

La circoncision

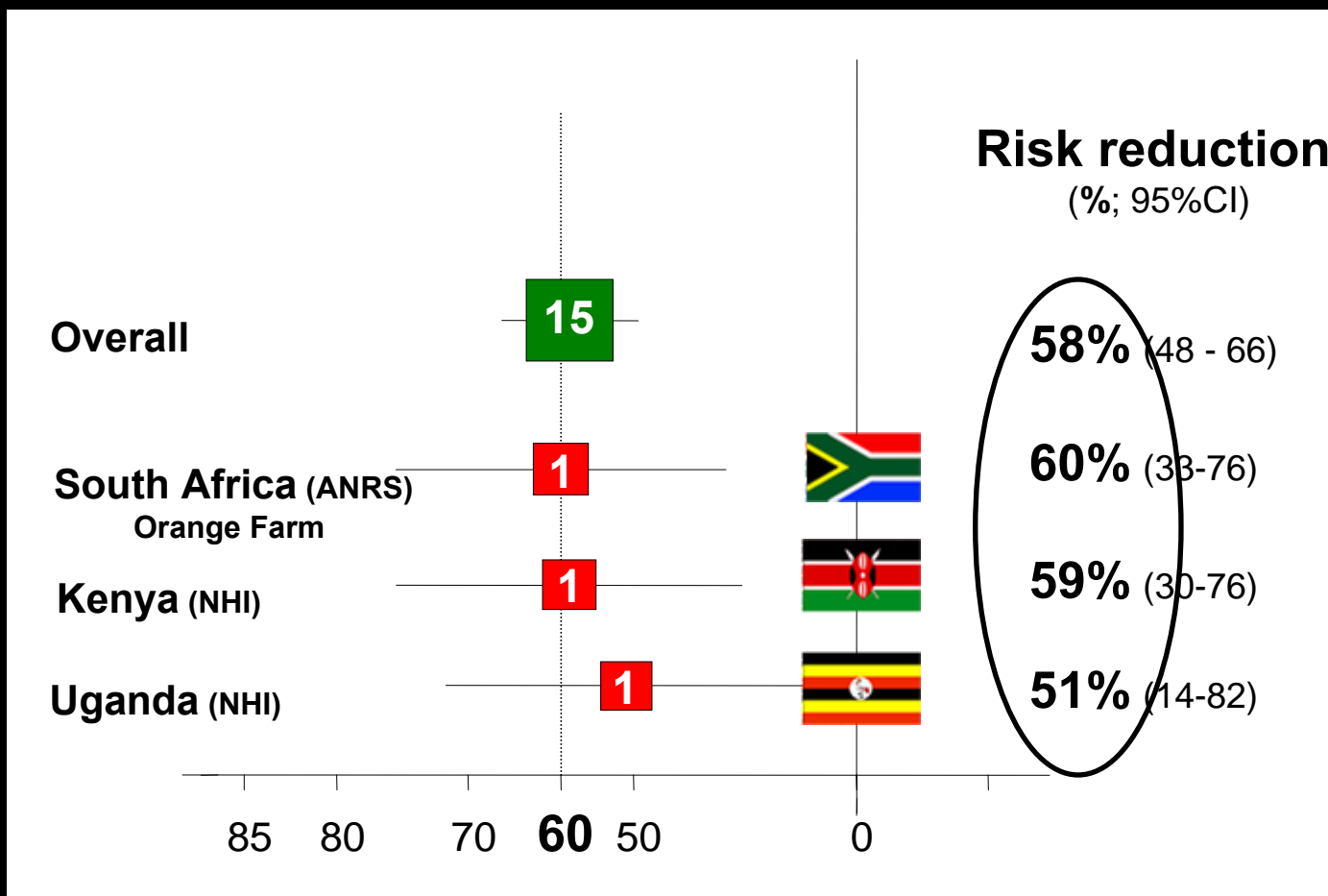
Bertran Auvert

Université de Versailles, France
INSERM U687 - APHP

JNI, Lyon, 10 juin 2009

- 1- Male circumcision (MC) and sexually transmitted infections (STI) in Africa: scientific evidence?**
- 2- MC as an HIV intervention**
- 3- Next steps?**

Impact of MC on HIV : Evidence from observational studies and RCTs



Weiss et al.
AIDS 2000, 14:2361-70

Auvert et al.
PLoS Med 2005(11): e298.2006

Bailey et al.
Lancet 2007; 369: 643-56

Gray et al.
Lancet, 2007, 657-66

Biological plausibility

HIV-1 target cells in the foreskin
(inner mucosal surface)

