Evaluating the potential impact of vaginal microbicides to reduce the risk of acquiring HIV in female sex workers

Robert J. Smith, Erin N. Bodine, David P. Wilson and Sally M. Blower

Objectives: The following questions were addressed: would the introduction of vaginal microbicides substantially reduce the risk of female sex workers (FSWs) acquiring HIV? Which factor would it be most important to maximize, microbicide efficacy or microbicide use? What level of microbicide efficacy and use would be necessary to counterbalance a possible reduction in condom use?

Design: Mathematical modeling, with parameter estimations from available literature.

Methods: Risk equations were developed and Monte Carlo simulations were performed to model a FSW's daily risk of HIV acquisition currently, and after, microbicide introduction. Uncertainty and sensitivity analyses were used as well as *tornado* plots for two ranges of microbicide efficacy (30–50%) and (50–80%). Risk was estimated for FSWs whose clients sometimes (10–50%) use condoms, and those whose clients never use condoms. An analytical threshold for which reducing condom use increases risk was estimated.

Results: For both groups of FSWs, daily risk would decrease by approximately 17% or approximately 28% using 30–50% or 50–80% effective microbicides, respectively. Increasing microbicide use would have greater impact on reducing risk than increasing microbicide efficacy. The microbicide efficacy and usage required to ensure that 'condom replacement' does not increase a FSW's risk of acquiring HIV was calculated.

Conclusions: Microbicides could substantially reduce FSWs' risk of acquiring HIV; absolute decrease in risk would be greatest in high-prevalence regions. The public health impact of microbicides will depend upon usage and efficacy. Even if the microbicides that become available are only low-to-moderately effective, the probability that risk in FSWs will increase (due to replacing condoms with microbicides) is low.

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Introduction

Vaginal microbicides are chemical compounds which can be applied topically to prevent or reduce the transmission of HIV [1–3], including neonatal transmission [4,5], and other sexually transmitted diseases [4,6]. Currently, there are around 60 candidate vaginal microbicides in development [7–9], 18 of which have advanced to clinical testing [7,9]. Two phase III microbicide trials are underway, with the prospect of at least one more this year in several African countries, including South Africa, Tanzania and Zambia [8]. The funding stream and enthusiasm for microbicides is high [10,11], but microbicides are not expected to be on the market before 2013 [7]. Current efforts are aimed at developing intravaginal topical formulations to curb mucosal and

From the Department of Biomathematics and UCLA AIDS Institute, David Geffen School of Medicine at UCLA, Westwood, California, USA.

Correspondence to Sally M. Blower, Department of Biomathematics and UCLA AIDS Institute, David Geffen School of Medicine at UCLA, 1100 Glendon Ave PH2, Westwood, CA 90024, USA.

E-mail: sblower@mednet.ucla.edu

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perinatal HIV transmission by directly inactivating HIV or preventing HIV from attaching, entering or replicating in susceptible target cells as well as dissemination from target cells present in semen or the host cells that line the vaginal wall [9,12,13]. Vaginal microbicides may provide an alternative mechanism of protection for women whose partners are unwilling to use condoms [2,3,8,13–17], and could also be applied in addition to condoms [2,3]. The hope is that microbicides can be added to lubricants for convenient use or combined with a contraceptive [3,9]. It has often been assumed that, initially, the efficacy of microbicides is likely to be significantly lower than condoms [18,19].

Worldwide, more than one-half of the 42 million people living with HIV/AIDS are women [1], with more than 90% of all adolescent and adult HIV infections resulting from heterosexual intercourse [9]. It has been reported that female sex workers (FSWs) in Central Java, Indonesia, accounted for 56% of HIV cases in the province at the end of 1998 [20]. Prevalence of HIV in high-risk zones in the developing world ranges from 13% in FSWs in Abidjan, Cote d'Ivoire [21] to 56% among truck drivers visiting FSWs in KwaZulu-Natal, South Africa [18]. Currently, condoms are the only method of protection available for individuals who have vaginal sex. Condoms are highly effective at preventing HIV transmission, with an estimated efficacy of 87% [22–26] (thus, condoms would prevent transmission in 87% of sexual acts between discordant partners), but studies suggest that condom use is often low [2,27,28]. A study in Central Java indicates that 30% of FSWs never use condoms with their clients during sex [20]. In the United States, it has been reported that 38% of heterosexuals who have multiple partners never use condoms [29]. Furthermore, when condoms are used, their use may be infrequent. Coital diaries of FSWs in Durban, South Africa, suggest that the mean weekly condom use is only 2.7 per 23.3 clients (12%) [30]. Clients perceive condoms as barriers to sexual pleasure and therefore pay less when condoms are used [31] sex without condoms in Durban, South Africa, was worth twice as much (US $20) as sex with condoms (US $10) [31].

