Vaginal disinfection for preventing mother-to-child transmission of HIV infection (Review)

Wiysonge CS, Shey MS, Shang JD, Sterne JAC, Brocklehurst P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Vaginal disinfection for preventing mother-to-child transmission of HIV infection (Review)

Wiysonge CS, Shey MS, Shang JD, Sterne JAC, Brocklehurst P

This record should be cited as:
Wiysonge CS, Shey MS, Shang JD, Sterne JAC, Brocklehurst P. Vaginal disinfection for preventing mother-to-child transmission of HIV infection. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003651. DOI: 10.1002/14651858.CD003651.pub2.

This version first published online: 19 October 2005 in Issue 4, 2005.
Date of most recent substantive amendment: 16 August 2005

ABSTRACT

Background
Mother-to-child transmission (MTCT) of HIV infection is one of the most tragic consequences of the HIV epidemic, especially in resource-limited countries, resulting in about 650 000 new paediatric HIV infections each year worldwide. The paediatric HIV epidemic threatens to seriously undermine decade-old child survival programmes.

Objectives
To estimate the effect of vaginal disinfection on the risk of MTCT of HIV and infant and maternal mortality and morbidity, as well as tolerability of vaginal disinfection in HIV-infected women.

Search strategy
We searched the Cochrane Controlled Trials Register, Cochrane Pregnancy and Childbirth Register, PubMed, EMBASE, AIDSLINE, LILACS, AIDSTRIALS, and AIDSDRUGS, using standardised methodological filters for identifying trials. We also searched reference lists of identified articles, relevant editorials, expert opinions and letters to journal editors, and abstracts and proceedings of relevant conferences, and contacted subject experts and pharmaceutical companies. There were no language restrictions.

Selection criteria
Randomised trials or clinical trials comparing vaginal disinfection during labour with placebo or no treatment, in known HIV-infected pregnant women. Trials had to include an estimate of the effect of vaginal disinfection on MTCT of HIV and or infant and maternal mortality and morbidity.

Data collection and analysis
Three authors independently assessed trial eligibility and quality, and extracted data. Meta-analysis was performed using the Yusuf-Peto modification of Mantel-Haenszel's fixed effect method.

Main results
Only two trials that included 708 patients met the inclusion criteria. The effect of vaginal disinfection on the risk of MTCT of HIV (OR 0.93, 95% CI 0.65 to 1.33), neonatal death (OR 1.38, 95% CI 0.30 to 6.33), and death after the neonatal period (OR 1.45, 95% CI 0.47 to 4.45) is uncertain. There was no evidence that vaginal disinfection increased adverse effects in mothers (OR 1.15, 95% CI 0.41 to 3.22), and evidence from one trial showed that adverse effects decreased in neonates (OR 0.14, 95% CI 0.07 to 0.31).

Authors' conclusions
Currently, there is no evidence of an effect of vaginal disinfection on the risk of MTCT of HIV. Given its simplicity and low cost, there is need for a large well-designed and well-conducted randomised controlled trial to assess the additive effect of vaginal disinfection on the risk of MTCT of HIV in antiretroviral treated women.

PLAIN LANGUAGE SUMMARY

Mother-to-child transmission (MTCT) of HIV is the primary way that children become infected with HIV. More than 2000 children worldwide are infected in this way every day. Researchers theorized that disinfecting the vaginal area of HIV-infected pregnant women would make it less likely that their babies would be born with HIV.

The primary objective of this review of clinical and randomised studies is to estimate the effect of vaginal disinfection during labour on the risk of mother-to-child transmission of HIV infection in HIV infected women. The secondary objectives are to determine the effect of vaginal disinfection on infant and maternal mortality and morbidity, and to describe its side effects to the mother and the new baby.

The authors of this review found that currently, there is no evidence of an effect of vaginal disinfection on the risk of MTCT of HIV. Given its simplicity and low cost, there is need for a large well-designed and well-conducted randomised controlled trial to assess the additive effect of vaginal disinfection on the risk of MTCT of HIV in pregnant, HIV-infected women, who are on antiretroviral therapy.

