Bias in Epidemiological Studies: the big picture

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The long road to causal inference (the “big picture”)

Causal Effect

Random Error

Confounding

Selection bias

Information bias (misclassification)

Bias in analysis & inference

Reporting & publication bias

Bias in knowledge use

RR_{causal}  
"truth"  
[counterfactual]

RR_{association}

the long road to causal inference…

Adapted from: Maclure, M, Schneeweis S. Epidemiology 2001;12:114-122.
“Bias is any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth” – Sackett (1979)

“Bias is systematic deviation of results or inferences from truth.” [Porta, 2008]
The key biases we look for when we read a paper, depends on the study design

- Sources of bias in RCTs:
  - Improper randomization
  - Lack of blinding
  - Attrition

- Sources of bias in case-control studies
  - How were cases and controls selected?
  - Was information collected using same methods in both cases and controls?
  - Was confounding addressed?
We have critical appraisal worksheets for each study design

https://www.teachepi.org/teaching-resources/worksheets/
Every single epidemiological study will have bias: we can try and reduce the amount & adjust for it in our analyses
Selection Bias
Sampling: recruited residents of Santa Clara county through ads on Facebook.

Potential for selection bias:

- Recruiting through Facebook likely attracted people with COVID-19–like symptoms who wanted to be tested (the ‘worried well’), boosting the apparent positive rate.
- The study also had relatively few participants from low-income and minority populations.
How (Not) to Do an Antibody Survey for SARS-CoV-2

Preprints from the first round of seroprevalence studies indicate that many more people have been infected with the virus than previously reported. Some of these studies also have serious design flaws.

Catherine Offord
Apr 28, 2020

Coronavirus: Nearly 15% India’s population may have antibodies, shows private lab data

Thyrocare conducted 60,000 antibody tests across 600 locations over 20 days.

“We have not chosen whom to test, we have only tested those who wanted it. 80% was the requirement of the corporates, 15 percent was the requirement of residential societies and 5% was the demand of individuals.”

https://scroll.in/latest/968224/coronavirus-nearly-15-indias-population-may-have-antibodies-shows-private-lab-data
Now lets define selection bias

“Distortions that result from procedures used to select subjects and from factors that influence participation in the study.”


Defining feature:
- Selection bias occurs at:
  - the stage of recruitment of participants
  - and/or during the process of retaining them in the study
- Difficult to correct in the analysis, although one can do sensitivity analyses

Who gets picked for a study, who refuses, who agrees, who stays in a study, and whether these issues end up producing a “skewed” sample that differs from the target [i.e. biased study base].
## Unbiased Sampling

<table>
<thead>
<tr>
<th>Disease</th>
<th>Exposure</th>
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<tr>
<td>-</td>
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</tr>
</tbody>
</table>

**REFERENCE POPULATION**
(source pop)

**STUDY SAMPLE**

Sampling fractions appear similar for all 4 cells in the 2 x 2 table.
Selection bias occurs when selection probabilities are influenced by exposure or disease status.

Szklo & Nieto. Epidemiology: Beyond the Basics. 2007
Biased sampling: Worried well might have a higher probability of being included

Exposed and healthy group has a higher probability of being included in the study: this leads to imbalance and bias.

REFERENCE POPULATION

STUDY SAMPLE
Selection bias in randomized controlled trials

Examples:

- Bias due to lack of allocation concealment
  - RCT on thrombolysis with alternating day allocation
  - RCT comparing open versus laparoscopic appendectomy
The trial ran smoothly during the day. At night, however, the attending surgeon's presence was required for the laparoscopic procedure but not the open one; and the limited operating room availability made the longer laparoscopic procedure an annoyance.

Reluctant to call in a consultant, and particularly reluctant with specific senior colleagues, the residents sometimes adopted a practical solution. When an eligible patient appeared, the residents checked the attending staff and the lineup for the operating room and, depending on the personality of the attending surgeon and the length of the lineup, held the translucent envelopes containing orders up to the light. As soon as they found one that dictated an open procedure, they opened that envelope. The first eligible patient in the morning would then be allocated to a laparoscopic appendectomy group according to the passed-over envelope.