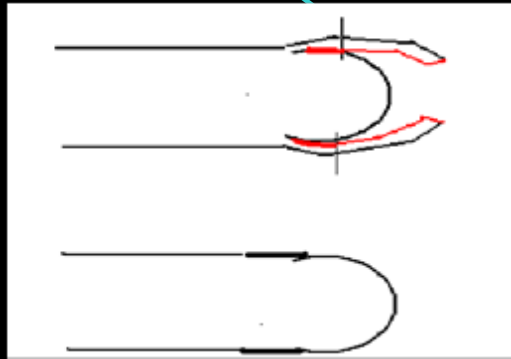


Figure 1



Figure 2

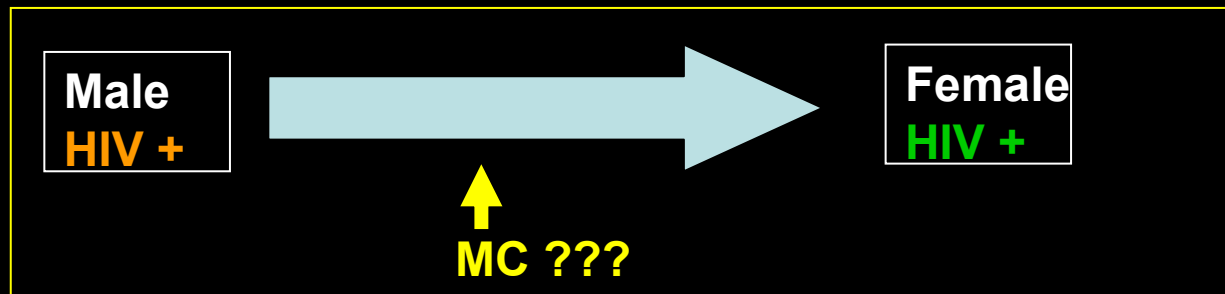
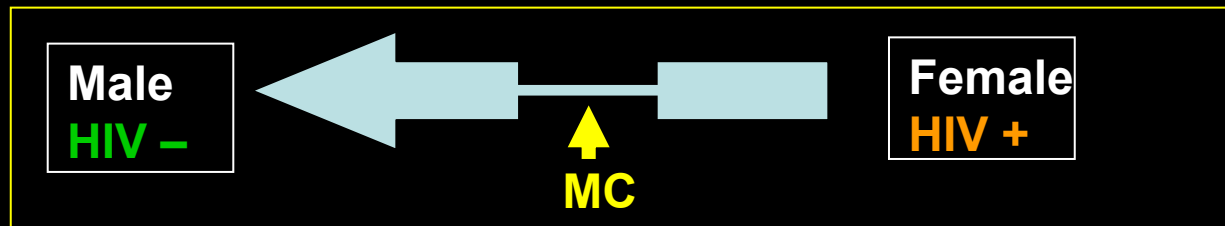


Figure 3

Explanation of the HIV heterogeneity?

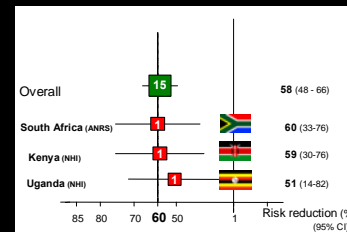
Observational studies (MC-HIV)

Ecological studies

Three RCTs

Biological plausibility

→ **Male circumcision is a key factor**

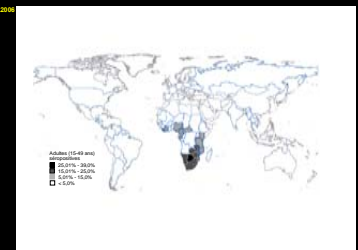


Wells et al.
AIDS 2000, 14:2361-70

Auerdt et al.
PLoS Med 2005(11): e298-300

Bailey et al.
Lancet 2007; 369: 643-50

Gray et al.
Lancet, 2007; 657-68



Other factors:

Sexual behavior (Cameroon – Uganda)

HSV-2 (HIV, MC) ?

...

Does MC explain the African situation?

Why do we have such a high HIV epidemic in Southern Africa?

Sexual behavior?

Age mixing, sexual mixing,...

Genetics?

Other STIs? (but then why?)

...

Still a mystery!

Effect of MC on *Neisseria gonorrhoeae* (bacterium)

NG prevalence at M21

| | NG prevalence % (positive/total) | OR (95% CI, p) | aOR (95% CI, p) |
|---------------------|-------------------------------------|---------------------------|---------------------------|
| Randomization group | | | |
| Control | 10.3% (91/881) | 1 | 1 |
| Intervention | 10.0% (89/886) | 0.97 (0.71 to 1.32, 0.84) | 0.91 (0.62 to 1.34, 0.64) |
| Circumcision status | | | |
| Uncircumcised | 10.0% (88/878) | 1 | 1 |
| Circumcised | 10.4% (92/887) | 1.04 (0.76 to 1.41, 0.81) | 1.04 (0.71 to 1.53, 0.84) |

→ No effect

Effect of MC on *Trichomonas vaginalis* (protozoon)

TV prevalence at M21

| | TV prevalence % (positive/total) | OR (95% CI, p) | aOR (95% CI, p) |
|---------------------|-------------------------------------|----------------------------|----------------------------|
| Randomization group | | | |
| Control | 3.1% (27/881) | 1 | 1 |
| Intervention | 1.7% (15/886) | 0.54 (0.29 to 1.03, 0.062) | 0.48 (0.22 to 1.06, 0.069) |
| Circumcision status | | | |
| Uncircumcised | 3.2% (28/878) | 1 | 1 |
| Circumcised | 1.6% (14/887) | 0.49 (0.25 to 0.93, 0.030) | 0.41 (0.18 to 0.91, 0.030) |

→ Border line protective effect

Effect of MC on TV

These results may explain why several studies* (including 1 RCT) have shown that women with circumcised partners are at lower risk of TV infection.

