A Dynamic HIV-Transmission Model for Evaluating the Costs and Benefits of Vaccine Programs

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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 and of therapeutic vaccines. We found that the effect of reductions in condom use is more important for therapeutic vaccines than for preventive vaccines. 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 vaccines, but the effects are more pronounced for preventive vaccines, which are more cost-effective in an early-stage epidemic than in a late-stage epidemic.

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, and Fauci 1996], many candidates have undergone phase I and II clinical trials [Dolin et

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al. 1991; Graham et al. 1996; Graham and Wright 1995; Redfield et al. 1991; Wintsch et al. 1991; World Health Organization 1995]. 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 possible vaccine programs to determine how combinations of various factors affect the cost-effectiveness of such programs. We considered the type of vaccine (preventive or therapeutic), the characteristics of the vaccine (efficacy, duration of protection, and 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 data from San Francisco, California. 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.

Methods

Building on the work of previous authors (the staged model of HIV progression developed by Brandeau et al. [1992], the model of HIV vaccines in a gay community developed by McLean and Blower [1993], and the model of life-prolonging therapies developed by Anderson, Gupta, and May [1991]), we developed a dynamic compartmental model [Edwards 1995; Edwards et al. 1995a, 1995b; Owens 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* (defined here to mean how well the vaccine prevents transmission of HIV in a partnership) between 10 and 90 percent, and mean *duration* (how long the protective effects of the vaccine persist) between five 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 revaccination. We chose a maximum mean duration of 50 years to include vaccines that provide lifetime protection for members of the population who live that long. We modeled the effect of therapeutic vaccines as an increase in the mean duration of the asymptomatic period of HIV infection; we varied this increase from one to 10 years. We also evaluated therapeutic-vaccine–induced reductions in *infectivity* (the probability of transmission of the virus in a sexual partnership) from zero (no reduction) to 90 percent. We define a sexual partnership to mean the entire duration of the relationship between the two individuals, not each particular act of sexual contact. 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), and

(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. Because we adopted a societal perspective for this analysis, population-based preferences (utilities) for the health states would be desirable. However, no such data were available; therefore, we used a surrogate—the results of a survey of physicians [Owens, Cardinalli, and Nease 1997; Owens and Sox 1990].

We present the results for a 20-year period and for a longer (150-year) time horizon. As other researchers have also discussed [Paltiel and Kaplan 1993], some of the effects of vaccine programs persist well beyond a 20-year period and contribute significantly to the costs and benefits for approximately 100 years, even though the effects are attenuated by the five percent discount rate. The reason that these effects persist is that the AIDS interventions alter the HIV seroprevalence in the population and thus have repercussions for many future generations. For example, in the case of preventive vaccines, cost savings due to infections prevented accrue for a certain period; beyond that, some of the cost savings diminish because the people in whom infection was prevented live a normal-length life, and thus incur costs of medical care for much longer than they would have if they had become infected. In the case of therapeutic vaccines, the benefits from delaying the progression of the disease save money and QALYs initially; later, however, the cost of treating the additional infections in the population erodes the previous dollar savings. Eventually, even the QALY savings diminish because of the additional infections, which result from longer periods during which people transmit HIV infection. We realize that there are many uncertainties in such a long time frame but present the results as an indicator of the potential long-term effects of vaccine programs.

Model Description

We modeled the adult male homosexual and bisexual population in San Francisco, which in 1987 consisted of an estimated 55,816 members with an estimated HIV seroprevalence of 49.3 percent [Lemp et al.

1990]. We considered only HIV transmission from sexual contact among the members of this population. The model (shown in Figure 1 and discussed more fully in the appendix) divides the population into eight mutually exclusive, collectively exhaustive states according to disease stage, screening status, and vaccination status. A set of deterministic differential equations describes the flows of individuals between 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.

We first describe the natural progression of disease without any vaccination program. Men enter the adult homosexual-male population at a constant rate into each of four unvaccinated states: unin-