If patients who presented at night were sicker than those who presented during the day, the residents' behavior would bias the results against the open procedure.

This story demonstrates that if those making the decision about patient eligibility are aware of the arm of the study to which the patient will be allocated -- if randomization is unconcealed (unblinded or unmasked) -- they may systematically enroll sicker -- or less sick -- patients to either treatment or control groups.

This behavior will defeat the purpose of randomization and the study will yield a biased result.
Selection bias in cohort studies

Sources:

- Bias due to a non-representative “unexposed” group
  - Key question: aside from the exposure status, are the exposed and unexposed groups comparable?

- Bias due to non-response
  - More likely if non-response is linked to exposure status (e.g. smokers less likely to respond in a study on smoking and cancer)

- Bias due to attrition (withdrawals and loss to follow up)
Healthy User and Healthy Continuer Bias: HRT and CHD

- HRT was shown to reduce coronary heart disease (CHD) in women in several observational studies.
- Subsequently, RCTs showed that HRT might actually increase the risk of heart disease in women.
- What can possibly explain the discrepancy between observational and interventional studies?
  - Women on HRT in observational studies were more health conscious, thinner, and more physically active, and they had a higher socioeconomic status and better access to health care than women who are not on HRT.
  - Self-selection of women into the HRT user group could have generated uncontrollable confounding and lead to "healthy-user bias" in observational studies.
  - Also, individuals who adhere to medication have been found to be healthier than those who do not, which could produce a "compliance bias" [healthy user bias]
Selection bias in case-control studies

Sources:

- Bias in selection of cases
  - Cases are not derived from a well defined study base (or source population)
- Bias in selection of controls
  - Controls should provide an unbiased sample of the exposure distribution in the study base
  - Control selection is a more important issue than case selection!
Controls in this study were selected from a group of patients hospitalized by the same physicians who had diagnosed and hospitalized the cases' disease. The idea was to make the selection process of cases and controls similar. It was also logistically easier to get controls using this method. However, as the exposure factor was coffee drinking, it turned out that patients seen by the physicians who diagnosed pancreatic cancer often had gastrointestinal disorders and were thus advised not to drink coffee (or had chosen to reduce coffee drinking by themselves). So, this led to the selection of controls with higher prevalence of gastrointestinal disorders, and these controls had an unusually low odds of exposure (coffee intake). These in turn may have led to a spurious positive association between coffee intake and pancreatic cancer that could not be subsequently confirmed.
Case-control Study of Coffee and Pancreatic Cancer: Selection Bias

Potential bias due to inclusion of controls with over-representation of GI disorders (which, in turn, under-estimated coffee drinking in controls)
Selection bias in cross-sectional studies

Sources:

- Bias due to sampling
  - Selection of “survivors” or “prevalent” cases
  - Non-random sampling schemes
  - Volunteer bias
  - Membership bias

- Bias due to non-participation
  - Non-response bias
Can selection bias be “fixed”?

- Not easy
  - Best avoided at the design stage; can try hard to retain participants in the study
- Can collect data to ‘estimate’ magnitude/direction of selection bias and do sensitivity analysis
  - e.g., collect data from a sample of non-respondents, and use this to do sensitivity analysis
- Effect estimates can be ‘adjusted’ if selection probabilities are known
Information Bias

EXCITING COVID STUDY

IT'S ALL JUST MEASUREMENT ERROR

@EpiEllie
Measurement error: a fact of life

- Measurement error in the ascertainment of:
  - Exposure
  - Outcome/disease
  - Covariates (e.g. confounders)

- Measurement error leads to misclassification bias:
  - Non-differential misclassification bias
  - Differential misclassification bias
Misclassification of exposure in laboratory studies

Example: Cumulative incidence of squamous intraepithelial lesions (SIL) among women with a normal Pap smear at entry

(Local cytology in Brazil)

Source: Eduardo Franco, McGill Univ.