Indeed, this study suggests that it is the result of a lower risk of TV infection among circumcised men in comparison with uncircumcised men.

* For example: Castellsague X et al. Am J Epidemiol 2005,162:907-916
Tobian A et al. Croi 2008, abstract 28LB

Effect of MC on HR-HPV

HR-HPV prevalence at M21

| | <i>HPV prevalence % (positive/total)</i> | <i>OR (95% CI; P)</i> | <i>aOR* (95% CI; P)</i> |
|---------------------|--|--------------------------|--------------------------|
| Randomization group | | | |
| Controlled | 24.8% (156/627) | 1 | 1 |
| Intervention | 15.8% (101/637) | 0.57 (0.43–0.75; <0.001) | 0.53 (0.36–0.78; 0.0012) |
| Circumcision status | | | |
| Uncircumcised | 25.5% (159/621) | 1 | 1 |
| Circumcised | 15.2% (98/643) | 0.52 (0.39–0.69; <0.001) | 0.44 (0.30–0.66; <0.001) |

→ Protective effect

Prevalence rate ratio=0.64 (0.50 – 0.82)

→ Protection : **36% (18% - 50%)**

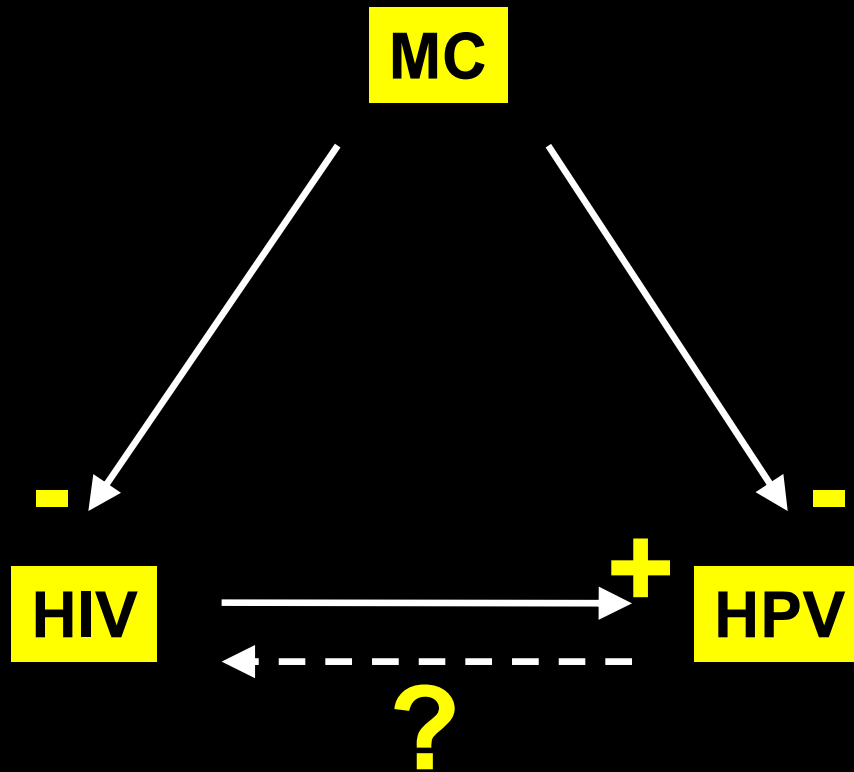
Effect of MC on HR-HPV

These results may also explain why several observational studies* have shown that women with circumcised partners are at lower risk of cervical cancer, most of them due to HR-HPV. (OR=0.42, CI, 0.23-0.79)

Indeed, this study suggests that it is the result of a lower risk of HPV infection among circumcised men in comparison with uncircumcised men.

* For example: Castellsague X et al. N Engl J Med 2002;346:1105-12
Castellsague X et al. J Infect 2007;55:91-3

HIV-HPV



MC-HSV2-HIV?

HSV-2 on HIV (statistical methods:GLM) :

J. Sobngwi-Tambekou, JID 2009

| | | |
|---------------------------------------|------------------|--------------------|
| HSV-2 on HIV (aIRR): | aIRR=3.3 | 1.5 – 7.4) p=0.004 |
| PAF (HIV incident cases to HSV-2): | PAF=27.8% | 17.7% – 37.2% |
| Effect of MC on HIV (HSV2+ vs HSV2-). | RR=0.38 vs. 0.37 | p=0.93 |

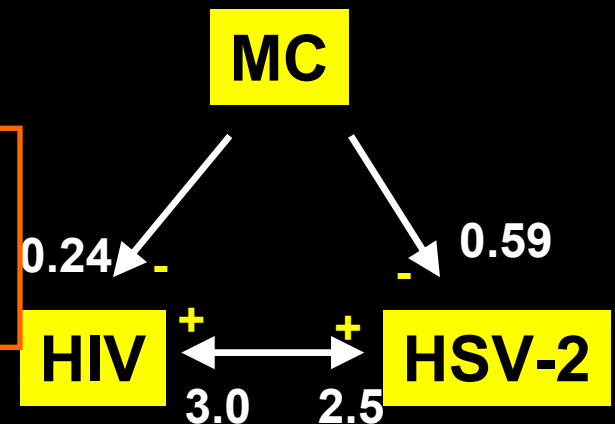
HSV2-HIV-MC (Specific mathematical modeling):

Mahiane S.G. AIDS 2009

| | | |
|----------------|---------|--------------|
| HIV FtoMTPs: | 0.0047 | 0.0014-0.017 |
| HSV-2 FtoMTPs: | 0.0067 | 0.0028-0.014 |
| HSV-2 on HIV → | RR=3.0 | 1.01-7.3 |
| HIV on HSV-2 → | RR=2.5 | 1.1-6.3 |
| MC on HIV → | RR=0.24 | 0.11-0.44 |
| MC on HSV-2 → | RR=0.59 | 0.36-0.91 |

Heterogeneity!

