Vaginal microbicides for preventing mother-to-child transmission of HIV infection – no evidence of an effect or evidence of no effect?

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Background. Vaginal disinfection is a simple, potentially effective strategy for reducing mother-to-child transmission (MTCT) of HIV that can be implemented in combination with antiretroviral therapy or even in the absence of prenatal HIV testing. We systematically reviewed currently available randomised controlled trials to estimate the benefits and risks of this intervention.

Methods. We conducted an exhaustive search for published and unpublished trials assessing the effect of vaginal microbicides on MTCT of HIV, extracted data in triplicate, assessed statistical heterogeneity between trial results, and conducted meta-analysis using Mantel-Haenszel's method.

Findings. Five potentially eligible studies were identified, two of which met eligibility criteria. Pooling the data shows that the effect of vaginal disinfection on the risk of MTCT of HIV (relative risk (RR) 0.94, 95% confidence interval (CI) 0.71 - 1.25) and neonatal death (RR 1.36, 95% CI 0.32 - 5.79) is uncertain. The combined data (two trials with 708 participants) had less than 80% power to detect a 30% reduction in the risk of MTCT of HIV from a baseline risk of 30%, and are compatible with a wide range of effects; from a 29% reduction to a 25% increase in risk. One trial, with 108 participants, showed no evidence that adverse effects increased in mothers (RR 1.02, 95% CI 0.87 - 1.20) and found that adverse effects decreased in neonates (RR 0.45, 95% CI 0.32 - 0.64).

Interpretation. At present there is insufficient and inconclusive evidence on the effect of vaginal microbicides on the risk of MTCT of HIV. This review identifies the need and provides the impetus for an adequately powered randomised controlled trial to assess the effect(s) of this inexpensive intervention.

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Nearly 2 000 children under the age of 15 are infected with the human immunodeficiency virus (HIV) each day in low- and middle-income countries.[1] These children acquire HIV infection primarily through mother-to-child transmission (MTCT), the risk (without intervention) of which ranges from 15 - 30% in Europe and North America to 30 - 45% in sub-Saharan Africa.[2]

Childhood illness and death resulting from HIV infection may seriously undermine successful child survival programmes, which have been promoted and supported by the international community over the years.[3] Together with the rising cost of comprehensive health care to treat HIV infection and AIDS, this has led to the development of numerous strategies to prevent MTCT of HIV.[2] Despite the benefits of antiretroviral therapy,[4,5] the costs associated with these interventions, their complexity, and the need for skilled personnel limit their availability in low- and middle-income countries, where most of the MTCT of HIV takes place.[1] In addition, the majority of infected women in these countries are not aware of their HIV infection status.[6] Simple, inexpensive, and effective interventions that could potentially be implemented in the absence of prenatal HIV testing programmes would be valuable.

In the absence of breastfeeding, most infant HIV infections occur during labour and delivery.[7] In addition, studies of twins indicate that first-born infants have a risk of infection at least twice that of second-born infants.[8,9] These observational data suggest that vaginal exposure might be an important route of infection, a hypothesis supported by the protective effect of caesarean delivery.[10] Disinfection of the birth canal during pregnancy and labour is therefore a potential low-cost strategy for reducing MTCT of HIV infection.

We conducted a systematic review of randomised controlled trials comparing vaginal disinfection with an appropriate control group conducted to date, to estimate the effect of vaginal disinfection on the risk of MTCT of HIV infection and infant mortality, and the safety of the intervention. Although the key to prevention of MTCT of HIV is primary prevention of HIV infection in women, prevention of HIV transmission from

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an infected mother to her child requires as much attention. The ultimate goal of this systematic review is to determine whether the use of vaginal microbicides during pregnancy and labour could be recommended as a public health policy to reduce MTCT of HIV infection and, as such, we have considered overall HIV infection in the child without differentiating between antenatal, intrapartum and postnatal infection.

Methods

Search strategy

We searched the following electronic databases for randomised trials published between 1980 and April 2006: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, and AIDSearch, by combining terms for the intervention (benzalkonium, betadine, chlorhexidine, 'vaginal antisept*-creams-foams-gel-jellies-OR-tablet*', 'vaginal cleansing-disinfection-OR-wash') and the health condition (pregnancy, labo*, birth, intrapartum, delivery). Standardised methodological filters for identifying controlled trials were applied,[11] as appropriate. We supplemented the search by searching reference lists of identified articles and abstracts presented by April 2006 at the International Conference on AIDS, the Conference on Retroviruses and Opportunistic Infections, and the Conference on Global Strategies for the Prevention of HIV Transmission From Mothers to Infants. For unpublished data and ongoing trials, we contacted current researchers and key agencies, organisations, and academic centres. Relevant editorials, expert opinions, and letters to the editor were also scrutinised for any additional relevant studies or unpublished data. There were no language restrictions to our search.

