Male circumcision and HIV prevention – Protection for the individual or the population?

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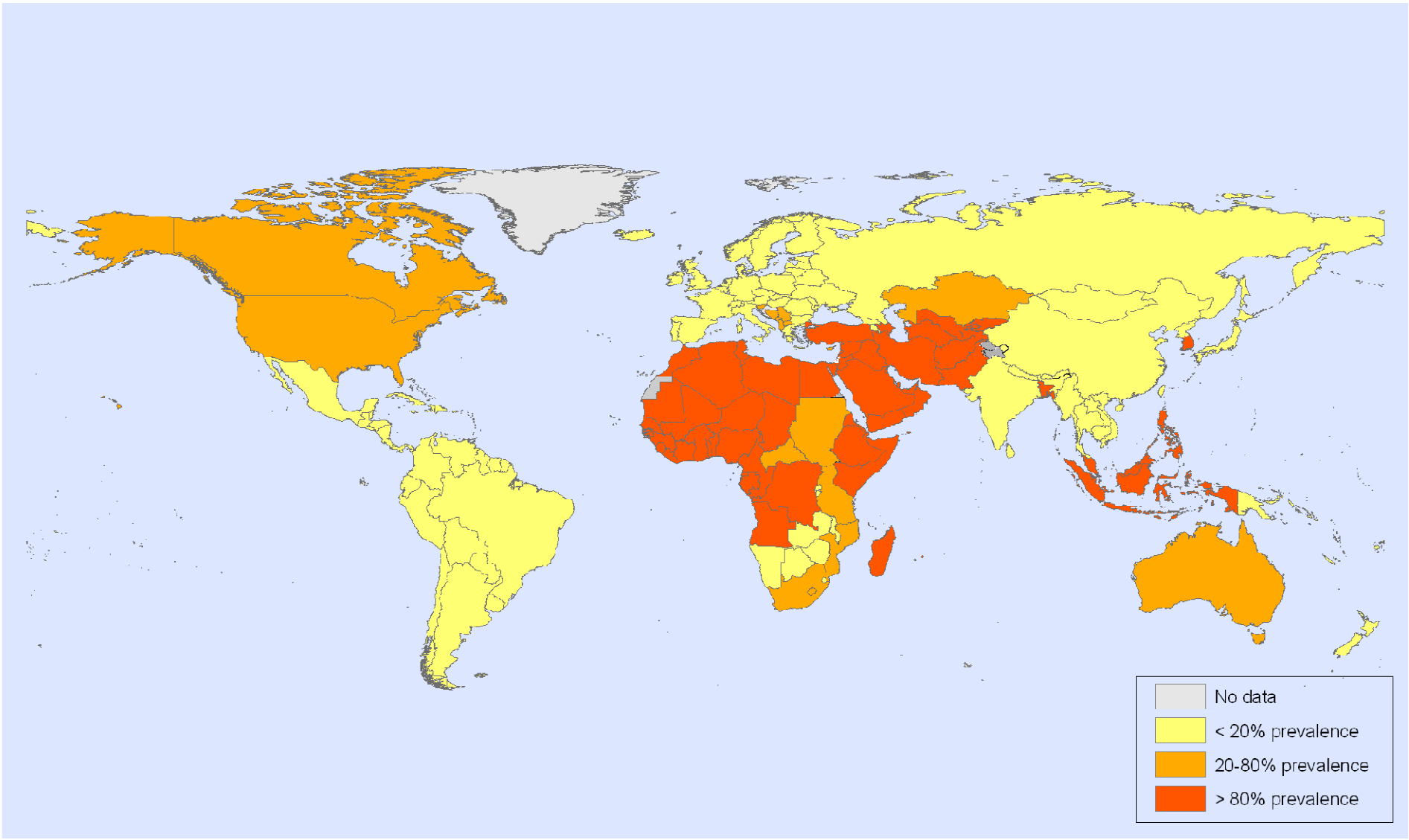
Global map of male circumcision prevalence at country level, as of December 2006



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Data Source: DHS and Other Publications
Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS), World Health Organization.

Male Circumcision and HIV Infection

- The evidence: male acquisition
  - Ecological
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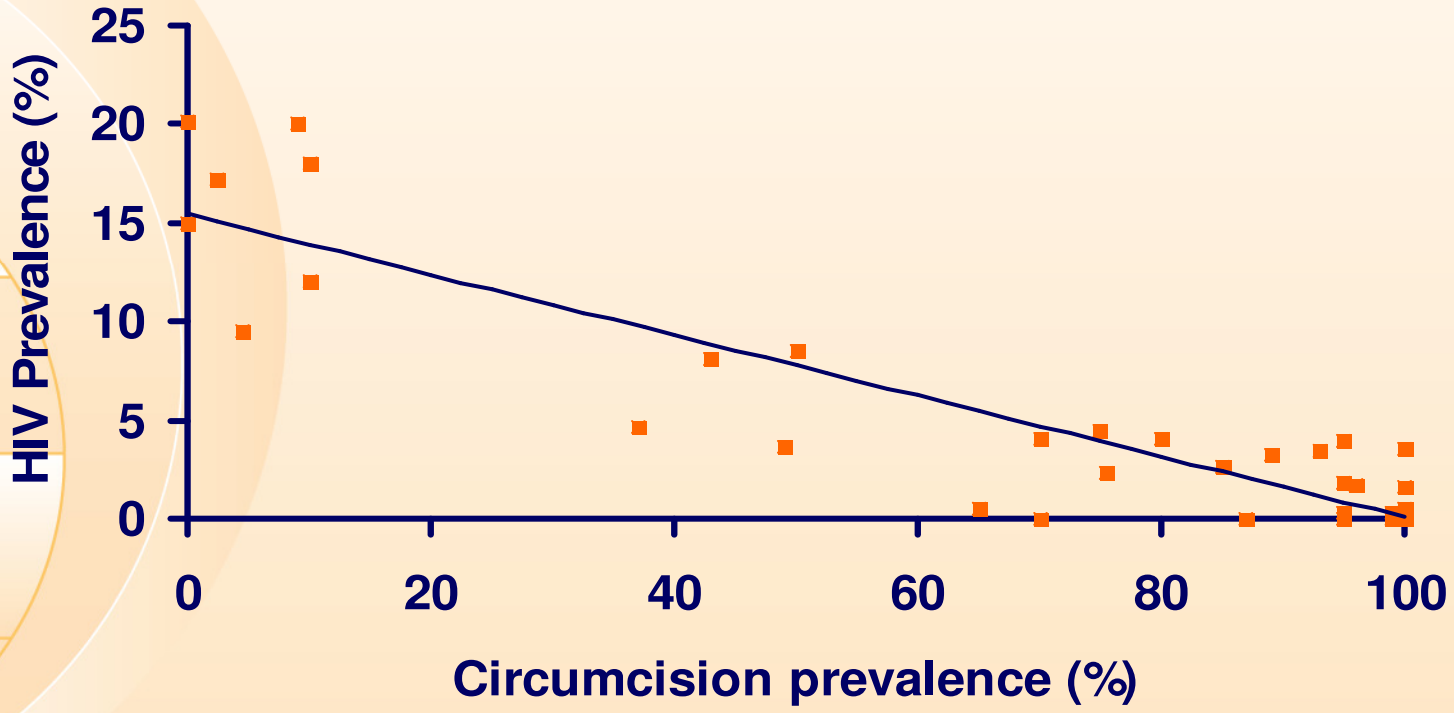
Male circumcision and HIV infection