BACKGROUND

The Joint United Nations Programme on HIV/AIDS and the World Health Organization estimate that about 7 million children 0-14 years of age had been infected with the human immunodeficiency virus (HIV) during the past two decades; 2.7 million of whom are still living with the virus (UNAIDS 2001). These children will have acquired the infection primarily through mother-to-child transmission (MTCT). HIV infection in women of childbearing age continues to fuel the paediatric HIV epidemic. An estimated 3 million HIV-infected women give birth worldwide yearly, resulting in 1800 new paediatric infections each day, 90% of which occur in sub-Saharan Africa. The risk of MTCT of HIV ranges from 15-30% in the industrialised countries of Europe and North America, to 30-45% in the breastfeeding populations of sub-Saharan Africa (De Cock 2000).

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. This, together with the rising cost of comprehensive health care to treat HIV infection and AIDS has led to the development of numerous strategies to prevent MTCT of HIV (De Cock 2000). The strategies, which have been researched over the last decade, include antiretroviral therapy, Caesarean section delivery, and avoidance of breastfeeding.

In 1994, it was demonstrated that administration of zidovudine (an antiretroviral drug) to the mother during pregnancy and to the infant for the first six weeks after birth reduced transmission by two-thirds (Connor 1994). In the well-resourced countries of Europe and North America, incorporation of this or more complex and expensive antiretroviral regimens to clinical practice coupled with Caesarean delivery and avoidance of breastfeeding has reduced the rate of MTCT of HIV to less than 2% (Wade 1998; MTCT Group 1999). Despite their benefits, the costs associated with these interventions, their complexity, and the need for skilled personnel limit their availability in under-resourced developing countries, where most of the MTCT of HIV takes place. Recently, high quality randomised controlled trials have shown several simpler and less expensive antiretroviral regimens to be effective in decreasing MTCT of HIV (Brocklehurst 2004). However, even short-course antiretroviral drugs may not be affordable or may be logistically difficult to deliver in many developing countries. One other major problem in these poorer areas of the world with the highest burden of MTCT of HIV is that the majority of infected women are not aware of their HIV infection status. 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 (70%) occur during labour and delivery (Simon 1994; Bertolli 1996; Bertolli 1996; Newell 1998; Mock 1999). In addition, studies of twins indicate that the first-born infants have a risk of infection at least twice that of the second-born infant (Goedert 1991; Duliege 1995). These observational data suggest that vaginal exposure might be an important route of infection; a hypothesis supported by the protective effect of Caesarean delivery (MOD 1999). Consequently, disinfection of the birth canal during labour has been proposed as a low-cost strategy for reducing MTCT of HIV infection (Newell 2000). Chlorhexidine is one such disinfectant. It is a powerful mucous membrane disinfectant that neutralises HIV (Harbison 1989) and is generally well tolerated (Burman 1992; Garland 1996). However, side effects have been reported (Autegarden 1999; Pham 2000). These include dermatological hypersensitivity reactions and anaphylactic shock. Benzalkonium chloride, another potential candidate for vaginal disinfection, inactivates HIV in vitro (Wainberg 1990), is not absorbed by mucosae and has been shown to be well tolerated when used as a spermicide (Erny 1983). This review aims to combine all randomised controlled and controlled clinical trials comparing vaginal disinfection conducted to date, with an appropriate control group, to estimate the effect of vaginal disinfection on the risk of mother-to-child transmission of HIV infection and infant and maternal mortality

and morbidity. Although the key to prevention of mother-to-child transmission of HIV is primary prevention of HIV infection in women, prevention of HIV transmission from an infected mother to her child requires as much attention. The ultimate goal of this review is to determine whether vaginal disinfection during 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 prepartum, intrapartum, and early postpartum infection.

The review is one of a group of reviews assessing the available evidence for preventing HIV transmission from an infected mother to her child. Other topics include antiretroviral therapies (Brocklehurst 2004), vitamin A supplementation (Wiysonge 2004), delivery by Caesarean section (Read 2004), and avoidance of breastfeeding (Tholandi 2004).

OBJECTIVES

The primary objective of the review is to estimate the effect of vaginal disinfection during labour on the risk of mother-to-child transmission of HIV infection in HIV infected women.

The secondary objectives are to determine the effect of vaginal disinfection on infant and maternal mortality and morbidity, and to describe its side effects to the mother and the neonate.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomised controlled trials and controlled clinical trials were eligible for inclusion in this review.

Types of participants

Known HIV-infected pregnant women (as diagnosed by an antibody test) of any age and clinical stage of HIV disease, whether exposed to another intervention aimed at reducing MTCT of HIV or not, during labour and delivery.

Trials assessing the effect of vaginal disinfection on adverse birth outcomes for HIV negative women or those of unknown HIV serostatus were not included in this review as they are already included in other Cochrane reviews in progress (Lumbiganon 2004, Stade 2004).

