Outline

- Evaluating microbicides using risk equations
- Will microbicides help?
- Which factors are most important?
- Condom replacement
- Effect of men's attitudes on microbicide introduction and use.

Microbicides

Microbicides are chemical compounds which can be applied topically to prevent or reduce

- HIV transmission in adults
- neonatal transmission
- other sexually transmitted diseases.

Microbicides

Microbicides can be applied

- vaginally
- rectally
- added to condoms.

Easy to use

Microbicides could be

- added to a lubricant
- combined with a contraceptive
- used when trying to become pregnant.

Alternatives

- Microbicides may provide an alternative for those unwilling or unable to use condoms

- Women will not have to negotiate condom use.

Candidates

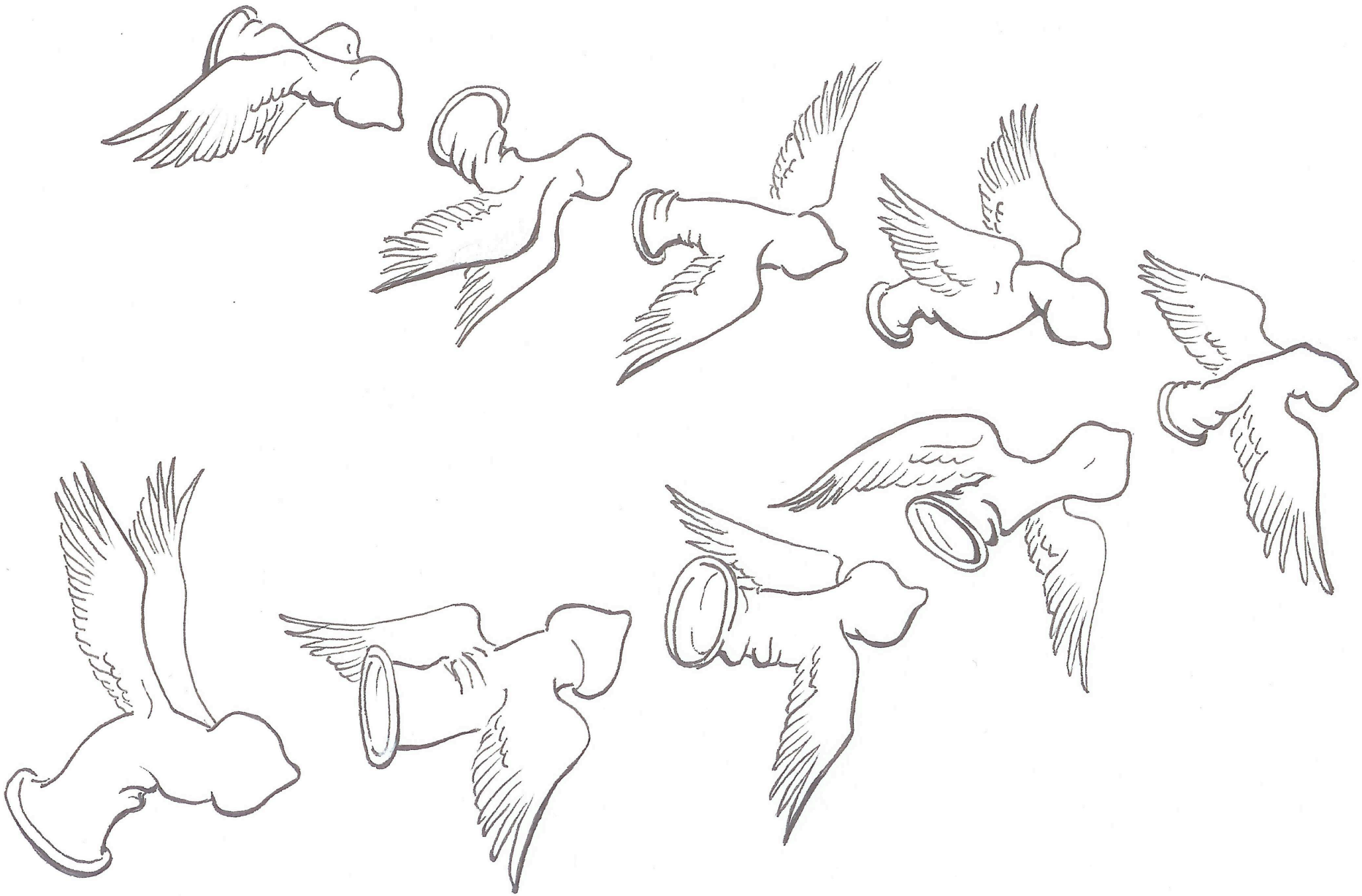
- Phase III microbicide trials are currently underway in South Africa, Tanzania and Zambia

- Not expected to reach the market for several years.

Possible consequences

- Microbicides → reduction in condom use?
- This has been termed “condom migration”

Condom migration?



Condom replacement

- We suggest an alternative term, “condom replacement”
- Couples who sometimes use condoms may replace condoms with microbicides some or all of the time
- Couples who do not use condoms currently are unlikely to later.

With no condom replacement…

Protection Options	
Before Microbicide Availability	**After Microbicide Availability**
Condom	Condom only
	Condom + Microbicide
No Protection	Microbicide only
	No Protection

Female sex workers

We chose to study female sex workers (FSWs) because they

- have been involved in early microbicide trials
- have reported high microbicide use
- are a high risk group of women.

Daily risk

- We developed risk equations to evaluate an FSW's daily risk of infection

- Both before and after the introduction of microbicides.

FSW = female sex worker

Crucial questions

Can vaginal microbicides *substantially* reduce the risk of a female sex worker acquiring HIV?

Which is more important to maximize: microbicide use or microbicide efficacy?

What level of microbicide use and efficacy is needed to counterbalance condom replacement?

