Male Circumcision and Microbicide Trials

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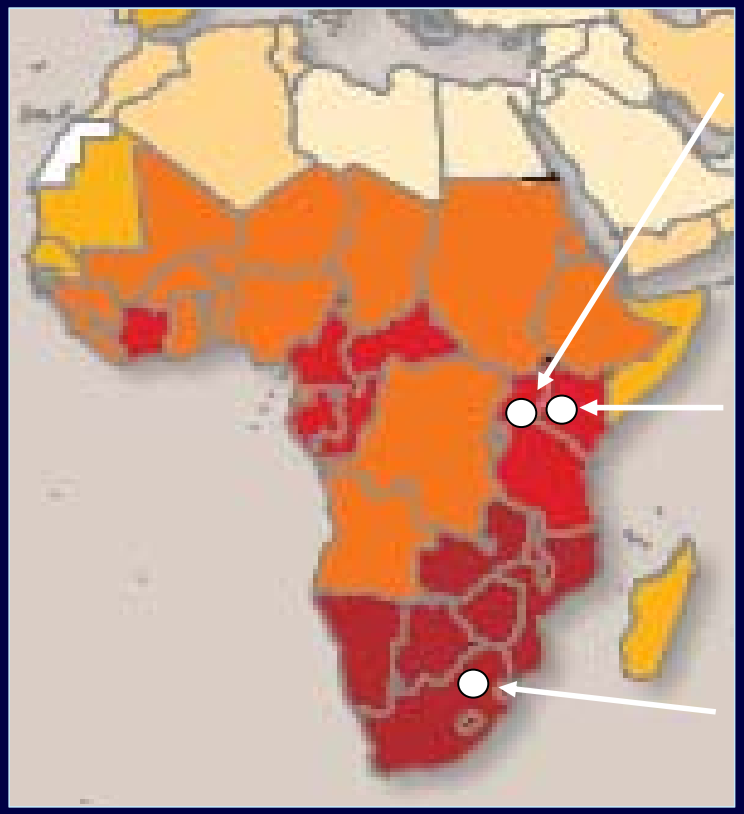
Male Circumcision Background Information

- Globally, 30%-35% of men are circumcised. In Africa, approximately 68%.
- It is a practice observed mostly for cultural and religious reasons, less often for health reasons.
- It is a simple procedure that may confer health benefits, but being a surgical procedure it entails risks.
- The benefits of MC must be weighed against the potential harm.

Randomised controlled trials of male circumcision to reduce HIV infections



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)