→ Protection : 41% (9% - 64%)



Rakai study...

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Potential impact?

J. Bongaarts et al. AIDS, 1989

Ecological study (Africa): Bongaarts (1989)

Rate of MC > 80% : HIV < 6%

Benin

Senegal

Cameroon

Kenya

DRG

...

Rate of MC < 40% : HIV > 20%

Zimbabwe

Swaziland

Botswana

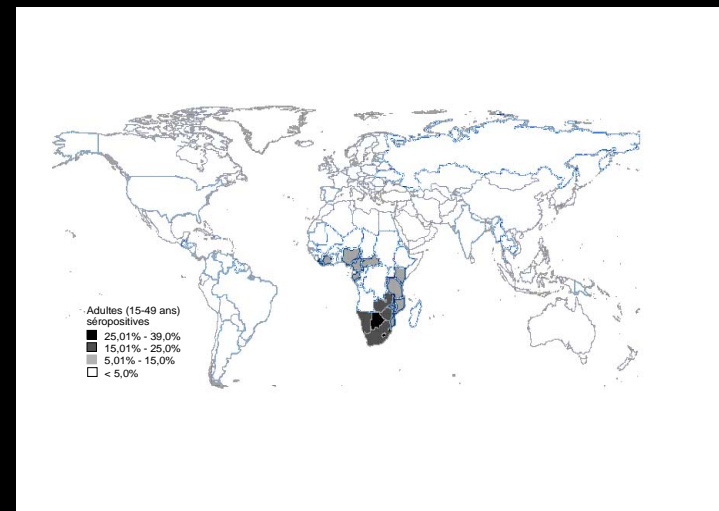
South Africa

Lesotho

Namibia

...

Southern Africa and East Africa



Countries with high HIV prevalence → **Strong potential impact**

2006: The Potential Impact of Male Circumcision on HIV in sub-Saharan Africa

Modeling study:

Over the next 10 years in sub-Saharan Africa, MC could avert :

2.0 (1.1–3.8) million new HIV infections (men and women)

0.3 (0.2–0.5) million deaths (men and women)

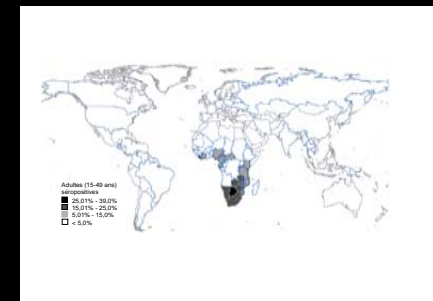
In the ten years after, a further :

3.7 (1.9–7.5) million new HIV infections (men and women)

2.7 (1.5–5.3) million deaths (men and women)

Williams et al. PLoS Med 2006

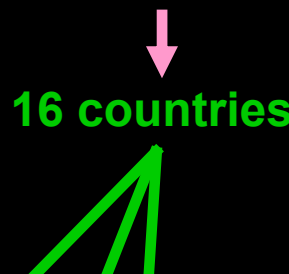
Other consistent studies.



Countries: 42 countries
 Uncircumcised men: 54 million
 HIV positive: 24 million

→ 16 countries (38%)
 → 30.5 million (56.5%)
 → 14.6 million (61%)

HIV > 5%
 MC < 80%



| Setting | MC (%) | Uncirc (Million; % total) | HIV (%) |
|--------------|--------|---------------------------|---------|
| Botswana | 25 | 0.34 (1.1%) | 37.3 |
| Burundi | 2 | 1.67 (5.5%) | 6.0 |
| CAR* | 67 | 0.3 (1%) | 13.5 |
| Kenya** | 10 | 0.97 (3.2%) | 24.0 |
| Lesotho | 0 | 0.43 (1.4%) | 28.9 |
| Liberia | 70 | 0.24 (0.8%) | 5.9 |
| Malawi | 17 | 2.26 (7.4%) | 14.2 |
| Mozambique | 56 | 1.98 (6.5%) | 12.2 |
| Namibia | 15 | 0.4 (1.3%) | 21.3 |
| Rwanda | 10 | 1.79 (5.9%) | 5.1 |
| South Africa | 35 | 7.95 (26.1%) | 24.6 |
| Swaziland | 50 | 0.13 (0.4%) | 38.8 |
| Tanzania | 70 | 2.71 (8.9%) | 8.8 |
| Uganda | 25 | 4.37 (14.3%) | 4.1 |
| Zambia | 12 | 2.15 (7.1%) | 16.5 |
| Zimbabwe | 10 | 2.82 (9.2%) | 24.6 |
| Total | - | 30.52 (100%) | - |