Study selection and characteristics

We included only randomised controlled trials, defined as a study in which the participants were assigned prospectively to one of two or more interventions by random allocation. Participants included were known HIV-infected women (as diagnosed by an antibody test) of any age and clinical stage of HIV disease, during labour and delivery. Trials assessing the effect of vaginal disinfection on adverse birth outcomes for HIV-negative women or those of unknown HIV status were not included in this review. The primary outcome measure was the HIV infection status of the child. The secondary outcome measures were neonatal mortality, death of the child after the neonatal period, and side-effects of vaginal disinfection in the mother and the neonate.

Data extraction and synthesis

We used the standard methods of the Cochrane HIV/AIDS Group (http://www.igh.org/Cochrane) to prepare the protocol, apply inclusion criteria, assess quality, and extract data. Quality assessment was based on the adequacy of allocation concealment, generation of allocation sequence, and blinding of study participants, investigators, and outcome assessors. Two authors (CSW and MSS) conducted the search with the assistance of the Cochrane HIV/AIDS Trial Search Coordinator and the rest of the reviewers were informed of its progress. Three authors (CSW, MSS and PB) independently assessed eligibility and quality, and extracted data on relevant outcome measures using a standardised data abstraction form. Disagreements were resolved by discussion. If a disagreement were to persist, the other authors would have arbitrated.

We expressed study results as relative risks (RR) with 95% confidence intervals (CI) and assessed statistical heterogeneity using the x^2-test of homogeneity, with a p-value ≤ 0.1 indicating significance. There was no significant heterogeneity between the two included studies ($I^2 = 0\%$, $p = 0.94$), and we pooled the study results using Mantel-Haenszel's fixed effect method.[12] We planned to use meta-regression to explore the effect of trial quality and other trial characteristics[13] on estimated treatment effects, but the number of trials was not sufficient for this type of analysis. No subgroup analyses based on patient characteristics were planned *a priori*, as these are better investigated using individual patient data meta-analysis.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit this manuscript for publication.

Results

Description and quality of included studies

Fig. 1 summarises the search and selection of identified studies. Of the five potentially relevant studies,[14-20] two[18,19] were included in this review. In one of the included studies, Gaillard *et al.*[21] allocated HIV-infected pregnant women in labour in Mombasa, Kenya, to either vaginal irrigation with 120 ml chlorhexidine (0.2% at the beginning and 0.4% towards the end of the trial) or no intervention, in alternating weeks. This approach to the generation of allocation sequence is inadequate and this trial is therefore considered of low quality. Women who delivered within 1 hour of admission, those in whom the time between first irrigation and delivery was less than 1 hour, and those for whom the time between the last irrigation and delivery was more than 4 hours, were excluded from the analysis.

There was adequate allocation concealment in the second trial, in which Mandelbrot *et al.*[19] randomly assigned HIV-infected pregnant women in Cote d'Ivoire and Burkina Faso to either 1% benzalkonium chloride or placebo using a