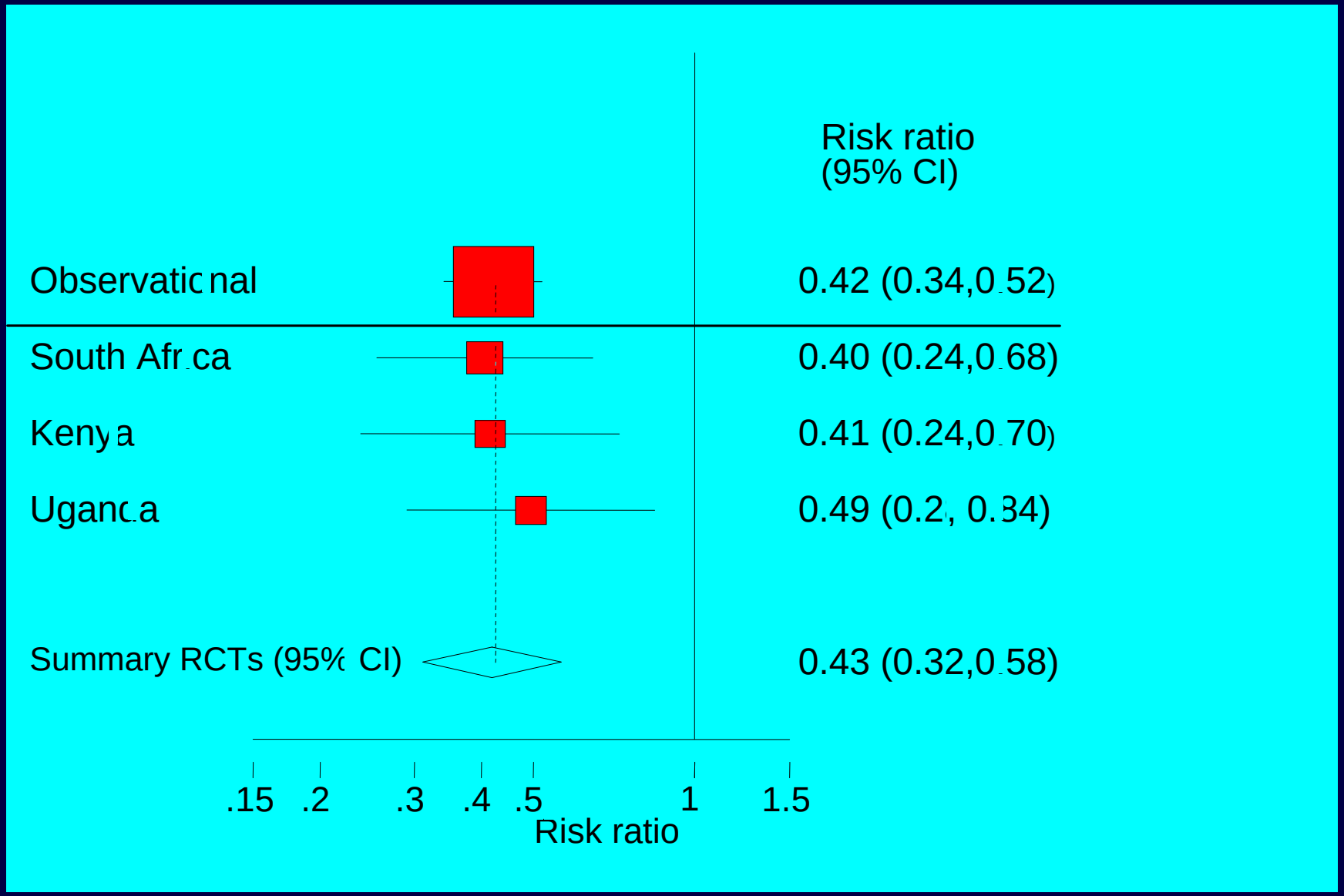
Lancet; 369: 643 – 56

Orange Farm, South Africa

Auvert *et. al.* (2005)

PLoS Med; 2 (11): e298

Effect of MC on HIV Incidence: Observational Studies and 3 RCTs




WHO/UNAIDS Consultation
Montreux, Switzerland
March 6, 2007

WHO/UNAIDS Statement March 28, 2007

- "The efficacy of male circumcision in reducing female to male HIV transmission has now been proven beyond reasonable doubt. This is an important landmark in the history of HIV prevention."
- "Scaling up male circumcision in *(certain)* countries will result in immediate benefits to individuals."
- "Male circumcision should be considered as part of a comprehensive HIV prevention package."

Other Benefits of Circumcision for Men

- **Urinary tract infections in infants**
  - 12 fold increased risk in uncircumcised boys
- **Phimosis and paraphimosis**

  Absent in circumcised men
- **Chancroid**
  - 2.5 fold increased risk in uncircumcised men
- **Invasive penile cancer in men**
  - 22 times more frequent in uncircumcised men

Cumulative % Infected with HSV-2 and HPV

	Circumcised	Not Circumcised	aRR (95% CI)
HSV-2 Rakai	7.8%	10.3%	0.72 (0.56-0.92)
HSV-2 Orange Farm	2.1%	3.7%	0.70 (0.49-0.99)
HPV Rakai	18.0%	27.9%	0.65 (0.46-0.90)
HPV Orange Farm	14.0%	23.2%	0.62 (0.47-0.80)
HPV Lu et al, 2009	Circumcised 6 times more likely to clear oncogenic infection		

Incidence of Non-ulcerative STI in Kisumu Cohort

	Circumcised	Uncircumcised
Gonorrhea	3.39 (2.68-4.29)	3.52 (2.80-4.42
Chlamydia	4.43 (3.97-5.87)	4.83 (3.52-5.35)
Trichonomas	1.05 (0.69-1.59)	1.45 (1.02-2.07)