Franco et al., PAJPH 1999; Ludwig-McGill Cohort (Follow-up data as of August 1997)
Example: Cumulative incidence of SIL among women with a normal Pap smear at entry
(Review cytology in Montreal)

Source: Eduardo Franco, McGill Univ.
Franco et al., PAJPH 1999; Ludwig-McGill Cohort (Follow-up data as of August 1997)
With better tests for HPV, the association between HPV and cervical cancer became stronger.

"Studies are ordered by year of publication, which underscores the transition from nonamplified hybridization techniques to detect HPV DNA, prevailing in the 1980s, to the new era of amplified target detection via polymerase chain reaction (PCR) protocols. The graph shows that the magnitude of the association increased substantially, from 2- to 5-fold risk increases in the early studies to triple digits in the most recent investigations."
What is information bias?

- “Bias in an estimate arising from measurement errors”

- Defining feature:
  - Information bias occurs at the stage of data collection
  - Misclassification of exposure and/or outcome status is the main source of error, and this, in turn, has the potential to bias the effect estimate
The ideal measurement tool (i.e. a diagnostic test) = no misclassification
Variations in test results

Overlap

Range of Variation in Disease free

Range of Variation in Diseased
If we used antibody tests for Covid-19, how accurate are they?

The pooled sensitivity of ELISAs measuring IgG or IgM was 84.3%.

Pooled specificities ranged from 96.6% to 99.7%.

https://www.bmj.com/content/bmj/370/bmj.m2516.full.pdf
Information bias in randomized controlled trials

**Sources:**

- Lack of blinding can cause **detection bias** (knowledge of intervention can influence assessment or reporting of outcomes)
  - Subjects ("participant expectation bias")
  - Investigators
  - Outcome assessors ("observer bias")
  - Data analysts

- Key issue: how “hard” is the outcome variable?
  - Strong versus “soft” outcomes
  - Blinding is very important for soft outcomes
Vit C and common cold

Bias File 5. How blind are the blind? The story of Vitamin C for common cold

Compiled by

Madhukar Pai, MD, PhD
Jay S Kaufman, PhD

http://www.teachepi.org/resources/bfiles.htm
Recall bias, MMR, and autism

N Andrews, E Miller, B Taylor, R Lingam, A Simmons, J Stowe, P Waight

Parents of autistic children with regressive symptoms who were diagnosed after the publicity alleging a link with measles, mumps, and rubella (MMR) vaccine tended to recall the onset as shortly after MMR more often than parents of similar children who were diagnosed prior to the publicity. This is consistent with the recall bias expected under such circumstances.

The self controlled case series method uses conditional Poisson regression to enable estimation of the R1 using only cases by comparison of the frequency of events within and outside specified post-immunisation risk periods. In these analyses the risk periods for autism onset considered were within 2, 4, 6, and 12 months of MMR. Age was adjusted for by stratification into one month groups. In the first analysis, cases were restricted to the subset of children with core or atypical autism in whom parents reported developmental regression, with onset defined...
Recall bias

OR = \frac{ad}{bc}

Cases

Controls

Exposed
Unexposed
Reducing information bias

- Use the best possible tool to measure exposure and outcomes
- Use objective ("hard") measures as much as possible
- Use blinding as often as possible, especially for soft outcomes
- Train interviewers and perform standardization (pilot) exercises
- Use the same procedures for collecting information from cases and controls & among exposed and unexposed
- Collect data on sensitivity and specificity of the measurement tool (i.e. validation sub-studies)
Confounding
Smokers seem less likely than non-smokers to fall ill with covid-19

That may point towards a way of treating it
Confounding: mixing of effects

“Confounding is confusion, or mixing, of effects; the effect of the exposure is mixed together with the effect of another variable, leading to bias” - Rothman, 2002

Latin: “confundere” is to mix together
Example

Association between birth order and Down syndrome

Data from Stark and Mantel (1966)

Source: Rothman 2002
Association between maternal age and Down syndrome

Data from Stark and Mantel (1966)
Association between maternal age and Down syndrome, stratified by birth order

