CORRESPONDENCE

Male circumcision and risk of HIV-1 infection

Sir—Steven Reynolds and colleagues (Mar 27, p 1039) have recast old data from the Mehendale group in Pune, India, on female-to-male transmission of HIV-1. They purport to show a significant reduction in female-to-male HIV-1. They purport to show a significant reduction in female-to-male infection if the man is circumcised.

The exhaustive Cochrane review of the evidence for possible protection from female-to-male sexual transmission of HIV-1 by circumcision concluded that "insufficient evidence exists to support an interventional effect of male circumcision in heterosexual males". In reviewing previous studies from the Mehendale group in Pune, the Cochrane review noted a low or unstartated participation rate, failure to control for religion, and an imbalance between circumcised and uncircumcised groups. As in these previous studies, Reynolds and colleagues’ report is also affected by selection bias because it involved high-risk groups from sexually transmitted disease clinics rather than the general population.

The present study also contains major statistical flaws. Although Reynolds and colleagues attempt to control for religion, a confounder remains because only three participants in the uncircumcised group (0·6%) were Muslim. As Reynolds and colleagues state, “When non-Muslim men were assessed separately, the protective effect was not significant”. Furthermore, the discrepancy in sample sizes (191 circumcised men vs 2107 genitally intact men) clearly suggests heterogeneity of variance, such that reported “statistically significant effects” might be little more than statistical artifacts, especially with the large overall sample size (n=2298) and resultant high level of experimental power.

Although multiple univariate effects are reported, the corresponding multivariate effects are not reported (in the absence of a significant multivariate effect, interpretation of univariate effects is likely to be difficult). At the very least, basic Bonferroni corrections should be done to keep to a minimum the risk of claiming “significant effects” that are due to chance alone. Also, I am surprised that no effect sizes are reported.

Researchers bias should not be ignored. There is a strong tendency to defend the culture of origin. The Cochrane review notes: “Circumcision practices are largely culturally determined and as a result there are strong beliefs and opinions surrounding its practice. It is important to acknowledge that researchers’ personal biases and the dominant circumcision practices of their respective countries may influence the interpretation of their findings.”

The study also notes a substantial failure to use condoms during visits with female sex workers. Clearly, irrespective of circumcision status, the HIV-1 infection rate would approach zero in both groups if condom use were universal.

The investigators tacitly acknowledge that circumcision would not be culturally acceptable to Hindu men. In addition, there are other factors to consider before taking any decision to introduce circumcision. These include potential adverse medical and psychological effects, as well as legal, ethical, and human rights issues.

The statistical inadequacies highlight weakened the validity of Reynolds and colleagues’ study. Therefore it would be prudent to await the results of the three randomised controlled trials now underway before any conclusions are drawn about HIV-1 transmission and male circumcision status.

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5 Boyle GJ. Issues associated with the introduction of circumcision into a non-circumcising society. Sex Trans Inf 2003; 79: 427–28.
likely that this, rather than any possible circumcision-dependent difference in the transmission rate, explains the difference in the rate of acquisition of HIV-1 by men of different religions. One could argue that HIV-1 prevalence among Muslims is low precisely because most Muslim men are circumcised, but this is the very point requiring proof. Pooling Muslim men with non-Muslims to find a lower incidence of HIV-1 in circumcised men obscures that requirement, besides introducing a host of confounding factors.

Throughout their study the authors refer to the “protective effect” of circumcision as though it were an established fact, rather than the hypothesis being tested. In a systematic review of published and unpublished studies, the Cochrane Library found insufficient evidence to support the claim, noting that observational studies are inherently limited by confounding.

It does not affect the internal validity of our investigation to understand the risk factors for HIV-1 infection in the context of any possible circumcision—definitive word on the epidemiological evidence exists from epidemiological review concluding that insufficient evidence exists from epidemiological studies of this nature, observational studies of this nature, and doctors have an ethical duty to act in monogamous, heterosexual, HIV-1-negative, high-risk behaviour with prostitutes from the same brothels. It is difficult to think of a confounder, restricted to Muslims, that would differentially block HIV-1 transmission, but not transmission of the other three pathogens considered (herpes simplex virus type 2, Treponema pallidum, and Neisseria gonorrhoeae).