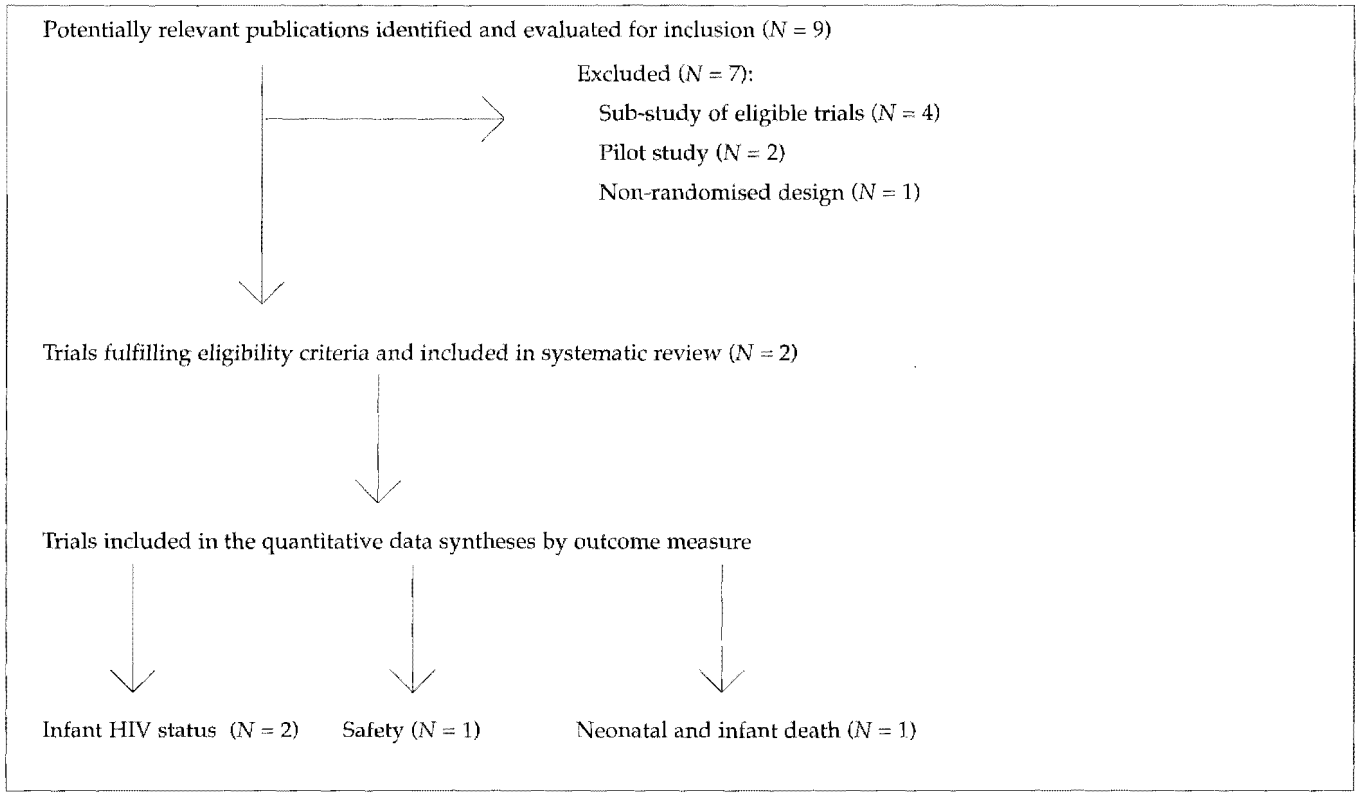

Fig. 1. Flow chart of randomised controlled trials through the systematic review.

computer-generated system by block-randomisation. Women self-administered the vaginal capsules daily from 36 weeks of pregnancy until labour. Another vaginal capsule was administered at the beginning of the delivery process in the maternity ward, under supervision of the study team. Finally, the neonate was bathed in either 1% solution of benzalkonium chloride or placebo within 30 minutes of delivery, in the delivery room. However, this trial was considerably underpowered to find a difference in transmission rates between treatment arms as it was designed as a phase II trial to evaluate the tolerability and acceptability of benzalkonium chloride, not its efficacy.

Quantitative data synthesis

Pooling the data from the two included trials (Fig. 2) with a total of 708 participants[20,21] shows no evidence of an effect of vaginal disinfection on the risk of MTCT of HIV (RR 0.94, 95% CI 0.71 - 1.25), neonatal death (RR 1.36, 95% CI 0.32 - 5.79), or death after the neonatal period (RR 1.39, 95% CI 0.52 - 3.71). The combined data have only 78% power to detect a 30% reduction in the risk of MTCT of HIV from a baseline risk of 30%, and are compatible with a wide range of effects, from a 29% reduction in risk to a 25% increase. One trial, with 108 participants, showed no evidence that adverse effects increased in mothers (RR 1.02, 95% CI 0.87 - 1.20) and found that adverse effects decreased in neonates (RR 0.45, 95% CI 0.32 - 0.64).

Discussion

We found no evidence of an effect of vaginal microbicides on the risk of MTCT of HIV infection and infant mortality. However, the scarcity of randomised controlled trials evaluating the effect of vaginal disinfection during labour on MTCT of HIV means that the database has limitations. The two included trials were considerably underpowered to find a significant difference in MTCT rates between treatment arms. Given the magnitude of the paediatric HIV epidemic in low- and middle-income countries of the world,[1] the suggestion that vaginal exposure might increase the risk of MTCT of HIV,[8-10] and the need for cheap, safe, and easy interventions to be used alone or in association with a short course of antiretroviral therapy,[5] there is need for high-quality adequately powered randomised controlled trials to investigate the effect of vaginal microbicides on MTCT of HIV, or more likely, the additive effect of vaginal microbicides in antiretroviral-treated women.