In the present study we addressed three questions: (1) would the introduction of vaginal microbicides substantially reduce the daily risk of FSWs acquiring HIV infection? (2) Which factor would it be most important to maximize, microbicide efficacy or microbicide use? (3) What level of microbicide efficacy and use would be necessary to counterbalance a possible reduction in condom use? We examined the potential impact of microbicide efficacy by considering both low-to-moderate (30–50%) and moderate-to-high (50–80%) efficacy microbicides. We also evaluated heterogeneity in FSWs by considering FSWs who sometimes use (FSW-Cs) and FSWs who never use (FSW-NCs) condoms with their clients. We defined a FSW's risk as the chance, per day, of becoming infected with HIV. We formulated risk equations for the probability of acquiring HIV, both currently and post-vaginal-microbicide introduction (post-VMI). Currently, the only protection options are condoms or no protection, whereas post-VMI, protection options would consist of condoms only, vaginal microbicides only, using vaginal microbicides with condoms, or no protection. It has been postulated [2,14] that the introduction of microbicides may lead to a reduction in condom use, where partners replace condoms with microbicides. This has been termed 'condom migration' [2]. We suggest the term 'condom replacement' is more appropriate and comprehensible than 'condom migration'. We calculated the microbicide efficacy and usage required to ensure that 'condom replacement' does not increase a FSW's risk of acquiring HIV.

Methods

We developed risk equations for a FSW, both currently and post-VMI, and we analyzed these risk equations for both FSW-Cs and FSW-NCs. These risk equations take into account the prevalence of HIV among FSWs' clients (P), the average number of vaginal sex partners per day (c), the transmission probability of HIV per vaginal sex act (β), the number of vaginal sex acts per partner per day (n), condom efficacy (e_c), and expected microbicide efficacy (e_m). Our risk equations also include the proportion of sex acts in which: (1) only condoms are used (p_0 currently, p_1, post-VMI); (2) only microbicides are used (p_2); or (3) both condoms and microbicides are used (p_3). The proportion of sex acts in which no protection is used currently is $(1-p_0)$ and will be $(1-p_1-p_2-p_3)$ post-VMI. The proportions of acts of all protection types sums to 1.

When a condom, microbicide, or a condom with microbicide is used during a single sex act, the probability that HIV is transmitted is reduced from the probability β to β' (where $\beta' < \beta$). We have modeled single coital acts and thus the transmission probability of each act is significantly less than the transmission probability over the duration of a long-term partnership. Our transmission probability range reflects this and is taken from the published literature [19,32,33]. If β' is the probability of transmission during a single sex act with a given protection type (condom, microbicide, both condom and microbicide, or no protection), then the probability of remaining uninfected during the single sex act is $(1-\beta')$. The probability of remaining uninfected after N *discordant* sex acts (sex acts with HIV-infected persons) is thus $(1-\beta')^N$. FSWs have n sex acts per partner with c sex partners per day who come from a client pool where HIV prevalence is P; thus $N = ncP$ is the total number of discordant sex acts per day. The number of discordant sex acts per day in which a given type of protection is used in a

proportion p of all sex acts is $pncP$. Thus, the probability of HIV acquisition for a FSW is

$$\text{Risk} = 1 - \prod_{i}^{\text{all protection option}} [1 - \beta']^{p_i ncP} \quad (1)$$

Currently (when the only protection options are condoms or no protection), a FSW's risk per day, r_1, is

$$r_1 = 1 - \left\{ [1 - (1 - e_c)\beta]^{p_0} [1 - \beta]^{(1-p_0)} \right\}^{ncP} \quad (2)$$

Post-VMI (when the available protection options are condoms, microbicides, both condoms and microbicides, or no protection), a FSW's risk per day, r_2, will be

$$\begin{aligned} r_2 = 1 - \{ & [1 - (1 - e_c)\beta]^{p_1} [1 - (1 - e_m)\beta]^{p_2} \\ & \times [1 - (1 - e_c)(1 - e_m)\beta]^{p_3} \\ & \times [1 - \beta]^{(1-p_1-p_2-p_3)} \}^{ncP} \end{aligned} \quad (3)$$

Initially, we assumed that after microbicides are introduced FSWs will continue to use condoms with their clients in the same proportion of sex acts ($p_0 = p_1 + p_3$) as pre-microbicides. We have assumed that current condom usage (p_0) is 10–50% [20,29,34–39] (see Table 1). To satisfy the condition of no 'condom replacement' (i.e. $p_0 = p_1 + p_3$), we set $p_1 = \alpha p_0$ (where α ranges from zero to one) and rearrange $p_0 = p_1 + p_3$ to find $p_3 = p_0 - p_1$. We also assumed microbicide only use would be similar to current condom use and thus gave p_2 the same range as p_0 (see Table 1).