Factors in risk equations

- Efficacy of protection used (condoms, microbicides)

- Proportion of each type of sex act in which protection (condoms only, microbicides only, or both) is used.

Other factors

- Transmissibility (male-to-female, per act)
- Number of sex acts per client
- Number of partners
- Prevalence of HIV among client population.

Developing risk equations

- β' = probability of transmission during a single sex act with a given protection type
- $(1-\beta')$ = probability of remaining uninfected during this sex act
- $(1-\beta')^N$ = probability of remaining uninfected after *N discordant* sex acts.

Sex acts per day

We assume

- *n* sex acts per partner
- *c* sex partners per day
- P = HIV prevalence

Hence $N=ncP$.

N=# discordant sex acts

Total risk

- The proportion of sex acts of a given type is denoted p_i
- Thus the probability of HIV acquisition is

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

β′ = transmission probability
n = # sex acts
c = # sex partners
P = prevalence.

Current risk

- Protection options: condoms or nothing
- The daily risk is thus

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

- e_c = efficacy of condoms
- p_0 = proportion of time condoms are used.

β = *transmission probability*
n = # sex acts
c = # sex partners
P = prevalence

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

Risk with microbicides

- The daily risk with microbicides will be

$$r_2 = 1 - \{[1 - (1 - e_c)\beta]^{p_1}[1 - (1 - e_m)\beta]^{p_2} \times [1 - (1 - e_c)(1 - e_m)\beta]^{p_3}[1 - \beta]^{(1-p_1-p_2-p_3)}\}^{ncP}$$

- e_m = efficacy of microbicides.

β = transmission probability
e_c = condom efficacy
p_i = proportion protection type used
n = # sex acts
c = # sex partners
P = prevalence

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

Analysis

We analysed our risk equations with uncertainty analysis using

- Monte Carlo simulations
- multivariate sensitivity analysis
- Latin Hypercube Sampling
- Partial Rank Correlation Coefficients.

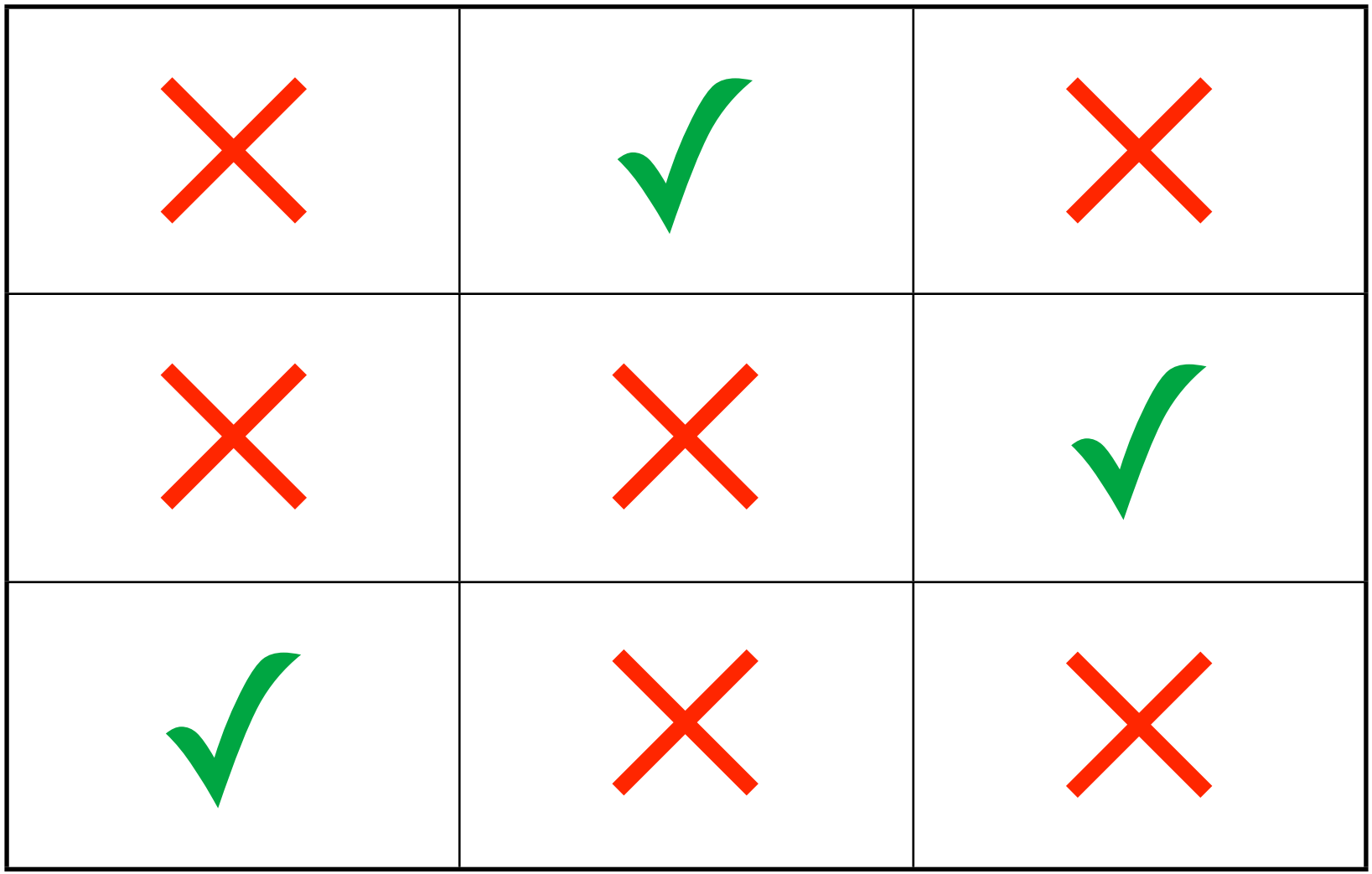
Latin Hypercube Sampling

Latin Hypercube Sampling

- samples parameters from a random grid
- resamples, but not from the same row or column

  (a bit like tic tac toe)
- runs 1,000 simulations.