Bongaarts, AIDS 1989



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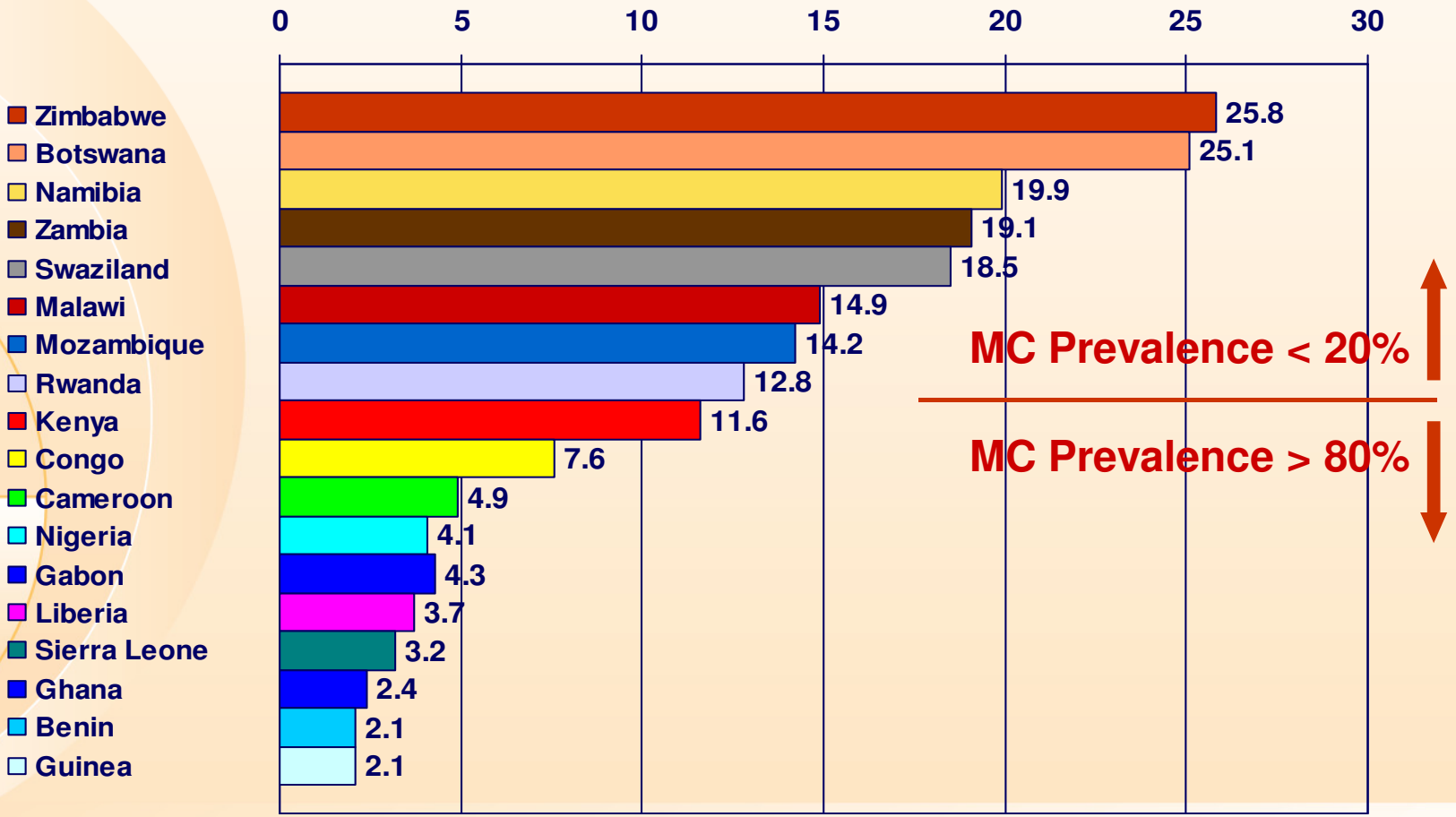
HIV and MC Prevalence – Africa

Adapted from Halperin & Bailey, *Lancet* 1999; **354**: 1813



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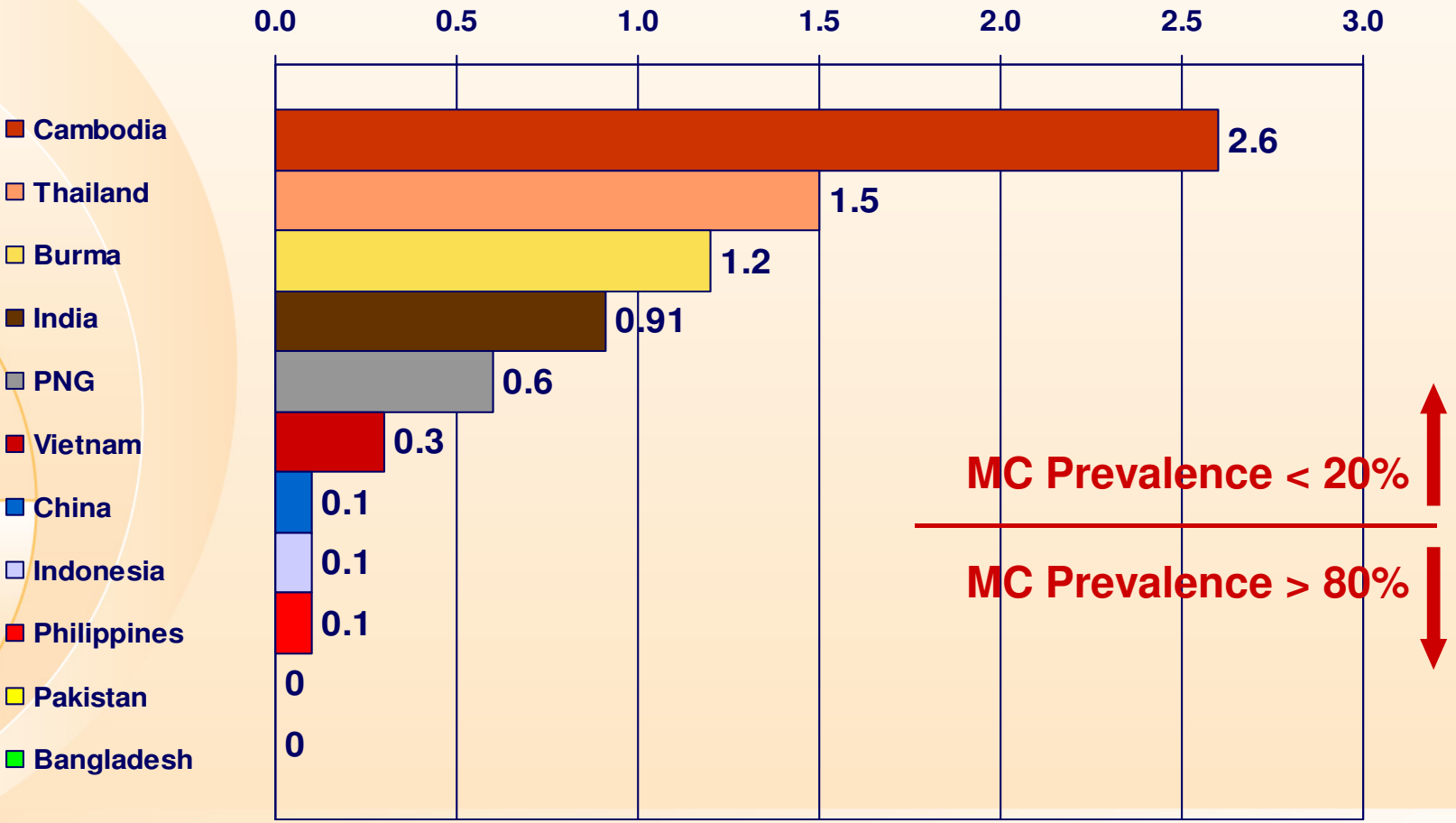
HIV and MC Prevalence – Asia