Types of intervention

Vaginal disinfection with any disinfectant during labour compared with placebo or no treatment.

Types of outcome measures

The primary outcome measure was the HIV infection status of the child (as defined by the authors).

The secondary outcome measures for the review were both infant and maternal:

Infant:
1. Neonatal sepsis (as defined by the authors).
2. Neonatal admissions
3. Death of the child within 28 days of birth
4. Later death of the child (as defined by the authors), and
5. Side effects in the neonate (as defined by the authors).

Mother:
1. Postpartum infection (as defined by the authors)
2. Postpartum admissions
3. Side effects in the mother (as defined by the authors)
4. Acceptability of intervention among women
5. Cost of the intervention.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Electronic searches were undertaken in CENTRAL/CCTR (Cochrane Library Issue 2, 2005), Cochrane Pregnancy and Childbirth register, PubMed (2001 onwards), EMBASE, AIDSLINE, LILACS, AIDSTRIALS, AIDSDRUGS, using the following terms: (benzalkonium OR betadine OR chlorhexidine OR "vaginal antisept*-creams-foams-gel-jellies-OR-tablet*" OR "vaginal cleansing-disinfection-OR-wash") AND (pregnancy OR labour OR labor OR birth OR intrapartum OR delivery). Standardised methodological filters for identifying controlled trials were applied (Lefebvre 2000; Higgins 2005), as appropriate. The methodological filter we used for PubMed was ("randomized controlled trial" [pt] OR "controlled clinical trial" [pt] OR "randomized controlled trials" [mh] OR "random allocation" [mh] OR "double-blind method" [mh] OR "single-blind method" [mh] OR "clinical trial" [pt] OR "clinical trials" [mh] OR (clinica* [tw] AND trial* [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (latin [tw] AND square [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR volunteer* [tw] OR "research design" [mh:noexp]) NOT (animal [mh] NOT human [mh]), and that for EMBASE was (CLINICAL-TRIAL (DE) OR RANDOMIZED-CONTROLLED-TRIAL (DE) OR trial* OR compar* OR DOUBLE-BLIND-PROCEDURE (DE) OR PLACEBO (DE) OR versus OR MULTICENTER-STUDY (DE) OR assign* OR allocat* OR singl* adj blind* OR CROSS-OVER-PROCEDURE (DE) OR PHASE-3-CLINICAL-TRIAL (DE) OR INTERMETHOD-COMPARISON (DE) OR volunteer* OR SINGLE-BLIND-PROCEDURE (DE)). The "Related articles" feature of PubMed was also used.

The above search strategy was supplemented by searching reference lists of identified articles and abstracts or proceedings

of 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. Investigators of identified trials and other content experts, agencies, organisations, academic centres, and pharmaceutical companies were contacted to locate any further trials (completed or ongoing, published or not) that may not have been included in the electronic databases or presented at the conferences. 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.

METHODS OF THE REVIEW

Five authors undertook the review. CSW conducted the literature search, noting the date each database was searched and years covered by the search, MSS cross-checked the search, and JDS, JACS and PB were informed of its progress.

Studies identified by the search strategy were scrutinised independently for eligibility by three authors (CSW, MSS, PB). Studies were included if they were controlled trials (study design) comparing vaginal disinfection during labour with placebo or no treatment (intervention) in HIV infected women (participants) and information was available on any of the outcomes listed above. CSW, MSS and PB then independently assessed included studies for methodological quality. Quality assessment was based on the method of assigning participants to interventions (Higgins 2005) as follows:

Category A - Adequate allocation concealment (such as centralised or pharmacy-controlled randomisation; pre-numbered or coded identical containers administered serially to patients; on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered; sequentially numbered, sealed, opaque envelopes);

Category B - Uncertainty about whether the allocation was adequately concealed (for example, merely stating that a list or table was used, that sealed envelopes were used, or that the participants were randomly assigned); and

Category C - Inadequate allocation concealment: if the approach used was alternation; use of case record numbers, dates of birth, day of the week, open list of random numbers, etc.