We have used suffixes NC and C to denote proportion of protection types used by the two groups of FSWs, namely FSW-NC and FSW-C respectively. It is assumed FSW-NCs will use microbicides for some proportion of their sex acts (p_2^{NC}), but will continue using no protection for the remainder of their sex acts ($1 - p_2^{NC}$). As FSW-NCs do not use condoms, $p_0^{NC} = 0$ and $p_3^{NC} = 0$. For comparison of FSW-Cs and FSW-NCs we have assumed that total microbicide use would be the same in both groups. Thus, we set the proportion of acts where only a microbicide is used for FSW-NCs equal to the proportion of acts where a microbicide is used (either solely or with condoms) for FSW-Cs (i.e., $p_2^{NC} = p_2^{C} + p_3^{C}$). As the

Table 1. Parameter values for female sex workers (FSWs).

Parameter	Description	Parameter range			Reference
		Min	Peak	Max	
c	Number of vaginal sex partners per day	1	–	8	[20,30,45–47]
P	Prevalence of HIV among men paying for sex	0.10	–	0.60	[18,21,48,49]
n	Number of vaginal sex acts per partner per day	1	–	2	[a]
e_c	Efficacy of condoms used during vaginal sex	0.60	0.87	0.95	[22–26]
e_m	Expected efficacy of vaginal microbicides	0.30 [19,32,33]	–	0.50	[b]
β	Transmissibility per vaginal sex act of HIV from male to female	0.50 0.0005	– 0.0009	0.80 0.001	
p_0	Proportion of vaginal sex acts where a condom is used (pre-VMI)	0.10	–	0.50	[20,29,34–39]
p_1	Proportion of vaginal sex acts where only a condom is used (post-VMI)		$p_1 = \alpha \cdot p_0$, where $0 < \alpha < 1$		[c]
p_2	Proportion of vaginal sex acts where only a vaginal microbicide is used (post-VMI)	0.10	–	0.50	[d]
p_3	Proportion of vaginal sex acts where a condom and a vaginal microbicide are used (post-VMI)		$p_3 = p_0 - p_1$		[c]
p_4	Proportion of vaginal sex acts where no protection is used		$p_4 = 1 - p_1 - p_2 - p_3$		[e]

[a]This parameter value was estimated by assuming that any client of a FSW would likely have only one or two sex acts per day.
[b]Since potential microbicide efficacy is still unknown we modeled both low (30–50%) and high (50–80%) efficacy microbicides.
[c]Equations defined such that 'condom replacement' does not occur.
[d]We assume microbicide use will be similar to current condom use.
[e]Ensures that the proportions of the four types of sex acts sum to 1.
VMI, vaginal microbicide introduction. All distributions in this table are uniform unless a peak value is given, in which case the distribution is triangular.

potential microbicide efficacy is still unknown we have modeled both low/moderate (30–50%) and moderate/high (50–80%) efficacy microbicides. Ranges for all other parameters (c, P, n, e_c, and β) were taken from current behavioral, clinical, experimental, and demographic literature (Table 1). All distributions in Table 1 are uniform unless a peak value is given, in which case the distribution is triangular.

To evaluate the potential impact of vaginal microbicides for reducing the risk of HIV acquisition in both groups of FSWs, we analyzed our risk equations with uncertainty analysis using Monte Carlo simulations and multivariate sensitivity analysis (as described in Refs [40–42]). In the uncertainty analysis we computed the value of risk over a wide parameter space to assess the variability of our dependent variable (risk per day of acquiring HIV). Parameter space was sampled using Latin Hypercube Sampling described in [40]. For our sensitivity analysis we calculated the partial rank correlation coefficients (PRCCs); see [40] for the discussion, and formula for calculating PRCCs.