Adapted from Halperin & Bailey, *Lancet* 1999; **354**: 1813



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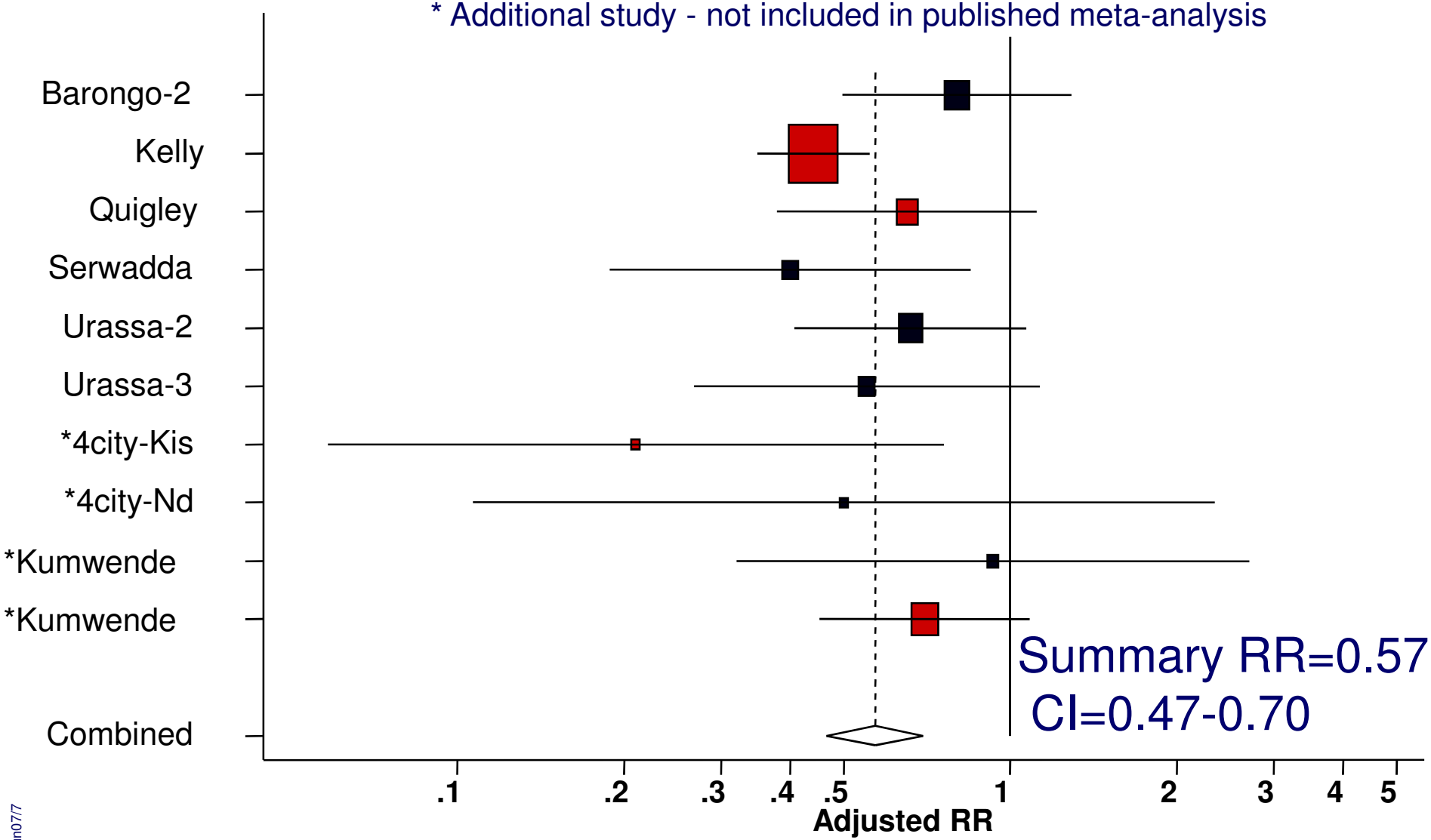
Population based studies - adjusted risk ratios

Weiss et al AIDS 2000 14:2361-2370

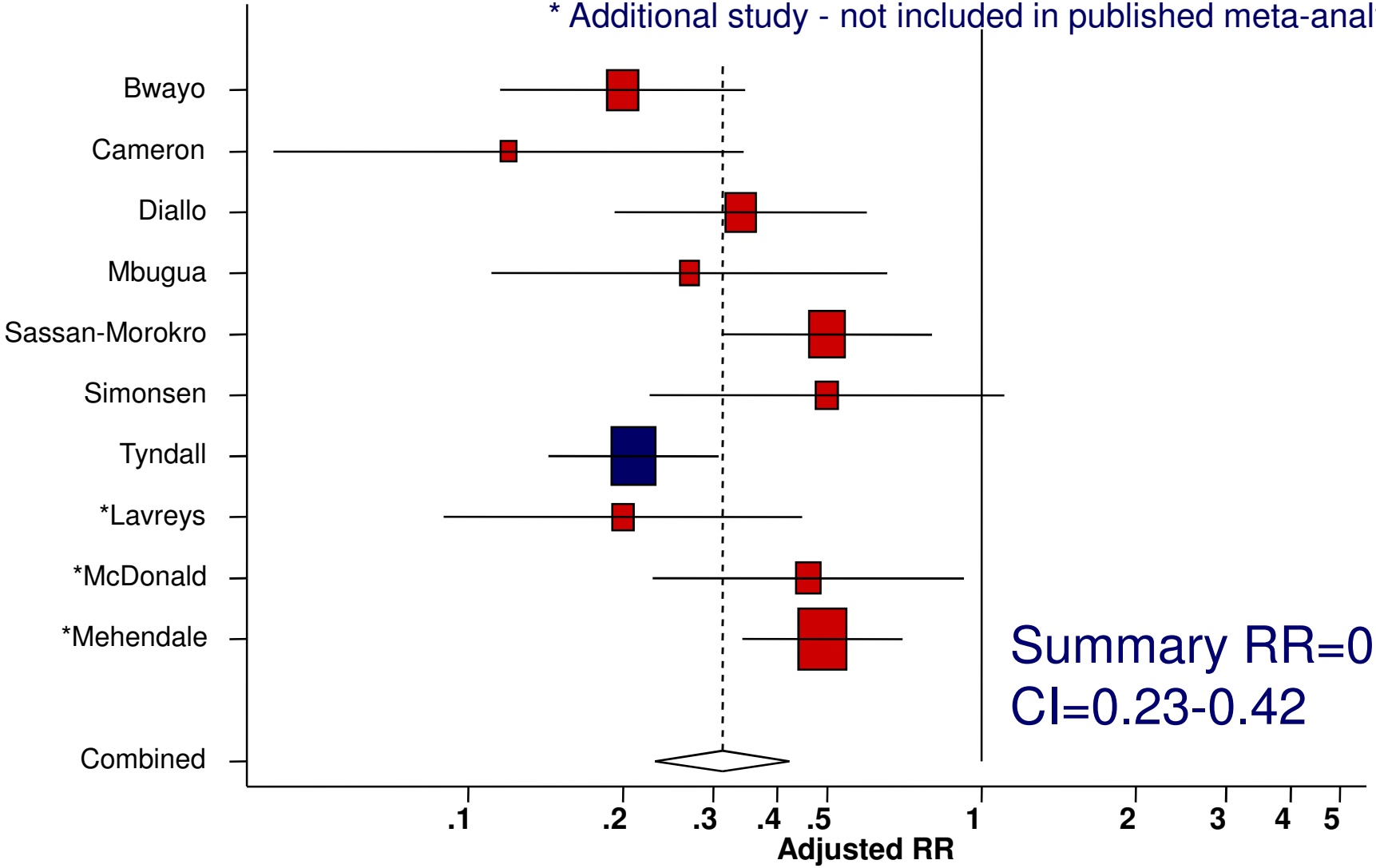
* Additional study - not included in published meta-analysis



High risk groups - adjusted RRs

Source: Weiss et al AIDS 2000 14:2361-2370

* Additional study - not included in published meta-analysis



Summary RR=0.31,
CI=0.23-0.42

Meta-analysis of prospective studies
Weiss et al. 2000

- Overall
  - Crude OR: 0.52 (95% CI: 0.40 to 0.68)
  - Adjusted OR: 0.42 (95% CI: 0.34 to 0.54)
- Population-based studies
  - Adjusted* OR: 0.57 (95% CI: 0.47 to 0.70)
- High risk groups
  - Adjusted* OR: 0.31 (95% CI: 0.23 to 0.42)