Boyle also claims that the discrepancy in sample sizes between circumcised and uncircumcised men in our study creates statistical artifacts. However, the statistical methods used are valid whether sample sizes are equal or not. Boyle also claims that “effect sizes” were not reported. However, such values were reported in table 2 in the column labelled “adjusted relative risks”. Circumcised men were shown to be at 0.15 times the risk of HIV-1 infection as uncircumcised men. The p value was less than 0.01, showing that even if a Bonferroni adjustment for the four pathogens examined was used, the effect would still be significant.

In answer to Marilyn Fayre Milos’s point about viral load, this variable has proved a major determinant of transmission among HIV-1-serodiscordant couples in Rakai, Uganda. Ours was not a discordant-couples study and we could not control for viral load given our methods. However, for viral load to be a potential confounder, the viral load of the sexual partner would need to be associated with our participant’s circumcision status, which we feel is not biologically plausible.

This study was done in patients attending STD clinics in Pune as part of an investigation to understand the risk factors for HIV-1 infection in the Indian setting. As with most observational studies of this nature, this limits the generalisability of the findings to other populations; however, it does not affect the internal validity of our findings.

Our objective was to add to worldwide information about the biology of sexual transmission of HIV-1, especially in view of the Cochrane review concluding that insufficient evidence exists from epidemiological studies of the protective effects of circumcision. The definitive word on the effects of male circumcision of HIV-1 transmission will probably come from three clinical trials currently in progress.
underway in Uganda, Kenya, and South Africa. Steven J Reynolds, Mary E Shepherd, Ronald S Brookmeyer, Sanjai M Mehendale,* Robert C Balbinger

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Species identification after treatment for taeniasis

Sir—Cesar Jeri and colleagues (March 20, p 949) report that purging with electrolut-polycethylene glycol salt (EPS) after niclosamide treatment of taeniasis is effective in expulsion of the intact worm for species identification. EPS purge could also be used in conjunction with other taeniid agents for exact speciation in case of niclosamide resistance.

We reported quinacrine or praziquantel treatment of niclosamide-unresponsive Taenia saginata infestation in which a purge was not routinely used. With quinacrine therapy, intact worms were passed by 53 of 86 treated patients, whereas with praziquantel, none of the 178 patients who provided a post-treatment stool sample passed the worm with scolex in the stools. Only five in the quinacrine group and eight in the praziquantel group continued with passage of viable eggs or proglottids; the rest were cured at 12 weeks of follow-up. Jeri and colleagues assume that a EPS purge is associated with a higher cure rate. However, this assumption requires substantiation by at least a 12-week follow-up. Such data are not available.

In Jeri and colleagues’ study, recovery of eggs was higher for patients who had the EPS purge than for those who received a standard purge, even when the recovery of intact worms with scolices and gravid proglottids remained high. By contrast, all but four of our 271 patients (three in the praziquantel group and one in the quinacrine group) had a drop in the egg count. The increase in the egg count in these four patients was presumably related to their release in the gut after digestion of the gravid proglottids. However, we did see a drop in egg viability (from 98–100% to less than 5%) in all these patients. It would be worthwhile to know if the egg counts in Jeri and colleagues’ study were higher in patients who did not expel proglottids after treatment, because expulsion of gravid proglottids would simply imply a purge-associated escape from disintegration. A pre-treatment egg count would certainly have been additionally helpful but is not available.

Finally, the non-expulsion of the worm in up to two-thirds of the patients makes other methods of distinguishing between the Taenia spp desirable. Whereas the data are an important addition to the therapeutic arsenal against taeniasis, more information would certainly have been handy.

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Authors’ reply

Sir—We concur with Parvaiz Koul that follow-up stool examinations 3 months after treatment might indeed have been useful. We routinely recommend follow-up at 1 and 3 months, but compliance is a limiting factor. It is important, however, to recognise the limitations of stool examinations. Tapeworms excrete eggs erratically and thus a single stool examination is poorly sensitive for taeniasis detection. Moreover, immunological assays have shown that less than 40% of tapeworm carriers had Taenia eggs in the same stool sample. For the same reason (erratic egg output) we did not measure egg counts before treatment. Also, a decrease in egg counts would not be indicative of cure since the tapeworm can lose the distal part of the strobila but remain alive and reproduce from the scolex.

In terms of Koul’s published studies, quinacrine might be better than niclosamide in preserving the parasitic specimens, but it is no longer recommended as the treatment of choice because of its side-effects (nausea, vomiting, abdominal pain, temporary yellow staining of the skin, and occasionally psychosis). Praziquantel works well, but, since it is absorbed, when used to treat Taenia solium taeniasis it can trigger the appearance of neurological symptoms in patients with occult neurocysticercosis (something that does not occur with T saginata).