To show which parameters the daily risk is most sensitive to, we used *tornado* plots [43] of PRCCs for each of the independent parameters for FSW-NCs and FSW-Cs. *Tornado* plots illustrate those parameters that have the greatest effect on the outcome, in descending order. Parameters with PRCC > 0 increase a FSW's daily risk as the parameter value increases, whereas parameters with PRCC < 0 decrease a FSW's daily risk as the parameter value increases. To determine whether it would be more important to maximize microbicide use or microbicide efficacy, we set all parameters except those which represent microbicide use or efficacy to their median value (calculated over all sampled values within the parameters given range in Table 1), and plotted microbicide use versus microbicide efficacy denoting the percentage decrease in daily risk for each Monte Carlo simulation.

Finally, we have calculated the microbicide efficacy and usage that would be necessary to offset 'condom replacement'. We consider the worst-case situation of complete 'condom replacement', that is, FSWs who are currently using condoms abandon condoms altogether post-VMI (and hence use only microbicides or no protection). Thus, post-VMI $p_1 = p_3 = 0$. Clearly, microbicides will be beneficial (i.e. decrease a FSW's risk per day) to a FSW if the risk of transmission after the introduction of microbicides is less than the current risk. By equating the current risk, r_1, and the risk post-VMI, r_2, we have calculated an analytical expression for the threshold level of microbicide efficacy and use that would be necessary to offset condom replacement. Accordingly, the outcome for FSWs will be beneficial if

$$[1-(1-e_m)\beta]^{p_2}[1-(1-e_c)\beta]^{-p_0}[1-\beta]^{(p_0-p_2)} > 1$$

and perverse (i.e. increase a FSW's risk per day) if the reverse inequality holds.

Results

Microbicides could reduce a FSW's risk significantly, whether her clients currently sometimes (FSW-Cs) or never (FSW-NCs) use condoms. Table 2 describes the distribution of the risk (currently and post-VMI) and percentage decrease in risk for FSW-Cs and FSW-NCs, for two ranges of microbicide efficacy: 30–50% (low/moderate efficacy) and 50–80% (moderate/high efficacy). For low/moderate efficacy microbicides, the median decrease in risk is 17% [interquartile range (IQR), 11.8–22.8%] for FSW-Cs and 17.5% (IQR, 12.8–22.4%) for FSW-NCs. For moderate/high efficacy microbicides, the median decrease in risk is 27.7% (IQR, 19.2–36.9%) for FSW-Cs and 28.5% (IQR, 20.8–36.4%) for FSW-NCs. Note that the median percentage decrease

Table 2. The daily distribution of risk of HIV acquisition currently [pre-vaginal microbicide introduction (pre-VMI)] and post-vaginal microbicide introduction (post-VMI) and the percentage decrease in risk for female sex workers who use condoms with their clients (FSW-C) and female sex workers who never use condoms with their clients (FSW-NC), calculated by Monte Carlo simulations of our risk equation.

	FSW-C			FSW-NC		
	Pre-VMI	Post-VMI	% Decrease	Pre-VMI	Post-VMI	% Decrease
$e_m = 30–50\%$						
Min	9.2157E-05	8.0500E-05	4.0	1.4970E-04	1.2253E-04	3.6
First IQ	0.00119	0.00097	11.8	0.00158	0.00130	12.8
Third IQ	0.00369	0.00305	22.8	0.00488	0.00399	22.4
Max	0.01982	0.01875	45.8	0.02331	0.02106	45.9
Median	0.00213	0.00175	17.0	0.00283	0.00232	17.5
$e_m = 50–80\%$						
Min	9.2157E-05	6.3041E-05	6.3	1.4970E-04	9.8661E-05	5.8
First IQ	0.00119	0.00082	19.2	0.00158	0.00110	20.8
Third IQ	0.00369	0.00265	36.9	0.00488	0.00344	36.4
Max	0.01982	0.01807	73.7	0.02331	0.02024	73.6
Median	0.00213	0.00149	27.7	0.00283	0.00198	28.5

Here, e_m denotes the microbicide efficacy and IQ is the statistical interquartile range from our uncertainty analysis.

for both FSW-Cs and FSW-NCs is similar in each case; however, median daily risk for each group is quite different. Furthermore, median decrease in risk for moderate/high efficacy microbicides is approximately 11% larger than for low/moderate efficacy microbicides. Even if microbicides become available and are used FSWs will still have approximately 0.2% chance of acquisition of HIV per day. Finally, although the daily risk appears small, the yearly risk would be substantial. Results are not shown for yearly risk because the number of clients that FSWs will have from week-to-week and over a year is not well known and could be highly variable.