*Including additional studies not included in published meta-analysis

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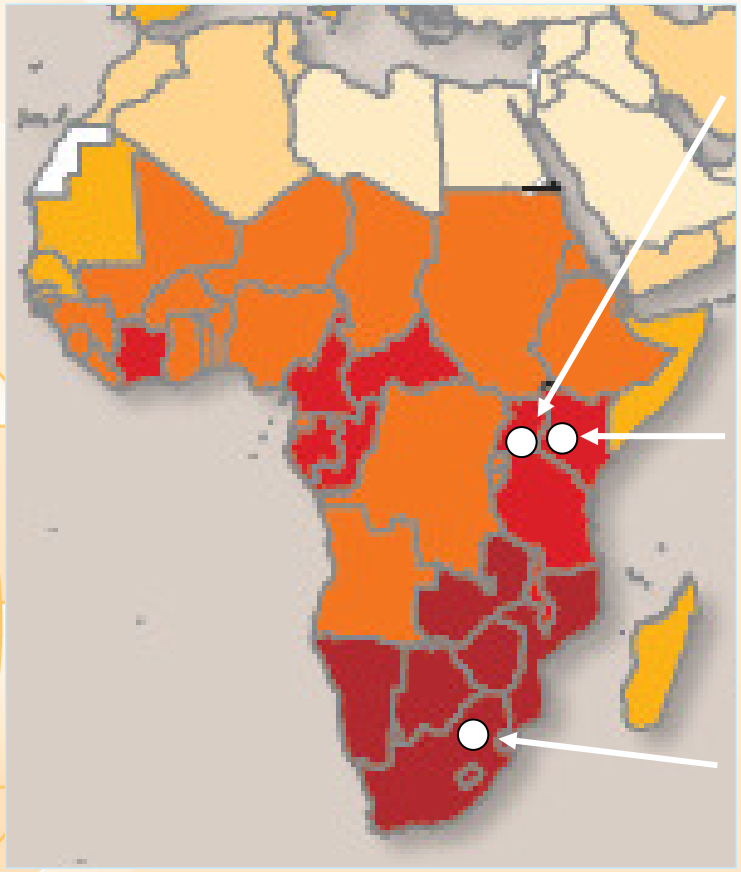
Randomised controlled trials of male circumcision to reduce HIV infection



Source: 2006 Report on the global AIDS epidemic (UNAIDS, May 2006)

Rakai, Uganda

Gray *et. al.* (2007)

Lancet; 369: 657 – 66

Kisumu, Kenya

Bailey *et. al.* (2007)

Lancet; 369: 643 – 56

Orange Farm, South Africa

Auvert *et. al.* (2005)

PLoS Med; 2 (11): e298

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Randomized Controlled Trials

- All three trials of a similar design
  - HIV-ve men randomized to immediate or delayed circumcision
  - All men given initial and refresher HIV and STI risk reduction counselling during follow-up
  - Followed prospectively and tested for HIV at regular intervals
  - Information recorded on sexual behaviour, condom use, incident STIs

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Features of Three RCTs

	Orange Farm	Rakai	Kisumu
Population	Semi-urban	Rural	Urban
MC prevalence	20%	16%	10%
Age range	18-24 yrs	15-49 yrs	18-24 yrs
Sample size	3,128	4,996	2,784
Schedule (months)	3, 12, 21	6, 12, 24	1, 3, 6, 12, 18, 24
First results	Jul 05	Dec 06	Dec 06

Results of RCTs

	Orange Farm	Rakai	Kisumu
Follow-up (p-yr)	4664	6,744	?
HIV infections	69	67	69
HIV+ control	49	45	47
HIV incid control (per 100 p-yr)	2.1	1.33	4.2
HIV+ circumcised	20	22	22
% reduction	60% (32-76)	51% (22-75)	53% (22-72)
P-value	P < 0.001	P = 0.006	P = 0.0065

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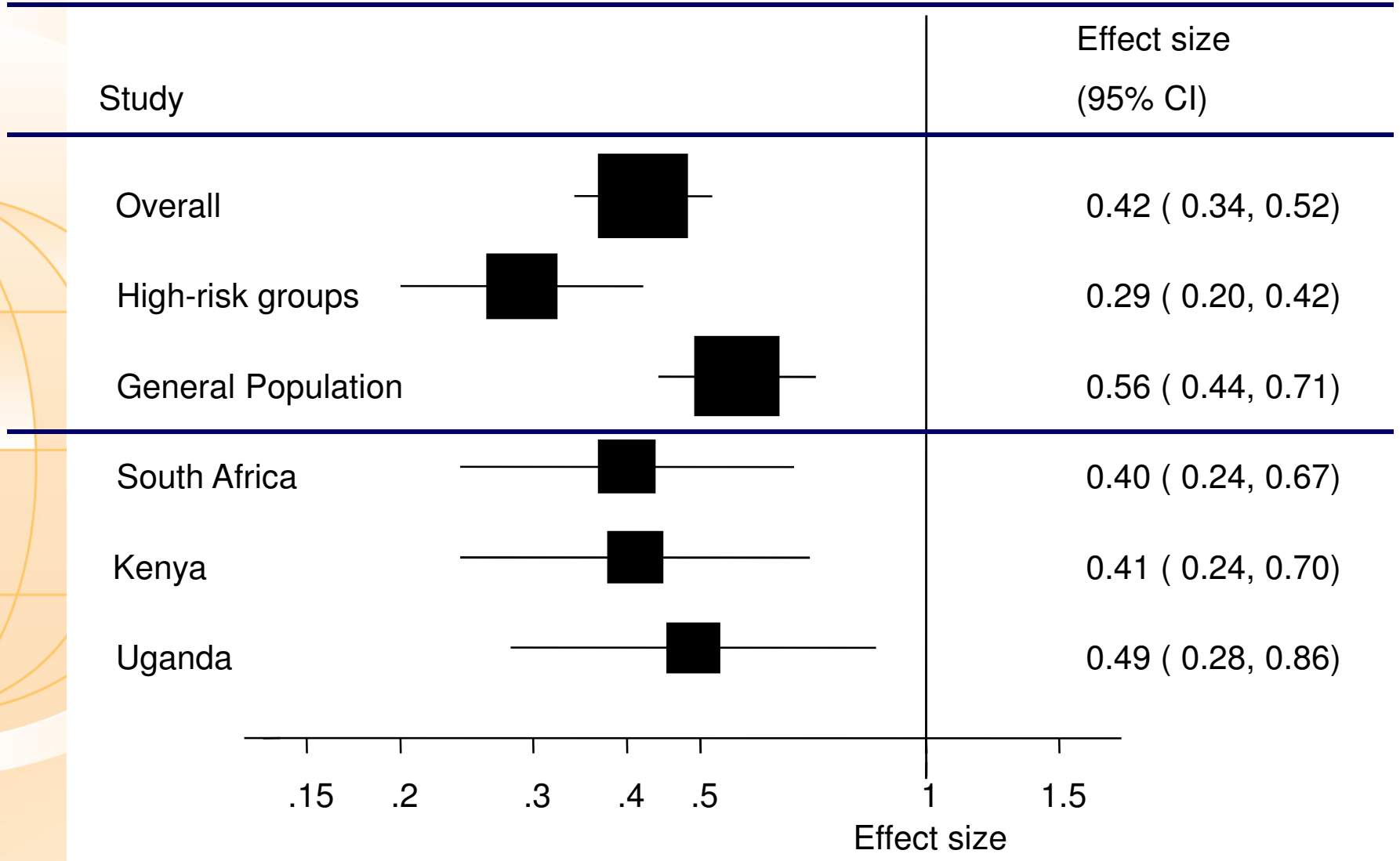
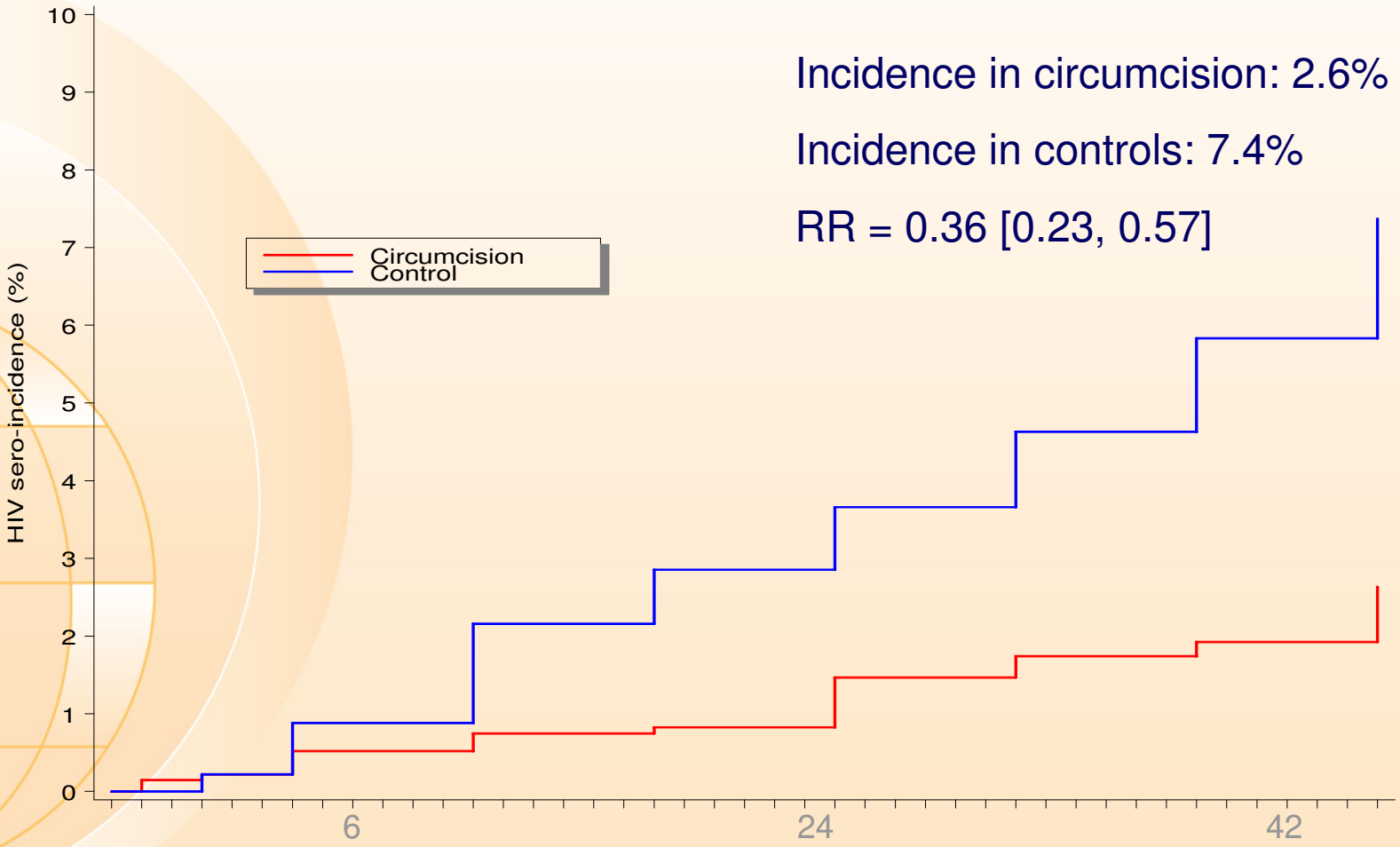
Impact on HIV incidence: Evidence from observational studies and RCTs



