Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men (Review)

Wilkinson D, Ramjee G, Tholandi M, Rutherford G

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

Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men (Review)

Wilkinson D, Ramjee G, Tholandi M, Rutherford G

This record should be cited as:
Wilkinson D, Ramjee G, Tholandi M, Rutherford G. Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men. *Cochrane Database of Systematic Reviews* 2002, Issue 1. Art. No.: CD003939. DOI: 10.1002/14651858.CD003939.

This version first published online: 21 January 2002 in Issue 1, 2002.
Date of most recent substantive amendment: 14 October 2001

ABSTRACT

Background
The incidence and prevalence of sexually transmitted infections (STI) and other reproductive tract infections (RTI) is high in much of the developing and parts of the developed worlds. STIs and RTIs are associated with the vaginal transmission of HIV. Additional strategies to improve STI control are needed, and vaginal microbicides are a possible strategy. One potential vaginal microbicide is the widely used spermicide, nonoxynol-9 (N-9).

Objectives
To determine the safety and effectiveness of N-9 in preventing vaginal acquisition of sexual transmitted infections (exclusive of HIV) by women from men.

Search strategy
Systematic search of electronic databases, conference abstracts, reference lists of relevant studies and contact with experts and funders.

Selection criteria
Randomised controlled trials meeting pre-determined quality criteria with STI as the outcome.

Data collection and analysis
Data were extracted by one reviewer and checked by another.

Main results
Ten of 12 identified randomised controlled trials were included and findings among them were broadly consistent. In meta-analysis, the risks of gonorrhoea (relative risk [RR] 0.91, 95%CI 0.67-1.24), cervical infection (RR 1.01, 0.84-1.22), trichomoniasis (RR 0.84, 0.69-1.02), bacterial vaginosis (0.88, 0.74-1.04), chlamydia (RR 0.88, 0.77-1.01) and candidiasis (RR 0.97, 0.84-1.12) were not statistically significantly different in women receiving N-9 compared with placebo. Genital lesions were more common in the N-9 users (RR 1.17, 95%CI 1.02-1.35).

Authors' conclusions
There is good evidence that nonoxynol-9 does not protect against sexually transmitted infections, and there is some evidence that it may be harmful by increasing the rate of genital ulceration. As such, this product cannot be recommended for STI prevention.

BACKGROUND

The epidemic of sexually transmitted infections (STI), reproductive tract infections (RTI) and HIV infection in the developing world is characterised by high incidence and high prevalence in many populations (WHO 1995). It is apparent that STIs and RTIs facilitate the transmission of HIV (Fleming 1999).

In recent years, the rapid spread of HIV worldwide among women has underscored their particular risk of infection. Women are particularly vulnerable to HIV infection for a number of reasons. Male-to-female transmission seems to be more efficient than female-to-male transmission (Padian 1991) and the subordinate social and cultural status of women in many countries makes it difficult for them to initiate sexual practices which would reduce the likelihood of HIV infection. Although male condoms provide good protection against HIV when used consistently, many women find it difficult to convince their male partners to use a condom for every sexual encounter (De Zoysa 1996). The urgent need for female-controlled HIV prevention strategies has been recognized for some time and focus has now been placed on the development of safe and effective microbicides (Elias 1996).

Importantly, among women STIs are frequently asymptomatic, unrecognised and/or untreated. Women also carry the large burden of the long term consequences of STIs, including pelvic inflammatory disease, infertility, chronic pelvic pain, and even death. Current STI control efforts are centered around case management, partner treatment, health promotion activities and the use of barriers such as condoms (WHO/UNAIDS 1997). There is substantial interest in the potential of vaginal microbicides to add to STI control efforts.

Microbicides are compounds formulated as gels, films, foams, suppositories, or creams and which, when inserted into the vagina, might prevent male to female transmission of HIV and other STIs. A perfect microbicide product would be safe and highly effective, it would not be messy, and it would be insertable several hours before coitus.

Several products are currently undergoing human testing. Different approaches to microbicide development are being explored. Among these are substances that: a) kill or otherwise immobilize pathogens (surfactants); b) block infection by creating a barrier between pathogens and the vagina or rectum; and c) prevent viral replication once the pathogen has entered the body. Only the first group, the surfactants, are in advanced testing (effectiveness studies against STIs and HIV), whilst the others are still undergoing Phase I and Phase II trials.