After quality assessment, the three authors extracted the data. We designed forms for data extraction and for requesting additional information from the investigators. On data abstraction forms was noted the review title, study reference and publication status, date of extraction, and review author's initials. Data were extracted under the following subheadings in the form: methods (method of randomisation and allocation concealment, blinding of those receiving and providing care and outcome assessors, losses to follow-up and how they were handled), participants (setting, number of women randomised), interventions (disinfectant, dose, type of control group, co-interventions), outcomes, and (other) notes. If data were available on MTCT of HIV at two or more periods, the more complete or later one was taken into account. All the outcome variables are dichotomous and the data extracted were the number of affected participants and the number of participants in the comparison group.

Disagreement between CSW, MSS and PB on the eligibility or quality of a trial or data extracted was resolved by discussion. If a disagreement were to persist, JDS and JACS would have arbitrated. We planned to reference any study that satisfied the design, intervention and participant criteria but for which none of the pre-specified outcomes could be obtained as one awaiting assessment. When we obtain the required information, such a trial would be included in the next update of the review. Authors assessing study eligibility and quality were not blinded to the names of the authors, their institutions, journals of publication, and results of the study.

We undertook statistical analysis using RevMan 4.2, expressed study results as odd ratios with 95% confidence intervals, and combined them using the Yusuf-Peto modification of Mantel-Haenszel's fixed effect method (Yusuf 1985). We examined heterogeneity between studies by graphical inspection of results followed by a chi-square test of homogeneity, and would have used meta-regression to explore the effect of trial quality, type of disinfectant, administered dose, method of administration, and type of control group, on estimated treatment effects if there were at least five trials included in the review. No subgroup analyses based on patient characteristics were planned, a priori, as these are better investigated using individual patient-data meta-analysis.

DESCRIPTION OF STUDIES

Studies are referred to according to the first author and the year of publication of the main report. The studies, which are briefly described below, are described in detail in the table of included studies.

Gaillard 2001
Eight hundred and ninety eight HIV-infected women in labour in a government hospital in Mombasa, Kenya, were allocated to intervention in alternating weeks. A regime of nine days of vaginal lavage followed by five days of non-lavage was introduced early on in the trial. This was followed by a regime of four days of vaginal lavage and 10 days of non-lavage at the end of the recruitment period. Women were allocated to the intervention in clusters, but analysed as individuals. Women who delivered within one hour of admission were excluded from the analysis. Also excluded from

the analysis were women in whom the time between first lavage and delivery was less than one hour, and those for whom the time between the last lavage and delivery was more than four hours.

Mandelbrot 2002
A simple randomised trial in which 108 HIV-infected pregnant women in Abidjan (Cote d'Ivoire) and Bobo-Dioulasso (Burkina Faso) were allocated to treatment strategies using a computer-generated system by block-randomisation with a block size of 10. Sequentially numbered identical sealed packages containing the treatments were prepared by an independent central pharmacy according to the randomisation list. Women self-administered either one percent benzalkonium chloride or placebo 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 a one percent solution of benzalkonium chloride or placebo within 30 minutes of delivery, in the delivery room. Analysis was by intention-to-treat. The study was designed as a phase II trial to observe a four-fold increase of genital ulcers from 5% in the placebo group to 20% in the treatment group, with an alpha error of 0.1 and 80% power. Therefore, it did not have adequate power to demonstrate a clinically significant difference in the risk of MTCT of HIV between the benzalkonium chloride and placebo arms.

METHODOLOGICAL QUALITY

Gaillard 2001
Alternation, which is the approach to allocation concealment used in this study, is considered inadequate by standard Cochrane criteria (Higgins 2005). The study is, thus, of low quality.

Mandelbrot 2002
The method of assigning participants to treatment strategies that is, a computer-generated list and sequentially numbered, identical sealed drug containers prepared by a central pharmacy is considered adequate by standard Cochrane criteria (Higgins 2005).

RESULTS

Only two small trials that included 708 patients met the inclusion criteria. There was no significant heterogeneity between the trials ($p = 0.94$). Combining the two trials show that the effect of vaginal disinfection on the risk of MTCT of HIV (odds ratio [OR] 0.93, 95% confidence interval [CI] 0.65 to 1.33), neonatal death (OR 1.38, 95% CI 0.30 to 6.33), and death after the neonatal period (OR 1.45, 95% CI 0.47 to 4.45) is uncertain. There was no evidence that vaginal disinfection increased adverse effects in mothers (OR 1.15, 95% CI 0.41 to 3.22), and evidence from one trial showed that adverse effects decreased in neonates (OR 0.14, 95% CI 0.07 to 0.31).

