Microbicides and HIV: Help or Hindrance?

Eran Karmon, Malcolm Potts, and Wayne M. Getz

Abstract: We present a simple mathematical model for assessing the effects of introducing a microbicide as an HIV infection protective method. As very little is known about the in vivo efficacy of microbicides, we ran sample scenarios for microbicides of various efficacies. We found that, in general, if existing condom usage in a community is low, introducing a microbicide will most likely have a positive impact on HIV incidence as abandonment of condom use in favor of microbicides will not play a significant role. If condom use in a community is high, though, attrition of condom users could play a role large enough to overwhelm any added risk reduction afforded new microbicide users. Our model illustrates the importance of knowing key behavioral parameters, such as the proportion of the population that uses condoms, before microbicides can be safely introduced. These parameters include the proportion of condom users likely to maintain condom use and the proportion of condom nonusers likely to adopt microbicides, as well as the efficacy of the candidate microbicide.

Key Words: HIV, prevention, microbicides, condoms, mathematical model

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The use of vaginal microbicides as HIV transmission barriers has been advocated for some time, but development has been slow.[1] A vaginal preparation inserted before intercourse may be more acceptable to a large number of women who know their sexual partner may be a risk of HIV infection but who cannot negotiate the use of condoms.[2] In the role of reaching out and empowering women for whom condom use is not possible, microbicides could be a significant force in reducing new HIV infections. At the same time, new intervention methods may lead to changes in risk behavior.[3,4] For example, a microbicide may be associated with some condom users switching away from condoms, with the possible consequence of putting those users at higher risk. Given that condoms are highly likely to be a more effective barrier against HIV transmission,[5] even a small reduction in their use can significantly affect the epidemic.

Clinical trials that accurately gauge microbicide efficacy in reducing HIV transmission risk are difficult to conduct.[6] Thus the variance associated with estimates of microbicide efficacy is likely to be fairly large. Further, predicting whether the availability of a microbicide will counteract any increased risk resulting from changes in condom use should prove to be difficult. The only completed clinical trials of microbicide efficacy in vivo are for the detergent nonoxynol 9. It was found to have no significant impact on HIV infection rates.[7] Apart from this trial, to the best of our knowledge, only in vivo tests of potential microbial compounds have been undertaken.

Here we address the concerns raised above by using a simple disease transmission model to examine how uncertainty in microbicide efficacy and switching away from condom use may affect the future course of an HIV/AIDS epidemic. We ask what level of abandonment of condoms would be needed to overwhelm the potential advantage of increased protection due to microbicides and also how microbicides of different efficacies could be expected to affect the future course of an HIV epidemic.

THE MODEL

The rate of production of new cases for an infectious disease in a homogeneous population is typically modeled as $\Gamma SI/N$,[8] where S is the number of susceptible individuals, I is the number of infected individuals, N the population size, and Γ the probability of infection given contact with an infected individual, or average risk of infection per partnership with an infected individual.

In a population in which condoms are used by a proportion γ_c of the population and prevent infection in a proportion ε_c of the contacts in which they are used, per exposure risk is:

$$\Gamma_c = \beta(1 - \varepsilon_c\gamma_c), \quad (1)$$

where β is the per exposure risk of HIV infection when no protection of any kind is used.

Equation 1 assumes that some proportion γ_c of a population uses condoms and some proportion $1 - \gamma_c$ uses no pro-

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From the Biophysics Graduate Group (Dr Karmon), School of Public Health (Dr Potts), and Department of Environmental Science, Policy and Management, University of California, Berkeley (Dr Getz).

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Reprints: Wayne M. Getz, Department of Environmental Science, Policy and Management, University of California, 201 Wellman Hall, Berkeley, CA, 94720-3112. (e-mail: getz@nature.berkeley.edu).

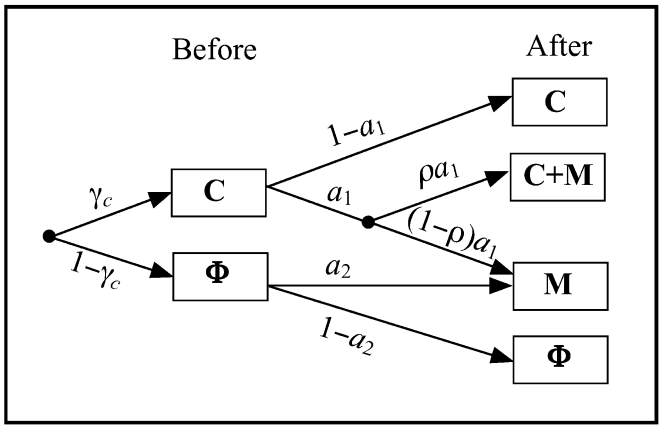

FIGURE 1. Flow rates between groups after microbicide introduction. Before introduction the population is divided into a proportion γ_c of condom users (group C) and $1 - \gamma_c$ nonusers (group Φ). After introduction, condom users can either maintain sole condom use (group C) or condom use concurrent with microbicide use (C + M), or they may abandon condom use in favor of sole microbicide use (group M). Condom nonusers either adopt microbicide use or remain protection nonusers.