Although one review of one potential vaginal microbicide, the widely used spermicide nonoxynol-9 (N-9), has been published (Cook 1998), indicating that N-9 protects against STIs, this review included observational studies and did not follow Cochrane methods (Roddy 1998b). Here, we provide a systematic review and meta-analysis of the randomised controlled trials that have studied the potential role of N-9 as a prophylactic against STIs (not including HIV). A separate Cochrane review studies the role of N-9 as a prophylactic against HIV.

OBJECTIVES

To determine the safety and effectiveness of N-9 in preventing vaginal acquisition of sexual transmitted infections (exclusive of HIV) by women from men.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials (RCTs) comparing an N-9 containing vaginal microbicide with a placebo or with no treatment, and with STI or RTI as an outcome.

Types of participants

Women in any setting.

Types of intervention

N-9 containing microbicides.

Types of outcome measures

STIs including gonorrhoea, chlamydia, trichomonas, bacterial vaginosis, candidiasis, and cervical infections (gonorrhoea and chlamydia combined).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Search strategies detailed below were used to identify studies in electronic databases.

Abstracts from international and major national HIV/AIDS and STI conferences and meetings (including unpublished, non-peer-reviewed data) were also searched. We included foreign language papers in our search.

The following electronic databases were searched:
AIDSLINE (1980- June 2001)
EMBASE (1974- January 2001)
MEDLINE/Pubmed(1966- June 2001)
Cochrane Library (2001, Issue 2)

Known published studies (including reviews) were examined along with their reference lists. Researchers and funding agencies were also contacted to identify further trials.

For MEDLINE we used the following strategy (last run on June 25, 2001):
1. Microbicide - (title word)
2. Nonoxynol-9 - (subject) OR spermicides - (subject) AND clinical trial (subject)
3. Microbicides - (title word) AND clinical study - (subject)
4. Nonoxynol-9 - (subject) OR spermicides - (subject) AND clinical trial (subject) AND safety (subject)
5. Nonoxynol-9 - (subject) OR spermicides - (subject) AND clinical trial (subject) AND HIV (subject)
6. Nonoxynol-9 - (subject) OR spermicides - (subject) AND clinical trial (subject) AND STD (subject)
7. Nonoxynol-9 - (subject) OR spermicides - (subject) AND clinical trial (subject) AND effectiveness (subject)
8. Nonoxynol-9 - (subject) OR spermicides - (subject) AND clinical trial (subject) AND administration (subject)
9. Nonoxynol-9 - (subject) OR spermicides - (subject) AND clinical trial (subject) AND dosage (subject)
10. Nonoxynol-9 - (subject) OR spermicides - (subject) AND clinical trial (subject) AND delivery (subject)

For AIDSLINE (last run June 21, 2001) we used:
1. Nonoxynol-9 - (subject) OR Spermicides - (subject) AND clinical trial (subject)
2. Microbicides - (title word) AND clinical trial - (subject)
3. Microbicides - (title word) AND clinical study - (subject)
4. Microbicides - (subject) AND randomised - (subject)
5. Nonoxynol-9 - (subject) AND HIV (subject) AND clinical trial (subject)
6. Nonoxynol-9 - (subject) AND sexually transmitted (subject) AND clinical trial (subject).

METHODS OF THE REVIEW

Study selection

Studies identified in the search were initially reviewed by title and abstract by two reviewers. Those identified as being of potential interest were further assessed using the full text to develop a list of RCTs. Having agreed on our list of trials one reviewer checked each trial carefully for quality according to criteria used by the Cochrane HIV/AIDS Group (http://hivinsite.ucsf.edu/cochrane/). A second reviewer checked the results. We planned to exclude studies that did not provide adequate detail on randomisation methods, allocation concealment, outcome data, or that had inadequate follow up rates.

Data extraction

One reviewer extracted data on the relevant outcome measures and a second reviewer checked this.

Studies reported outcome in a variety of ways. Some reported the number of individual infections while others reported gonorrhoea and chlamydia combined as "cervical infections". Some studies provided data on first infection only, while others studied the number of each type of infection experienced. Some studies excluded women following the first incident infection while others allowed re-admission to the study following proof of cure.