Kisumu RCT: Cumulative HIV Incidence over 42 Months: Circumcision Group versus Controls



Incidence in circumcision: 2.6%

Incidence in controls: 7.4%

RR = 0.36 [0.23, 0.57]

Bailey et al AIDS 2008 presentation

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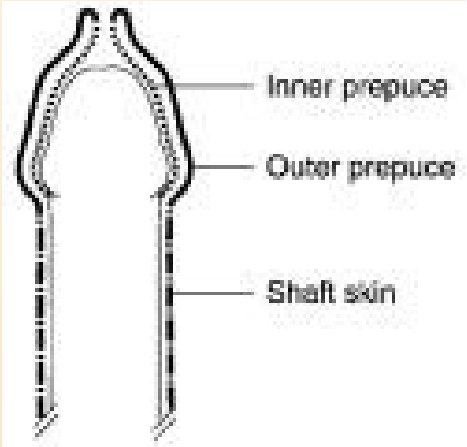
Biological Rationale for HIV link

Biological plausibility

- Inner mucosa of foreskin is rich in HIV target cells
- External foreskin/shaft keratinized and less vulnerable
- After circumcision, remaining inner aspect of foreskin quickly keratinizes, density of target cells is reduced and cells are less accessible

Foreskin is retracted over shaft during intercourse

- Large inner mucosal surface exposure
- Vulnerable to micro-tears, especially of frenulum



Intact foreskin associated with infections

- Genital ulcer disease
- Balanitis
- Possible increased HIV entry or shedding

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Foreskin Surface Area and HIV Incidence

965 initially HIV-negative men in Rakai population cohort subsequently enrolled in one of two randomised trials of immediate vs. delayed circumcision and foreskin surface area estimated at time of operation.

Foreskin surface area	Follow-up (years)	HIV infections	Incidence (/100 py)
<= 26.3 cm^2	994.9	8	0.80
26.4 – 35.0 cm^2	975.3	9	0.92
35.1 – 45.5 cm^2	888.5	8	0.90
>= 45.6 cm^2	926.8	23	2.48 IRR 2.37 (1.05 – 5.31)

Ref: Kigozi *et al.*, ***AIDS*** 2009 (ePub)

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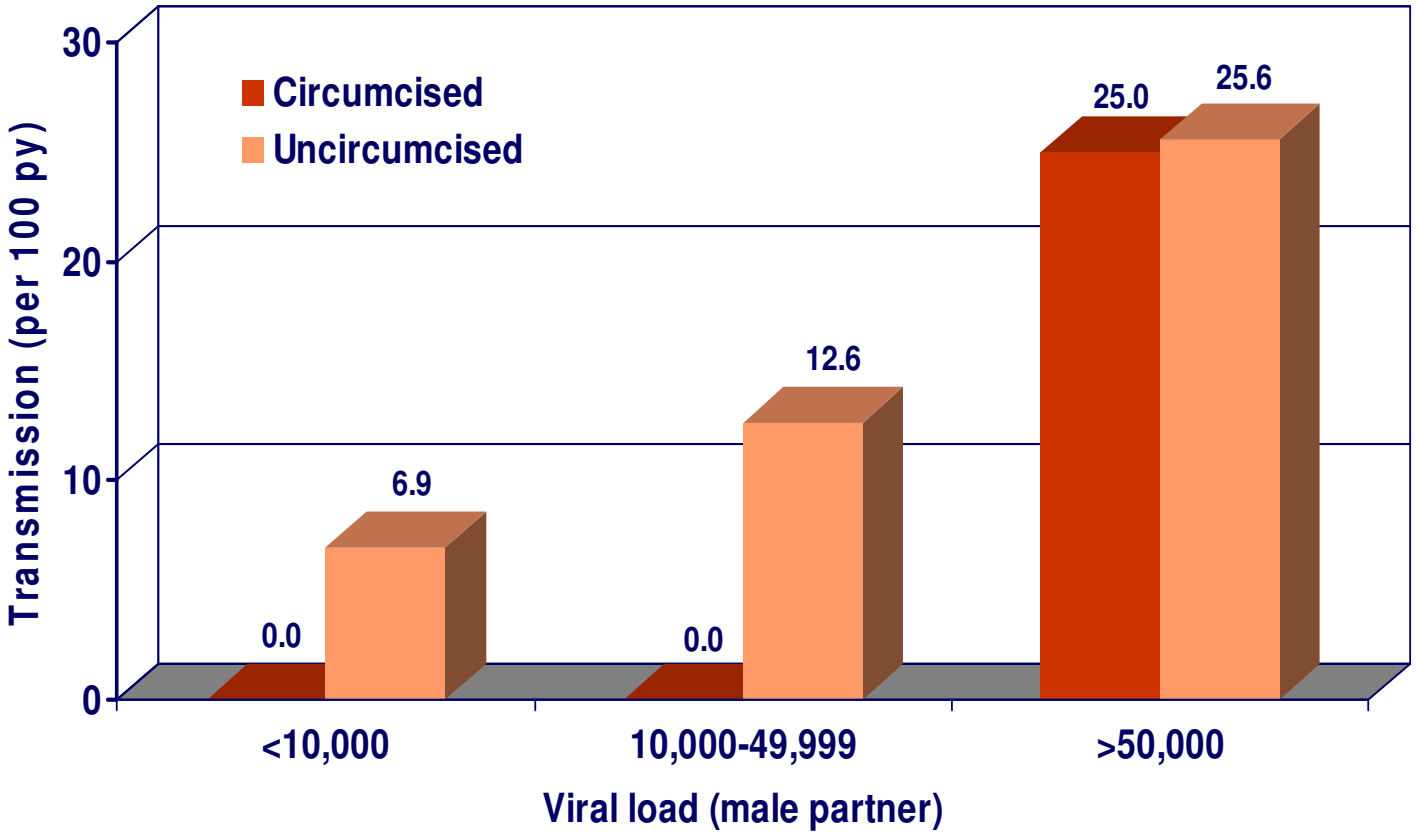
Circumcision and transmission to women