Latin Hypercube Sampling



PRCCs

Partial Rank Correlation Coefficients (PRCCs)

- tests individual parameters while holding other parameters at median values
- ranks parameters by amount of effect on the outcome.

Crucial question #1

Can vaginal microbicides *substantially* reduce the risk of a female sex worker acquiring HIV?

- Yes! (unlike vaccines)
- 17% risk reduction for low efficacy (30-50%) microbicides
- 28% risk reduction for high efficacy (50-80%) microbicides.

Risk & risk reduction results

e_m = 30-50%	FSW-C			FSW-NC		
	Pre-VMI	Post-VMI	% Decrease	Pre-VMI	Post-VMI	% Decrease
Min	9.2157E-05	8.0500E-05	4.0	1.4970E-04	1.2253E-04	3.6
1st I.Q.	0.00119	0.00097	11.8	0.00158	0.00130	12.8
3rd I.Q.	0.00369	0.00305	22.8	0.00488	0.00399	22.4
Max	0.01982	0.01875	[illegible]	0.02331	0.02106	[illegible]
median	0.00213	0.00175	17.0	0.00283	0.00232	17.5

e_m = 50-80%	FSW-C			FSW-NC		
	Pre-VMI	Post-VMI	% Decrease	Pre-VMI	Post-VMI	% Decrease
Min	9.2157E-05	6.3041E-05	6.3	1.4970E-04	9.8661E-05	5.8
1st I.Q.	0.00119	0.00082	19.2	0.00158	0.00110	20.8
3rd I.Q.	0.00369	0.00265	36.9	0.00488	0.00344	36.4
Max	0.01982	0.01807	[illegible]	0.02331	0.02024	[illegible]
median	0.00213	0.00149	27.7	0.00283	0.00198	28.5

Tornado plots

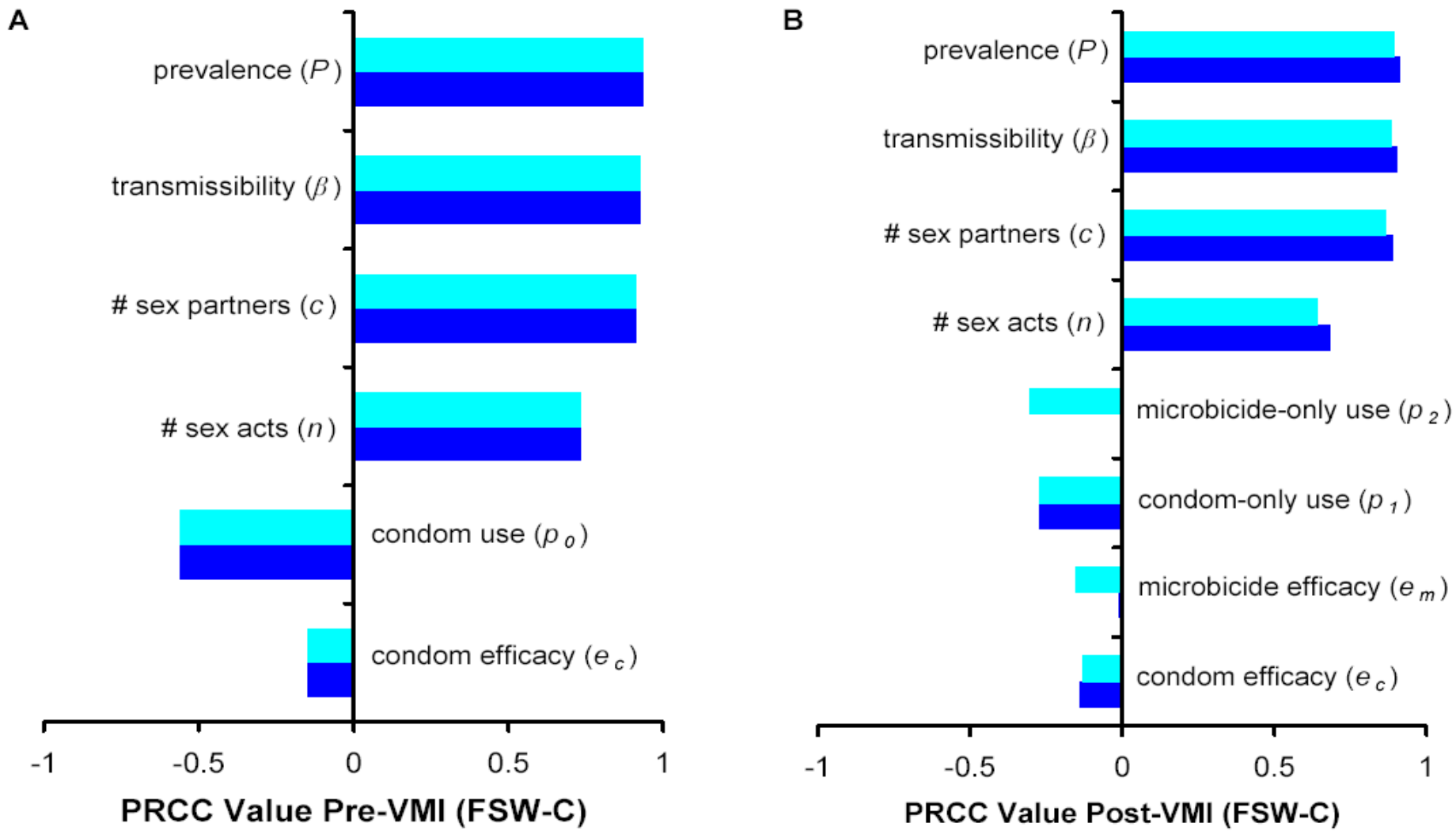
- *Tornado* plots illustrate those parameters that have the greatest effect on the outcome, in descending order

- PRCC>0 → parameter increases the risk

- PRCC<0 → parameter decreases the risk.