DISCUSSION

We found no evidence of an effect of vaginal disinfection on the risk of MTCT of HIV infection and infant mortality. However, the scarcity of randomised controlled trials that evaluate the effect of vaginal disinfection during labour on the risk of MTCT of HIV means that the database has limitations. The two included trials had only 78% power to detect a 30% reduction in the risk of MTCT of HIV, and less than 10% power to detect a significant effect of the order observed (that is, 6% reduction in the risk of MTCT of HIV), from a baseline transmission rate of 30%. Given the magnitude of the paediatric HIV epidemic in under-resourced countries (UNAIDS 2001), the suggestion that vaginal exposure might increase the risk of MTCT of HIV (Goedert 1991; Duliege 1995; MOD 1999), and the need for effective, cheap, safe, and easy interventions to be used alone or in association with a short course of antiretroviral therapy (Brocklehurst 2004), there is need for high quality randomised controlled trials to investigate the effect of vaginal disinfection on MTCT of HIV; or more likely, the additive effect of vaginal disinfection in antiretroviral treated women.

AUTHORS' CONCLUSIONS

Implications for practice

At the moment, there is no high-quality evidence to use vaginal disinfection to reduce the risk of mother-to-child transmission of HIV infection.

Implications for research

Given the simplicity and low cost of vaginal disinfection, there is a need for a large high-quality randomised controlled trial to assess the additive effect of this intervention on the risk of MTCT of HIV in antiretroviral treated women.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

We are grateful to Prof Aubrey Sheiham, Sir Iain Chalmers, Dr Phil Alderson, Prof Justus Hofmeyr, the staff of the Cochrane Collaboration Secretariat and the UK Cochrane Centre, and the editorial base of the Cochrane HIV/AIDS and Pregnancy and Childbirth Groups for their support in the course of preparing and updating this review.

SOURCES OF SUPPORT

External sources of support

- Aubrey Sheiham Cochrane Collaboration Scholarship (CSW) UK
- Department of Health (PB) UK

Internal sources of support

- Department of Social Medicine, University of Bristol (JAS) UK
- Ministry of Public Health (CSW) CAMEROON
- University of Yaounde I (MSS, JDS) CAMEROON
- University of Cape Town (CSW) SOUTH AFRICA

REFERENCES

References to studies included in this review

Gaillard 2001 *{published data only}*

* Gaillard P, Mwanyumba F, Verhofstede C, et al. Vaginal lavage with chlorhexidine during labour to reduce mother-to-child HIV transmission: clinical trial in Mombassa, Kenya. *AIDS* 2001;**15**:389–396.

Mandelbrot 2002 *{published data only}*

* Mandelbrot L, Msellati P, Meda N, et al. 15 Month follow up of African children following vaginal cleansing with benzalkonium chloride of their HIV infected mothers during late pregnancy and delivery. *Sex Transm Infect* 2002;**78**:267–270.

Msellati P, Meda N, Leroy V, et al. Safety and acceptability of vaginal disinfection with benzalkonium chloride in HIV-infected pregnant women in West Africa: ANRS 049b phase II randomized, double blinded placebo-controlled trial. *Sex Transm Infect* 1999;**75**:420–425.

References to studies excluded from this review

Biggar 1996

* Biggar RJ, Miotti PG, Taha TE, et al. Perinatal intervention trial in Africa: effect of a birth canal cleansing intevention to prevent HIV transmission. *Lancet* 1996;**347**:1647–1650.

Taha T, Biggar RJ, Broadhead RL, et al. Effect of cleansing the birth canal with antiseptic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial. *BMJ* 1997;**315**:216–219.

Additional references

Autegarden 1999

Autegarden JE, Pecquet C, Huet S, Bayrou O, Leynadier F. Anaphylactic shock after application of chlorhexidine to unbroken skin. *Contact Dermatitis* 1999;**40**:215.

Bertolli 1996

Bertolli J, St Louis ME, Simonds RJ, et al. Estimating the timing of mother to child transmission of human immunodeficiency virus in a breastfeeding population in Kinshasa Zaire. *J Infect Dis* 1996;**174**:722–26.

Brocklehurst 2004

Brocklehurst P, Volmink J. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection (Cochrane Review). *The Cochrane Library* 2004, Issue 1. Art. No.: CD003510. DOI: 10.1002/14651858.CD003510.pub2.

Burman 1992

Burman LG, Christensen P, Christensen K, et al. Prevention of excess neonatal morbidity associated with group B streptococci by vaginal chlorhexidine disinfection during labour. The Swedish Chlorhexidine Study Group. *Lancet* 1992;**340**:65–9.