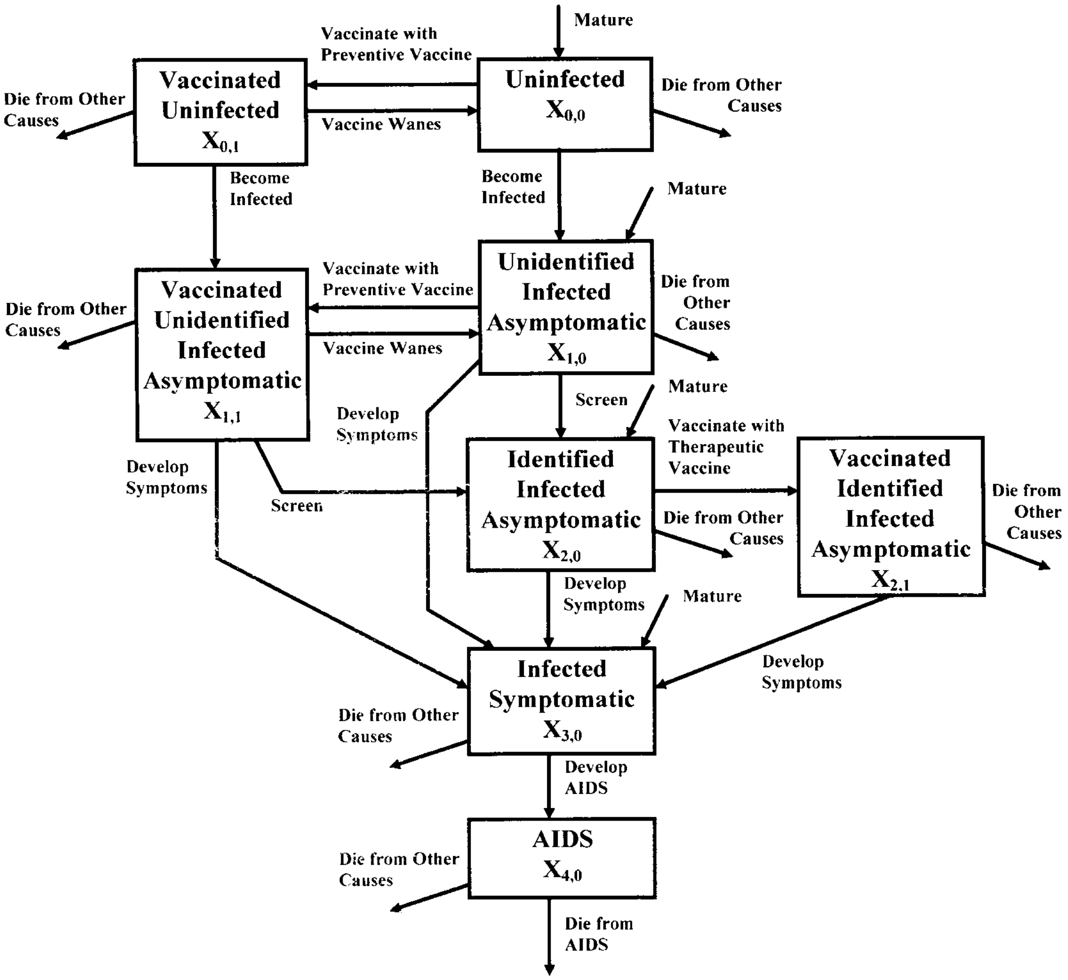


Figure 1: In this model of the transmission and progression of HIV in a population of homosexual men under a vaccine program, the population is divided into eight compartments according to disease stage and vaccination status. The arrows represent transitions into and out of the population and between compartments.

fected, unidentified infected asymptomatic, identified infected asymptomatic, and infected symptomatic. Uninfected men may become infected through their interactions with infected men and move to the unidentified infected asymptomatic state. Infected men are initially asymptomatic, then develop symptoms, progress to AIDS, and eventually die of AIDS if they do not die of non-AIDS–related causes first. Some infected asymptomatic men may learn that they are infected with HIV 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 timing of intervention programs can affect their cost effectiveness.

A preventive-vaccine program (in the absence of additional screening) targets people who appear uninfected; thus both uninfected and unidentified infected asymptomatic men may receive the vaccine and move to corresponding vaccinated states. Vaccinated men (uninfected or infected) may alter their sexual behavior in response to the vaccination program; they may decrease their risky behavior in response to counseling that accompanies the administration of the vaccine, or they may increase their risky behavior because they feel more protected. The vaccine has no biochemical effect on the infected men, but the extra state models the potential behavior change.

A preventive vaccine may fail in one of two ways [McLean and Blower 1993]: it may not provide lifetime protection, and it may not confer perfect immunity. For vaccines that do not provide lifetime protection, vaccinated people move back to the corresponding unvaccinated states at the rate indicated by the duration of protection. For vaccines that do not confer perfect immunity, some vaccinated men may become infected through their interactions with infected men. These men move to the vaccinated unidentified infected asymptomatic state, because in the asymptomatic state of disease, their behavior is the same as that of men who were unidentified infected asymptomatic when they received the vaccine. From the vaccinated unidentified infected asymptomatic state, men may become identified through a screening program and move to the identified infected asymptomatic state, or they may develop symptoms and move directly to the infected symptomatic state. We have assumed that the preventive vaccine has no effect on the progression of the disease after a vaccinated person has become infected.

A therapeutic-vaccine program targets identified infected asymptomatic people and moves them to the vaccinated identified infected asymptomatic state. Vaccinated people develop symptoms at a slower rate than do unvaccinated people. Furthermore, the vaccine may change the chance that infected men will transmit the virus to uninfected men because of either a decrease in infectivity or a change in risky sexual behavior. We have assumed that the therapeutic vaccine may lengthen the duration of the asymptomatic period of disease, but that it does not affect the symptomatic or AIDS stages of disease.

Outcome Measures

We calculated the total discounted economic costs and the total discounted QALYs gained. We determined the total discounted costs and QALYs accrued in the population without a vaccine program and used that as a reference point for our analyses. Thus we considered the difference in the total discounted costs and QALYs accrued in the population with and without a vaccine program.

We present the total incremental discounted costs and QALYs of each vaccine program as a point on a cost-effectiveness graph (Figure 2, originally developed by Shepard and Thompson [1979]). We com-

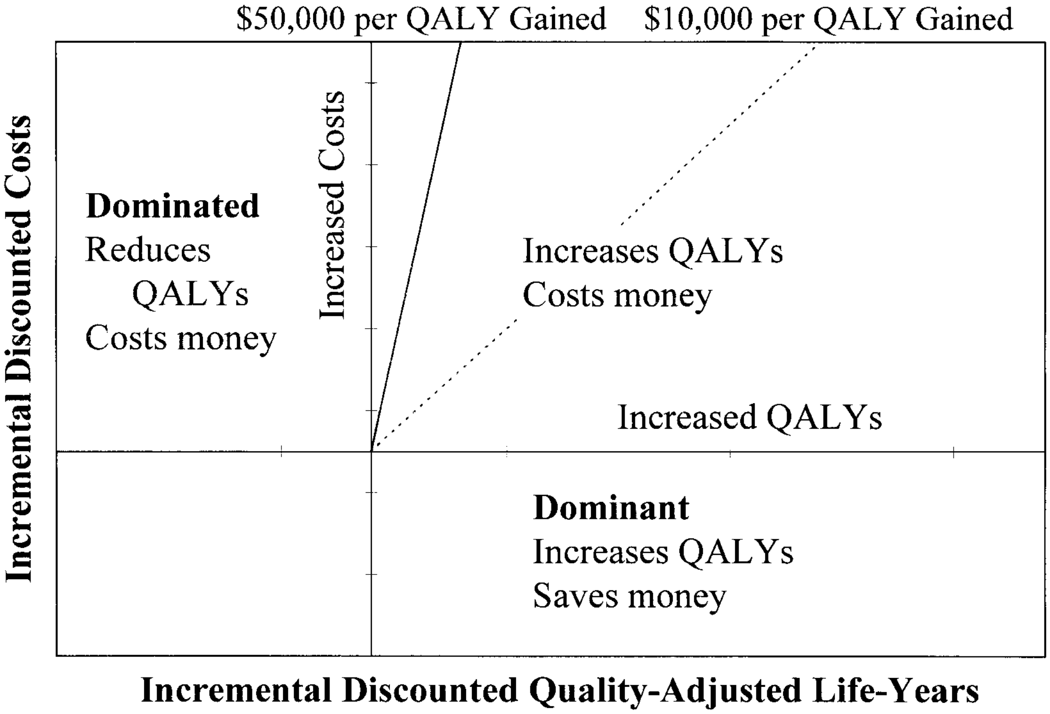


Figure 2: In this cost-effectiveness graph for evaluating vaccine programs, the total incremental discounted costs and quality-adjusted life-years (QALYs) of a vaccine program would be represented by a point on the graph. Because we record the difference in the total discounted costs and QALYs between 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. Programs that appear in the lower right quadrant—dominant programs—reduce expenditures and increase QALYs and should be implemented without reference to any cost-effectiveness threshold. Programs that fall in the upper right region increase QALYs and cost money, and their implementation must be considered in the context of value for money. The slope of the line connecting the program outcomes to the origin is the cost-effectiveness ratio of the program: programs with flatter slopes are more cost-effective. Programs that fall in the upper left region are dominated by the status quo of no vaccine program and should never be implemented. In the lower left region, programs would decrease costs and decrease QALYs, but none of the HIV-vaccine programs that we analyzed falls in this region.

pared the programs to a reference cost-effectiveness line of $50,000 per QALY for illustrative purposes, but we recognize that there is no standard cost-effectiveness threshold, and that other cost-effectiveness thresholds are valid as well.