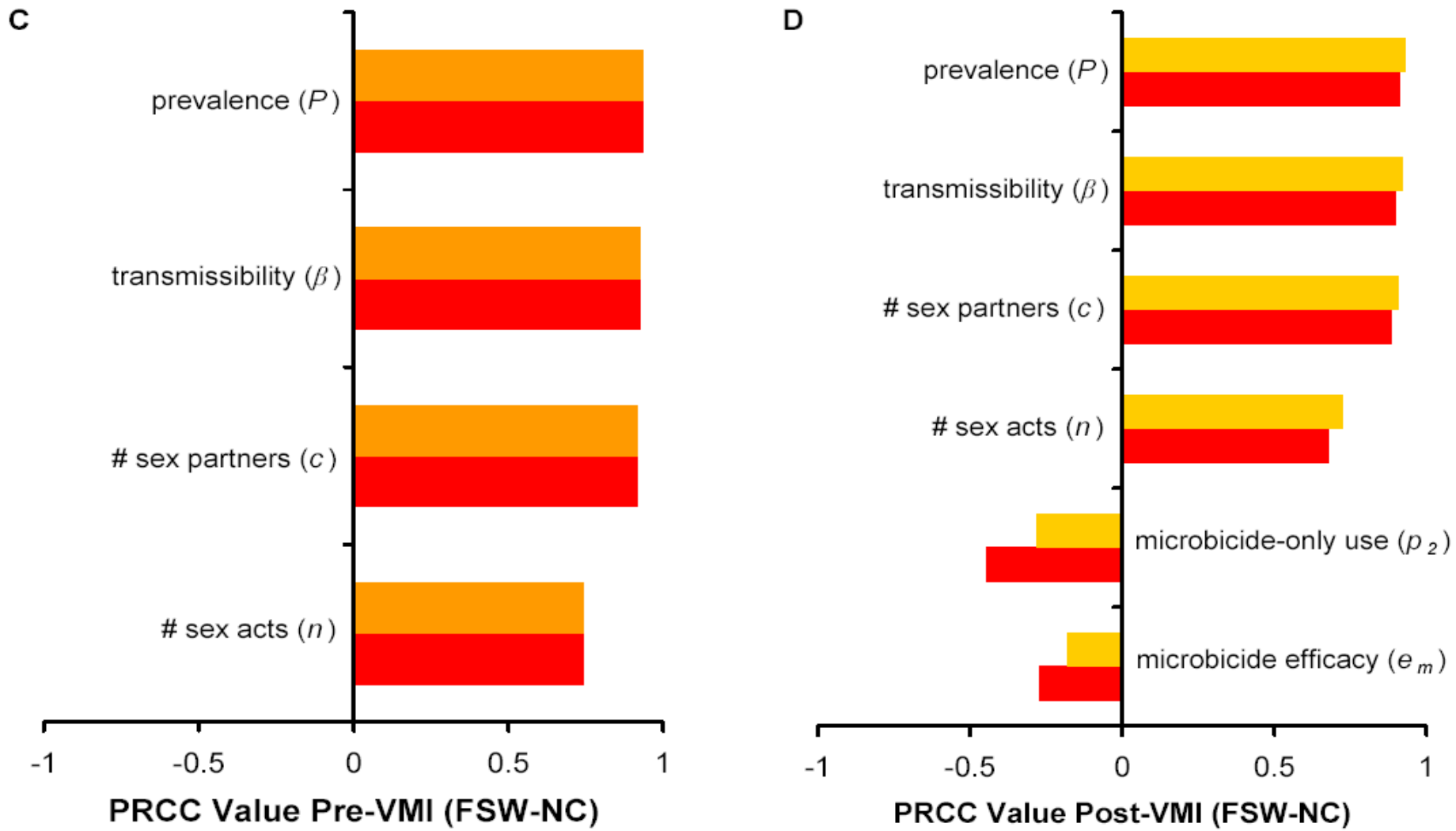
PRCC = partial rank correlation coefficient