HR of GC or Ct = 0.96 (0.89-1.04), p=0.33

No Protective Effect Against Syphilis Acquisition

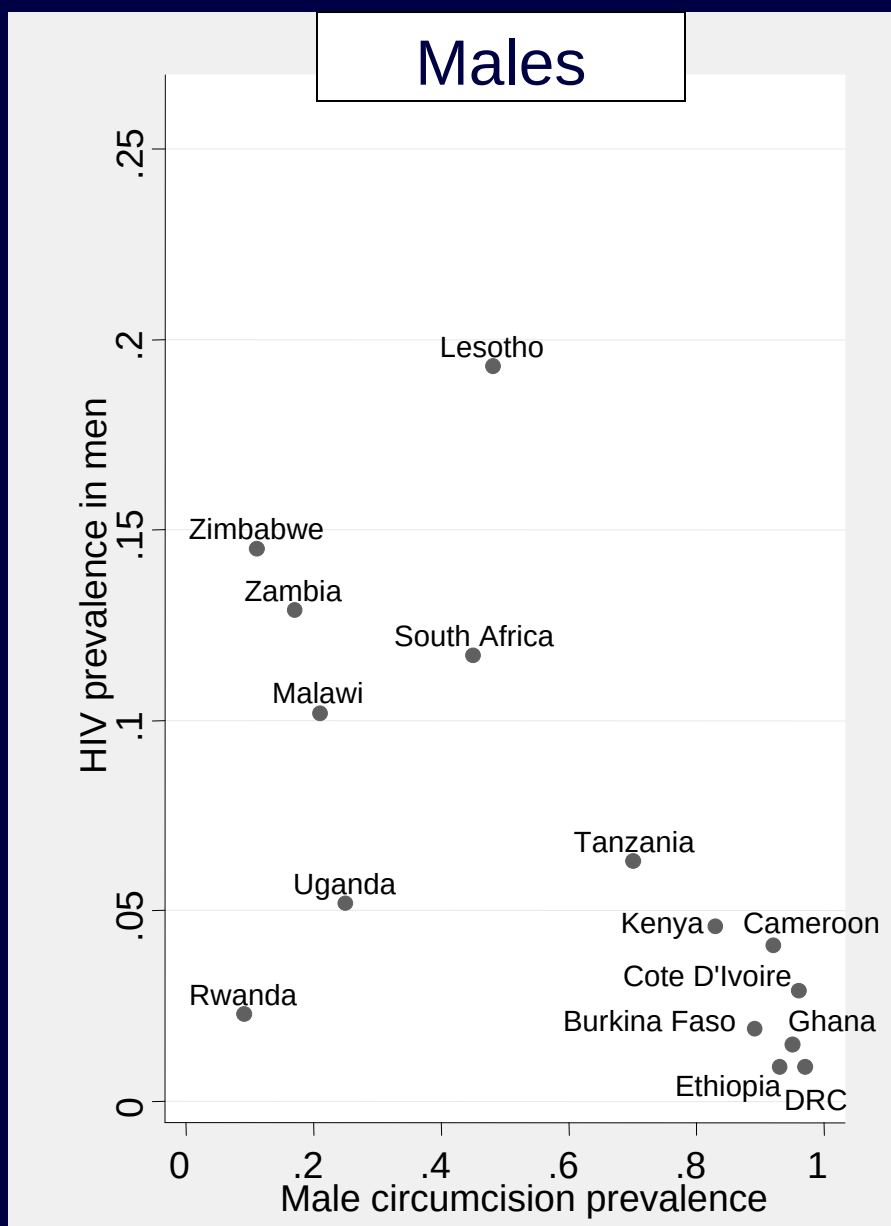
- Kisumu
  - RR = 1.68 (0.40 – 7.03)
- Rakai
  - aHR = 1.10 (0.75 – 1.65)

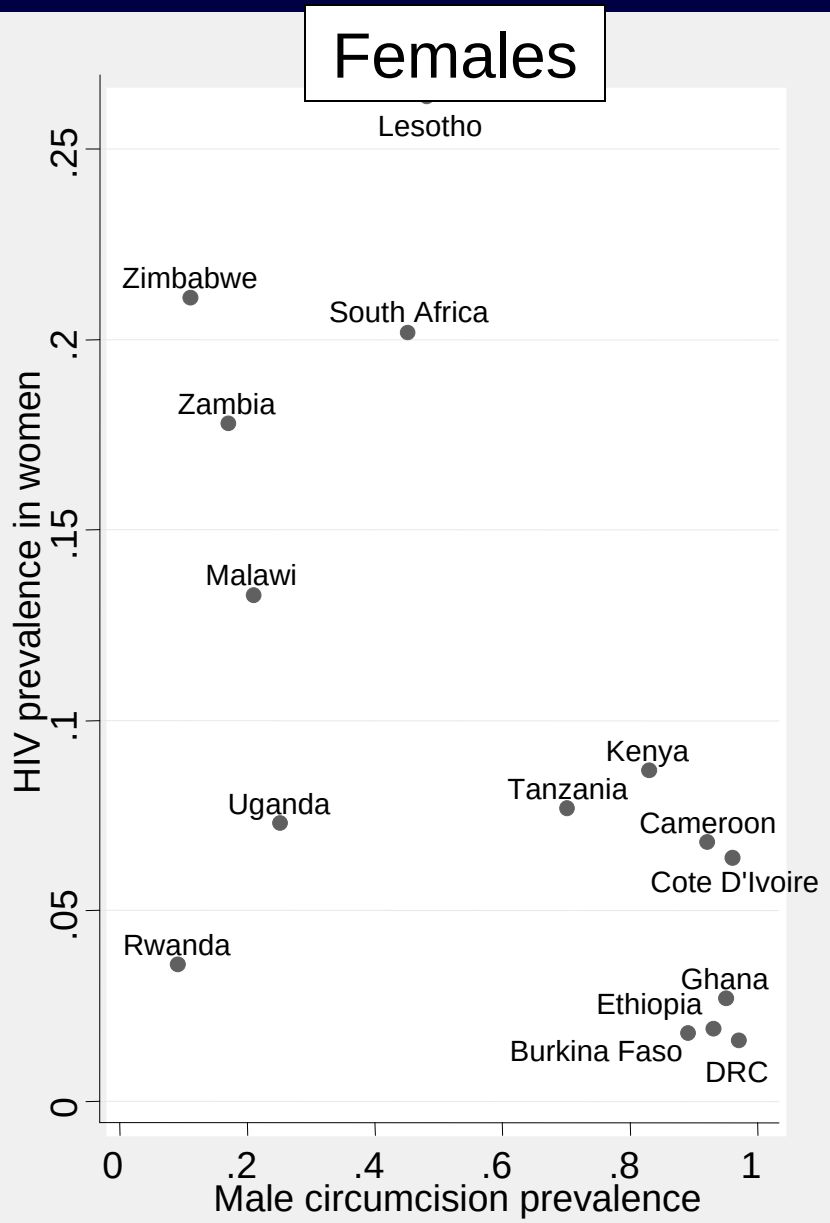
Signs and Symptoms of Selected STIs Over Follow-up Visits Kisumu