Data from Stark and Mantel (1966)
Mixing of Effects: the water pipes analogy

Exposure and disease share a common cause (‘parent’)

Mixing of effects – cannot separate the effect of exposure from that of confounder

Adapted from Jewell NP. Statistics for Epidemiology. Chapman & Hall, 2003
Mixing of Effects: “control” of the confounder

If the common cause (‘parent’) is blocked, then the exposure – disease association becomes clearer (“identifiable”)

Successful “control” of confounding (adjustment)

So, a confounder is a parent of exposure & outcome

![Confounder Diagram]

Confounding Schematic

Confounding factor: Maternal Age

Birth Order \[\rightarrow\] Down Syndrome

C

E \[\rightarrow\] D
Are confounding criteria met?

Association between balding and Covid19

Confounding factor: Age

Balding → Covid-19
Counterfactual model explains how confounding occurs

- Ideal “causal contrast” between exposed and unexposed groups:
  - “A causal contrast compares disease frequency under two exposure distributions, but in one target population during one etiologic time period”
  - If the ideal causal contrast is met, the observed effect is the “causal effect”

Maldonado & Greenland, Int J Epi 2002;31:422-29
Ideal counterfactual comparison to determine causal effects

Exposed cohort

Counterfactual, unexposed cohort

\[ \text{RR}_{\text{causal}} = \frac{I_{\text{exp}}}{I_{\text{unexp}}} \]

“A causal contrast compares disease frequency under two exposure distributions, but in one target population during one etiologic time period”

“Initial conditions” are identical in the exposed and unexposed groups – because they are the same population!

Maldonado & Greenland, Int J Epi 2002;31:422-29
A substitute will usually be a population other than the target population during the etiologic time period. - INITIAL CONDITIONS MAY BE DIFFERENT
Counterfactual definition of confounding

Exposed cohort

Counterfactual, unexposed cohort

 Substitute, unexposed cohort

$RR_{causal} \neq RR_{assoc}$

“Confounding is present if the substitute population imperfectly represents what the target would have been like under the counterfactual condition”

“An association measure is confounded (or biased due to confounding) for a causal contrast if it does not equal that causal contrast because of such an imperfect substitution”

Maldonado & Greenland, Int J Epi 2002;31:422-29
Simulating the counter-factual comparison: Experimental Studies: RCT

Randomization helps to make the groups “comparable” (i.e. similar initial conditions) with respect to known and unknown confounders. Therefore confounding is unlikely at randomization - time $t_0$. 
Simulating the counter-factual comparison:
Experimental Studies: Cross-over trials

Although cross-over trials come close to the ideal of counterfactual comparison, they do not achieve it because a person can be in only one study group at a time; variability in other exposures across time periods can still introduce confounding (Rothman, 2002)
Simulating the counter-factual comparison: Observational Studies

In observational studies, because exposures are not assigned randomly, attainment of exchangeability is impossible – “initial conditions” are likely to be different and the groups may not be comparable.

Confounding is ALWAYS a concern with observational designs!
Example: Does male circumcision reduce risk of HIV?

HIV and male circumcision—a systematic review with assessment of the quality of studies

N Siegfried, M Muller, J Deeks, J Volmink, M Egger, N Low, S Walker, and P Williamson

This Cochrane systematic review assesses the evidence for an interventional effect of male circumcision in preventing acquisition of HIV-1 and HIV-2 by men through heterosexual intercourse. The review includes a comprehensive assessment of the quality of all 37 included observational studies. Studies in high-risk populations consisted of four cohort studies, 12 cross-sectional studies, and three case-control studies; general population studies consisted of one cohort study, 16 cross-sectional studies, and one case-control study. There is evidence of methodological heterogeneity between studies, and statistical heterogeneity was highly significant for both general population cross-sectional studies ($\chi^2=132.34; \text{df}=15; p<0.00001$) and high-risk cross-sectional studies ($\chi^2=29.70; \text{df}=10; p=0.001$). Study quality was very variable and no studies measured the same set of potential confounding variables. Therefore, conducting a meta-analysis was inappropriate. Detailed quality assessment of observational studies can provide a useful visual aid to interpreting findings. Although most studies show an association between male circumcision and prevention of HIV, these results may be limited by confounding, which is unlikely to be adjusted for.