Increasing microbicide usage would have a greater impact on reducing HIV acquisition in FSWs than increasing microbicide efficacy; results shown for 30–50% and 50–80% efficacy (Fig. 1). Prevalence of HIV among FSW clients has the greatest effect on risk uncertainty (pre- and

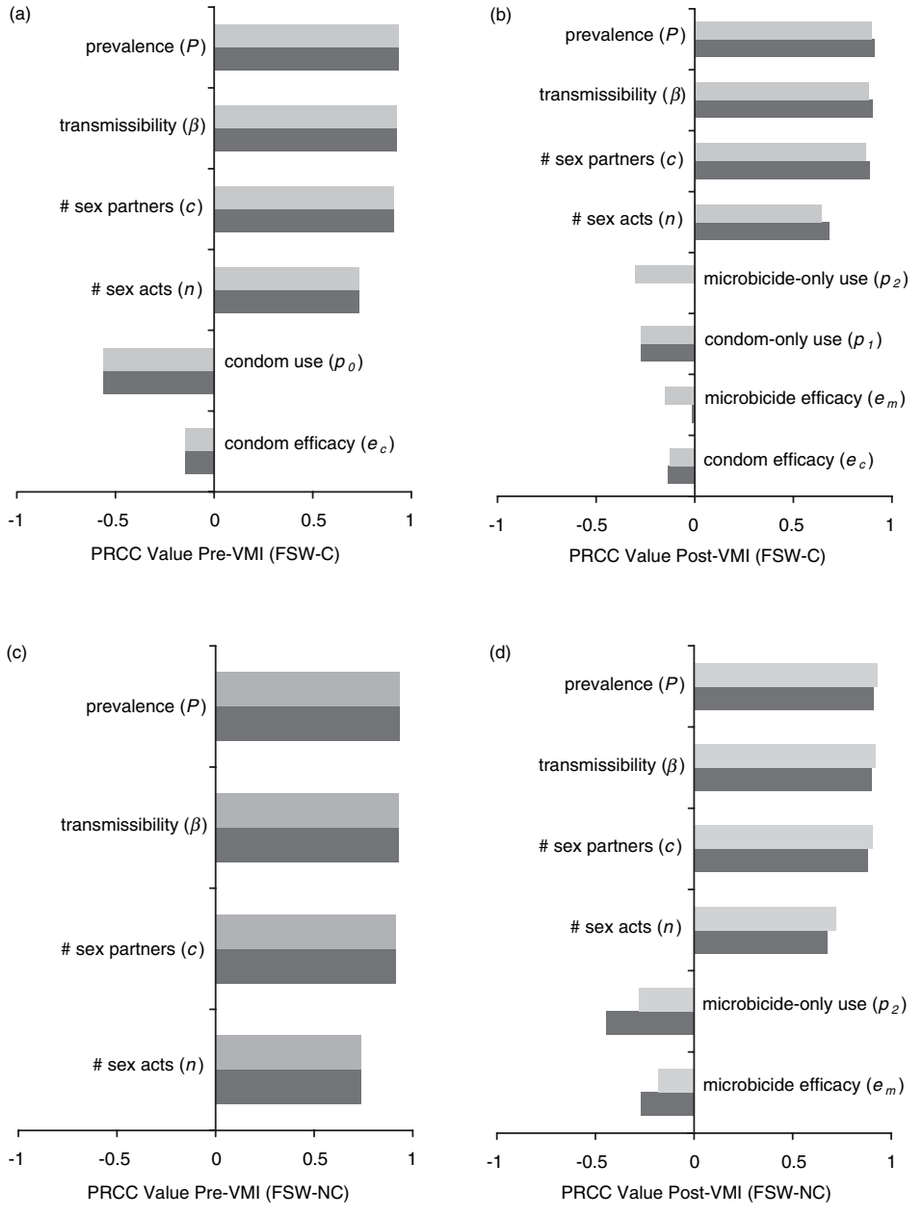

Fig. 1. *Tornado* plots of partial rank correlation coefficients for each of the parameters in the risk equations for (a) female sex workers who use condoms with their clients (FSW-Cs) currently [pre-vaginal-microbicide introduction (pre-VMI)]; (b) FSW-Cs post-VMI; (c) female sex workers who never use condoms with their clients (FSW-NCs) currently; and (d) FSW-NCs post-VMI. In each case, the lighter color is for microbicide efficacy of 30–50% and the darker color is for microbicide efficacy of 50–80%. Parameters with partial rank correlation coefficient (PRCC) > 0 will increase an individual's risk as they are increased, whereas parameters with PRCC < 0 will decrease an individual's risk as they are increased.