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. By joining the extreme points into a polygon, we formed the production possibility frontier for the vaccine programs. Although we omitted the interior points from the graphs for clarity, the reader can infer their positions by connecting the corresponding points on the edges of the 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.

Model Implementation

We developed the model and performed the initial analyses using the software package STELLA II [Newcomb et al. 1996]. To perform sensitivity analyses and to achieve faster performance, we translated the model into MATLAB [The MathWorks 1992, 1994] in a UNIX environment. Both software packages project compartment sizes using Runge-Kutta algorithms.

Input Data and Sources

Tables 1 and 2 show the input data and sources for our parameters. We assumed a per-person vaccine cost of $1,000 for all analyses. We further assumed that this cost incorporates 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 vac-

Variable	Value	Source
Initial size of total population ($Y0$)	55,816	[Lemp et al. 1990]
Initial prevalence of HIV ($\phi 0$)	49.3%	[Lemp et al. 1990]
Non-AIDS–related annual death rate (μ)	0.0222	[Chan and Oreglia 1993, p. 28]
Fraction of population that is screened annually for HIV (σ)	0.15	[Communication Technologies in association with the San Francisco AIDS Foundation 1990]
Annual discount rate (r)	5%	
True-positive rate of screening process (ξ)	0.983	[Brandeau et al. 1993]
Annual % of uninfected people who receive preventive vaccine ($\nu_p(t)$)	75% ($t \leqq 20$), % ($t > 20$)	assumption
Annual % of infected people who receive therapeutic vaccine ($v_t(t)$)	75% ($t \leqq 20$), 0% ($t > 20$)	assumption
Per-person cost of the preventive vaccine (κ_p)	$1,000	assumption
Per-person cost of the therapeutic vaccine (κ_t)	$1,000	assumption

Table 1: Input values.

Disease stage and vaccination status (i, j)	Infectivity ($\beta_{i,j}$)[1]	Contact rate (p_i partners per year)[2]	Mean duration of disease stage ($1/\mu_{i,j}$, *in years*)[3]	Quality-adjustment for a year of life (q_i)[4]	Annual cost of medical treatment (c_i)[5]	Annual immigration ($I_{i,j}$)[6]
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_ν	2	$8.1 + 1/\mu_\nu$	0.83	$5,467	0

[1] Samuel et al. [1994] estimate that the infectivity of unprotected anal receptive intercourse is 0.099. Brandeau et al. [1993] provide reasoning that supports the assumption that infectivity in the asymptomatic stage of infection is 45 percent of the infectivity in the symptomatic and AIDS stages of disease. These numbers together with the mean duration of disease stage ($1/\mu_{i,j}$), which indicates the proportion of people in each stage in an advanced epidemic, result in the infectivity parameters shown.

[2] Laumann et al. [1994] report the mean number of sex partners for homosexual men to range from two to four. We use two partners per year for the late-stage epidemic and four partners per year for the early-stage epidemic. We assume that men with AIDS decrease their number of sexual partners by 1/3.

[3] Estimated from a Markov model [Beck and Pauker 1983; Sonnenberg and Beck 1993] fitted to epidemiologic cohort data [Longini et al. 1989; Owens et al. 1995; Owens and Nease 1994].

[4] Owens, Cardinelli, and Nease [1997].

[5] Hellinger [1992]; Hellinger [1993]; Owens et al. [1995].

[6] 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 percent of immigrations are to the uninfected state.

Table 2: Input values for disease-stage specific variables.

cine costs between $100 and $2,000. The different vaccine costs alter the absolute costs of the vaccine programs, but because the conclusions stem from comparisons between scenarios, it is the relative costs that are most interesting, not the total costs of the vaccine programs.

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 percent and compared the model results to published and unpublished data for the years 1990 through 1994. The number of AIDS cases by year matches published data within 15 percent [San Francisco Department of Public Health 1995], except in 1992, where the difference is 25 percent. The HIV seroprevalence predicted by the model for the year 1992 (41 percent) compares favorably to the published estimate of 43 percent [San Francisco Department of Public Health 1992]. We compared our results to San Francisco data to verify that our model produces results that are within the range of the data, not to attempt to match the data exactly. Our purpose was not to predict the course of the epidemic in a particular population but rather to predict changes caused by vaccine programs and examine ranges of parameters to determine results that are generalizable to many populations.

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. Because our purpose was to make general recommendations about vaccines under a wide variety of circumstances, we considered several scenarios based on the stage of the epidemic and possible changes in condom-use behavior. For the first scenario, we considered vaccine programs in a late-stage epidemic (in which the initial HIV seroprevalence is 43 percent and men have decreased their annual number of partners to an average of two) in which vaccinated men decrease their condom use by 25 percent. To understand the sensitivity of the results to changes in condom-use behavior, we compared the results of the initial scenario to results for the case in which vaccinated men increase their condom use by 25 percent. (We use changes of 25 percent, but the degree to which condom use would actually change is not known.) The resulting graphs show the impact of such changes on the overall outcomes of vaccine programs. Similarly, we compared the results from the initial scenario to vaccine programs in an early-stage epidemic (in which the initial HIV seroprevalence is 10 percent and the average annual number of partners is four).

Results

Table 3 shows the total outcomes for no vaccine program, a preventive-vaccine program, and a therapeutic-vaccine program, as well as the incremental outcomes for the two vaccine programs.