* Central African Republic
 ** Nyanza province

Cost of the roll-out (public model, MC→85%)

Cost of 1 MC=US\$32

Total :

| | |
|----------------------|----------------------------------|
| In years 1-5 | mUS\$ 919 (726 – 1 245) |
| In years 6-10 | mUS\$ 184 (145 – 249) |
| Cost 1-10 | mUS\$ 1 077 (855 - 1 448) |

Per adult:

| | |
|----------------------|--------------------------|
| In years 1-10 | US\$ 14 (10 – 19) |
|----------------------|--------------------------|

Cumulative net cost

After adjustment for averted HIV medical costs: +=expenses -=saving

| | |
|--------------------|--|
| At 10 years | mUS\$ + 672 (+437 to +1021) |
| At 20 years | mUS\$ - 2 274 (-3 318 to -1416) |

→ saving!

Cost per HIV infection averted (cost-effectiveness)

| | | |
|--------------------|-----------------|--------------------|
| In 10 years | US\$ 338 | (266 - 456) |
| In 20 years | US\$ 168 | (133 - 23) |

Number of circumcisions to avoid one HIV infection

| | | |
|--------------------|-------------|---------------------|
| In 10 years | 10.1 | (9.0 – 11.2) |
| In 20 years | 5.6 | (5.1 – 6.2) |

Acceptable in sub-Saharan Africa?

**2006: review of 13 acceptability studies
in 9 sub-Saharan countries with low MC prevalence:**

| | |
|-----------------------------------|--------------|
| Uncircumcised men for themselves: | 65% (29-87%) |
| Women (for their partners): | 69% (47-79%) |
| Men for their son: | 71% (50-90%) |
| Women for their son: | 81% (70-90%) |

Westercamp et al. AIDS Behav. 2006

Not surprising: Zulus, Twanas ...

Uptake

Among “Uncircumcised”:

If MC was done by a doctor and free of charge would you be willing to become circumcised?

82.1%

709/864

Among those willing to become circumcised:

Went for circumcision:

72.1%

511/709

Among “Uncircumcised”:

Uptake 59.1% (55.8 – 62.4%) 511/864

Is it a recommended intervention?

WHO-UNAIDS policy meeting in March 2007

Recommendations (28 March 2007)

"Male circumcision should now be recognized as an efficacious intervention for HIV prevention."

Arguments against the use of MC as a prevention method against HIV: (1/3)

One can say:

MC is a cultural practice: it cannot be changed!

One can reply:

It is because it is cultural practice that it can be changed and become sustainable! In South Korea, MC rate was 0% in 1940. It is now close to 60%. The Zulus are now mostly uncircumcised, but they were circumcised before the time of Dingiswayo.

Arguments against the use of MC as a prevention method against HIV: (2/3)

One can say:

MC can only protect men!

One can reply:

In African countries where all men are circumcised, HIV is low among men and women!

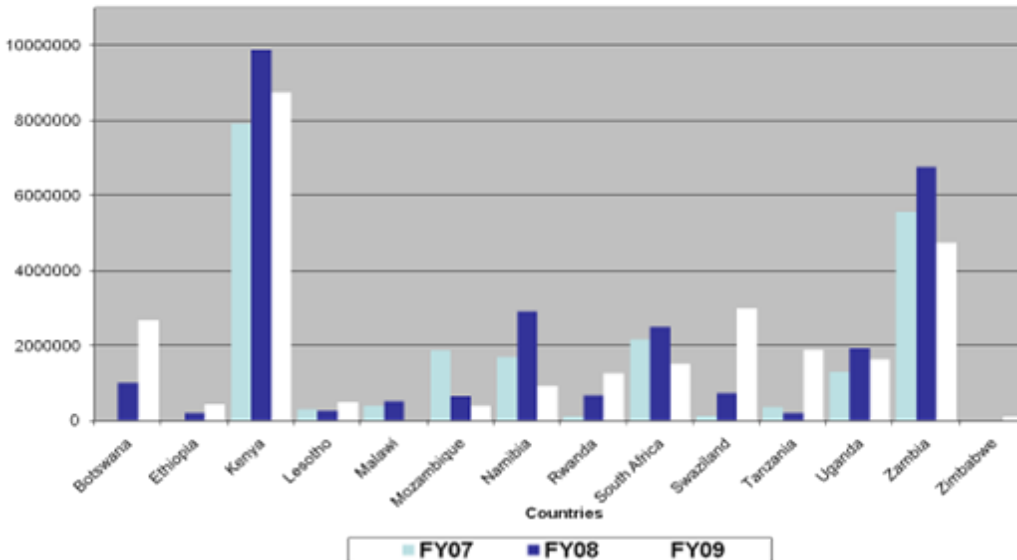
Women will indirectly benefit of the roll out of MC.

Indeed, with the roll out of MC, the HIV incidence among men will decrease, HIV prevalence among men will then decrease, reducing the risk of infection of women...

Women have a very important role to play...