Observational studies had major limitations, especially confounding
Confounders considered in the Cochrane review

**Panel: Potential confounding factors**

- Age
- Location of study (e.g., rural, urban)
- Religion
- Education, occupation, and socioeconomic status
- Sexual behaviour (e.g., measured by age at first intercourse, number of sexual partners, contact with sex workers)
- Any STIs
- Condom use
- Migration status
- Travel to different countries
- Other possible exposures (e.g., injections, blood transfusions, homosexual intercourse)

Siegfried N et al. Lancet Infect Dis 2005
In 2005, first RCT gets published

Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial

Bertran Auvert1,2,3,4*, Dirk Taljaard5, Emmanuel Lagarde2,4, Joëlle Sobngwi-Tambekou2, Rémi Sitta2,4, Adrian Puren6

1 Hôpital Ambroise-Paré, Assistance Publique—Hôpitaux de Paris, Boulogne, France, 2 INSERM U 687, Saint-Maurice, France, 3 University Versailles Saint-Quentin, Versailles, France, 4 IFR 69, Villejuif, France, 5 Progressus, Johannesburg, South Africa, 6 National Institute for Communicable Disease, Johannesburg, South Africa

Competing Interests: The authors have declared that no competing interests exist.

Author Contributions: BA designed the study with DT, EL, and AP. DT and AP were responsible for operational aspects, including laboratory and field work and in-country administration of the study. BA monitored the study with input from EL and wrote the paper with input from all authors. BA analyzed the data with RS, with inputs from JST. RS conducted the interim analysis.

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ABSTRACT

Background

Observational studies suggest that male circumcision may provide protection against HIV-1 infection. A randomized, controlled intervention trial was conducted in a general population of South Africa to test this hypothesis.

Methods and Findings

A total of 3,274 uncircumcised men, aged 18–24 y, were randomized to a control or an intervention group with follow-up visits at months 3, 12, and 21. Male circumcision was offered to the intervention group immediately after randomization and to the control group at the end of the follow-up. The grouped censored data were analyzed in intention-to-treat, univariate and multivariate, analyses, using piecewise exponential, proportional hazards models. Rate ratios (RR) of HIV incidence were determined with 95% CI. Protection against HIV infection was calculated as 1 − RR. The trial was stopped at the interim analysis, and the mean (interquartile range) follow-up was 18.1 m0 (13.0–21.0) when the data were analyzed. There were 20 HIV infections (incidence rate = 0.85 per 100 person-years) in the intervention group and 49 (2.1 per 100 person-years) in the control group, corresponding to an RR of 0.40 (95% CI: 0.24%–0.68%; p < 0.001). This RR corresponds to a protection of 60% (95% CI: 32%–76%). When controlling for behavioural factors, including sexual behaviour that increased slightly in the intervention group, condom use, and health-seeking behaviour, the protection was of 61% (95% CI: 34%–77%).

Conclusion

Male circumcision provides a degree of protection against acquiring HIV infection, equivalent to what a vaccine of high efficacy would have achieved. Male circumcision may provide an important way of reducing the spread of HIV infection in sub-Saharan Africa. (Preliminary and partial results were presented at the International AIDS Society 2005 Conference, on 26 July 2005, in Rio de Janeiro, Brazil.)
Randomization resulted in highly comparable distribution of potential confounders; so confounding is not an issue (at baseline)
Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial

Ronald H Gray, Godfrey Kimbugwe, David Serwadda, Frederick Makumbi, Stephen Watya, Fred Nalugoda, Noah Kwirendi, Lawrence H Houtinon, Mohammed A Zaidi, Michael Z Chen, Nekson M Sewankambo, Fred Wabwire-Mangen, Melanie C Bacon, Carolyn M Williams, Pius Opondo, Steven J Reynolds, Oliver Lueydenken, Thomas C Quinn, Maria J Wawer

Summary

Background Ecological and observational studies suggest that male circumcision reduces the risk of HIV acquisition in men. Our aim was to investigate the effect of male circumcision on HIV incidence in men.