Preventive-Vaccine Programs

Table 3 shows the results of our analysis of a preventive vaccine administered to 75 percent of the asymptomatic (both uninfected and unidentified infected asymptomatic) population in a late-stage epidemic during a 20-year period from 1995 to 2015. For this base-case analysis, we used a vaccine efficacy of 75 percent, a mean duration of vaccine efficacy of 10 years, assumed that vaccine recipients know that the effects of the vaccine last for 10 years, and examined the case in which vaccinated men decrease their condom use by 25 percent. Over a 20-year horizon, this vaccine program results in 2,520 infections

	No vaccine		Preventive vaccine		Therapeutic vaccine	
	20-year outcomes	150-year outcomes	20-year outcomes	150-year outcomes	20-year outcomes	150-year outcomes
Total outcomes						
Number of infections	37,680	38,750	35,160	35,800	38,720	40,230
Total QALYs gained	838,670	1,123,790	846,680	1,149,660	841,080	1,118,500
Total cost ($M)	6,037.1	7,195.7	6,027.7	7,176.8	6,046.3	7,241.5
Incremental outcomes						
Infections prevented	—	—	2,520	2,950	−1,040	−1,480
Incremental QALYs gained	—	—	8,010	25,870	2,410	−5,290
Incremental cost ($M)	—	—	−9.4	−18.8	9.2	45.8
Cost-effectiveness ($/QALY)	—	—	dominant*	dominant*	3,810	dominated†

*dominant = saves QALYs (quality adjusted life years) and saves money
†dominated = decreases QALYs and costs money

Table 3: Health and economic outcomes of vaccine programs.

prevented, an increase of 8,010 QALYs, and a savings of $9.4 million. Extending the time horizon of the analysis to 150 years to examine the effects on future generations indicated that the vaccine may prevent an additional 430 infections and 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 percent and mean duration of protection from five to 50 years (Figure 3a). All preventive vaccines with efficacy of 25 percent or greater cost less than $50,000 per QALY. The preventive-vaccine program is dominant—reduces expenditures and increases QALYs—in two cases: (1) when the efficacy is at least 75 percent and the mean duration is at least 10 years, or (2) when the efficacy is 50 percent and the mean duration is 50 years. Extending the time horizon of the analysis enhances the benefits of the preventive-vaccine programs.

These analyses were for the case in which vaccinated men decrease their condom use by 25 percent. Counter to that case, we examined the case in which men increase their condom use by 25 percent in response to counseling that accompanies the administration of the vaccine. This response would enhance the benefits of the preventive vaccine. Researchers have concluded previously that changes in risk behavior have a substantial impact on the ability of preventive vaccines to eradicate HIV [Blower and McLean 1994]. We examined the effect of changes in risk behavior on the QALY- and cost-savings associated with preventive vaccines, regardless of their ability to eradicate the epidemic. For preventive vaccines with efficacy of 10 percent, the results are sensitive to changes in condom-use behavior, but the sensitivity decreases with increasing efficacy of the vaccine (Figure 3b). This finding is expected because, at the extreme, the results for a perfect (100 percent effective) vaccine would not depend on changes in condom use.

We compared the results of a preventive-vaccine program in an early epidemic and a late epidemic (Figure 3c). In the early epidemic, preventive vaccines provide more benefit for a given level of expenditure than in the late epidemic and are dominant in more cases as well. These results are consistent with intuition. In an early epidemic, in which the HIV seroprevalence is low and increasing, there are more uninfected people to protect than there would be in a late-stage epidemic; thus, preventive vaccines prevent more infections, avoid more AIDS treatment, and result in more QALYs saved and lower total costs than they would in a late-stage epidemic.

Therapeutic-Vaccine Programs

In our analysis of a base-case therapeutic vaccine administered to 75 percent of the identified infected asymptomatic population in a late-stage epidemic during a 20-year period from 1995 to 2015, we used a vaccine that increases the asymptomatic period of infection by five years and does not change infectivity, and we examined the case in which vaccinated men decrease their condom use by 25 percent. 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 1,040 infections

(Table 3). The losses from these additional infections are offset by the gains in additional QALYs in the infected men. Thus, the program results in an increase of 2,410 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 decrease of 5,290 QALYs at a cost of $45.8 million. Clearly, if we consider the long-term effects, this vaccine program decreases 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 percent 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 one and 10 years and the reduction in infectivity from zero to 90 percent (Figure 4a). Therapeutic vaccines are dominant in the following cases: (1) when they add at least 10 years of life, (2) when they decrease infectivity by at least 50 percent, or (3) when they add at least five years of life with at least a 25 percent decrease in infectivity. Therapeutic vaccines cost less than $50,000 per QALY in the following cases: (1) when they add at least five years of life, (2) when they de-