Implications for practice

At the moment, there is no high-quality evidence to develop practice guidelines for use of vaginal microbicides to reduce the risk of MTCT of HIV infection.

Implications for research

There is a need for well-designed adequately powered randomised controlled trials to estimate the effect of vaginal

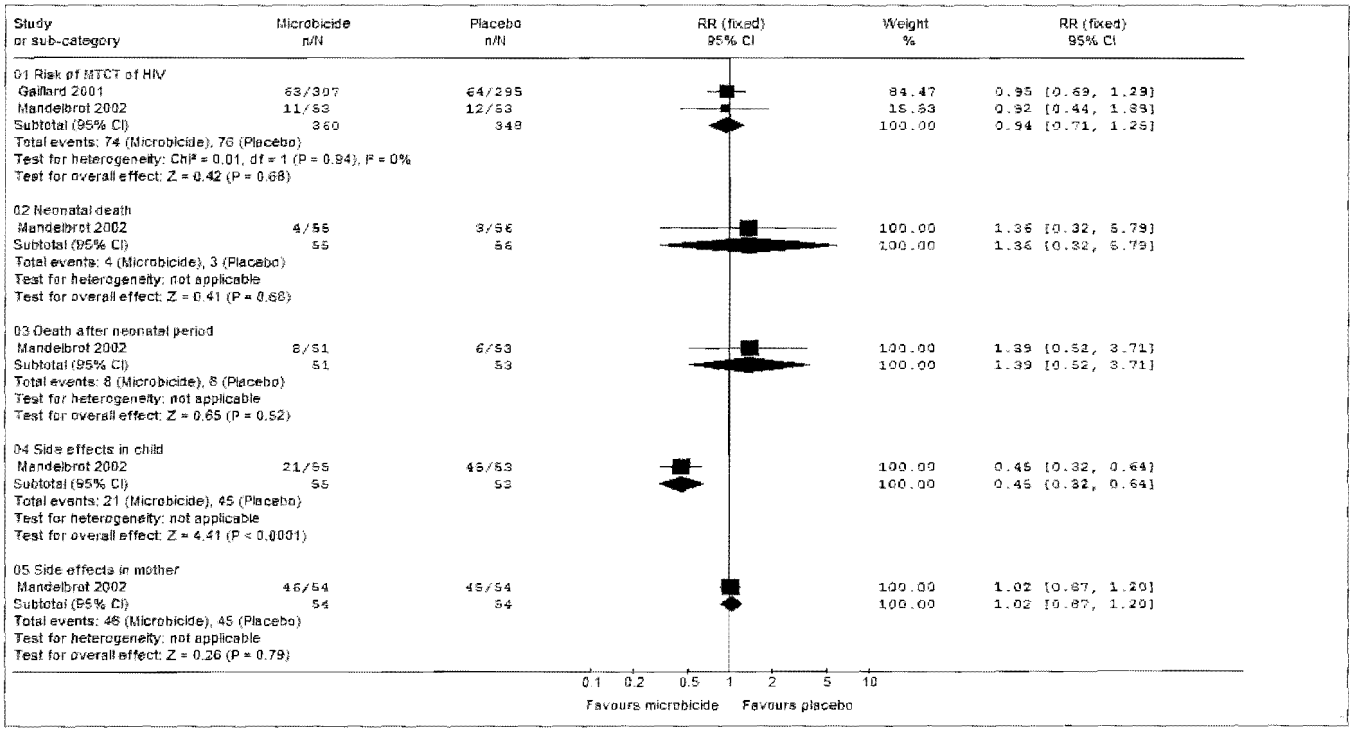

Fig. 2. Summary of the meta-analyses.

microbicides on the risk of MTCT of HIV infection. Ethically, women in either arm of such trials should be provided a short course of antiretroviral therapy.

CSW and PB conceived the study, CSW, MSS, and PB did data extraction, CSW and MSS conducted the analysis, and all authors participated in the interpretation of the data. CSW wrote the first draft of the paper and all the authors contributed intellectualiy to and approved the final version. The authors have no conflict of interest.

This review will be regularly updated in the Cochrane Library (http://www.cochrane.org/reviews/clibintro.htm).

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