In the meta-analysis, we were restricted to including only those studies that reported the number of events (and we used only first events in this review) and the number of women studied. Some studies provided outcomes as incidence density rates, and we used this to estimate the number of women affected. One study (Kreiss 1992) used a non-standard outcome measure (number of events/number of follow-up visits) and these data could not be used in the meta-analysis but were included in the systematic review. Rosenberg 1987 used a cross-over design, but, as only approximately one third of women agreed to the cross-over, we have used data from the initial parallel phase only.

Adverse effects are reported as genital lesions and these adverse outcome are reported in the meta-analysis. Some studies also reported on rates of more non-specific complaints raised and on numbers of women who dropped out of the study due to adverse events. Due to the inconsistency to which this data was reported, this is included only in the systematic review.

We used the relative risk for outcomes and employed a fixed effect model as the test for heterogeneity did not reach statistical significance.

DESCRIPTION OF STUDIES

Roddy 1998 conducted a double blind RCT among 1,170 HIV-negative, female sex workers in Cameroon. They compared 70 mg N-9 in a film with a placebo film. 2,290 women were screened, 1,317 enrolled and 1,292 randomised (the balance had indeterminate HIV status). Of these, 1,170 returned at least once for follow-up and hence were included in the primary analysis. These women had been sex workers for around 4 years (at least 4 partners per month), rarely used contraception (about 12%), often douched (about 25%), frequently used other vaginal substances (around 45%), and only about half reported using a condom with their last client. Around 10% had gonorrhoea, and 10% had chlamydia infection at screening. About 25% reported oral sex and about 16% anal sex. All women were urged to use, and were provided with, male condoms during the study and were advised to insert the film prior to each episode of intercourse. All were regularly screened and treated for STIs, and all regularly received intensive counseling for HIV prevention. Women were randomised by computer generated permuted blocks of eight. Allocation was concealed by opaque envelope. The placebo product was identical in appearance to the N-9 product. Women were interviewed monthly during follow-up, and 73% were followed-up for 1 year with a mean follow-up of 14 months. Withdrawals and reasons for

withdrawal were similar in each arm of the trial. At these follow-up visits women were examined by colposcope for genital lesions. Gonorrhoea and chlamydia were both detected using the DNA PACE 2 assay (Gen-Probe). Condom use was reported by 90%, approximately 10% reported oral sex and 5% reported anal sex during the study (rates were similar in each trial arm).

Kreiss 1992 did an unblinded RCT in Nairobi, Kenya, among 116 HIV negative female sex workers. They compared 1000 mg N-9 in a sponge (Today Sponge) with placebo glycerine vaginal suppository or cream (as no placebo sponge could be manufactured). 138 women were randomised, but 22 did not return for follow-up and were excluded from the primary analysis. Commercial sex workers in this area average 34 partners per week. Prevalence of gonorrhoea was around 20%, and chlamydia was around 12%. All women received male condoms, STI treatment, and regular HIV prevention advice. Women were randomised by computer-generated list, but the method of allocation concealment was not reported. Those randomised to sponge were advised to insert it prior to the first partner each day, to replace it after every 2-3 partners, and to remove it 6 hours after the last partner. Mean follow-up was for 14-17 months (range 1-46 months), with a mean of 9 follow-up visits. STIs were detected through microbiological culture of endocervical specimens. Condom use was reported as about 60%, with 90% compliance with the intervention, and no anal or oral sex was reported.

Van Damme 2001 did a triple-blind RCT among 765 HIV-negative female sex workers from Benin, Cote d'Ivore, South Africa, and Thailand. They compared 52.5 mg N-9 as a gel (COL-1492; Advantage S) with placebo (vaginal moisturiser; Replens) of the same components (except the N-9) and identically packaged. 892 women were randomised with 765 attending at least one follow-up visit and hence included in the primary analysis. In the introductory phase of the trial all women were colposcoped at all visits but not during the full phase III trial. Women were aged over 18 years (16 years in South Africa) and were recruited directly from place of work, via STI clinics, or through clinics for sex workers. Condom use varied from around 100% in Thailand to less than 50% in South Africa. Anal sex varied from 40% in South Africa to less than 5% in Cote d'Ivoire. Approximately 5% of women had gonorrhoea, and 5% had chlamydia at baseline. Condom use was promoted and STI treatment provided at all visits. Women were asked to use male condoms for each episode of intercourse and to apply the gel for every episode if they had cleaned the vagina after the last intercourse (there was no limit to the number of gels used each day). In all, 68% of women remained in the study at 48 weeks. STIs were detected through the NG/CT combined Amplicor PCR (Roche).