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PEPFAR Funding for Male Circumcision

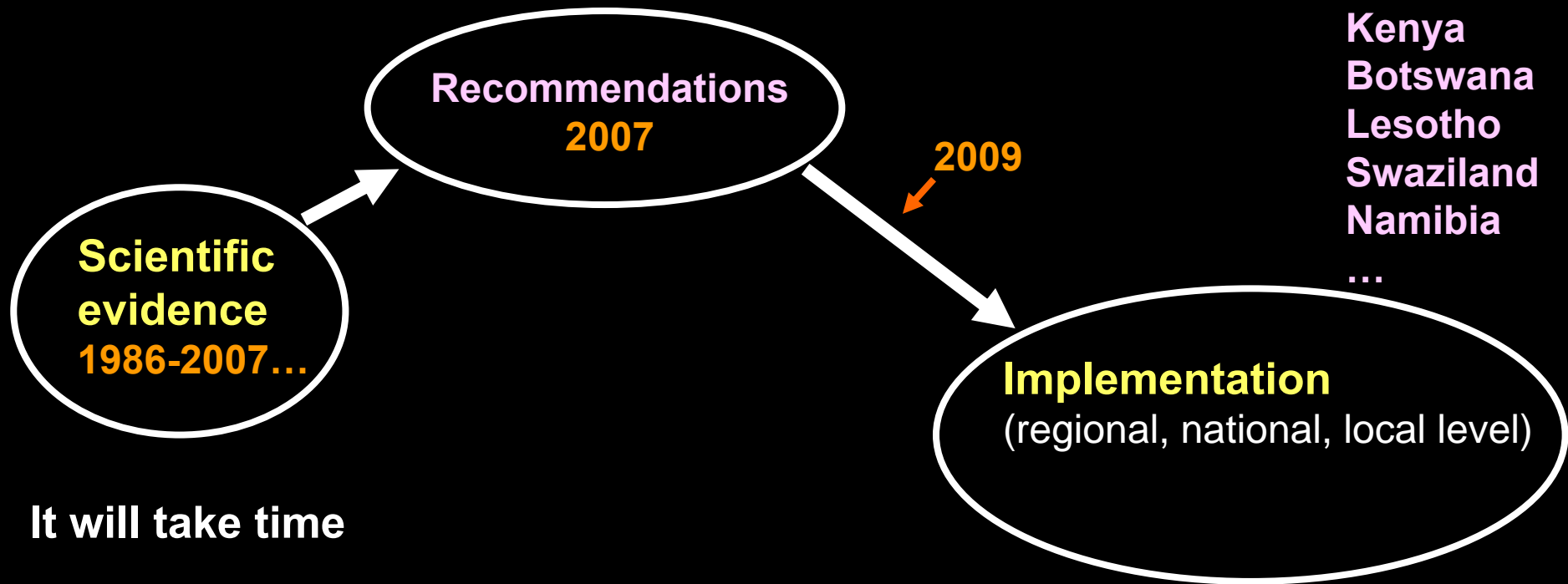


2008: \$5.4 billion for the President's Emergency Plan for AIDS Relief

FY09: ~\$28,000,000

BMGF...

- In the FY08 and 09 there **was no funding limitation** for male circumcision activities; activities must follow lead of host country government and be consistent with local norms and policies
- Now supporting male circumcision activities in **14 countries** , working with host countries, WHO, and other partners and donors in program planning and implementation



It will take time

Ongoing activities: meetings, country consultations, toolkits...

What can the research community do during this time?

Basic research

Phase-4 studies

Operational research

With the aim

To improve our knowledge in MC (HIV, STI, condom, sexual behavior...)

To contribute to guide implementation

Example of a phase-4 study

Offer free and safe MC in a community (OF)

Uptake?

Effect on HIV (time) among men and women?

Risk compensation?

Condom use?

5 000 000 Euros
67 people



Does it work in the real world ?

Ongoing studies in South Africa, Kenya, Uganda,...



ANRS-12126



Preparation

Community advisory board

CAB: Local NGO's, Political structures, local leaders, scientists, interested parties