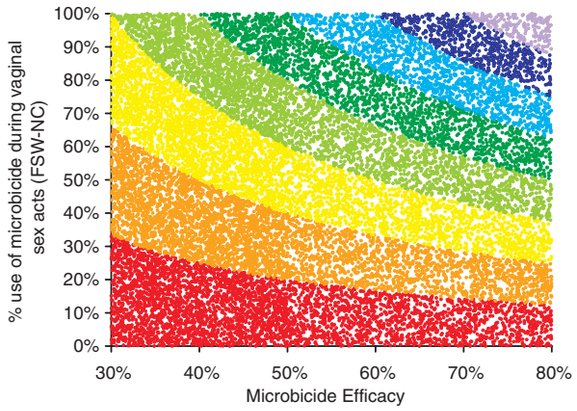

Fig. 2. The relationship between microbicide efficacy and microbicide use for female sex workers who never use condoms with their clients (FSW-NCs). The bands of color represent grades of percentage reduction in an individual's daily risk of acquisition of HIV (red = 0–10%, orange = 10–20%, yellow = 20–30%, light green = 30–40%, dark green = 40–50%, light blue = 50–60%, dark blue = 60–70%, purple = 70–80%).

post-VMI), followed by increasing transmissibility, increasing the number of sex partners and increasing the number of sex acts. Figs 1b and 1d both show microbicide use has a higher PRCC value than microbicide efficacy (the PRCC value for microbicide-only use for FSW-Cs for 50–80% efficacious microbicides is 0.0006, so it does not appear on the graph).

Figure 2 quantifies the relationships among potential microbicide efficacy, potential microbicide use, and the percentage reduction in daily risk for FSW-NCs. Bands of color represent grades of percentage reduction in risk. For example, if a 70% effective microbicide were introduced, a FSW-NC who used this microbicide only 50% of the time would reduce her risk by 30–40%. However, if she used this microbicide 100% of the time, she would reduce her risk by 60–70%. The slopes of the bands indicate that percentage changes in microbicide use would have a greater effect on reducing risk than the same percentage change in microbicide efficacy. For example, if a 70% effective microbicide were introduced, the percentage reduction in a FSW's risk could be anywhere from 0–70%, depending on microbicide usage. However, given a fixed microbicide usage of 70%, changing the efficacy would mean that the percentage reduction in a FSW's risk could only range from 20–50%. The results for FSW-Cs are similar (but data not shown). Note also that for low microbicide usage levels, the risk is nearly independent of the efficacy.

To determine the level of microbicide efficacy and the usage necessary to counterbalance a possible reduction in condom use we considered the 'worst-case situation' of FSWs who abandon condoms altogether. Figure 3 shows how much microbicide usage would be required to reduce risk (i.e., produce a beneficial outcome) if 'condom replacement' occurs and if a 30% (Fig. 3a), 50% (Fig. 3b), or 80% (Fig. 3c) effective microbicide was available. To make these calculations, we used an analytical threshold expression derived from our risk equation (see methods). Assuming that microbicide efficacy will be lower than condom efficacy, then (if FSWs abandon condoms) they will have to use microbicides more frequently than they previously used condoms in order not to increase their risk of acquiring HIV (Fig. 3). The necessary frequency usage of microbicides will depend upon pre-microbicide condom usage and microbicide efficacy (Fig. 3). For example, if pre-microbicide-availability condoms were used in 30% of acts and a 30% effective microbicide became available, then the FSW would have to use the microbicide in at least 82% of sex acts to ensure that her risk did not increase (Fig. 3a). However, if a 50% effective microbicide became available, she would only need to use the microbicide in slightly less than 50% of acts to ensure that her risk did not increase (Fig. 3b). Finally, if a 80% effective microbicide became available, her risk would not increase if she used the microbicide only slightly more often than she had used condoms (Fig. 3c).

Our results show that whereas microbicides could decrease the risk of HIV acquisition in FSWs, it would also be possible for the introduction of microbicides to increase the risk of HIV acquisition in FSWs (Fig. 3). The chance of increasing the risk of acquiring HIV will be greatest if low-efficacy microbicides are introduced, and the risk will be greatest in the group of FSWs who are currently using condoms fairly frequently (Fig. 3). For example, our results show that if a 30% effective microbicide is used by FSWs who are currently using condoms fairly frequently (for any pre-VMI condom use to the right of the dot-dashed line in Fig. 3a) then their risk of acquiring HIV would increase even if they used the microbicide in 100% of sex acts (Fig. 3a). Thus, although change in risk is more sensitive to microbicide use than efficacy, microbicide efficacy is a critical factor in determining whether use will be beneficial (i.e., decrease risk of HIV acquisition) or perverse (i.e., increase risk of HIV acquisition) if condom use is abandoned.