Also, in the T solium model, eggs and proglottids are found much less frequently, precluding any comparison of technique performance between species.

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The politics of terror

Sir—Tom Parfitt’s Medicine and health policy article (Apr 17, p 1291) on the sexual violence experienced by Chechen asylum seekers in the UK is of great interest. The fact that sexual abuses are occurring against men and women is crucial to an understanding of the realities of living in Chechnya at this time.

The findings of the report reinforce the view of our organisation, and that of many others working in the north Caucasus, that an unacceptable high level of brutality and violence remains in Chechnya. Extreme violence, abductions, assassinations, torture and “cleansing” operations persist. These realities run contrary to the repeated mantra of “normalisation” put out by the Russian authorities, who are keen to uphold the illusion that the war is over. In response to the global war on terror, Russia has been able to position the Chechen conflict within the framework of the international fight against terrorism. The subsequent silence of the international community with respect to war crimes in Chechnya has shattered the hopes of many that the situation will improve.
Chechnya is currently witnessing a health and humanitarian crisis. Years of war have left medical services in chaos. Unable to cope, they are propped up by donations from the international aid community so that local medical staff can continue to treat patients. Available drugs and services are insufficient to treat key causes of morbidity and mortality: cardiovascular disease, cancer, and tuberculosis. Many medical staff have fled the country. Those who remain are frustrated at the lack of equipment and poor access to new and improved protocols.

Because of the repeated kidnapping of expatriate workers, Chechnya remains closed off to international scrutiny. Our colleague, Arjan Erkel, Médecins Sans Frontières’ Head of Mission in Dagestan, was released by captors on April 11, 2004, after 20 months as a hostage. Arjan’s long detention, and the abduction of more than 50 international humanitarian aid workers since 1995, has crippled the ability to provide aid to war affected civilians in this region.

It is almost impossible to deal effectively with medical emergencies because the risks involved in moving around prevent medical staff and patients from reaching the hospitals. Health centres are too dangerous for the war wounded and are consequently avoided. Many staff express fear for their own personal safety because they work in hospitals where guns and violence are commonplace.

Despite the violence and intimidation in their homeland, the forced return of thousands of Chechen refugees living in temporary camps and shelters in the neighbouring republic of Ingushetia continues. As part of the normalisation strategy, the authorities are attempting to close all tent camps by mid-2004. Such camps have provided refuge for more than 200 000 Chechens since the start of the second Chechen war in 1999. Measures include intimidation, deregistration of refugee status, and cutting off electricity and water supplies. Access to the camps for humanitarian aid workers has been severely restricted. Although many Chechens are living here in appalling and desolate conditions, most say they are too frightened to return to Chechnya.

The basic right of Chechens to take refuge in Ingushetia must be respected by the authorities until the situation in Chechnya is safe. For those living in Chechnya, the international community must ensure that medical and humanitarian aid reaches them, and they must be reassured that they have not been forgotten.

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Autoimmune disease and other potential side-effects of statins

Sir—According to the hypothesis of Bernd Moosmann and Christian Behl (March 13, p 892),1 myopathy and some other side-effects of statins might be attributable to inhibition of selenoprotein synthesis. However, severe autoimmune diseases have been reported, suggesting that statins could have immunomodulator effects too.

An unexpected number of autoimmune diseases (more than 20 cases) have been reported in patients treated with statins in the past few years. Most of these patients had systemic lupus erythematosus (SLE) but dermatomyositis, autoimmune hepatitis, and pemphigoid have also been reported,2 and a lethal outcome has been recorded in one patient.3 Unlike usual drug reactions, skin eruptions have been noted months or even years after starting treatment. Side-effects generally improve after drug discontinuation, but not necessarily in serological disease. In many reported cases, antinuclear antibodies are still positive many months after interruption of drug treatment. The causal relation between drug intake and autoimmune disease can, therefore, be difficult to establish and many cases are probably not reported.