tection whatsoever. Suppose that once microbicides are introduced into a population, a proportion α_1 of the condom users starts using microbicides and a proportion α_2 of the nonusers starts using microbicides (Fig. 1). Of the proportion of condom users adopting microbicides, some proportion ρ ceases using condoms. Under these assumptions, it follows that the risk per contact is:

$$\Gamma_{cm} = \beta(1 - \varepsilon_c\gamma_c(1 - a_1) - \gamma_c\rho a_1\varepsilon_{cm} - \varepsilon_m(\gamma_c a_1(1 - \rho) + a_2(1 - \gamma_c))), \quad (2)$$

where

$$\varepsilon_{cm} = (1 - (1 - \varepsilon_c)(1 - \varepsilon_m)). \quad (3)$$

In the absence of data to the contrary we assume that condoms and microbicides confer protection independently.

For risk before the introduction of microbicides to be lower than risk after introduction, the conditions $\Gamma_{cm} < \Gamma_c$ must hold. This corresponds to the following threshold condition that the proportion ρ of condom users abandoning condoms must satisfy:

$$\rho < \rho_{thresh} = \frac{a_2\varepsilon_m(1 - \gamma_c) + a_1\gamma_c(\varepsilon_m - \varepsilon_c)}{a_1\varepsilon_c(\varepsilon_m - 1)\gamma_c} \quad (4)$$

to ensure that the average per contact risk in the population will be less after microbicide introduction.

SAMPLE SCENARIOS

The efficacy of condoms ranges between 0.85–0.98[5] (i.e., $0.85 < \varepsilon_c < 0.98$). Additionally we assume that the efficacy of a microbicide is somewhere between 0.2–0.6. The actual in vivo efficacy of candidate microbicides, however, is not yet known. Because clinical trials of microbicide efficacy are very difficult to conduct, the variance surrounding any estimate of their efficacy will be high. Our analysis here is conducted in the vein of a tale cautioning that if microbicide efficacy is substantially less than that of condoms, i.e., around 0.3–0.7, then a public health education campaign must stress that they cannot be used as a substitute for condoms, only as an additional weapon in the fight against the transmission of HIV. With this in mind, we present several scenarios using different parameter values—actually distributions of values because high variance is likely to be associated with estimates of microbicide efficacy and some of the other model parameters. The precise shape of the parameter distributions is not critical to our analysis. Rather, we seek to provide a sense of the degree to which microbicide introductions could exacerbate AIDS epidemics in various communities if the message of this paper is not heeded.

In our first scenario we consider a distribution of microbicide efficacies over the range $0.2 < \varepsilon_m < 0.6$ (see model in the Appendix and Fig. 1 for details of how this and other parameters mentioned below enter into the model equations). In sub-

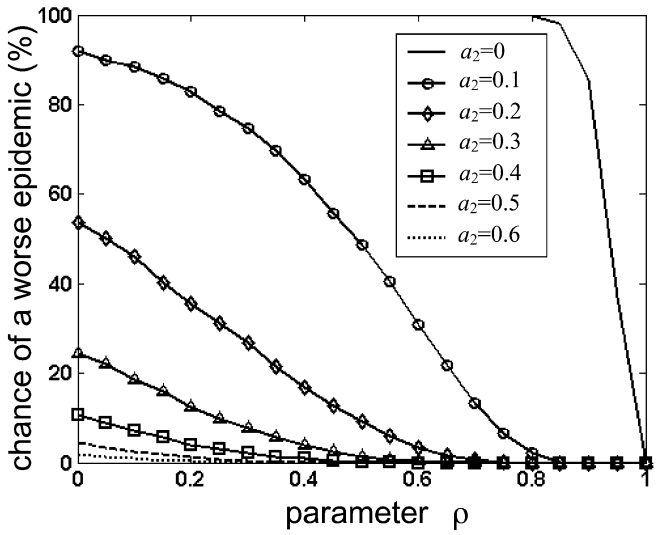

FIGURE 2. The probability of a worse epidemic for various values of parameter ρ, the proportion of condom users adopting microbicides while maintaining condom use, and parameter a_2, the proportion of condom nonusers adopting microbicides. Probabilities were found by counting the number of times out of 20,000 draws of the remaining model parameters from triangular distributions that resulted in per-exposure average HIV infection risk growing after microbicide introduction. Parameters were drawn over the following intervals: $0.85 < \varepsilon_c < 0.98$, $0.2 < \varepsilon_m < 0.6$, $0.4 < a_1 < 0.6$, and $0.1 < \gamma_c < 0.4$.