Discussion

We evaluated the potential impact that the introduction of vaginal microbicides could have on reducing the risk of HIV acquisition in FSWs (a high-risk group of women). We considered FSWs whose clients had HIV prevalence ranging from 10–60%, reflecting data from high-risk clients in the developing world. We considered two groups of FSWs (as defined by their condom usage) and two ranges of microbicide efficacy (30–50% and 50–80%). We found that moderate/high effective (50–80%)

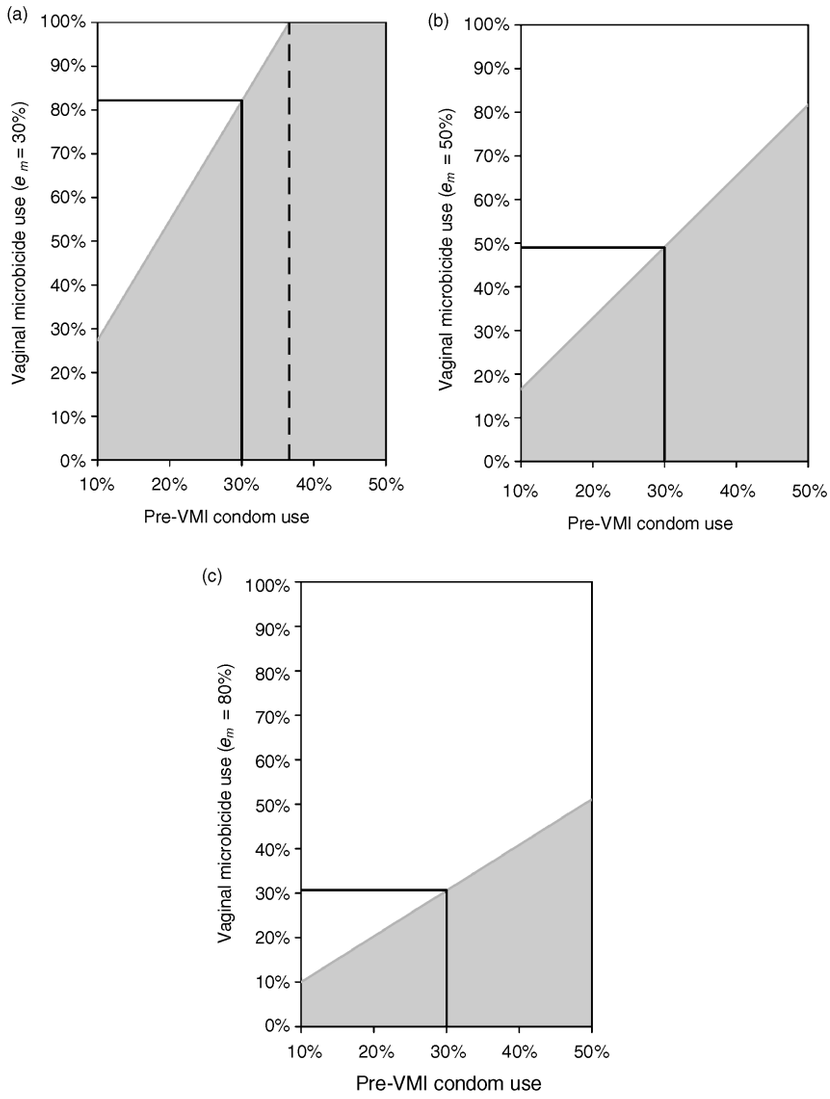

Fig. 3. The level of microbicide use required to produce a beneficial outcome (i.e., to decrease risk of HIV acquisition) when 'condom replacement' occurs. (a) The level of microbicide use required to reduce the risk of HIV acquisition (i.e. produce a beneficial outcome) for a female sex worker (FSW) who abandons condoms altogether [post-vaginal-microbicide introduction (post-VMI)] assuming a 30% effective microbicide is available. (b) The level of microbicide use required for a FSW who abandons condoms altogether (post-VMI) in favor of a 50% effective microbicide to have a beneficial outcome. (c) The level of microbicide use required for a FSW who abandons condoms altogether (post-VMI) in favor of an 80% effective microbicide to have a beneficial outcome. Parameter values chosen to generate the curves were the medians of the ranges presented in Table 1, except for microbicide use, microbicide efficacy, and pre-VMI condom use. The line between the grey and white areas is the analytical threshold between an increase or decrease in risk, with the shaded area showing when the risk decreases. The black lines indicate the vaginal microbicide usage necessary to offset abandonment of 30% condom use. The dashed line in (a) demonstrates the pre-VMI condom threshold (38%) such that no level of microbicide use can produce a decrease in risk for a 30% effective microbicide.