	Circumcision N (%)	Control n (%)	RR [95% CI]	p-value
Present on Study Visits or Symptom in Previous 6 Months				
GUD	59 (5.4%)	106 (10.1%)	0.56 [0.40,0.77]	0.001
Urethral Discharge	85 (7.9%)	105 (9.4%)	0.79 [0.59,1.05]	ns
Genital Warts	4 (0.4%)	28 (2.7%)	0.14 [0.05,0.41]	0.001

Benefits of Circumcision for Women

- **Chlamydia** (Castellsague et al., 2005)
  - OR = 0.18 (95%CI, 0.05-0.58)
- **Cervical cancer in female partners** (Castellsague et al., 2002)
  - 5.5% if partner circumcised; 19.6% if partner uncircumcised
  - OR = 0.37 (95%CI, 0.16-0.85)
- **Bacterial vaginosis** (Gray et al., 2009)
  - aRR = 0.82 (95%CI, 0.74-0.91)
- **GUD** (Gray et al., 2009)
  - aRR = 0.78 (95%CI, 0.61-0.99)

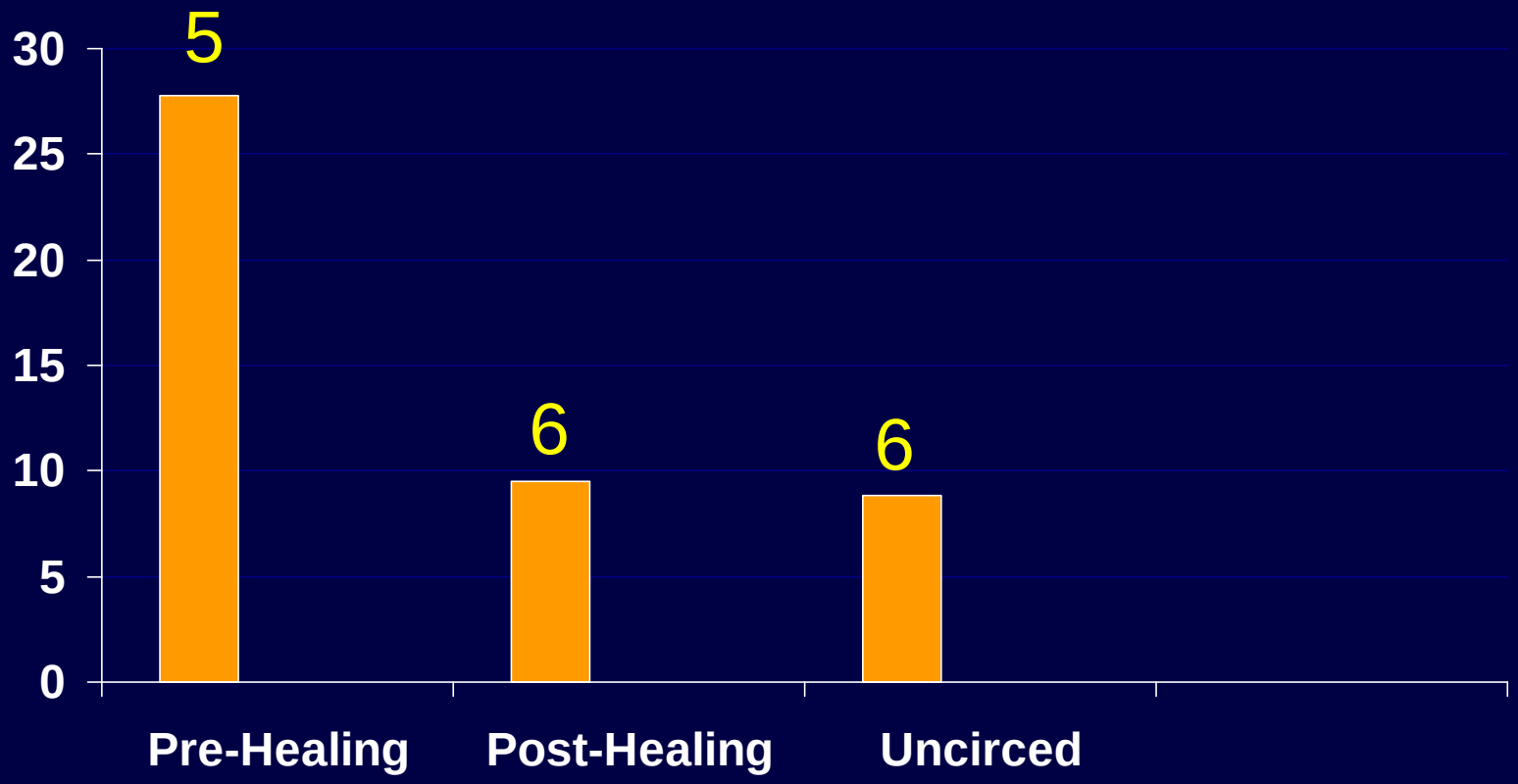

Males
HIV prevalence in men
0
.05
.1
.15
.2
.25
Lesotho
Zimbabwe
Zambia
South Africa
Malawi
Tanzania
Uganda
Kenya
Cameroon
Cote D'Ivoire
Rwanda
Burkina Faso
Ghana
Ethiopia
DRC
0
.2
.4
.6
.8
1
Male circumcision prevalence


Females
HIV prevalence in women
0
.05
.1
.15
.2
.25
Lesotho
Zimbabwe
South Africa
Zambia
Malawi
Kenya
Tanzania
Uganda
Cameroon
Cote D'Ivoire
Rwanda
Ghana
Ethiopia
Burkina Faso
DRC
0
.2
.4
.6
.8
1
Male circumcision prevalence