Roddy 2001 did an unblinded RCT among 1,241 HIV negative women (not sex workers) in Cameroon. They compared N-9 100 mg in a gel (Conceptrol contraceptive gel) with no gel (i.e. the comparison was gel plus condoms vs condoms alone). Women were aged over 17 years, typically single, with high education, had 1-2 partners in the preceding month, and averaged 3 coital acts per week. Around 40% douched, and around 5% had gonorrhoea and chlamydial infection at screening. All women received male condoms and HIV prevention messages together with treatment for any STIs. These were women with symptoms of STIs and were recruited from 10 clinics and 10 pharmacies (they also had STIs before). Women were randomly assigned by computer generated random number list in permuted blocks of 4, 8 and 12. During the study, condom use was reported by approximately 85% of women and gel use was reported by 76%; sexual activity was not reported to have changed during the study. Follow-up was carried out for up to 6 months. Gonorrhoea and chlamydia were detected by ligase chain reaction test of urine (or cervical specimen, if gynaecological examination was required).

Barbone 1990 and Louv 1988 report on the same double-blind randomised controlled trial. Women, aged 19-29 years, non-pregnant and using contraception, were recruited from the STD clinic in Birmingham, Alabama, USA, in 1984-6. Women free of cervical infections were randomised to 150 mg N-9 gel(Koromex) or identical placebo, and products were to be used for each episode of intercourse. Follow-up was monthly for 6 months. Endocervical specimens were cultured for N. gonorrhoea, while chlamydia infection was confirmed with staining by flourescent monoclonal antibodies. Trichomoniasis was diagnosed by wet preparation microscopy, candidiasis by potassium hydroxide preparation showing yeast and / or hyphae, and bacterial vaginosis diagnosed as the presence of any two of the following: a positive amine test, a wet preparation showing clue cells, or an abnormal grayish discharge. 818 women were randomised (408 to N-9 and 410 to placebo). Subjects were young (median age 23 years), mainly black (89%) and unmarried (82%). They had a median of one sex partner per month (range 0-12), and five episodes of sex per month (0-49). Follow-up for 6 months was completed for 78% of participants.

Niruthisard 1992 compared the 70 mg N-9 film with placebo among female sex workers recruited from six massage parlours in Bangkok, Thailand in 1990. Of 507 women screened, 31% had either gonorrhoea or chlamydial infection. Women without any microbiological evidence of STIs were recruited. The trial was single blind with the placebo being an inert, non-film lubricant. 186 women were randomised to N-9 and 157 to placebo. Women were asked to use the products and male condoms each time they had sex. Women were followed-up weekly for nine weeks. Gonorrhoea was diagnosed by culture of an endocervical specimen. Chlamydia was diagnosed by an enzyme immunoassay (IDEIA Chlamydia test). Women were treated, but not re-enrolled, if an incident infection was identified. Most women were young (80% less than 25 years), unmarried (>90%) and of low educational status. Approximately two-thirds of participants had a previous STI and around 70% had 8 or more partners each week. Follow-up was completed for 75% of participants.

Rendon 1980 compared 150 mg N-9 suppository with a placebo suppository among women aged 18-55 years without STIs in a double blind randomised trial in Mexico. Mean age was 32 years. 24 women were included in the N-9 group and 29 in the placebo group. Women were followed-up monthly for 6 months. Follow-up was complete in 55% of participants.

Rosenberg 1987 studied female sex workers in Bangkok, Thailand recruited from massage parlours in an unblinded randomised trial. They compared 1000 mg N-9 sponge with non-users (no placebo). Women were young (65% less than 25 years), had limited education, were single (about 70%), and had had an STI in the last 3 months (30%). About 75% had more than 7 partners each week. Twenty percent of those screened had either gonorrhoea or chlamydia. Women were randomised according to a computer-generated list and allocation was concealed by means of an opaque envelope. Sponge users were advised to insert the sponge before the first partner, replace it after every three partners and leave it in place for 6 hours after the last partner. STIs were diagnosed using conventional microbiological microscopy and culture techniques. Chlamydia was diagnosed with fluorescent monoclonal antibodies. Women were followed up weekly for 6 weeks and were re-admitted to the study following cure of incident infections. 149 women were included in the N-9 group and 168 in the non-user group. After 6 weeks, women were offered continuation of the intervention through cross-over into the alternate group but only about one-third agreed to this.