sequent scenarios we will also consider efficacies over the range $0.4 < \varepsilon_m < 0.8$. We continue with our first scenario by supposing that 40–60% of condom users start using microbicides (i.e., $0.4 < a_1 < 0.6$) and 10–40% of the population uses condoms before microbicides are available (i.e., $0.1 < \gamma_c < 0.4$). This latter range is consistent with African communities where condom use rates have been measured.[9]

In Figure 2 we plot results from model simulations of the chances that a worse epidemic occurs as a function of the proportion ρ of condom users that abandons condoms once microbicides are introduced. We do this for specific proportions a_2, ranging from 0.0–0.6, of condom nonusers that begin using the introduced microbicides. As expected, if no condom nonusers adapt microbicides ($a_2 = 0$) then any attrition of condom users results in a worse epidemic. More instructive is the fact that the probability of a worse epidemic remains positive even when 60% of condom nonusers adopt microbicides, provided the proportion of condom users abandoning condoms upon the in-

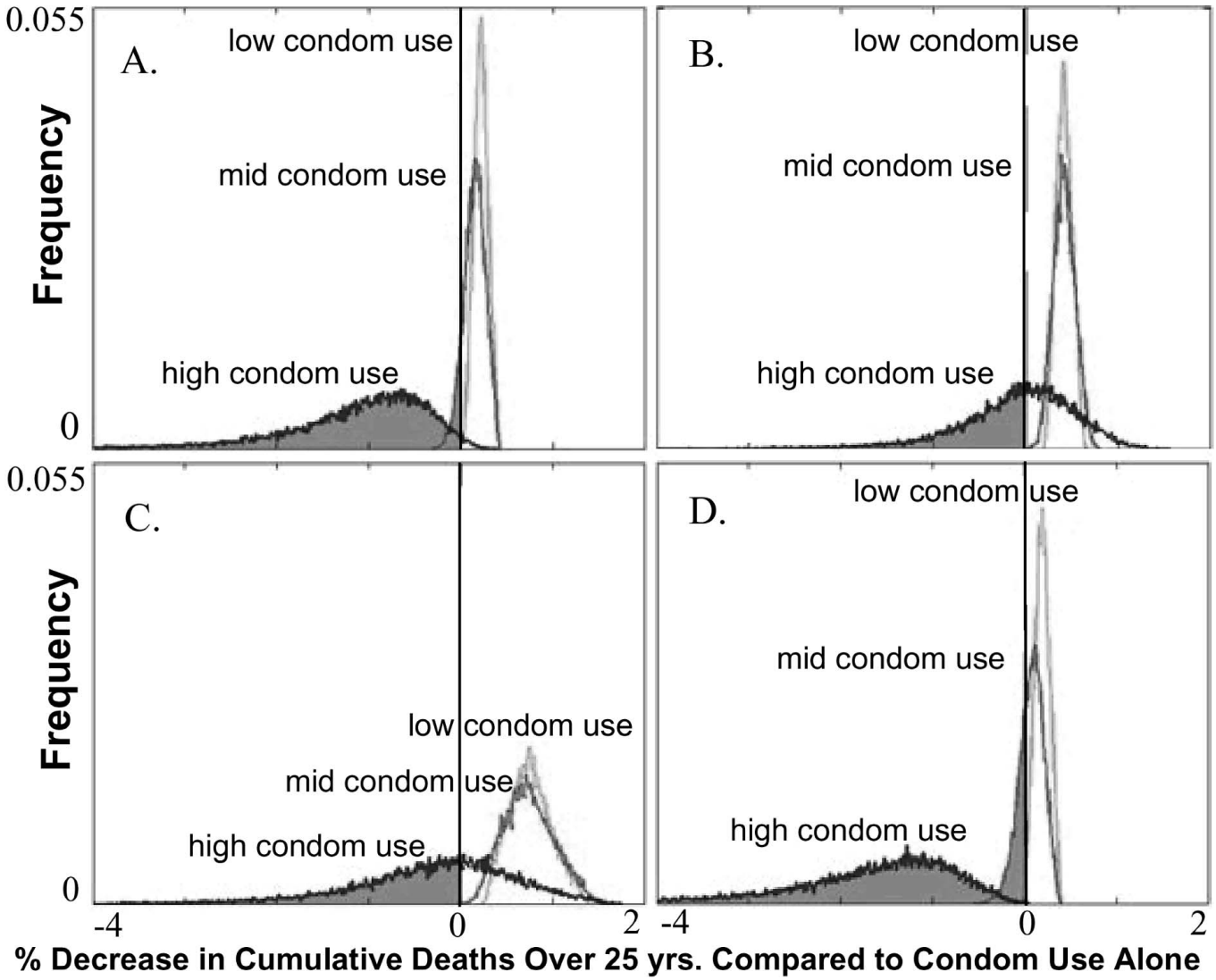

FIGURE 3. Probability distributions of percent reduction in cumulative deaths over 25 years under microbicide and condom use compared with condom use alone for low (5–20%), medium (10–40%), and high (50–80%) proportions of the population using condoms before microbicides become available: viz. the area under the curve to the left of any negative percent value on the abscissa represents the probability that number of deaths will exceed that percent value if microbicides are introduced. (Note negative values correspond to % increase in deaths so that the gray area represents greater deaths under microbicide.) Parameters were drawn from triangular distributions over the indicated intervals or given the indicated fixed values (for explanation of parameters see Table 1). **A**, $0.2 < \varepsilon_m < 0.6$, $\alpha_2 = 0.2$, and $\rho = 0.5$. **B**, $0.4 < \varepsilon_m < 0.8$, $a_2 = 0.2$, and $\rho = 0.5$. **C**, $0.2 < \varepsilon_m < 0.6$, $a_2 = 0.5$, and $\rho = 0.5$. **D**, $0.4 < \varepsilon_m < 0.8$, $a_2 = 0.5$, and $\rho = 0.3$. In all cases, $0.85 < \varepsilon_c < 0.98$, $0.1 < \gamma_c < 0.4$, and $0.4 < a_1 < 0.6$. Also for all cases, epidemic model parameters were set as follows: $\delta = 7\text{yr}$, $\Delta = 5000\text{yr}^{-1}$, $\mu = 1/34\text{yr}$, $c = 12\text{yr}^{-1}$.