Methods 4996 uncircumcised, HIV-negative men aged 15–49 years who agreed to HIV testing and counselling were enrolled in this randomised trial in rural Rakai district, Uganda. Men were randomly assigned to receive immediate circumcision (n=2474) or circumcision delayed for 24 months (2522). HIV testing, physical examination, and interviews were repeated at 6, 12, and 24 month follow-up visits. The primary outcome was HIV incidence. Analyses were done on a modified intention-to-treat basis. This trial is registered with ClinicalTrials.gov, with the number NCT00425984.

Findings Baseline characteristics of the men in the intervention and control groups were much the same at enrolment. Retention rates were much the same in the two groups, with 90–92% of participants retained at all time points. In the modified intention-to-treat analysis, HIV incidence over 24 months was 0.66 cases per 100 person-years in the intervention group and 1.33 cases per 100 person-years in the control group (estimated efficacy of intervention 51%, 95% CI 16–72; p=0.006). The as-treated efficacy was 55% (95% CI 22–75; p=0.002); efficacy from the Kaplan-Meier time-to-HIV-detection as-treated analysis was 60% (30–77; p=0.003). HIV incidence was lower in the intervention group than in the control group in all sociodemographic, behavioural, and sexually transmitted disease symptom subgroups. Moderate or severe adverse events occurred in 8.5% (3–6%) circumcisions; all resolved with treatment. Behaviours were much the same in both groups during follow-up.

Interpretation Male circumcision reduced HIV incidence in men without behavioural disinhibition. Circumcision can be recommended for HIV prevention in men.

Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial

Robert C Bailey, Stephen Moses, Corette B Parker, Kwenango Agot, Ian Mckee, John NKiege, Carolyn M Williams, Richard T Campbell, Jackson O Korope-Achola

Summary

Background Male circumcision could provide substantial protection against acquisition of HIV-1 infection. Our aim was to determine whether male circumcision had a protective effect against HIV infection, and to assess safety and changes in sexual behaviour related to this intervention.

Methods We did a randomised controlled trial of 2784 men aged 16–24 years in Kisumu, Kenya. Men were randomly assigned to an intervention group (circumcision; n=1391) or a control group (delayed circumcision, 1393), and assessed by HIV testing, medical examinations, and behavioural interviews during follow-up at 1, 3, 6, 12, 18, and 24 months. HIV seroconversion was estimated in an intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, with the number NCT00093371.

Findings The trial was stopped early on December 12, 2006, after a third interim analysis reviewed by the data and safety monitoring board. The median length of follow-up was 24 months. Follow-up for HIV status was incomplete for 240 (8.5%) participants. 22 men in the intervention group and 47 in the control group had tested positive for HIV when the study was stopped. The 2-year HIV incidence was 2.1% (95% CI 1.2–3.0) in the circumcision group and 4.2% (3.0–5.4) in the control group (p=0.004); the relative risk of HIV infection in circumcised men was 0.47 (0.28–0.78), which corresponds to a reduction in the risk of acquiring an HIV infection of 53% (22–72). Adjusting for non-adherence to treatment and excluding four men found to be seropositive at enrolment, the protective effect of circumcision was 60% (32–77). Adverse events related to the intervention (21 events in 1.5% of those circumcised) resolved quickly. No behavioural risk compensation after circumcision was observed.