Gray *et al., AIDS* 2000, **14**: 2371-81



Of 47 couples in whom circumcised *male partner was HIV+* AND whose viral load was <50,000 particles, *0 female partners were infected* after two years, compared with 26 of 143 female partners of uncircumcised HIV+ men (9.6/100 py) (p = 0.02)

RCT Female HIV Acquisition
Wawer *et al*., *Lancet* 2009; 374: 229-237

- Trial conducted in Rakai in parallel with trial among HIV -ve men
- Men screened for eligibility and willingness to participate in RCT of male circumcision
  - HIV –ve men ➔ enrolled in acquisition RCT
  - HIV +ve men
    - if CD4 count > 350, enrolled in transmission RCT
    - Partners linked through Rakai demographic surveillance programme
    - Consenting HIV –ve partners followed and included

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RCT Female HIV Acquisition

Wawer *et al.*, *Lancet* 2009; 374: 229-237

	Partners of circumcised men	Partners of un-circumcised men
Number of women	92	67
Incident HIV infections	17	8
Cumulative HIV infection rate (24m)	21.7% (12.7-33.4%)	13·4% (6·7–25·8%)
Risk ratio	1·58 (0·68–3·66); p=0·287	

1. Circumcision of HIV-infected men did not reduce HIV transmission to female partners over 24 months
2. Longer-term effects could not be assessed
3. Particular concern of excess risk of M ➔F transmission if resumption of sex before full wound healing (3x higher risk)

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Biological Plausibility for Effects of Circumcision on HIV Acquisition in Women

- Female partners of circumcised men have lower prevalence of bacterial vaginosis (risk factor for HIV acquisition)
- Observational data referred to men circumcised many years previously, but long follow-up in cohort not practical
- Possibility of later protective effect, but cannot be confirmed
- Potential short-term increased risk of HIV transmission

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Models to Assess Impact and Cost-Effectiveness

- Population groups
  - Circumcised men
  - Uncircumcised men
  - Women
- Age groups for simulating epidemic
  - Either 5- or 10-year intervals
- Targets for intervention
  - Neonates, men before sexual debut, all men, "high risk" men, …
- Population structure, HIV prevalence and incidence, sexual mixing, … typical of high-HIV low-circumcision population
  - e.g. Kisumu (Kenya), Zimbabwe, Botswana, …

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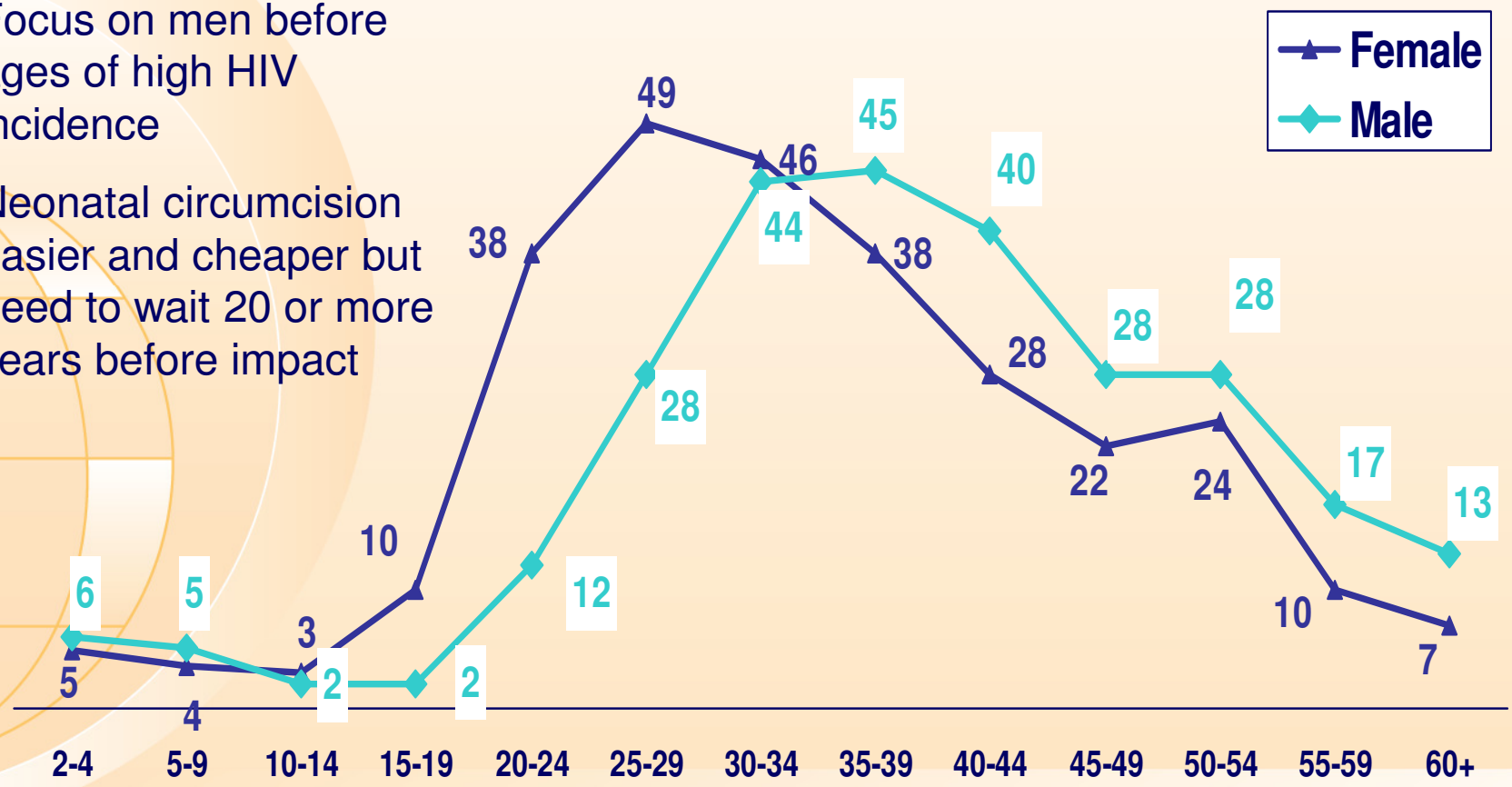
HIV Prevalence by Age and Sex

[Swaziland Demographic and Health Survey 2006]

Focus on men before ages of high HIV incidence

Neonatal circumcision easier and cheaper but need to wait 20 or more years before impact