Several pathogenic mechanisms have been postulated in statin-induced SLE. Cellular apoptosis—which has an important role in SLE—might be exacerbated or triggered by second-generation statins, which are potent pro-apoptotic agents. Release of nuclear antigens into the circulation could cause production of pathogenic autoantibodies. The same mechanism has been implicated for other environmental factors such as ultraviolet light, which is a well known trigger in SLE. Likewise, the direct immunomodulator effect of statins on T cells is possibly involved. SLE is characterised by a shifting of T helper 1 to T helper 2 immune responses, causing B-cell reactivity and production of pathogenic autoantibodies. Statins and selenoprotein inhibition can aggravate this event.4

Epidemiological study and clinical trial findings suggest that selenoprotein inhibition might heighten the risk of prostate and colon cancer.5 If Moosmann and Behl’s hypothesis is confirmed, statins could not only trigger autoimmune diseases but also contribute to the development of some types of cancer. Further studies are, therefore, warranted to determine the long-term safety of these lipid-lowering agents.

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Malaria intermittent preventive treatment and EPI coverage

Sir—I was interested to read the Rapid review on malaria intermittent preventive treatment (IPTi) in infants and childhood vaccinations by Jennifer Rosen and Joel Breman (April 24, p 1380).1 Although I also see the great potential for this innovative approach towards malaria control in infants and young children, I would like to add some comments of caution.

According to the latest available figures, more than 90% of all deaths due to malaria in children younger than 5 years occur in sub-Saharan Africa (table).2,3 Similarly, at our remote 400-bed hospital in a rural area in northern Tanzania, malaria is the leading cause for admissions and deaths in children younger than 5 years. Thus, preventive measures should focus on this age-group in Africa first.

Although combination of the IPTi approach with the existing Extended Programmes of Immunisation (EPI) is currently being planned,1,4 immunisation coverage in these countries should be analysed carefully. For sub-Saharan Africa as a whole, EPI coverage rates (except for BCG) are not more than 58% (table).5 There are also substantial

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### Mortality rates in children younger than 5 years and EPI coverage at 1 year in different WHO regions

<table>
<thead>
<tr>
<th></th>
<th>Sub-Saharan Africa region</th>
<th>Western Pacific region</th>
<th>Southeast Asia region</th>
<th>Eastern Mediterranean region</th>
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<tr>
<td><strong>Under 5 mortality</strong></td>
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</tr>
<tr>
<td>Total</td>
<td>4610 (22%)</td>
<td>1368 (13%)</td>
<td>3603 (2%)</td>
<td>559 (4%)</td>
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<tr>
<td>Malaria-attributable</td>
<td>1050 (22%)</td>
<td>14 (1%)</td>
<td>72 (2%)</td>
<td>23 (4%)</td>
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<tr>
<td><strong>EPI coverage</strong></td>
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<tr>
<td>DPT3</td>
<td>55%</td>
<td>78%</td>
<td>71%</td>
<td>86%</td>
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<tr>
<td>Polio3</td>
<td>55%</td>
<td>79%</td>
<td>73%</td>
<td>86%</td>
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<tr>
<td>Measles</td>
<td>58%</td>
<td>80%</td>
<td>67%</td>
<td>87%</td>
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DPT = diphtheria, tetanus, pertussis. *In thousands.

### Spontaneous subdural haemorrhage in newborn babies

Sir—In their study of the frequency and natural history of subdural haemorrhages in term newborn babies, E H Whitby and colleagues (March 13, p 846)\(^1\) conclude that the presence of subdural haemorrhage is not necessarily indicative of excessive birth trauma, and that subdural haemorrhages that completely resolve by age 4 weeks are mostly benign, clinically asymptomatic, and of no long-term importance. Although we agree with their conclusions, one should be alert to possible underlying causes, including coagulation abnormalities, that might contribute to the development of subdural haemorrhage in uneventful perinatal courses.

A term baby girl was born by non-instrumented, vaginal delivery. Her mother (gravida 2, para 1) had an unremarkable pregnancy apart from a previous early miscarriage. The girl's birthweight was 2855 g (3rd percentile), length 49 cm (50th percentile), and head circumference 33 cm (25–50th percentile). The placenta was small but unremarkable otherwise. Striking satura
diastasis (1·7 cm) with full, opened anterior and posterior fontanelles were noted. She was neurologically normal and clinically asymptomatic.

Cranial ultrasonography and subsequent CT scans diagnosed subdural haemorrhage (figure). Preliminary investigations revealed a low haemoglobin concentration (111 g/L), normal platelet counts, normal international normalised ratio, but a slightly long partial thromboplastin time (51 s). Subsequent coagulopathy work-up showed that both the baby girl and her mother were heterozygous for the prothrombin 20210 mutation.

**Cranial ultrasound (top) and subsequent CT examination (bottom) of neonate**

Ultrasonography shows 6-mm thick subdural collection along left outer cortex associated with mild shifting of midline structures to right and smaller left lateral ventricle. CT shows subdural haemorrhage.