Connor 1994

Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994;**331**:173–80.

De Cock 2000

De Cock KM, Fowler MG, Mercier E, et al. Prevention of mother to child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA* 2000;**283**:1175–82.

Duliege 1995

Duliege AM, Amos CI, Felton S, Biggar RJ, Goedert JJ. Birth order, delivery route and concordance in the transmission of human immunodeficiency virus type 1 from mothers to twins. *J Pediatr* 1995;**216**:625–32.

Erny 1983

Erny R, Siboni C. Les tampons au chlorure de benzalkonium: tolerance locale et effets sur la glaire cervicale. *J Gynecol Obstet Biol Reprod* 1983;**12**:767–774.

Garland 1996

Garland JS, Alex CP, Mueller CD, Cisler-Kahill LA. Local reactions to a chlorhexidine gluconate-impregnated antimicrobial dressing in very low birth weight infants. *Pediatr Infect Dis J* 1996;**15**:912–4.

Goedert 1991

Goedert JJ, Duliege AM, Amos CI, Felton S, Biggar RJ. High risk of HIV-1 infection for first-born twins. *Lancet* 1991;**338**:1471–75.

Harbison 1989
Harbison MA, Hammer SM. Inactivation of human immunodeficiency virus by betadine products and chlorhexidine. *J Acquir Immune Defic Syndr* 1989;**2**:16–20.

Higgins 2005
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.4 [updated March 2005]. *http://www.cochrane.org/resources/handbook/hbook.htm (accessed 31st March 2005)*. 2005.

Lefebvre 2000
Lefebvre C, Clarke MJ. Identifying randomised trials. In: EggerM, Davey SmithG, AltmanDG editor(s). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2000.

Lumbiganon 2004
Lumbiganon P, Thinkhamrop J, Thinkhamrop B, Tolosa JE. Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV) (Protocol for a Cochrane Review). *The Cochrane Library* 2004, Issue Issue 1.

Mock 1999
Mock PA, Shaffer N, Bhadrakom C, et al. Maternal viral load and timing of mother to child HIV transmission, Bangkok, Thailand. *AIDS* 1999;**13**:407–414.

MOD 1999
The European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999;**353**:1035–9.

MTCT Group 1999
The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1-a meta-analysis of 15 prospective cohort studies. *N Engl J Med* 1999;**340**:977–87.

Newell 1998
Newell ML. Mechanisms and timing of mother to child transmission of HIV-1. *AIDS* 1998;**12**:831–7.

Newell 2000
Newell ML. Vertical transmission of HIV-1 infection. *Trans R Soc Trop Med Hyg* 2000;**94**:1–2.

Pham 2000
Pham NH, Weiner JM, Reisner GS, Baldo BA. Anaphylaxis to chlorhexidine. Case report. Implication of immunoglobulin E antibodies and identification of an allergenic determinant. *Clin Exp Allergy* 2000;**30**:1001–7.

Read 2004
Read JS, Newell M-L. Cesarean delivery for prevention of mother-to-child transmission of HIV. *Cochrane Library* 2004, Issue 1.

Simon 1994
Simon A, Lepage P, Karita E, et al. An assessment of the timing of mother to child transmission of human immunodeficiency virus type 1 by means of polymerase chain reaction. *J Acquir Immune Defic Syndr Hum Retrovirol* 1994;**7**:952–957.

Stade 2004
Stade B, Shah V, Ohlsson A. Vaginal chlorhexidine during labour to prevent neonatal group B streptococcal infection (Protocol for a Cochrane Review). *The Cochrane Library* 2004, Issue 1.

Tholandi 2004
Tholandi M, Wilkinson D, Dabis F, et al. Interventions to drecrease the risk of mother-to-child transmission of HIV-1 through breast milk (Protocol). *Cochrane Library* 2004, Issue 1.

UNAIDS 2001
UNAIDS/WHO. AIDS epidemic update. Geneva: Joint United Nations Programme on HIV/AIDS. UNAIDS/01.74-WHO/CDS/CSR/NCS/2001.2. (English original, December 2001).

Wade 1998
Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med* 1998;**339**:1409–14.

Wainberg 1990
Wainberg MA, Spira B, Bleau G, et al. Inactivation of human immunodeficiency virus type 1 in tissue culture fluid and in genital secretions by the spermicide benzalkonium chloride. *J Clin Microbiol* 1990;**28**:156–158.