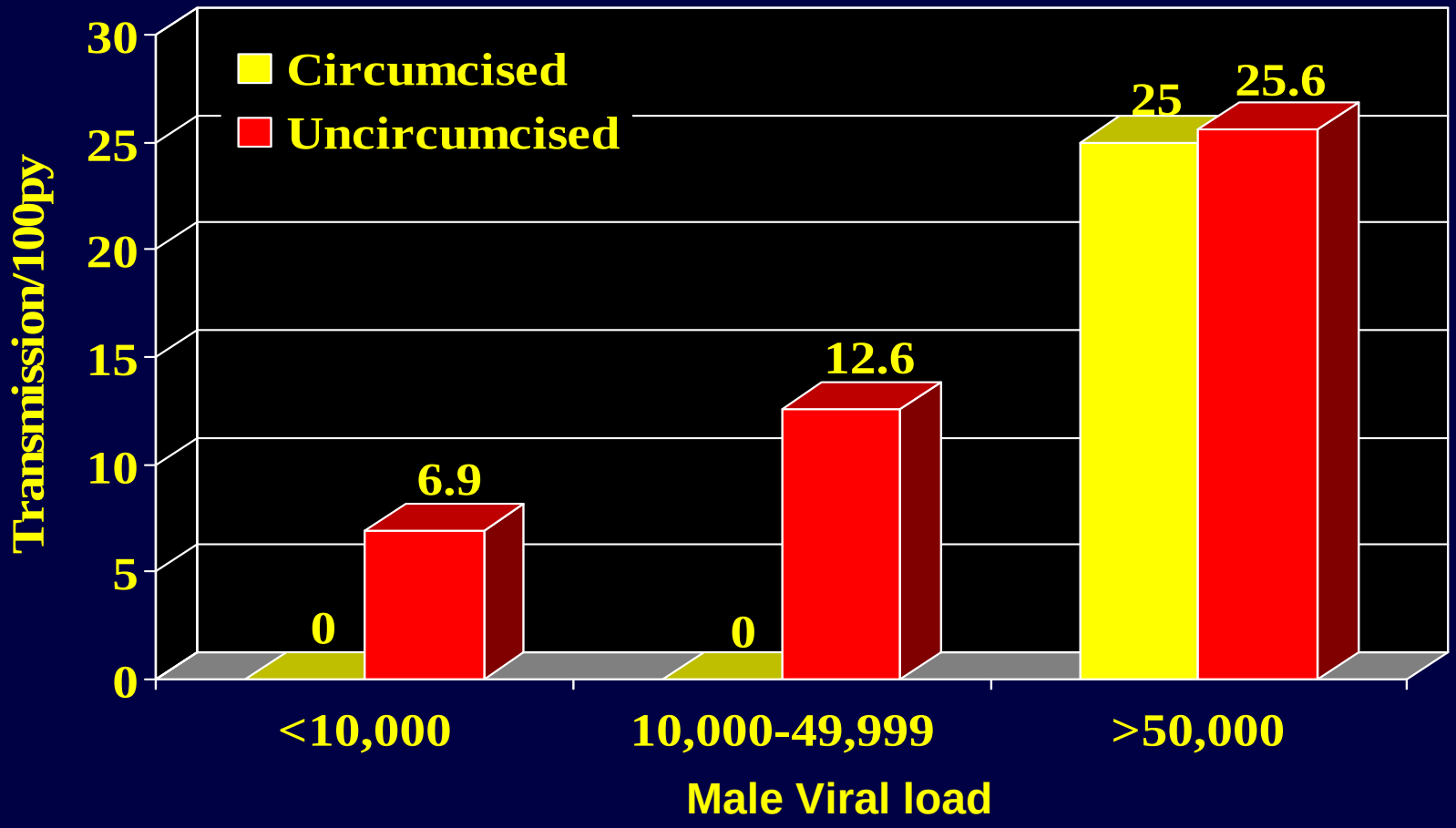
HIV Transmission to Women

- One RCT (Rakai) has evaluated the impact of MC on HIV acquisition in women.
- Recruitment was stopped at interim analysis due to futility.
  - No answer possible by end of planned two-year follow-up
- RR = 1.59 (95%CI, 0.7-4.3) at six months
- Some suggestion that HIV+ men who resumed sex early transmitted HIV to partner in 1st six months.

% of Seroconversions in Female Partners by Time of Resumption of Sex after Circumcision