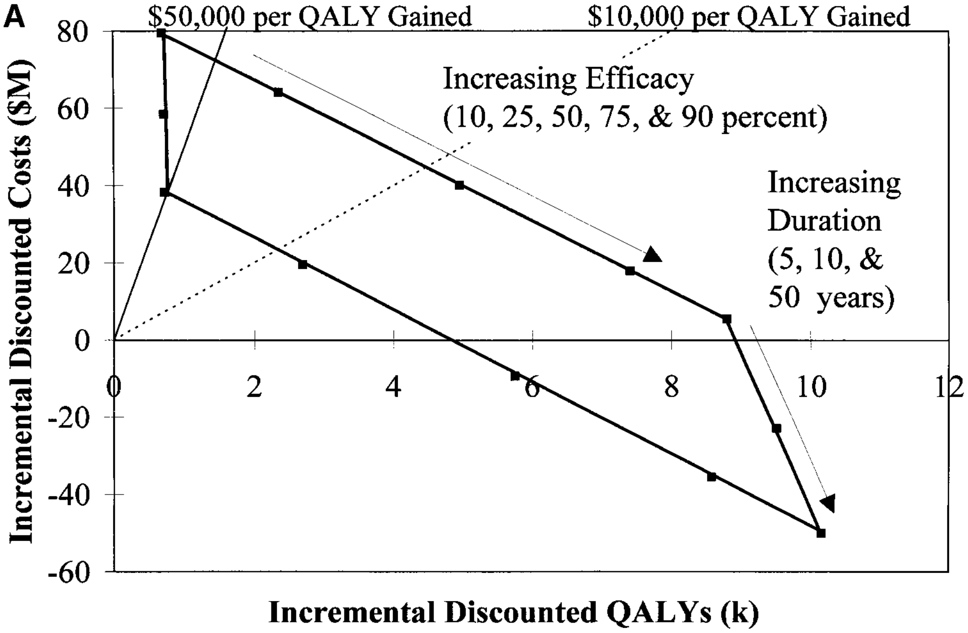
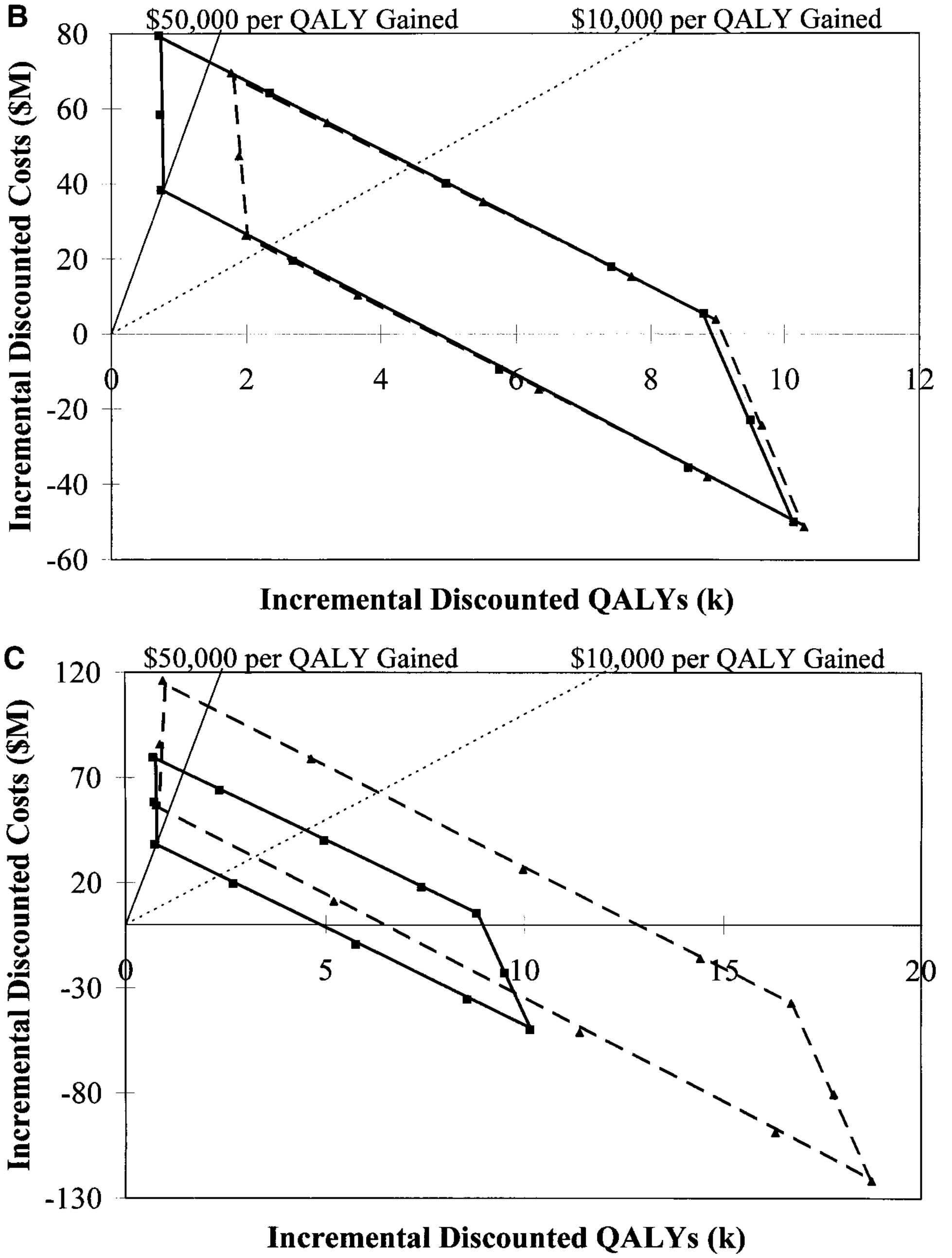


Figure 3: These graphs show the outcomes for a range of preventive-vaccine programs: (a) In this graph of base-case preventive-vaccine programs, each point represents the total discounted net costs and quality-adjusted life-years (QALYs) for a vaccine program using a vaccine with efficacy of 10, 25, 50, 75, or 90 percent and mean duration of five, 10, or 50 years. (We have omitted the interior points from the graphs for clarity, but the reader can infer their positions by connecting the corresponding points on the edges of the polygon.) (b) The graph of sensitivity to changes in condom use shows the results for the full range of preventive-vaccine pro-



grams under two conditions: that vaccinated individuals increase their condom use by 25 percent (dashed polygon) and that vaccinated individuals decrease their condom use by 25 percent (solid polygon). (c) This graph of sensitivity to stage of the epidemic shows 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.

crease infectivity by at least 50 percent, or (3) when they add at least two years of life with at least a 25 percent 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 percent or (2) add at least five years of life with at least a 25 percent decrease in infectivity.

These analyses were for the case in which vaccinated men decrease their condom use by 25 percent. Counter to that case, we examined the case in which men increase their condom use by 25 percent. This response would enhance the benefits of the therapeutic vaccine to the extent that any therapeutic-vaccine program would save both QALYs and dollars and thus would be dominant (Figure 4b).

We compared the results under a late epidemic and an early epidemic (Figure 4c). Therapeutic vaccines that reduce infectivity by 25 percent or less are more efficient in the late epidemic than in the early epidemic. Therapeutic vaccines that reduce infectivity by 75 to 90 percent and add less than two years of life are dominant in both an early epidemic and a late epidemic but save even more money in the early epidemic; 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