Coagulation abnormalities including factor V Leiden and prothrombin 20210 mutations are not uncommon in those with haemostatic and thromboembolic complications.\(^3\) Petaja and colleagues\(^1\) suggested intraventricular haemorrhage as one of the disease states triggered by thrombophilic coagulation abnormalities. The G20210A polymorphism in the prothrombin gene is not rare in white populations (1–2%)\(^4\) and has been associated with recurrent miscarriages and lower birthweight in newborn babies of heterozygous mothers.\(^5\)

In our case, several factors, including maternal obstetric history, small but unremarkable placenta, low birthweight, and a slightly long partial thromboplastin time raised the possibility of this mutation. The presence of thrombophilic risk factors in this uneventful delivery might have been coincidental or a real predisposition for the development of idiopathic subdural haemorrhage. Nonetheless, our case illustrates the importance of identifying potential causes of subdural haemorrhage in newborn babies. Furthermore, it shows that cranial ultrasonography in...
experienced hands can be a low-cost, convenient alternative to MRI imaging.

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Novel means of spread of bloodborne infections in Pakistan

Sir—Use of oxytocin injections immediately before cattle milking increases milk production, and is a widespread practice.1 We recently found that people in many villages in Pakistan’s Charsadda district were obtaining used medical syringes for this purpose. Children were being asked to acquire used syringes from local dispensers or primary-care workers who provide much of the health-care services in Pakistan, and most of whom receive no formal medical training.2 The elders were replacing the used needles with larger needles needed for animals such as buffalos and cows. 21 dispensers or primary-care workers we interviewed gave out an average of 4–7 syringes per day, mostly to children. They claimed that the practice had been in existence for many years and existed all over Pakistan.

Handling of contaminated needles by children and their elders exposes them to dangerous bloodborne infections such as HIV/AIDS and hepatitis B and C. The issue is particularly important because Pakistan already has a very heavy burden of hepatitis B and C, mainly because of unnecessary injections, reuse of inadequately sterilised needles, and improper disposal of hazardous waste.3,4 Research is needed to assess the extent of the problem and its effects. We urge WHO, UNICEF, and the Government of Pakistan to take immediate steps to educate health-care workers and the general public about the dangers of such practices.

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Need for national level outbreak control in Austria

Sir—On Nov 30, 2001, the Austrian Ministry of Health was informed by the German Ministry of Health that a 44-year-old man had fallen ill with legionellosis on Oct 8 of that year, after a vacation in a small Austrian village (population about 1500). A further case of legionellosis in a 55-year-old Dutch woman (onset of disease Feb 26, 2002) was reported to the Austrian National Reference Centre for Legionella Infections by EWGLINET (European Working Group for Legionella Infection Network). This tourist had stayed in a different hotel in the same village as the first. In September and October, 2002, four more cases (one male, three female, one of whom died) were also reported by EWGLINET. Two patients had stayed in the same hotel as each other. A seventh case, a 44-year-old man had fallen ill with legionellosis in Lugano. Apart from the close proximity of the dates of onset of illness of the third, fourth, fifth, and sixth cases suggests one source of infection; two patients even had an overlap of their holiday periods.

Although local health authorities were immediately informed of each case by the National Reference Centre, official notification of this outbreak of travel-related legionellosis did not reach the general population, the local physician, or the hospital serving this tourist village. However, a flyer was sent by the community authority to all private households informing them that, on Dec 2, 2002, chlorination of the village’s water system was necessary as a general disinfection measure “after finishing comprehensive repair work”. In Austria, which consists of nine federal states, the individual counties (n=83 plus Vienna) are responsible for local infection control. The state in which this village is located has been the source of 19 of the 40 cases of travel-associated legionellosis related to Austrian hotels reported between 1987 and 2003. From 1998 to 2003, the period prevalence of travel-associated Legionnaires’ disease seen in this state was 0·08 per 1 million overnight stays, compared with 0·03 per 1 million overnight stays for the remaining eight states.

In our opinion, this outbreak clearly shows the need for higher independent health authorities capable of implementing early investigative and preventive public-health measures. At the local level—eg, in a small village that relies on tourism as the main source of income—conflicts of interest could represent an insurmountable barrier for implementing appropriate outbreak controls. The creation of the Austrian Agency for Health and Food Safety in June, 2002, with the legal mandate to investigate outbreaks might be the first step in this direction.

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