Community meetings

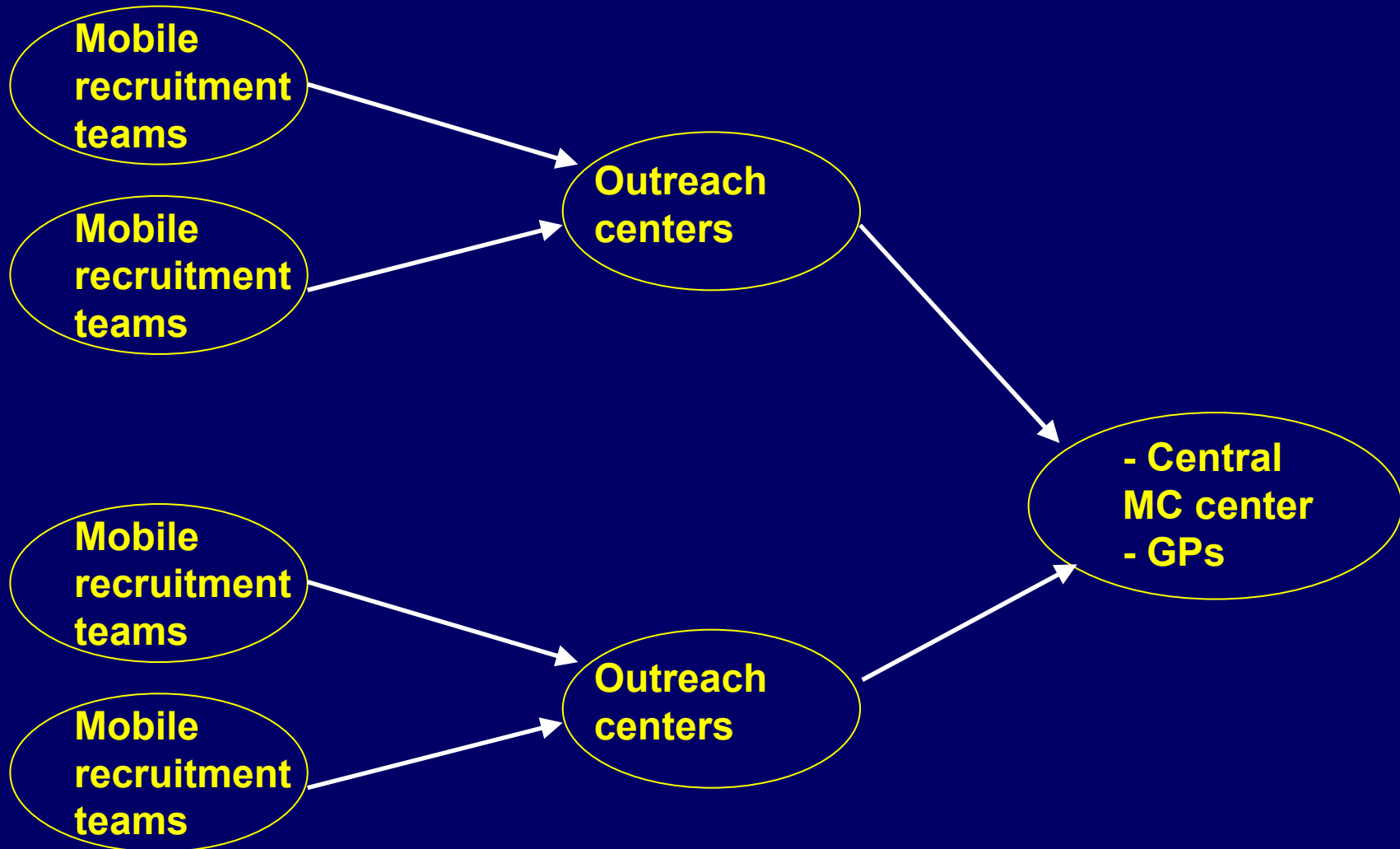


General information

household visits
shopping centers
railways station
taxi ranks
clinics

Detailed information
Counseling
VCT, MC card

Surgery
Follow-up



Recruitment Outreach activities

- Schools, churches, community leaders
- Local radio station: Thetha FM
- Community outreach activities: all households
 - “What women should know about MC”
 - “What men should know about MC”
- Community stakeholder workshops i.e. loveLife
- Local GPs
- In the clinics (STI patients)



Local radio



Door-to-door outreach



Inclusion activities



- Information session, anyone can attend, parents, spouses, partners
 - Safe sex messaging
 - Section on MC
 - Partial protection for men only
 - 6-week period of abstinence
 - Individual counselling
- VCT is recommended and offered
- CD4 count test (on site) → ARVs
- Paper work (minimum) for Inclusion, including Informed consent