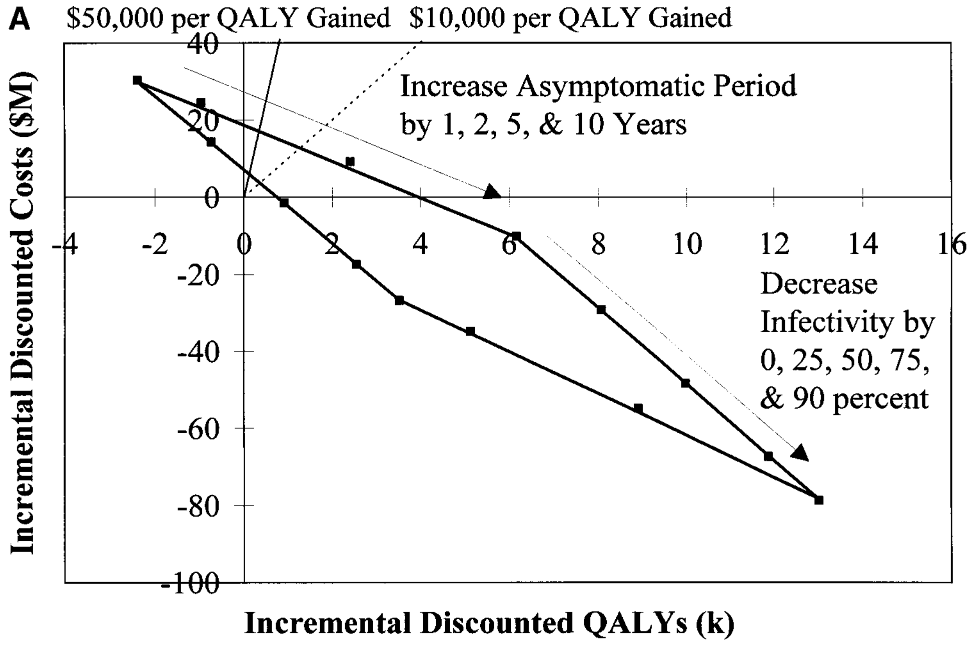
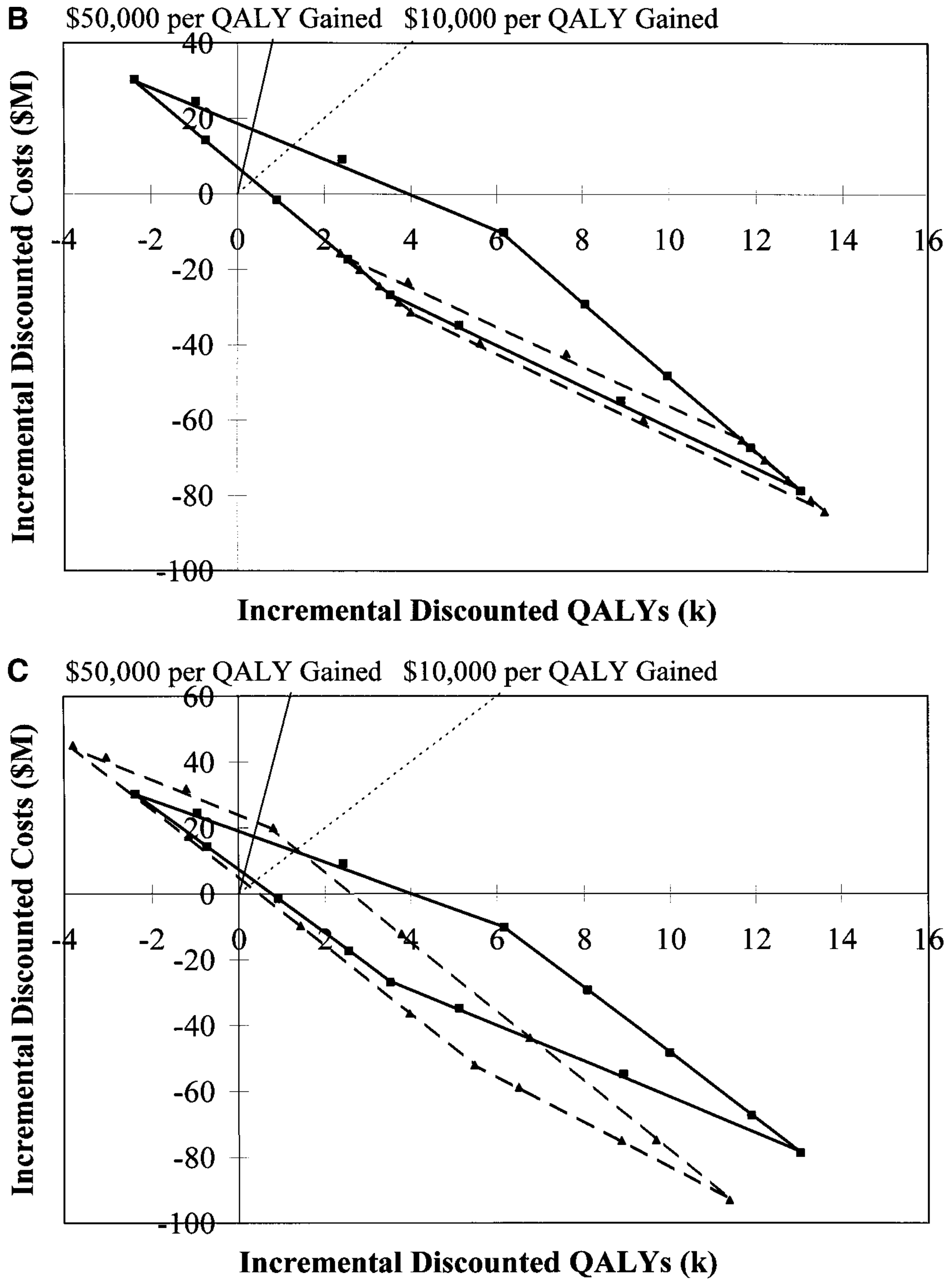


Figure 4: These graphs show the outcomes for a range of therapeutic-vaccine programs: (a) For base-case therapeutic-vaccine programs, each point represents the total discounted net costs and quality-adjusted life-years (QALYs) for a vaccine program using a vaccine that increases the period of asymptomatic HIV infection by one, two, five, or 10 years and decreases infectivity by zero, 25, 50, 75, or 90 percent. (We have omitted the interior points from the graphs for clarity, but the reader can infer their position by connecting the corresponding points on the edges of



the polygon.) (b) This graph of sensitivity to changes in condom use shows the results for the full range of therapeutic-vaccine programs under two conditions: that vaccinated individuals increase their condom use by 25 percent (dashed polygon) and that vaccinated individuals decrease their condom use by 25 percent (solid polygon). (c) This graph of sensitivity to stage of the epidemic shows the results for the full range of therapeutic-vaccine programs under both an early-stage (dashed polygon) and a late-stage epidemic (solid polygon).

infectivity by 75 to 90 percent 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) when the vaccine adds 10 years of life, (2) when the vaccine reduces infectivity by at least 50 percent, or (3) when the vaccine adds at least five years of life and reduces infectivity by at least 25 percent. In a 150-year time horizon, some of these benefits erode: to cost less than $50,000 per QALY, the therapeutic vaccine must reduce infectivity by at least 50 percent.