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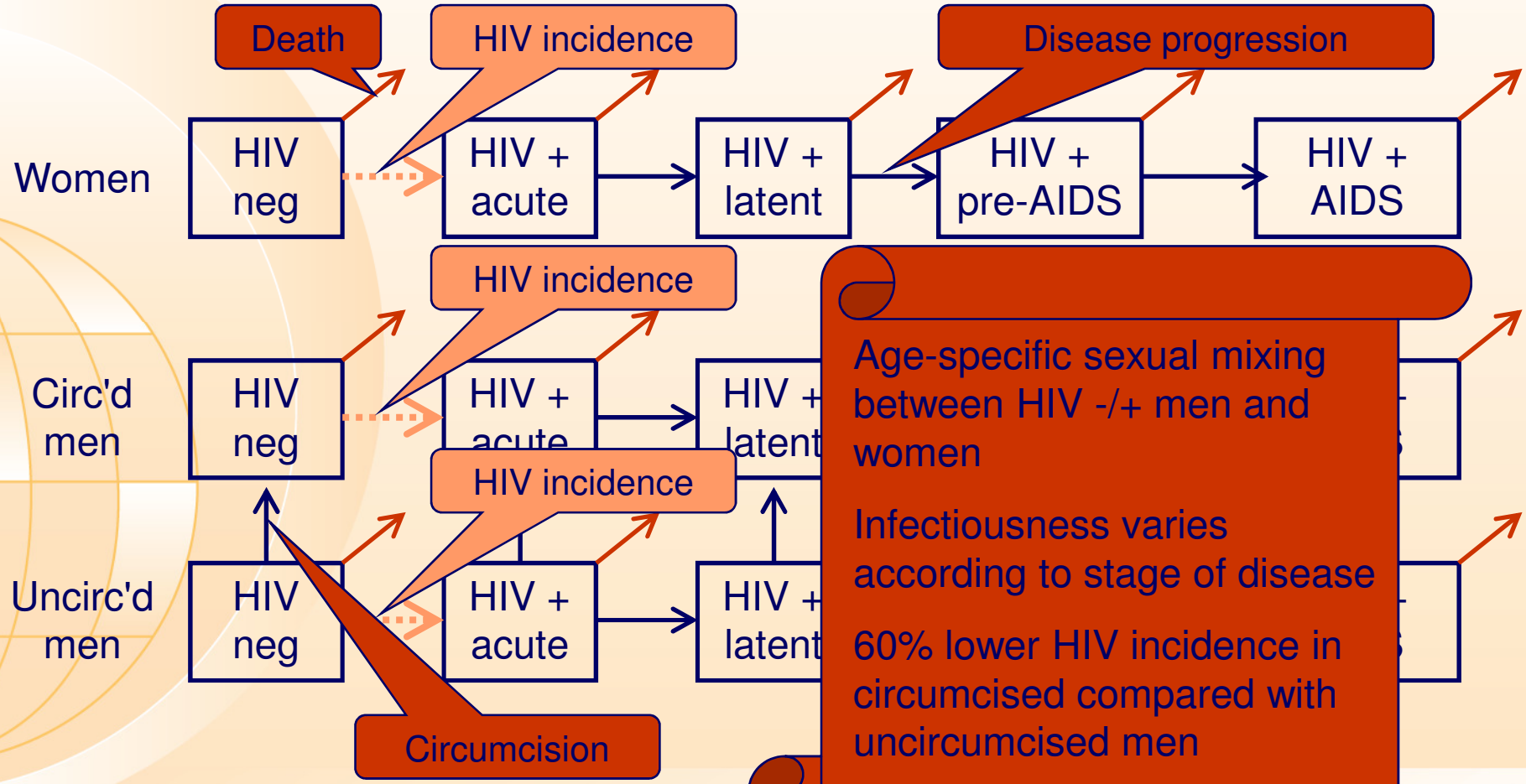
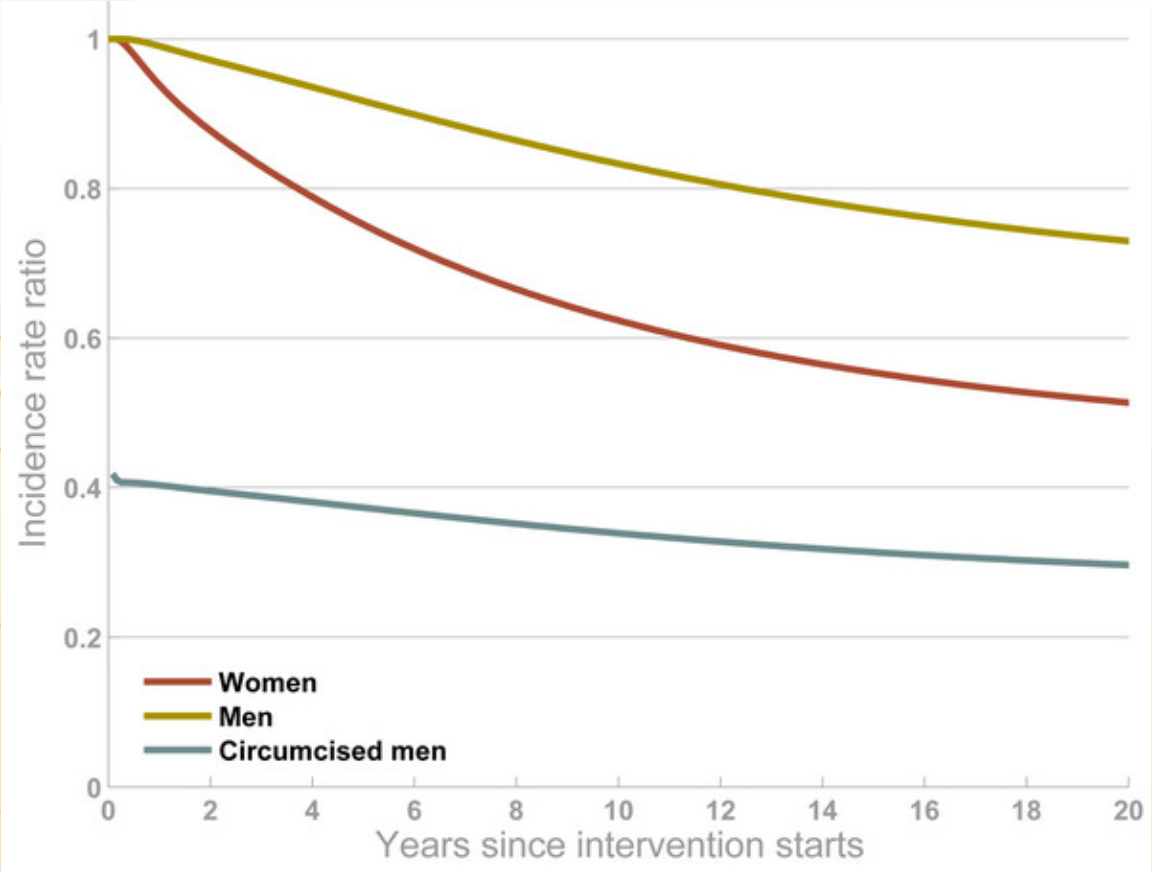
Model Flow Diagram

Hallett *et al.*, PLoS ONE 2008; 3(5): e2212



Impact of Circumcision on HIV Incidence



1. Immediate impact on HIV incidence in circumcised men (primary [direct] effect)
2. Delayed and somewhat attenuated impact in women (secondary [indirect] effect)
3. Impact in uncircumcised men (tertiary effect)
4. Additional impact in circumcised men

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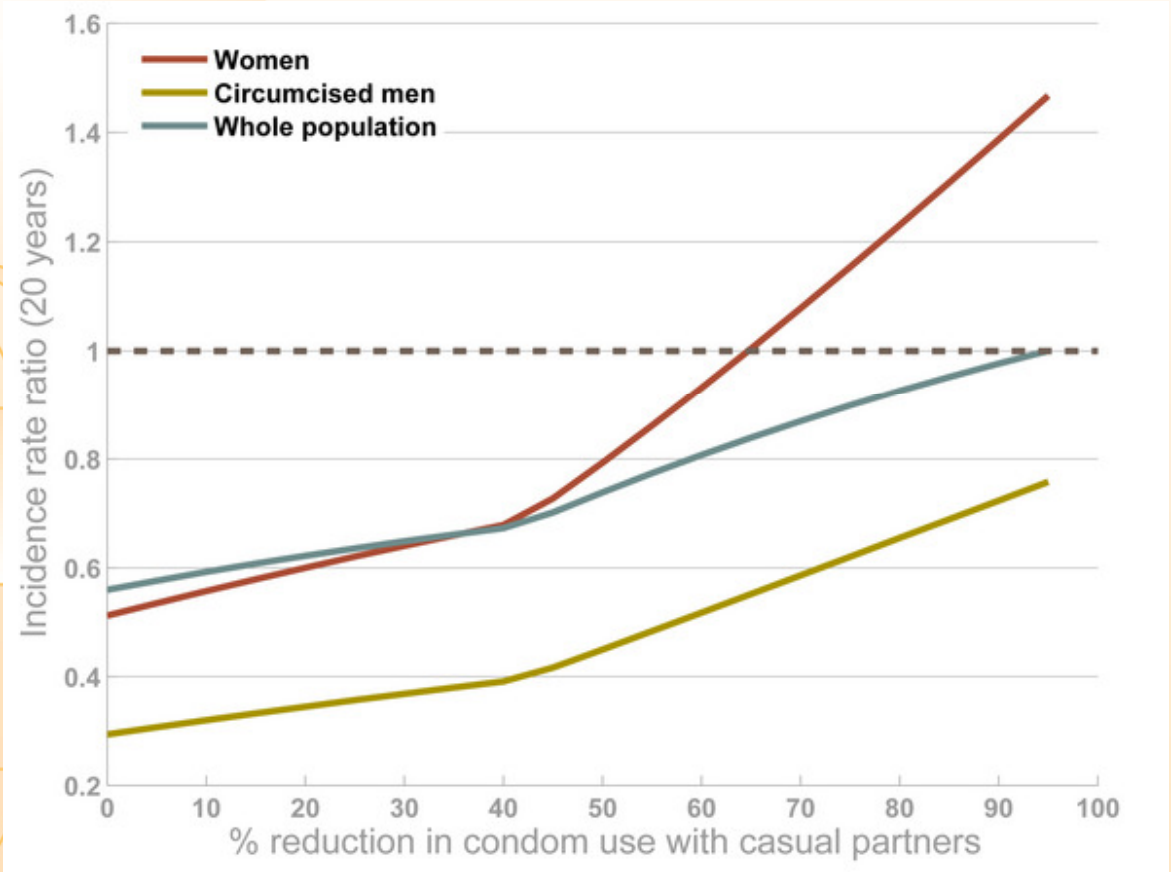
Risk Compensation