Condom users



30-50% microbicide efficacy, 50-80% efficacy

Non-condom users



30-50% microbicide efficacy, 50-80% efficacy

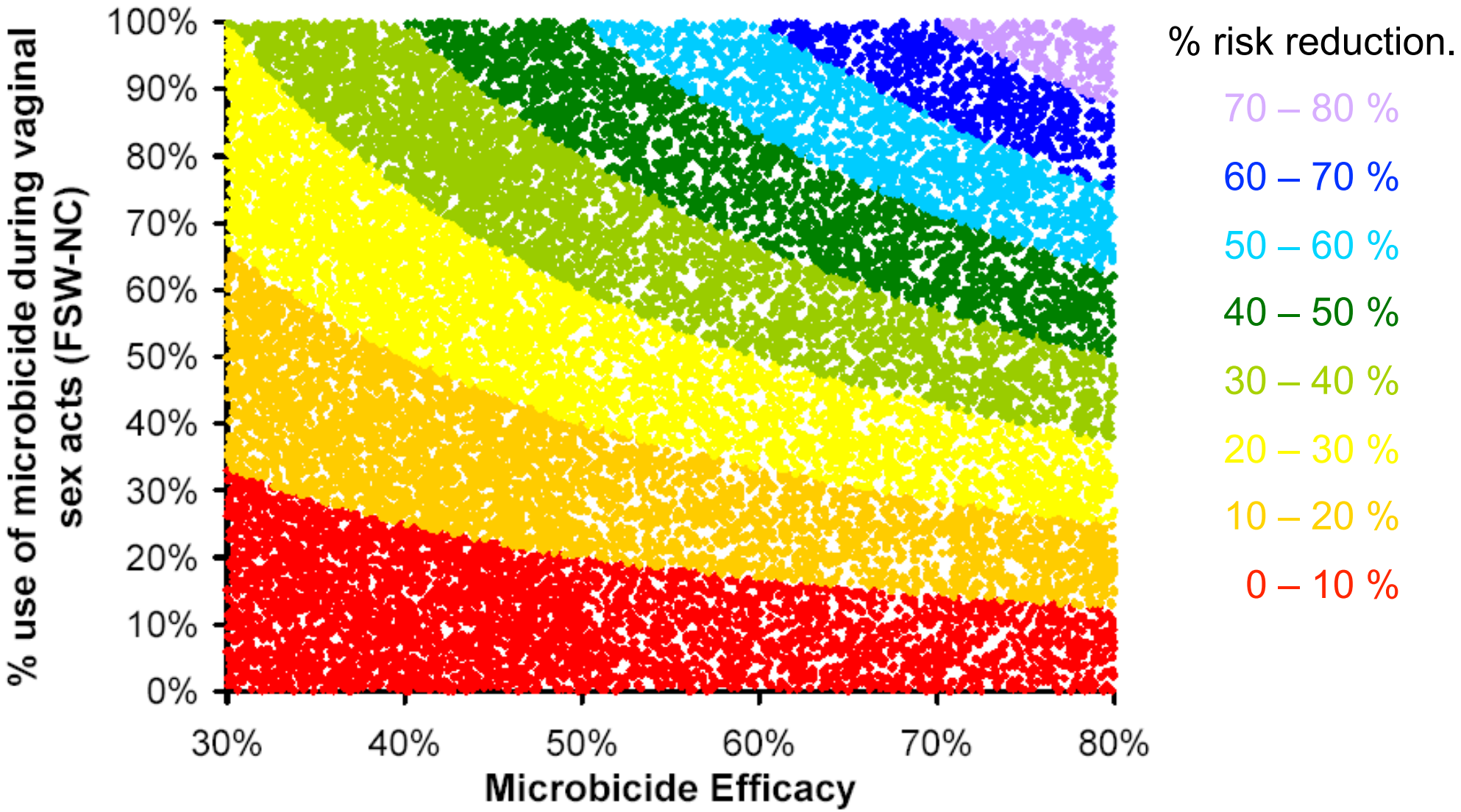
Crucial questions #2

Which is more important to maximize: microbicide use or microbicide efficacy?

- Microbicide Use!

- To quantify the relationship between use and efficacy, we set all other parameters to their median values and plotted use vs. efficacy for each Monte Carlo simulation.

Microbicide use vs. efficacy



Use vs. efficacy

- Changes in microbicide use have more of an impact than changes in efficacy
- For low efficacy microbicides, moderate levels (20-30%) of risk reduction can be obtained with high use.

Crucial questions #3

What level of microbicide use and efficacy is needed to counterbalance condom replacement?

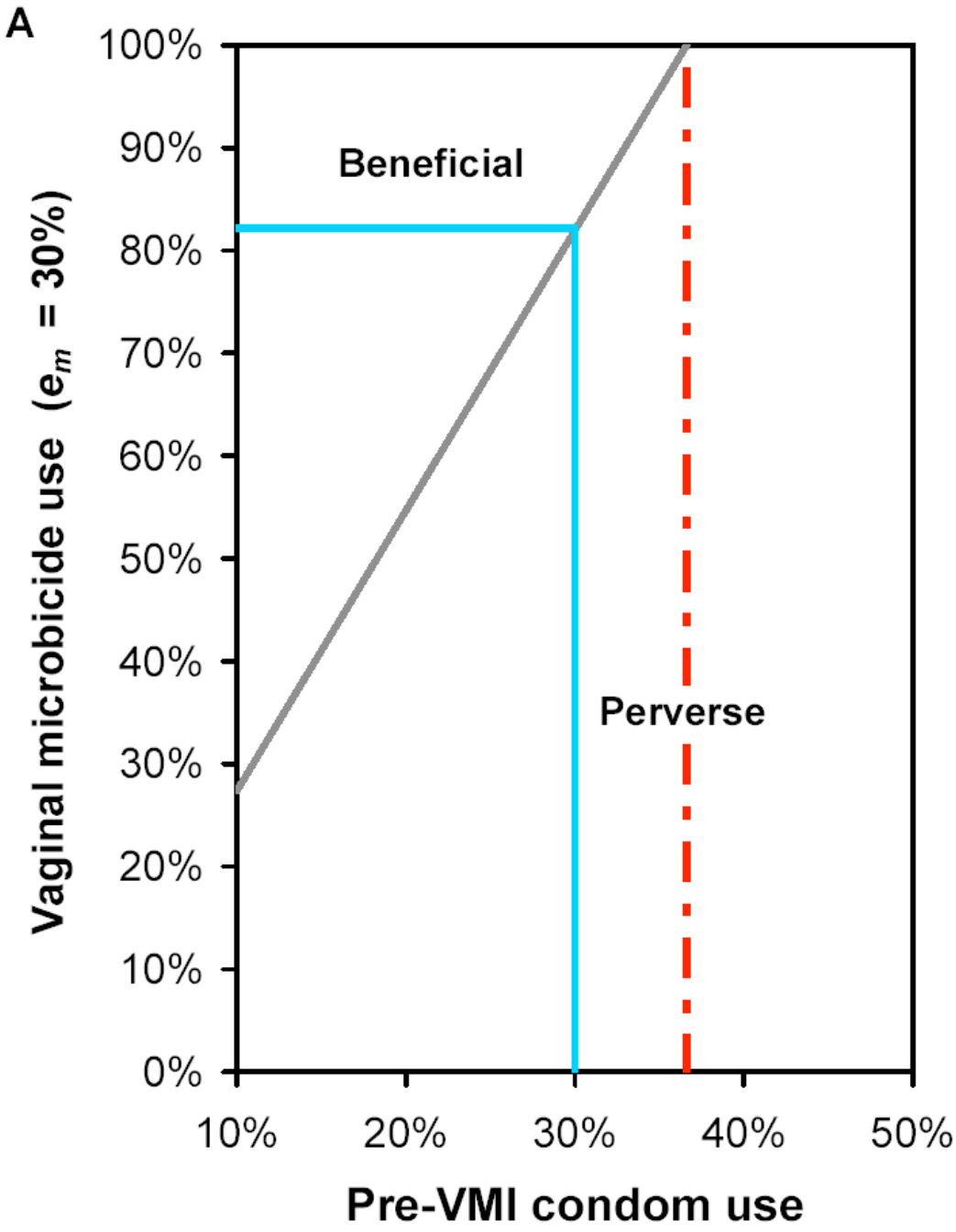
- The level of microbicide use needed to counterbalance *condom replacement* depends on
  - microbicide efficacy
  - level of condom use prior to microbicide use.