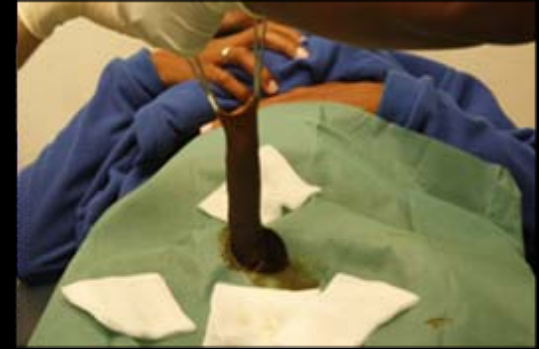


**Wait 3 days before surgery!
(7 days for smokers!)**

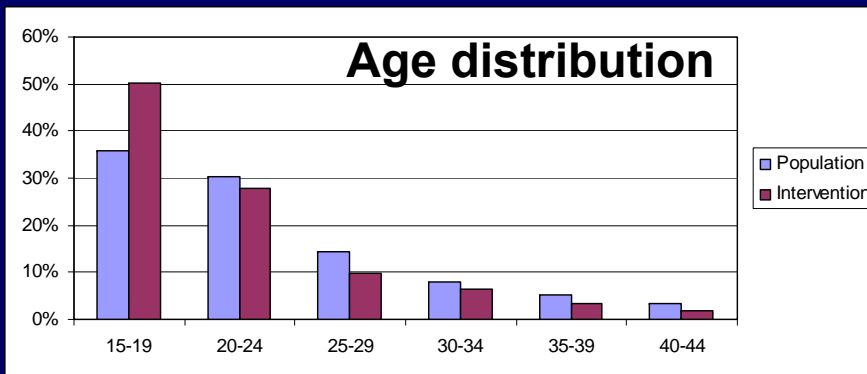
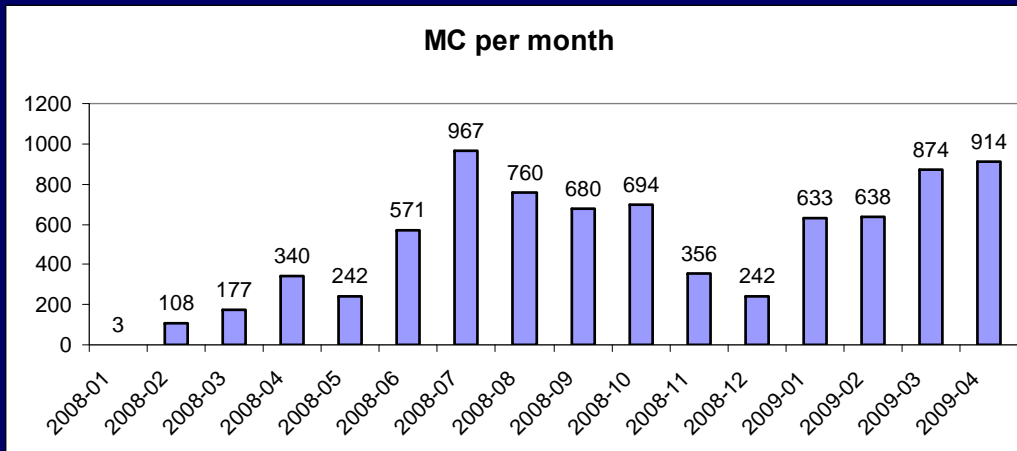
Surgery

WITS Urology Department Study Site

- There is a **follow-up visit** 2-3 days after surgery
- **Emergency response** for participant after surgery



What are the characteristics of the men being circumcised within the project?



| Language | OF Male pop | Already circ | MC cards |
|----------|-------------|--------------|----------|
| Sesotho | 41.0% | 15.4% | 46.0% |
| IsiZulu | 54.5% | 15.4% | 45.1% |
| Other | 4.5% | 24.1% | 8.9% |

Conclusion

Public Health problem: HIV in Africa

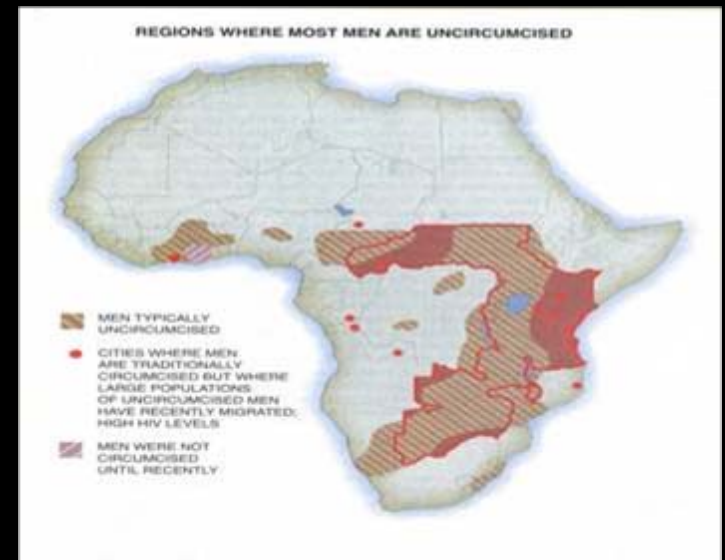
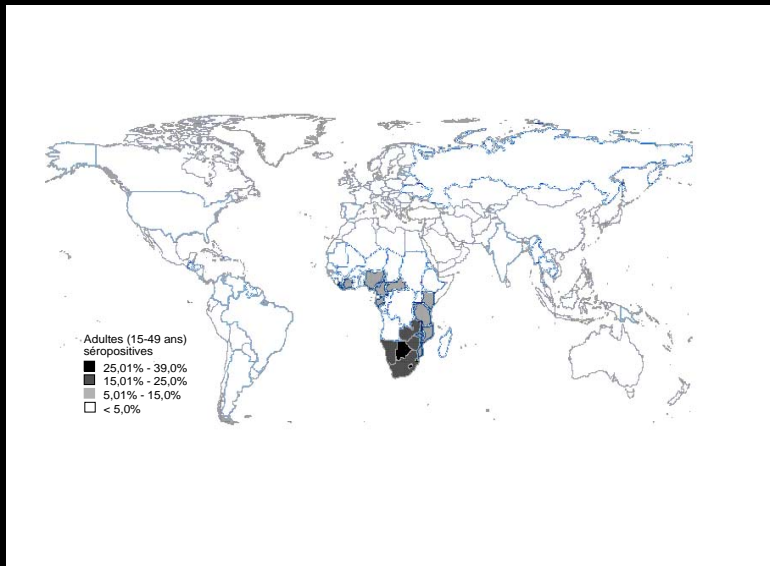
Methods:

**Epidemiology
Biology**

**Health economics
Biomathematics**

**Social science
Virology**

→ **Better understanding**
→ **Intervention**



Merci de votre attention 😊

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Richard Hayes

Jim Kahn

Emmanuel Lagarde

Camille Legeai

France Lert

David Lewis

Pascale Lissouba

Guy Mahiane

Sylvia Males

Nancy padian

Adrian Puren

Jamie Robinson

Rémi Sitta

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