Circumcision Status and HIV Transmission to Women



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

Quinn et al NEJM 2000

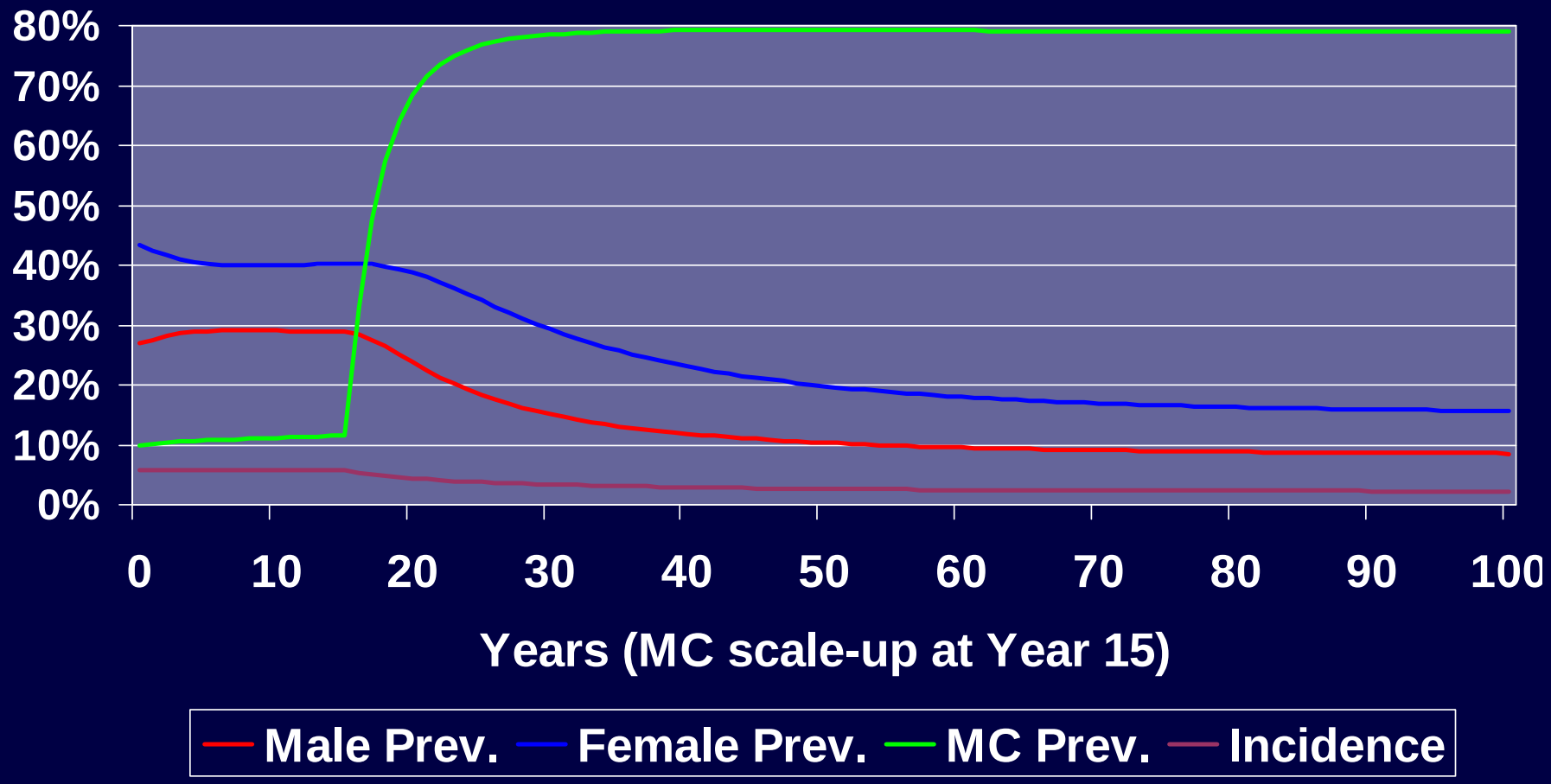
Implications for Trial Design

- Women should be part of the pre and post-op counseling.
  - MC is only partially protective for the male
  - Do not resume sex before full wound healing
- Power analyses should include possibility that MC is 33% protective for female partners.
- Effect could be stronger in high risk women.

Modeling the Impact of MC on HIV Prevalence/Incidence

- Williams et al., 2006
  - 100% uptake of MC could avert 2.0 million new infections and 0.3 million deaths over ten years in sub-Saharan Africa