A condom replacement threshold

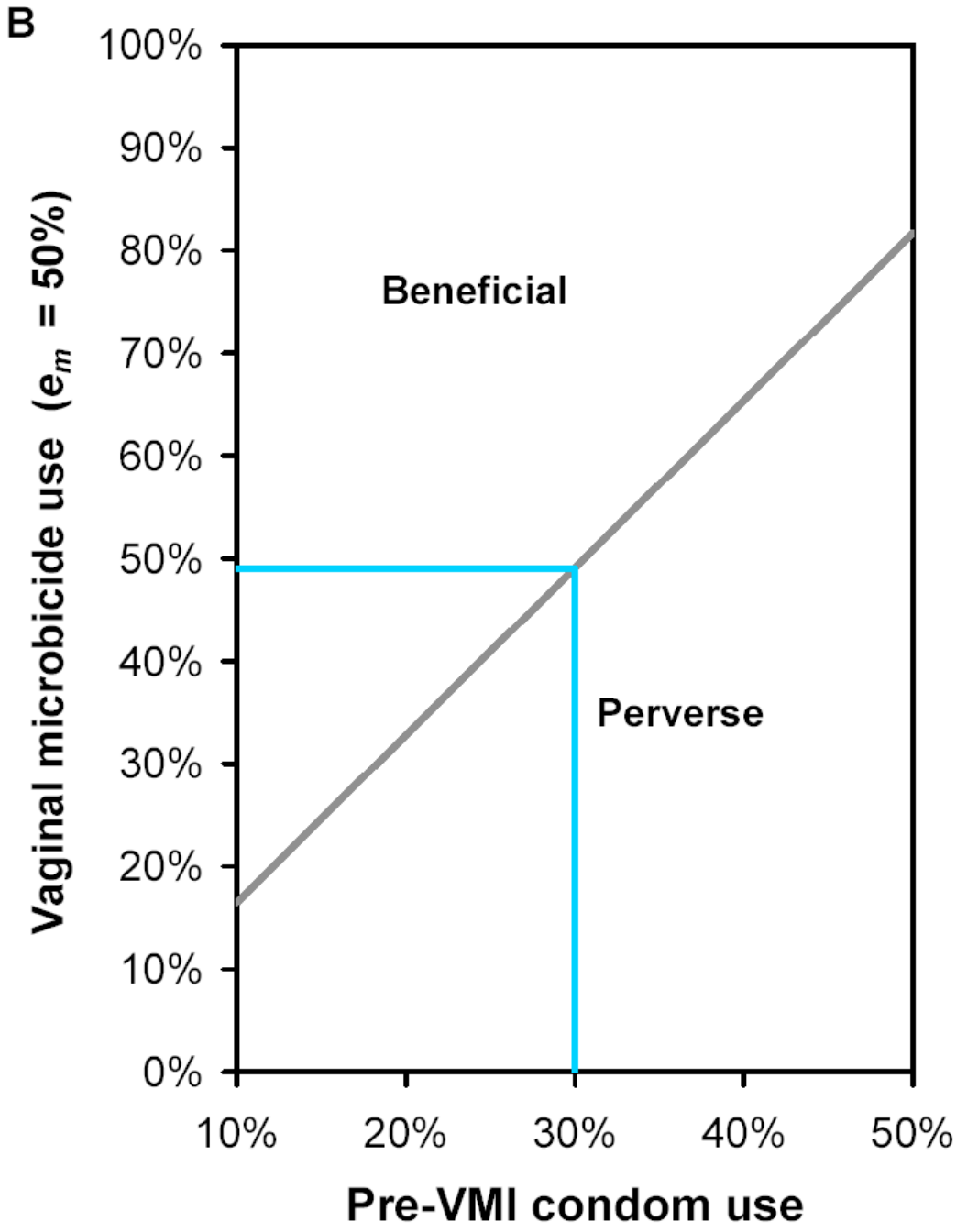
- The outcome will be beneficial if the risk decreases, i.e. if $r_1 > r_2$
- Solving, this gives the threshold

$$[1-(1-e_{\mathrm{m}})\beta]^{p_2}[1-(1-e_{\mathrm{c}})\beta]^{-p_0}[1-\beta]^{(p_0-p_2)} > 1$$

