveness and cost effectiveness. Our analysis of therapeutic vaccines indicates that the reduction in infectivity (if any) caused by the vaccine, and the behavioral changes that accompany vaccination, exert a critical influence on epidemic outcomes. Thus, clinical trials of therapeutic vaccines should evaluate changes in high-risk behavior and in infectivity of vaccine recipients, to ensure that the vaccine program does not inadvertently increase transmission of HIV.

ACKNOWLEDGMENTS

Dr. Owens is supported by a VA Health Services Research and Development Career Development Award. Dr. Edwards was supported by the United States Department of Energy through the Doctoral Studies Program at Sandia National Laboratories. We thank Lyn Dupré for comments on the manuscript.

APPENDIX

Table A1. Condom-use parameters [1]

Disease stage of Infected Partner (i,j)	Probability of condom use in partnership between uninfected and infected ($n_{00,i,j}$)	Probability of condom use in partnership between vaccinated uninfected and infected ($n_{01i,j}$)
1, 0	0.53	$n_{00,10} * \Delta_p$
1, 1	$n_{00,10} * \Delta_p$	$n_{00,11} * \Delta_p$
2, 0	0.35	$n_{00,20} * \Delta_p$
2, 1	$n_{00,20} * \Delta_t$	$n_{00,21} * \Delta_p$
3, 0	0.28	$n_{00,30} * \Delta_p$
4, 0	0.28	$n_{00,40} * \Delta_p$

[1] Derived from (Communication Technologies in association with The San Francisco AIDS Foundation 1990)

Table A2. Model equations

$$\lambda(t) = \frac{\sum_{j=0}^{j=1}\sum_{i=1}^{i=4} p_i \beta_{i,j} n_{00,i,j} Y_{i,j}(t)}{\sum_{j=0}^{j=1}\sum_{i=0}^{i=4} p_i Y_{i,j}(t)}$$

$$\lambda_v(t) = \frac{\sum_{j=0}^{j=1}\sum_{i=1}^{i=4} p_i \beta_{i,j} n_{01,i,j} Y_{i,j}(t)}{\sum_{j=0}^{j=1}\sum_{i=0}^{i=4} p_i Y_{i,j}(t))}$$

Table A3. Initial conditions

$$Y_{0,0}(0) = (1-\phi 0) Y0$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_j 1/\mu_{j,0}} \phi 0 \cdot Y0 \text{ , for } i=1,2,3,4$$

$$Yi,1(0) = 0, \text{ for } i=0,1,2,3,4$$

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