troduction of microbicides remains <40%. As suggested by Eq. 2, Figure 2 shows that the threshold for the proportion of condom users abandoning condom use falls as the proportion of condom nonusers adopting microbicides rises. For example, if half of the condom users who have taken on microbicides abandon condoms ($\rho = 0.5$) then the chance of a worse epidemic is just <50%.

Apart from the simple probability of a worse epidemic under microbicide use, health authorities would want to have some inkling of the magnitude of any increases or decreases in deaths due to AIDS that could be expected to result from microbicide introduction. The intricacies of a real HIV epidemic, such as differences in the sexual behavior of individuals and the presence of other disease cofactors (e.g. *Chlamydia* or tuberculosis), make it impossible to predict such numbers with precision. However, estimates from single-group SIR models,[10] modified to include frequency rather than mass-action transmission[11] (Appendix), provide a rough first-cut at such numbers. This cut establishes a baseline set of values for comparison with more sophisticated analysis; and these baseline values are generally more useful for assessing relative (i.e., percentage) than absolute (i.e., total number) changes due to the introduction of a particular microbicide.

We used stochastic simulations of our model to generate distributions of the percent of additional (cumulative) deaths after 25 years under both microbicide and condom use compared with condom use alone (20,000 simulations for each distribution with initial conditions set by running the model without any intervention method until steady state was reached). We did this for low, medium, and high levels of condom usage under a variety of scenarios (Fig. 3) to assess the degree to which the potential impact of a microbicide is strongly affected by the amount of condom use in a population prior to microbicide introduction.

In a low-use population (5–20%) the probability of a worse epidemic is virtually zero after introduction of a microbicide with an efficacy of 20–60% (Fig. 3A) while in a high-use population (50–80%) it is a staggering 98%. In this latter case, the increase in cumulative deaths could be as high as 6%. These results indicate the importance of only introducing microbicides into communities where existing condom use is either very low or a strong educational campaign stresses that microbicides are a supplement to condom use and should be used alone only in cases where condom use is impossible.