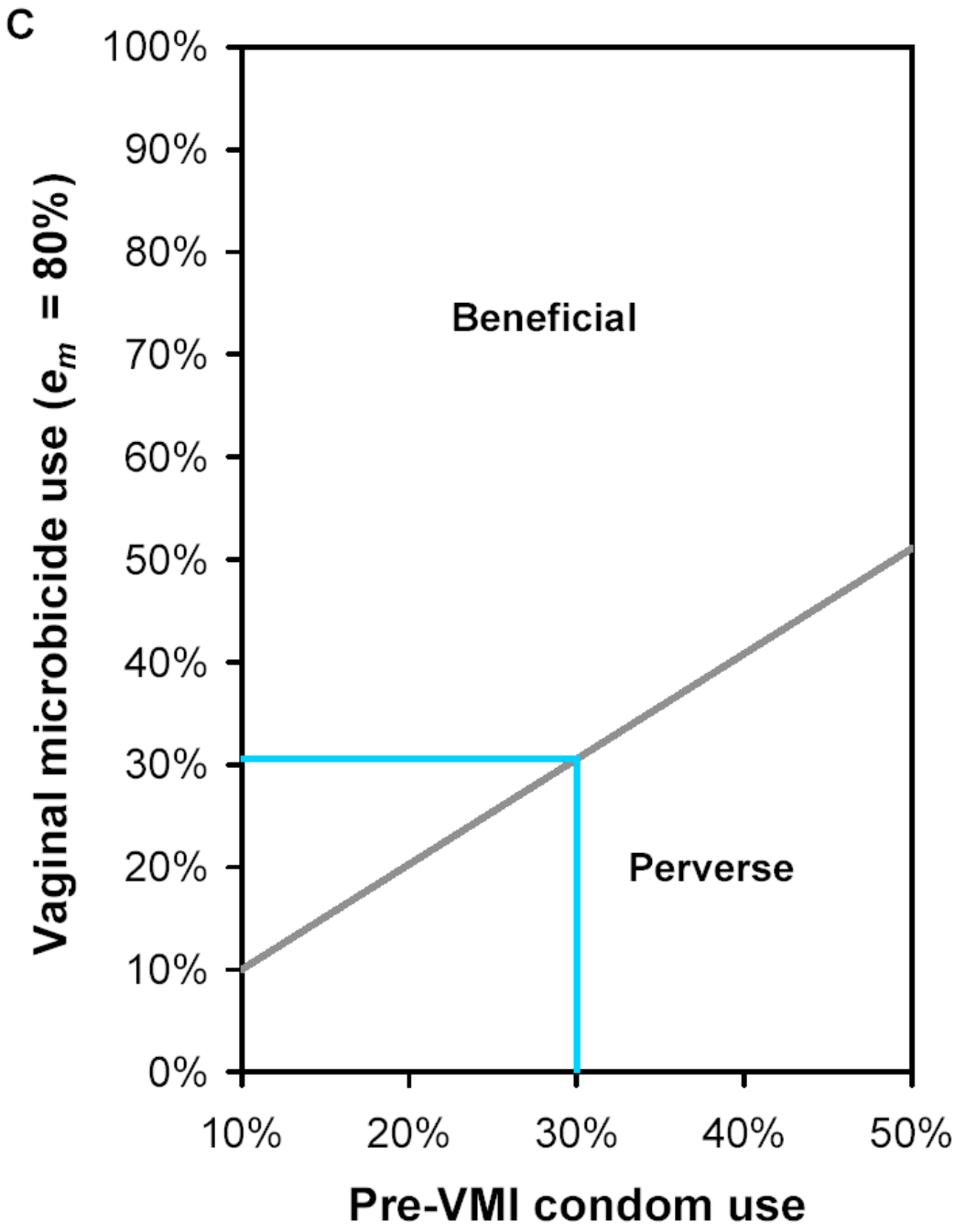
β = *transmission probability*
e_c = *condom efficacy*
e_m = *microbicide efficacy*
p_0 = *proportion condoms used currently*
p_2 = *proportion microbicides used.*


A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Beneficial
Perverse
Vaginal microbicide use (e_m = 30%)
10%
20%
30%
40%
50%
Pre-VMI condom use