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 cost and effectiveness? 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 influence the desirability of the program, particularly for therapeutic vaccines. This finding is consistent with that of Blower and McLean [1994], who showed that a vaccine program could not eradicate HIV in San Francisco unless vaccinated people also reduced high risk behaviors. 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 preventive and therapeutic HIV vaccines cost less than $50,000 per QALY 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). This 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 HIV transmission during the additional years that vaccine recipients live [Anderson, Gupta, and May 1991; Paltiel and Kaplan 1991]. In our base-case analysis, we assumed that condom use among vaccine recipients would decrease by 25 percent. Given this assumption, therapeutic HIV vaccines that extend life by less than five 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 percent 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 dominant. These findings underscore the profound effect that changes in risk behavior have on the course of the HIV epidemic [Blower and McLean 1994].

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 percent) that is growing rapidly, preventive vaccines with low efficacies save more QALYs at lower cost than they do in late-stage, slow-growing epidemics (prevalence approximately 40 percent) (Figure 3c). This finding suggests that initiating immunization early in an HIV epidemic with a preventive vaccine of lower efficacy may be a superior strategy to immunization late in an epidemic with a better vaccine. Therapeutic vaccines that reduce infectivity by less than 25 percent are more cost effective in the late epidemic than in the early epidemic (Figure 4c). Therapeutic vaccines that reduce infectivity by 75 percent or more are dominant in both early- and late-stage epidemics.

We note several limitations of our analysis. First, we modeled only the effect of sexual transmission within a closed homosexual population. Although HIV transmission among the homosexual population would also occur via needle sharing or interaction with other population subgroups, these effects would not change our primary conclusions about the effect of vaccine programs within the homosexual population. Second, both the frequency and type of sexual behavior varies among populations and within the same population over time. In addition, data on high-risk sexual behavior depend on self-reports and are therefore uncertain and difficult to verify. Furthermore, such data may be age related, and that is not reflected in the model. 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. Developing 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 program's 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.

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APPENDIX

We provide a mathematical description of the model. The model variables are defined in Table 4, the equations are shown in Table 5, and the initial conditions are shown in Table 6.

Equation 1 represents the change in time in the number of uninfected men ($dY_{0,0}(t)/dt$). The term $I_{0,0}$ represents the constant rate at which young uninfected homosexual men mature into adulthood (reach 18 years of age). The second term, $\nu_p(t)Y_{0,0}(t)$, equals the total number of uninfected people who receive the preventive vaccine, where $\nu_p(t)$ is the time-dependent percentage of the same. (We set $\nu_p(t)$ equal to a constant percentage for 20 years and then equal to zero afterward.) The third term, $\mu Y_{0,0}(t)$, equals the number of uninfected people who die of non-AIDS–related causes, where μ is the non-AIDS–related death rate. (We use life-expectancy to determine μ, which assumes that men remain sexually active for their entire lifetime. Sensitivity analysis on this parameter indicates that the total health and economic outcomes are within 10 percent of the final results.) The fourth term, $p_0\lambda(t)Y_{0,0}(t)$, is the annual number of uninfected people who become infected, where p_0 is the average annual number of partnerships and $\lambda(t)$ is the probability of acquiring the infection from any one partner. The final term, $\omega Y_{0,1}(t)$, equals the number of vaccinated uninfected people who return to the uninfected state because the preventive effects of the vaccine wear off; the parameter 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. 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 several terms in common, which we explain here. Each equation for an unvaccinated state ($Y_{i,0}(t)$) has an immigration term ($I_{i,0}$) that represents the number of young homosexual men that enter state (i,0) when they reach the age of 18 years. Each equation has a term that represents the number of deaths due to non-AIDS–related causes ($-\mu Y_{i,j}(t)$) 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 immigration, 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 infected, 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 correctly identified as HIV-infected through a screening program ($-\sigma\xi Y_{1,0}(t)$), because they receive the preventive vaccine and thus alter their risk behavior ($-\nu_p(t)Y_{1,0}(t)$), because the disease progresses, or because they die of non-AIDS–related causes.

Equation 4 represents the change in time

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	
$Y_{i,j}(t)$	Number of people in disease stage i with vaccination status j at time t
$\lambda(t)$	Probability of acquiring the infection at time t from any one partner
$\lambda_{\nu}(t)$	Probability of acquiring the infection at time t from any one partner, under behavior modifications due to vaccination
$\beta_{i,j}$	Per-partner infectivity (chance of transmitting HIV) of individual in disease stage i with vaccination status j (note that this is per-partner, and not per-contact, infectivity)
p_i	Contact rate (number of new partners per year) of individual in disease stage i
$1/\mu_{i,j}$	Mean duration (in years) of disease stage i under vaccination status j
q_i	Quality-adjustment for a year of life in disease stage i
c_i	Annual cost of medical treatment for a person in disease stage i
$I_{i,j}$	Annual immigration of people in disease stage i with vaccination status j
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]
Population variables	
μ	Non-AIDS–related annual death rate
σ	Fraction of population that is screened annually for HIV
Other variables	
r	Annual discount rate
ξ	True-positive rate of screening process
Preventive-vaccine variables	
$\nu_p(t)$	Annual percent of uninfected people who receive preventive vaccine
κ_p	Per-person cost of the preventive vaccine
ε	Vaccine efficacy (percent of partnerships protected from infection)
$1/\omega$	Mean vaccine duration (years)
Δ_p	Change in condom use after preventive vaccine ($1.25 = 25$ percent increase, $0.75 = 25$ percent decrease)
Therapeutic-vaccine variables	
$\nu_t(t)$	Annual percent of identified asymptomatic infected people who receive therapeutic vaccine
κ_t	Per-person cost of the therapeutic vaccine
$1/\mu_{\nu}$	Additional years asymptomatic under vaccine therapy
β_{ν}	Change in infectivity of asymptomatics due to vaccine ($1 =$ no change, $0.75 = 25$ percent decrease)
Δ_t	Change in condom use after therapeutic vaccine ($1.25 = 25\%$ increase, $0.75 = 25$ percent decrease)

Table 4: Definition of model variables

State equations

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

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

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

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

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

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

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

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

$$\lambda(t) = \frac{\sum_{j=0}^{j=1}\sum_{i=1}^{i=4} p_i\,\beta_{i,j}n_{00,ij}Y_{i,j}(t)}{\sum_{j=0}^{j=1}\sum_{i=0}^{i=4} p_iY_{i,j}(t)} \quad (9) \qquad \lambda_\nu(t) = \frac{\sum_{j=0}^{j=1}\sum_{i=1}^{i=4} p_i\,\beta_{i,j}n_{01,ij}Y_{i,j}(t)}{\sum_{j=0}^{j=1}\sum_{i=0}^{i=4} p_iY_{i,j}(t)} \quad (10)$$