  - Could avert 5.7 million new infections over 20 years
- Mesesan et al., 2006
  - 50% uptake of MC could avert 32,000 – 53,000 new infections in Soweto, SA over 20 yrs. Prevalence would decline from 23% to 14%.
- Nagelkerke et al., 2007
  - Prevalence in Nyanza Province, Kenya would decline from 18% to 8% with 50% uptake of circumcision over 10 years.
- Gray et al., 2007
  - Assuming 50% uptake in Rakai, incidence would decline from 1.4% to .81%, and R_o would decline to 0.89.

Botswana – MC uptake 80% over 10 years, relative risk = 0.40



Nagelkerke et al, BMC Inf. Dis. 2007

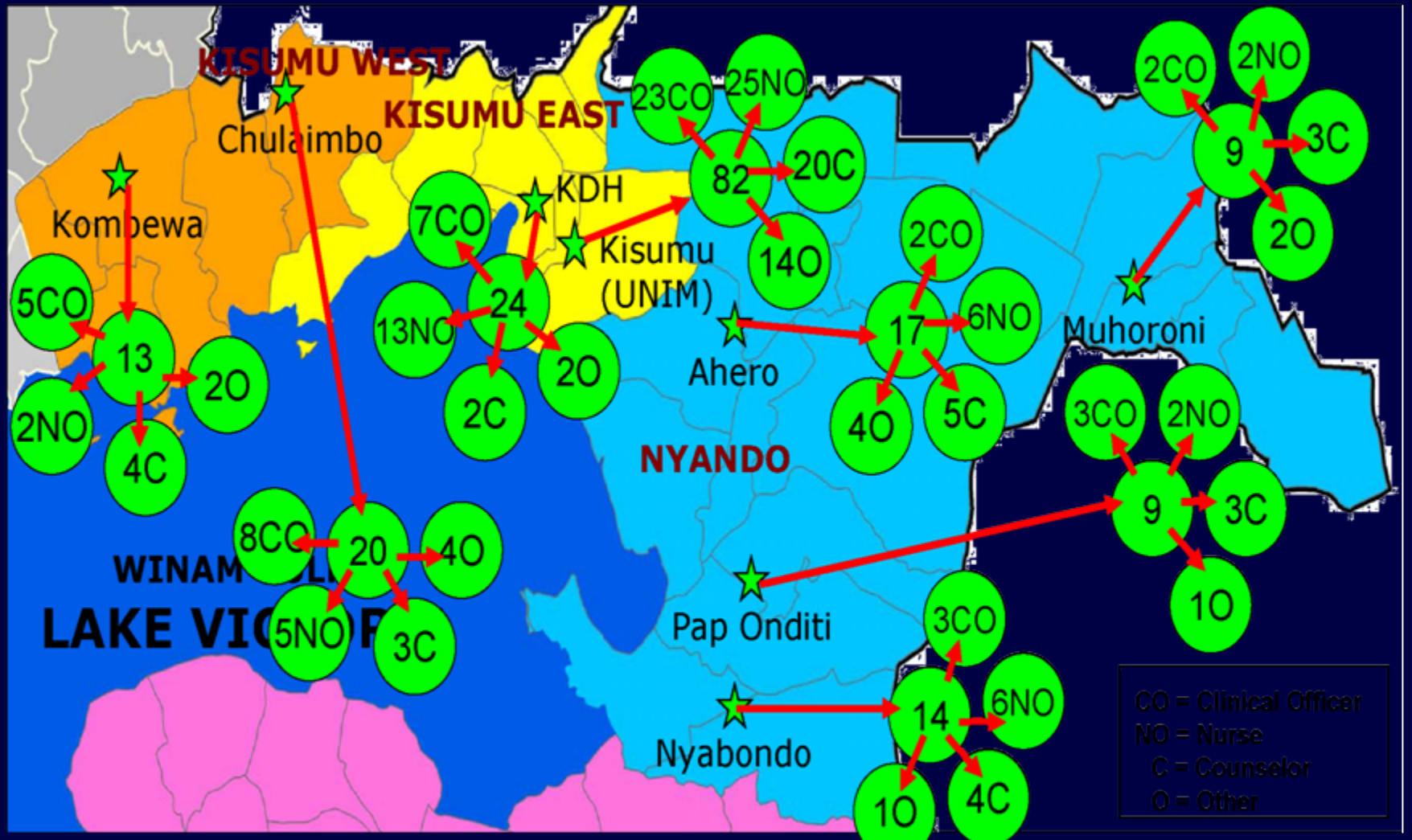
MC Training and Service Provision in Nyanza Province, Kenya