30% efficacy

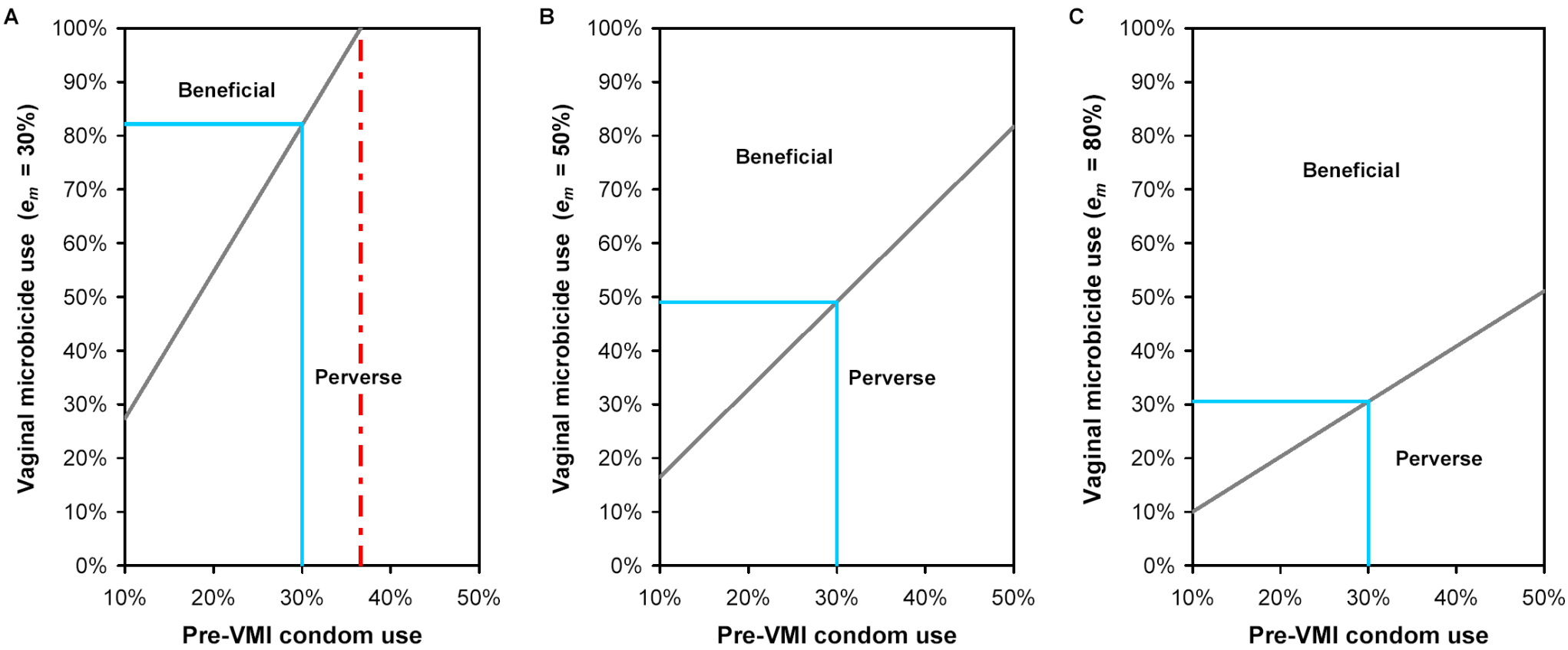

B
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Vaginal microbicide use (e_m = 50%)
Beneficial
Perverse
10%
20%
30%
40%
50%
Pre-VMI condom use

50% efficacy


C
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Vaginal microbicide use (e_m = 80%)
Beneficial
Perverse
10%
20%
30%
40%
50%
Pre-VMI condom use

80% efficacy

Balancing condom replacement



Note: We consider *complete* condom replacement (i.e. all condom use is replaced with some level of vaginal microbicide use). This is the most extreme possible case.

Consequences

- As prevalence increases, so does the absolute reduction in risk
- Thus, microbicides would be more beneficial when prevalence is high
- This includes developing countries and within certain high-risk communities.

Low efficacy microbicides

- Low efficacy microbicides are likely to be beneficial, so long as they are used with sufficient frequency

- This is true whether they replace condoms or not.

The importance of education

- The introduction of low efficacy microbicides must be tightly linked to education strategies
- eg advertising, marketing, state-sponsored education programs
- How do these strategies depend on men's attitudes and their relationships with women?

Consequences of condom replacement

Surveys with men in urban South Africa indicated:

- 82% preferred a vaginal microbicide to a condom
- 61% preferred sole microbicide use over sole condom use or concurrent use of both.

Cultural/urban/rural differences

Urban and rural men in Zimbabwe, Mexico and the US were surveyed:

- Both populations in Zimbabwe desired the man's permission for microbicide use
- Only the rural population in Mexico desired male permission
- Neither population in the US thought men's permission was needed
- All groups thought microbicides should be targeted primarily towards women.

Male perceptions

Perceptions about the efficacy of microbicides may lead to:

- higher male risk taking
- decreased condom use
- health ramifications for both men and women

Thus, condom replacement may shift the burden of responsibility for HIV/STI prevention solely onto women.

Acceptability factors

- Physiological acceptability and physical tolerance of microbicides are crucial
- Factors include:
  - taste
  - lubrication
  - packaging (eg gel packs that fit in wallets)
- Without appropriate education campaigns, men may be left with the illusion of risk-free, condom-free sex.

Cultural awareness

- Neo-colonial agendas aimed at population control (eg coercive sterilisation) have led to scepticism among communities to whom they are targeted
- Microbicides in development can be
  - combined with a contraceptive, or
  - used when pregnancy is intended;
  - added to lubricants, or
  - added to powders, to account for “dry sex”.

Covert application

- While a female-controlled protection option is empowering for women, the realities of relationships and imbalances of power may make this less useful
- The potential repercussions of discovery could nullify the advantages of covert application
- A microbicide that is undetectable during vaginal intercourse may be discovered during oral sex if it has a distinct taste.

Moving beyond sex workers

- Thus far, the model of microbicide use has been the female sex worker
- If a women's partner is a client, there may be no need to inform him of microbicide use
- However, within relationships this is no longer so clear-cut
- In particular, FSWs testing microbicides have felt the need to inform their steady male partners of microbicide use.

FSWs' discursive legacy

- FSWs have traditionally been imagined as carriers and especially vulnerable to HIV
- This is despite their long-standing professional knowledge and activism about AIDS
- Yet their discursive legacy is that they are imagined to be so contaminated that their bodies are seen as virtual laboratories for viral replication (Treichler, 1999).

Sexuality is complex

- Rectal microbicide development lags behind vaginal microbicides
- Due to heteronormativity, vaginal sex acts are seen as more worthy of protection than anal sex acts
- This is true, regardless of which types carry the greatest risk of infection
- Lesbian sex is often ignored altogether by vaginal microbicide research.

Complexities of identity

Thus far, microbicide development has

- considered historic cultural differences
- limited gender considerations to stereotypes about women
- ignored class and sexuality

Eg, a vaginal microbicide that cannot be tolerated anally, or offers no rectal protection, may result in decreased condom use for heterosexual anal sex if condoms are replaced by vaginal microbicides.

Including men

Factors that must be considered include:

- impact of microbicides on sensitive penile/ anal tissue
- risk of female-to-male HIV transmission
- risk of female-to-male transmission of other STIs.

Specific issues

Other issues that must be studied before microbicides can be effectively introduced:

- diversity of sexual acts performed
- acceptance of microbicides in male-male discussions
- overlap between men who have relationships with women and who have sex with men
- interaction of microbicides with sexual pleasure.

Summary

- Education is crucial
- The effect of microbicides must be considered beyond the model of the female sex worker and her clients
- Men's attitudes towards microbicides may be crucial to their acceptance among women.

Conclusion

- Unless men are included in education and marketing of microbicides, women may be asked to shoulder the entire burden of protection
- This is dangerous for both women and men and self-defeating for epidemic control.