Outcome equations

$$C = \int_0^T [\kappa_p\nu_p(t)(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t\nu_t(t)Y_{2,0}(t)]e^{-rt}\,dt + \int_0^T \sum_{j=0}^{j=1}\sum_{i=0}^{i=4} c_iY_{i,j}(t)e^{-rt}\,dt \quad (11)$$

$$Q = \int_0^T \sum_{j=0}^{j=1}\sum_{i=0}^{i=4} q_iY_{i,j}(t)e^{-rt}\,dt \quad (12)$$

Table 5: Model equations

in the number of vaccinated unidentified infected asymptomatic men (state 1,1). Men enter state (1,1) through infection despite the vaccine ($p_0(1 - \varepsilon)\lambda_\nu(t)Y_{0,1}(t)$), or because they receive the preventive vaccine and thus alter their risk behavior ($\nu_p(t)Y_{1,0}(t)$). Men leave state (1,1) because they believe that the protective effects of a vaccine have waned ($-\omega Y_{1,1}(t)$), because they have been correctly identified as HIV-infected through a screening program ($-\sigma\xi Y_{1,1}(t)$), because the disease progresses, or because they die of non-AIDS–related causes.

Equation 5 represents the change in time in the number of identified infected asymptomatic men (state 2,0). Men enter state (2,0) through immigration, or because they have been correctly identified as HIV-infected through a screening program ($\sigma\xi(Y_{1,0}(t) + Y_{1,1}(t))$). They leave state (2,0) because they receive a therapeutic vaccine ($-\nu_t(t)Y_{2,0}(t)$), because the disease progresses, or because they die of non-AIDS–related causes.

Equation 6 represents the change in time in the number of vaccinated identified infected asymptomatic men (state 2,1). Men

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

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

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

Table 6: Initial conditions

enter state (2,1) because they receive a therapeutic vaccine ($\nu_t(t)Y_{2,0}(t)$). They leave state (2,1) because the disease progresses, or because they die of non-AIDS–related causes.

Equation 7 represents the change in time in the number of infected symptomatic men (state 3,0). Men enter state (3,0) through immigration or 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. ($\Sigma_{i=1}^{i=2}\Sigma_{j=0}^{j=1}\mu_{i,j}Y_{i,j}(t)$). They leave state (3,0) because the disease progresses, or because they die of non-AIDS–related causes.

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 ($\mu_{3,0}Y_{3,0}(t)$). They leave state (4,0) because the disease progresses, or because they die of non-AIDS–related causes.

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. We mention them solely to avoid confusion about the double summation notation in Equations 11 and 12.

Equations 9 and 10 describe $\lambda(t)$, the probability of acquiring the infection at time t from any one partner, and $\lambda_v(t)$, the probability of acquiring the infection at time t from any one partner under behavior modifications due to vaccination. These two probabilities are simply the sum over all infected states, $\Sigma_{j=0}^{j=1}\Sigma_{i=1}^{i=4}$, of the chance of selecting an infected partner in state (*i,j*) (e.g., $p_iY_{i,j}(t)/\Sigma_{j=0}^{j=1}\Sigma_{i=0}^{i=4}p_iY_{i,j}(t)$) multiplied by the probability that the virus will be transmitted in that partnership, $\beta_{i,j}n_{00,ij}$, where $\beta_{i,j}$ is the per-partner infectivity of a person in state (*i,j*) and the parameters $n_{00,ij}$ and $n_{01,ij}$ are the probability that a partnership between an uninfected person and a person in disease stage *i*, vaccination status *j*, is not protected by condoms, and the probability that a partnership between a vaccinated uninfected person and a person in disease stage *i*, vaccination status *j*, is not protected by condoms, respectively.

These last two parameters, $n_{00,ij}$ and $n_{01,ij}$, are derived from the data in Table 7 as follows. Table 7 gives the probability (based on his own disease stage and vaccination status) that an individual uses condoms in his partnerships. We assume that in a partnership between an individual in disease stage and vaccination status *ij* and an individual in disease stage and vaccination status *k, l,* the probability that the two of them will use condoms in their partnership ($g_{ij,kl}$) is the maximum of their individual probabilities:

$$g_{ij,kl} = \max(h_{ij}, h_{kl})$$

Disease stage and vaccination status (*i,j*)	Probability of condom use (h_{ij})
0, 0	0.55
0, 1	$h_{0,0}{}^{*} \Delta_p$
1, 0	0.55
1, 1	$h_{0,0}{}^{*} \Delta_p$
2, 0	0.77
2, 1	$h_{2,0}{}^{*} \Delta_t$
3, 0	0.85
4, 0	0.85

Derived from Communication Technologies in association with the San Francisco AIDS Foundation [1990] assuming that if a person says he always uses condoms, he actually uses them 95 percent of the time, and that if a person says he sometimes uses condoms, he actually uses them 50 percent of the time.

Table 7: Condom-use data

Then the probability that a partnership between an uninfected person and a person in disease stage i, vaccination status j, is not protected by condoms ($n_{00,ij}$) is:

$$n_{00,ij} = fg_{00,ij} + (1 - g_{00,ij}),$$

where $f = 10$ percent is the per-partnership probability of condom failure [Trussell et al. 1990]. Similarly, the probability that a partnership between a vaccinated uninfected person and a person in disease stage i, vaccination status j, is not protected by condoms ($n_{01,ij}$) is:

$$n_{01,ij} = fg_{01,ij} + (1 - g_{01,ij})$$

Equation 11 calculates the total discounted economic costs. The first term, $\int_0^T [\kappa_p \nu_p(t)(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t(t) Y_{2,0}(t)]e^{-rt}dt$, represents the discounted direct cost of the vaccine program, where κ_p and κ_t are the per-person direct costs of vaccination, $\nu_p(t)(Y_{0,0}(t) + Y_{1,0}(t))$ and $\nu_t(t)Y_{2,0}(t)$ are the numbers of people who receive the preventive and therapeutic vaccines each year, r is the discount rate, and T is the time-horizon of interest. The second term, $\int_0^T \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j}(t) e^{-rt}dt$, is the discounted cost of medical treatment, where the double sum is over all states and c_i is the annual cost to treat a patient in disease stage j.

Equation 12 calculates the total discounted QALYs lived by the population. The form is the same as that of the second term in Equation 11, with c_i replaced by q_i, the QALY adjustment for a year of life in disease stage j.

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