microbicides could reduce both groups of FSWs' median daily risk by approximately 28%, thus substantially reducing the risk of HIV acquisition for a FSW; the absolute decrease in risk would be greatest for the highest risk women who are currently not using condoms. However, we found that even if microbicides become available and are used FSWs will still be at high risk for the acquisition of HIV (approximately 0.2% chance of acquisition per day). We examined daily risk of HIV acquisition, since the number of clients FSWs will have over a much longer period of time is not well known.

As we have shown the prevalence of HIV in FSWs' clients is of major importance in determining the magnitude of the overall risk in acquiring HIV infection. In our model,

the prevalence (*P*) is in the exponent of our expression for risk. As *P* increases, not only does the risk of transmission increase, but so does the absolute reduction in risk. Therefore, we predict that, post-VMI, the absolute decrease in risk will be greater in regions where HIV prevalence amongst clients is high (such as in developing countries, and in certain communities in developed countries).

We have used an individual-level model to examine the potential daily impact of vaginal microbicides, of varying efficacies and use on FSWs, a high-risk group of women. We used a range of values for unknown microbicide use and efficacy parameters, in the absence of data. As such data becomes available our results could be further refined to provide more accurate estimates for specific geographical locations. Although our model could be applied to many sets of parameters, our specific results are dependent upon the range of parameters chosen. Further analysis could be done for other parameter ranges, applying the model we have developed to specific places and populations, or could include a population study to assess the dynamic impact of microbicides on an entire group.

A previous study on the potential effect of vaginal microbicides and 'condom replacement' has been done by Foss *et al.* [2]. Their results provide only point estimates for the estimated protection provided; however, we have conducted an uncertainty analysis (and hence have provided a wide range of outcomes) that are based upon considering heterogeneity in all parameters. Furthermore, our model differs from the model presented by Foss *et al.* [2] in several important ways. Foss *et al.* compare condoms plus microbicides with condoms alone to obtain a threshold expression for a beneficial or perverse outcome, and they consider the risk per sex act. Our model considers an individual's risk per day and is more comprehensive as (unlike Foss *et al.*) we include the proportion of time that no protection is used, the prevalence and the number of sex partners. Our model thus applies to a greater range of circumstances than that of Foss *et al.*

In the case of 'condom replacement', we calculated an analytical threshold for the level of microbicide usage that would be required to offset a given amount of 'condom replacement'. We determined that the microbicide usage required to offset 'condom replacement' is dependent upon both the expected microbicide efficacy and the pre-VMI condom usage. If microbicide efficacy is substantially lower than condom efficacy (which appears likely), then FSWs who directly replace condom usage with microbicide usage will always increase their risk (i.e., have a perverse outcome). Thus, whereas microbicide use is a more important factor to maximize than microbicide efficacy for FSWs who continue to use condoms at the same rate, for FSWs who abandon condoms post-VMI, microbicide efficacy is critical. Therefore, if low/moderate efficacy microbicides become available then it will be critical to ensure that FSWs who are currently using condoms fairly frequently do not choose to replace condoms with microbicides. However, for low/moderate efficacy microbicides, the risk of HIV acquisition in FSWs will be reduced – even if complete condom abandonment occurs – if prior condom use was low.

Behavioral scientists will need to explore the acceptability and perceived ease of use of microbicides; the introduction of microbicides should be linked to education campaigns promoting both condom and microbicide use. It is important to note that we have shown that even low/moderate efficacy microbicides could significantly decrease a FSW's risk of acquisition of HIV. The impact of microbicides on risk reduction is a function of both microbicide efficacy and microbicide usage [44]. We found that risk reduction is more sensitive to increases in microbicide usage than microbicide efficacy. Although it may not be possible to achieve high-efficacy microbicides, our results show that even low/moderate efficacy microbicides could have a substantial impact on risk reduction if usage is high. Furthermore, (unlike with condoms) it may well be possible to achieve high usage of microbicides, since FSWs will not have to negotiate microbicide use with their clients. Thus, even if high-efficacy microbicides cannot be developed, high use of low/moderate efficacy microbicides could still have a significant impact if they are used sufficiently frequently. We have shown that microbicides could substantially decrease the risk of HIV infection in a group of women (FSWs) who are at great risk for HIV, particularly in high-prevalence regions.

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