Wiysonge 2004
Wiysonge CSU, Brocklehurst P, Sterne JAC. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Library* 2004, Issue 3. Art. No.: CD003648. DOI:10.1002/14651858.CD003648.pub2.

Yusuf 1985
Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Progress in Cardiovascular Diseases* 1985;**27**(5):335–71.

** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Gaillard 2001
Methods	Selected women were allocated to intervention in alternating weeks. Women who delivered within one hour of admission were exluded from the analysis. Also excluded were women in whom the time between first

	vaginal lavage and delivery was less than one hour, and those for whom the time between the last lavage and delivery was more than four hours.
Participants	898 HIV-infected women in labour in a government hospital in Mombassa, Kenya.
Interventions	Vaginal irrigation with 120ml chlorhexidine (0.2% during the first 17 months, then 0.4% during the subsequent 11 months) or no intervention.
Outcomes	HIV infection status of the child at 6 and/or 14 weeks.
Notes	Women were allocated to the intervention in clusters, but analysed as individuals.
Allocation concealment	C – Inadequate

Study	**Mandelbrot 2002**
Methods	Patients were allocated to drug regimens using a pre-established computerised list drawn by an independent statistician. Block randomisation was used for the random allocation of patients, with block size of ten. Sequentially numbered sealed drug packages containing the appropriate treatments indentical in appearance were prepared by an independent central pharmacy according to the randomisation list. Analysis was by intention-to-treat.
Participants	108 HIV infected pregnant women recruited before 36 weeks of pregnancy in Abidjan (Cote d'Ivoire) and Bobo-Dioulasso (Burkina Faso), mean age 24.6 years, mean parity 1.8
Interventions	Self-administration of 1% benzalkonium chloride or placebo 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 a 1% solution of benzalkonium chloride or placebo within 30 minutes of delivery in the delivery room.
Outcomes	Reproductive tract symptoms and signs in women; Irritation of the skin, mucosae, or eyes for neonates; HIV infection status and death of the child within 15 months
Notes	The study was designed as a phase II trial to assess the tolerability of vaginal benzalkonium chloride in HIV-infected pregnant women.
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	**Reason for exclusion**
Biggar 1996	Not randomized - women enrolled in large blocks of time of 2-3 months. No account taken of clustering of women within blocks. Forty one percent loss to follow-up for determing HIV status of children.

ANALYSES

Comparison 01. Vaginal disinfection compared with non-disinfection

Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 HIV infection status of the child	2	708	Peto Odds Ratio 95% CI	0.93 [0.65, 1.33]
02 Neonatal sepsis	0	0	Peto Odds Ratio 95% CI	Not estimable
03 Neonatal admissions	0	0	Peto Odds Ratio 95% CI	Not estimable
04 Neonatal death	1	111	Peto Odds Ratio 95% CI	1.38 [0.30, 6.33]
05 Deaths after neonatal period	1	104	Peto Odds Ratio 95% CI	1.45 [0.47, 4.45]
06 Side effects in the child	1	108	Peto Odds Ratio 95% CI	0.14 [0.07, 0.31]
07 Maternal postpartum infection	0	0	Peto Odds Ratio 95% CI	Not estimable

08 Maternal postpartum admissions	0	0	Peto Odds Ratio 95% CI	Not estimable
09 Maternal death	0	0	Peto Odds Ratio 95% CI	Not estimable
10 Side effects in the mother	1	108	Peto Odds Ratio 95% CI	1.15 [0.41, 3.22]
11 Maternal complaints	0	0	Peto Odds Ratio 95% CI	Not estimable

INDEX TERMS

Medical Subject Headings (MeSH)

Disease Transmission, Vertical [*prevention & control]; Disinfection [*methods]; HIV Infections [prevention & control; *transmission]; Irrigation; Labor, Obstetric; Randomized Controlled Trials; Risk; Vagina [*virology]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Vaginal disinfection for preventing mother-to-child transmission of HIV infection
Authors	Wiysonge CS, Shey MS, Shang JD, Sterne JAC, Brocklehurst P
Contribution of author(s)	CSW, PB, and JACS designed the protocol, CSW and MSS did the literature search, CSW, PB and MSS scrutinised the trials for eligibility and quality and extracted the data, CSW and MSS entered the data, and all the authors contributed to the text of the review. CSW and PB are guarantors of the review.
Issue protocol first published	/
Review first published	1995/2
Date of most recent amendment	23 August 2005
Date of most recent SUBSTANTIVE amendment	16 August 2005
What's New	When this review was first published in 2002, only one study (Gaillard 2001) was included. A new study (Mandelbrot 2002) has been added to the current update of the review.
Date new studies sought but none found	16 October 2004
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	10 January 2003
Date authors' conclusions section amended	01 May 2004
Contact address	Dr Charles Shey Wiysonge Deputy Permanent Secretary Central Technical Group Ministry of Public Health EPI c/o BP 25125 Messa Yaoundé CAMEROON E-mail: wiysonge@yahoo.com