Interpretation Male circumcision significantly reduces the risk of HIV acquisition in young men in Africa. Where appropriate, voluntary, safe, and affordable circumcision services should be integrated with other HIV preventive interventions and provided as expeditiously as possible.
Male circumcision for the prevention of heterosexually acquired HIV infection: a meta-analysis of randomized trials involving 11,050 men*

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1St Paul's Hospital, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, 2Division of Infectious Diseases, Ottawa Hospital, University of Ottawa, ON, Canada and 3Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

UNAIDS endorsed this intervention in 2007

Press release

EMBARGOED: Wednesday, 28 March, 12:00 GMT, 14:00 CET

WHO AND UNAIDS ANNOUNCE RECOMMENDATIONS FROM EXPERT MEETING ON MALE CIRCUMCISION FOR HIV PREVENTION

Paris, 28 March 2007 — In response to the urgent need to reduce the number of new HIV infections globally, the World Health Organization (WHO) and the UNAIDS Secretariat convened an international expert consultation to determine whether male circumcision should be recommended for the prevention of HIV infection.

Based on the evidence presented, which was considered to be compelling, experts attending the consultation recommended that male circumcision now be recognized as an additional important intervention to reduce the risk of heterosexually acquired HIV infection in men.

The international consultation, which was held from 6-8 March 2007 in Montreux, Switzerland, was attended by participants representing a wide range of stakeholders, including governments, civil society, researchers, human rights and women’s health advocates, young people, funding agencies and implementing partners.

“The recommendations represent a significant step forward in HIV prevention”, said Dr Kevin De Cock, Director, HIV/AIDS Department, World Health Organization. “Countries with high rates of heterosexual HIV infection and low rates of male circumcision now have an additional intervention which can reduce the risk of HIV infection in heterosexual men. Scaling up male circumcision in such countries will result in immediate benefit to individuals. However, it will be a number of years before we can expect to see an impact on the epidemic from such investment.”

There is now strong evidence from three randomized controlled trials undertaken in Kisumu, Kenya, Rakai District, Uganda and Orange Farm, South Africa that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 50%. This evidence supports the findings of numerous observational studies that have also suggested that the geographical correlation long described between lower HIV prevalence and high rates of male circumcision in some countries in Africa, and more recently elsewhere, is, at least in part, a causal association. Currently, an estimated 0.65 million men, or 5% of men worldwide, are estimated to be circumcised.

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**Meta-analysis of 3 RCTs in 2008**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Risk ratio and 95% CI</th>
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<tr>
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<td>Risk Lower Upper p-Value</td>
<td>0.01 0.1 1 10 100</td>
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<tr>
<td></td>
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<td>Favours Circumcision</td>
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<td>Auvert, RSA</td>
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<td>Bailey, Kenya</td>
<td>0.41 0.24 0.70 0.0001</td>
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<tr>
<td>Gray, Uganda</td>
<td>0.50 0.30 0.83 0.007</td>
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<tr>
<td>Combined</td>
<td>0.44 0.33 0.60 &lt;0.0001</td>
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*For full details, please refer to the full article.
Control of confounding:

- **Control at the design stage**
  - Randomization
  - Restriction
  - Matching

- **Control or ‘adjustment’ at the analysis stage**
  - Conventional approaches
    - Stratified analyses
    - Multivariate analyses
Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial

Wei Tang,1,2 Zhujun Cao,3 Mingfeng Han,4 Zhengyan Wang,5 Junwen Chen,6 Wenjin Sun,7 Yaojie Wu,8 Wei Xiao,9 Shengyong Liu,10 Erzhen Chen,11 Wei Chen,1,2 Xiongbiao Wang,12 Jiuyong Yang,13 Jun Lin,14 Qinxia Zhao,15 Youqin Yan,16 Zhibin Xie,17 Dan Li,18 Yaofeng Yang,19 Leshan Liu,20 Jieming Qu,1,2 Guang Ning,21 Guochao Shi,1,2 Qing Xie3

P=0.34 by log rank

SOC plus HCQ

SOC

Days from randomisation

Patients with positive SARS-CoV-2 RT-PCR test (%)
In our analysis, we adjusted for likely confounders, including age, race and ethnic group, body-mass index, diabetes, underlying kidney disease, chronic lung disease, hypertension, baseline vital signs, Pao2 :Fio2 , and inflammatory markers of the severity of illness. Despite this extensive adjustment, it is still possible that some amount of unmeasured confounding remains.