- UNIM Training and Research Center
  - MC Training Team
  - Train Mobile Training Teams
    - Mobile Training Teams train staff at MOH health facilities
  - Train outreach teams
    - Provide MC services at lower capacity facilities
  - Train mobile service provision teams
    - Provide MC services in villages

Assessments and Capacity Building at Health Facilities

- Assessments of approx. 60 health facilities
  - Minor Renovations
  - Autoclaves
  - Instruments & Supplies
- Training of staff
  - Medical Officers
  - Clinical Officers
  - Nurses
  - Counselors
  - Cleaners, public health educators

Training and Capacity Building



The in-house, Nyando and Kisumu training team up to date trained: 1 Medical Officer, 48 Clinical Officers, 48 Nurses, 43 Counselors, and 18 Cleaners, Public Health Officers, and Community Health Workers – a total of 191 MC providers

MC Service Provision

- Comprehensive Services
  - Integrated with fixed site VCT or home-based VCT
  - STI diagnosis and treatment
  - Couples counseling and testing
  - Pre-op counseling, informed consent
  - Surgery
  - Post-op counseling & follow-up
    - Wound care
    - Abstinence from sex for 6 weeks
    - Partner reduction, condom use

Three Models of MC Service Provision

- Fixed sites (District Hospitals and Health Centers)
- Outreach sites – health facilities with less capacity
- Mobile Teams

Integrating MC into Microbicide Trial Designs

- Provide information about the risks and benefits of MC to women
  - Not sufficient
- Provide information plus referral
  - Must ensure access to service
  - Must ensure quality of service
  - Service must be free
  - Must be comprehensive (VCT, STI treatment, counseling)
- Should provide couples counseling about MC

Adverse Events by Setting

Facility	n	# AEs	%
Public Facility	111	12	10.8
Private Facility	346	78	22.5
Traditional	426	146	34.3
Total	883	236	26.6

R.C. Bailey and O. Egesah, Bungoma, Kenya, 2005

Integrating MC into Microbicide Trial Designs

- Trials with discordant couples
  - If male is known positive
    - Advise that MC is unlikely to have significant benefit
    - If he is healthy and wants circumcision, he should not be denied the service
- Trials with high-risk women
  - Comprehensive, safe, free MC services should be available to male partners.
  - Seek prevention partners with funding/expertise
  - Contract for training in appropriate health facilities

Increasing the Uptake of MC

- Barriers
  - **Cost (money and time from work)**
  - **Fear of pain**
  - **Fear of infection**
  - **MC framed as a cultural or religious practice only**
- **Facilitators**
  - **Political endorsement, national and local leadership**
  - **MC not just for HIV prevention**
    - **Hygiene, reduction of STIs, protection for women**
  - **Superior services – friendly, clean, safe**

MC and Microbicide Trials

- MC clinics provide opportunities for recruitment of discordant couples
- Should include circumcision status of male partner as a risk factor
  - observe the circumcision status of the man
- Include measurement of:
  - Risk compensation related to MC status of partner and reasons for changes in risk behaviors
  - Timing of resumption of sex after circumcision

Summary

- MC is a proven means of reducing incidence of HIV acquisition in heterosexual men
- MC has many other benefits for men
- There is not good evidence that there is a direct protective effect of MC against female HIV acquisition
- MC reduces women's risks of acquisition of STIs other than HIV
- MC is likely to reduce substantially HIV prevalence in women in countries with currently low circumcision and high HIV prevalence.
- MC services can be offered in a variety of settings: fixed site, outreach, mobile.

Summary

- MC services must be offered in the context of a full package of HIV prevention services
- Implications for trials:
  - May require larger sample sizes
  - Should provide MC services: free, safe, comprehensive
  - Uptake can be improved
    - Political leadership
    - MC not just for HIV prevention
    - Provision of superior services

The End