Tel: +237 223 09 42
Fax: +237 223 09 47

DOI 10.1002/14651858.CD003651.pub2

Cochrane Library number CD003651

Editorial group Cochrane HIV/AIDS Group

Editorial group code HM-HIV

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Vaginal disinfection compared with non-disinfection, Outcome 01 HIV infection status of the child

Review: Vaginal disinfection for preventing mother-to-child transmission of HIV infection

Comparison: 01 Vaginal disinfection compared with non-disinfection

Outcome: 01 HIV infection status of the child

Study	Vaginal disinfection n/N	No disinfection n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Gaillard 2001	63/307	64/295		84.7	0.93 [0.63, 1.38]
Mandelbrot 2002	11/53	12/53		15.3	0.90 [0.36, 2.25]
Total (95% CI)	360	348		100.0	0.93 [0.65, 1.33]

Total events: 74 (Vaginal disinfection), 76 (No disinfection)

Test for heterogeneity chi-square=0.01 df=1 p=0.94 I^2 =0.0%

Test for overall effect z=0.42 p=0.7

Analysis 01.04. Comparison 01 Vaginal disinfection compared with non-disinfection, Outcome 04 Neonatal death

Review: Vaginal disinfection for preventing mother-to-child transmission of HIV infection

Comparison: 01 Vaginal disinfection compared with non-disinfection

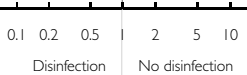
Outcome: 04 Neonatal death

Study	Vaginal disinfection n/N	No disinfection n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Mandelbrot 2002	4/55	3/56		100.0	1.38 [0.30, 6.33]
Total (95% CI)	55	56		100.0	1.38 [0.30, 6.33]

Total events: 4 (Vaginal disinfection), 3 (No disinfection)

Test for heterogeneity: not applicable

Test for overall effect z=0.41 p=0.7



Analysis 01.05. Comparison 01 Vaginal disinfection compared with non-disinfection, Outcome 05 Deaths after neonatal period

Review: Vaginal disinfection for preventing mother-to-child transmission of HIV infection

Comparison: 01 Vaginal disinfection compared with non-disinfection

Outcome: 05 Deaths after neonatal period

Study	Vaginal disifection n/N	No disinfection n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Mandelbrot 2002	8/51	6/53		100.0	1.45 [0.47, 4.45]
Total (95% CI)	51	53		100.0	1.45 [0.47, 4.45]
Total events: 8 (Vaginal disifection), 6 (No disinfection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.65 p=0.5					

Analysis 01.06. Comparison 01 Vaginal disinfection compared with non-disinfection, Outcome 06 Side effects in the child

Review: Vaginal disinfection for preventing mother-to-child transmission of HIV infection

Comparison: 01 Vaginal disinfection compared with non-disinfection

Outcome: 06 Side effects in the child

Study	Vaginal disinfection n/N	No disinfection n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Mandelbrot 2002	21/55	45/53		100.0	0.14 [0.07, 0.31]
Total (95% CI)	55	53		100.0	0.14 [0.07, 0.31]
Total events: 21 (Vaginal disinfection), 45 (No disinfection)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.96 p<0.00001					

Analysis 01.10. Comparison 01 Vaginal disinfection compared with non-disinfection, Outcome 10 Side effects in the mother

Review: Vaginal disinfection for preventing mother-to-child transmission of HIV infection

Comparison: 01 Vaginal disinfection compared with non-disinfection

Outcome: 10 Side effects in the mother

Study	Vaginal disinfection n/N	No disinfection n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Mandelbrot 2002	46/54	45/54		100.0	1.15 [0.41, 3.22]
Total (95% CI)	54	54		100.0	1.15 [0.41, 3.22]
Total events: 46 (Vaginal disinfection), 45 (No disinfection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.26 p=0.8