The potential negative impacts are, of course, less if microbicide efficacy is increased from the range 20–60% to 40–80% (Fig. 3B). In the high-condom-use category, however, the probability of a worse epidemic is still >50% (Fig. 3B) and in the worst cases cumulative deaths over 25 years will increase by >4%. Another way to reduce the chance of a worse epidemic is by increasing the proportion of condom nonusers who take up microbicides from 20% (Fig. 3A) to 50% (Fig. 3C) (α_2). Figure 3C shows results for a 20–60% effective microbicide, but with $a_2 = 0.5$. In this case the probability of a worse epidemic is reduced to just below 60%.

TABLE 1. Parameters Used in the Model

γ_c	Proportion of population using condoms before microbicide introduction
a_1	Proportion of condom users adopting microbicides
ρ	Proportion of condom users adopting microbicides who abandon condoms
a_2	Proportion of condom nonusers adopting microbicides
ε_c	Efficacy of condoms (percent by which condom use reduces HIV transmission probability)
ε_m	Efficacy of microbicides (percent by which microbicide use reduces HIV transmission probability)
c	Average number of contacts per year
δ	Average time from infection to death in years
Λ	Number of immigrants into population per year
μ	Average residence time in population in years

Any decrease in the proportion of condom users abandoning condom use in favor of microbicides would not only have dire consequences for the individuals involved but could potentially be disastrous from a public health point of view. For example, a decrease in condom users from $\rho = 0.5$ to $\rho = 0.3$ for the more effective microbicide case (compare Fig. 3D with B) results in a dramatic increase in chance of a worse epidemic from virtually 0 to 27% in populations that have medium condom use. This bleak scenario illustrates the importance of maintaining condom use reduction to an absolute minimum.

CONCLUSIONS

We developed a simple model for assessing the potential effects of microbicide introduction and demonstrated the dangers posed by nontarget groups (e.g., condom users) taking up microbicides in favor of condoms. Simple models cannot predict real outcomes with precision because they omit many features certain to affect the course of an epidemic. Even the most complex models, however, omit details that could prove critical in predicting outcomes. Thus dramatic predictions from models—whether from simple models such as ours or from models more complex than ours—serve more as a call to action for careful surveillance and assessment of a population before microbicides are introduced than as a way of foretelling the future. Variables such as the proportion of condom users abandoning condoms (ρ) and the proportion of the target group of condom nonusers adopting microbicides (a_2) are very difficult to anticipate, but as our simulations show, their values greatly affect the probability of worsening an AIDS epidemic. Thus, until microbicides have efficacies comparable to condoms, they can only be used to complement, rather than substitute for, condom use.

APPENDIX

Modified SIR Model

Let S be the number of susceptible individuals in a perfectly mixing, homogeneous population, I be the number of infected individuals, and R be the number of individuals who have died due to AIDS ($R = 0$ at time = 0). Further, N is total population size $S + I$, c is the average number of new sexual partners per person per year, Λ is annual immigration, μ is the annual per capita attrition rate, and δ is average time from infection until death. Γ is the method-specific risk of infection per contact term. $\Gamma = \Gamma_c$ (Eq. 1) in a population in which only condoms are available, Γ_{cm} (Eq. 2) for a population in which both condoms and a microbicide are available, and 1 if neither method is available. The SIR[10] model modified to include frequency rather than mass action transmission[11] comprises the following three equations:

$$\frac{dS}{dt} = \Lambda - \frac{cSI}{N}\Gamma - \mu S \quad (5)$$

$$\frac{dI}{dt} = \frac{cSI}{N}\Gamma - \frac{1}{\delta}I - \mu I \quad (6)$$

$$\frac{dR}{dt} = \frac{1}{\delta}I. \quad (7)$$

For this study, the following parameter values are used: δ = 7yr,[12] Λ = 5000yr^{-1}, μ = 1/34yr, c = 12yr^{-1}. β, the risk of infection per contact given no protection is used, is set to 0.2. Initial conditions were found by running a model with no protection methods and the following initial conditions to equilibrium: $S_o = 100{,}000$, $I_o = 25000$. The initial number of deaths R_o was set to 0 for the simulations including protection methods.

Triangular Distributions

The sum of 2 random variables each uniformly distributed on an interval $[x_1, x_2]$ has a triangular distribution on $[x_1, x_2]$ with mean and mode $(x_1 + x_2)/2$. We use triangular rather than uniform distributions because a triangular, unlike a uniform, distribution is continuous when defined to be 0 for $x \leq x_1$ and $x \geq x_2$.

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