Lower condom use with casual partners by circumcised men



1. Impact of circumcision (both direct and indirect effects) sufficiently large that even 50% reduction in condom use results in minimal dilution of effect

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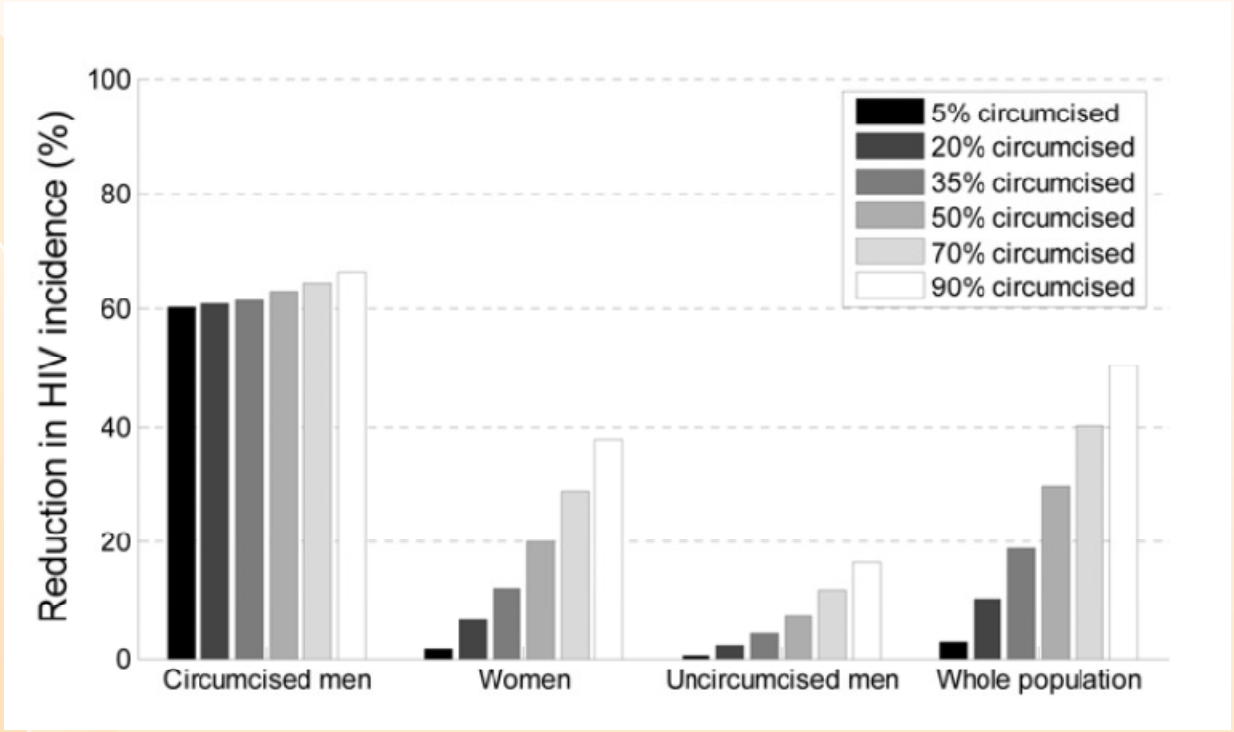
Impact of Circumcision Coverage



UNAIDS/WHO/SACEMA Expert Group on Modelling the Impact and Cost of Male Circumcision for HIV Prevention (2009) Male Circumcision for HIV Prevention in High HIV Prevalence Settings: What Can Mathematical Modelling Contribute to Informed Decision Making? PLoS Med 6(9): e1000109.

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Model for Circumcision Service Expansion

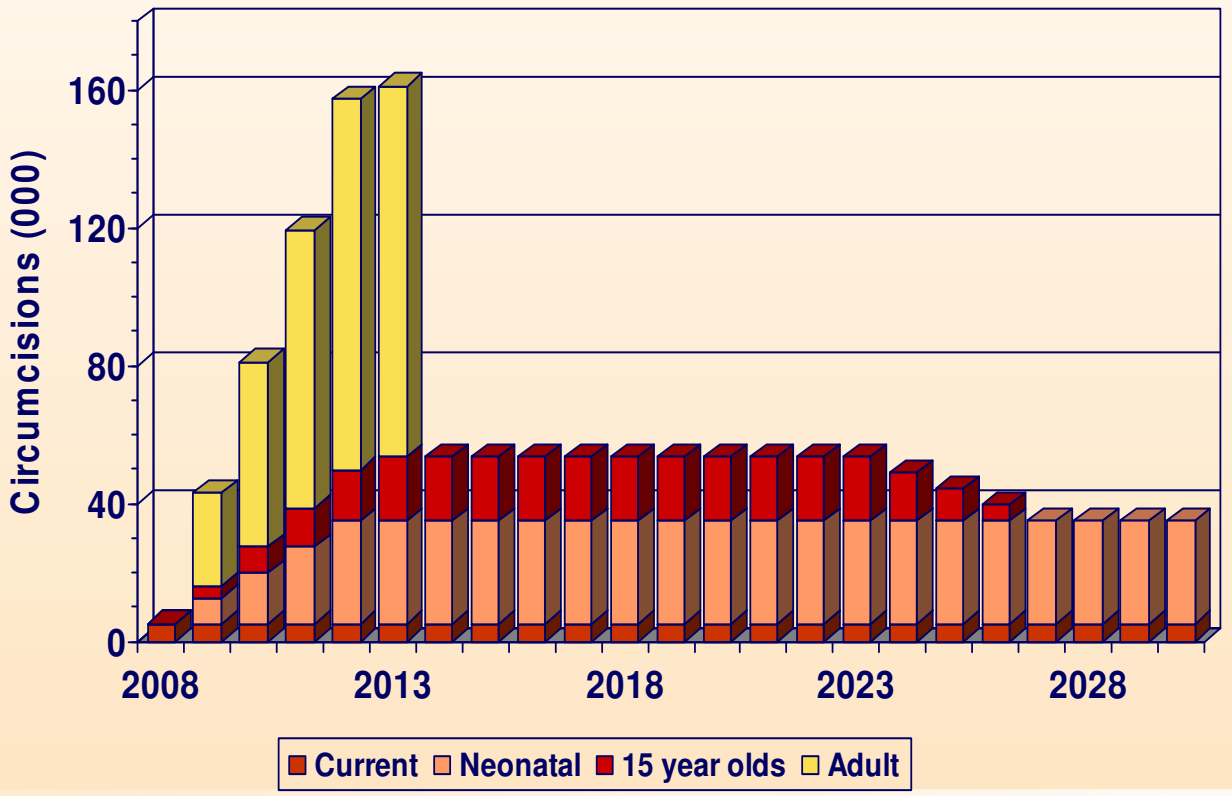
[informed by Botswana demographic information]

Adult, 15-year and Neonatal Programme

523,000 males 15-49y (80% coverage within 5y)

Maintain age 15y programme until youngest cohorts sufficiently old

23,700 male births annually (80% coverage within 4y)



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Conclusion:
Protection for Individual or Population?

- High-level generalised epidemics only seen in populations where few men circumcised
- Strong evidence of large individual level effect of circumcision (60% risk reduction)
- Modelling shows important secondary and tertiary effects as HIV incidence and prevalence drop
- Challenge is to support countries with high HIV incidence and little or no tradition of circumcision to scale up services rapidly

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