Richardson 2001 did a double blind RCT among 278 female sex workers in Mombasa, Kenya. They compared 52.5mg N-9 gel (COL-1492; Advatage S) with a placebo gel (very similar to the N-9 carrier gel). About half of the women were married, median age was 28 years and median duration of sex work was 3 years. Reported median weekly sex acts was 2. Douching was reported by 86% and 29% used lubricants for sex. Most (94%) returned for at least one follow-up visit and the median folow-up was for 50.1 weeks. At 12 weeks, 69% of the N-9 group and 61% of the placebo group were still being followed-up. Women were seen monthly and had a full clinical examination with colposcopy and evaluation for STIs and HIV. Median compliance with N-9 was reported to be 75%, but only 34% reported 100% compliance. In addition, 50% of the N-9 group reported 100% condom use.

METHODOLOGICAL QUALITY

Trials were generally of fair to high quality with methods of randomisation and allocation concealment made clear, with double or triple blinding where possible. Some studies were unblinded, as appropriate placebo products could not be manufactured.

The trial reported by Barbone 1990and Louv 1988 did not report on allocation concealment. Rendon 1980 reported that women were unaware of their assignment, but did not describe the method of concealment.

Follow-up rates were generally acceptably high and similar in intervention and control arms. Rendon 1980 had a low follow-up rate of only 55% and provided limited information on study participants.

RESULTS

Of 12 identified trials that were eligible for inclusion, 10 trials were included in the review. One trial (Cutler 1977) was excluded as there was no description of allocation concealment, and entry criteria and criteria for analysis were changed mid-way through the trial. Another trial (Sacks 1990) was excluded as the intervention comprised N-9 plus low dose interferon-alpha with recurrent herpes as the outcome. Nine trials (excluding Kreiss et al) contributed to the meta-analysis.

Roddy 1998 reported a rate ratio for gonorrhoea of 1.1 (95%CI 0.8-1.4) in the N-9 group compared with placebo and a rate ratio for chlamydia of 0.9 (0.7-1.3). Women receiving N-9 film were more likely to have genital lesions, most of which were on the vulva and included excoriation, fissures, and ulcers (129/410 vs 107/393).

Kreiss 1992 reported an adjusted relative risk (RR) for gonorrhoea of 0.4 (21% vs 32%, calculated as the number of events/number of examinations, $p<0.001$) among N-9 users. The rate of chlamydia was not significantly different (RR 0.6, 2 vs 4%). The adjusted relative risk for ulcers at any site was 3.3 among N-9 users (15% vs 8%). Ulcers were most frequently identified on the vulva. Spermicide-attributed complaints, mainly vulvar irritation, burning, and ulceration, were reported by 47% of N-9 users compared with 7% of placebo users.

Van Damme 2001 reported a small and statistically non significant increase in the risk of gonorrhoea (RR 1.2, 95%CI 0.9-1.6) and chlamydia (RR 1.16, 95%CI 0.8-1.6) among N-9 users. The estimated number of women experiencing genital lesions (from proportions given in the article) was 132 in the N-9 group and 117 in the placebo group. Incidence of lesions was greater among women who used the gel most frequently (close to double that among low users).

Roddy 2001 reported 116 gonorrhoea and chlamydia infections in the N-9 group and 100 in the non-user group yielding a relative risk of 1.2 (95%CI 0.9-1.6). Women were not routinely examined in this study and so there is no report of genital lesions. It is, however, reported that 214 women in the N-9 group and 215 women in the control group had at least one adverse event, but the nature of these events is not specified.

Louv 1988 found that the risk of first gonorrhoea infection was slightly lower among N-9 users (RR 0.84, 0.63-1.1) and was significantly lower for any episode of gonorrhoea infection (RR 0.75, 0.58-0.96). Similar results were shown for first chlamydia infection (RR 0.72, 0.58-0.9) and any chlamydia episode (RR 0.79,

0.64-0.97). Adverse effects were uncommon (reported by three women using N-9 and one using placebo) , mild and did not prevent continued use. Barbone 1990 found no statistically significant change in rates of trichomoniasis (RR 0.83, 0.61-1.12), candidiasis (RR 1.02, 0.77-1.35) or bacterial vaginosis (RR 0.86, 0.69-1.07).

Niruthisard 1992 showed that overall, N-9 reduced the incidence of cervical infection (gonorrhoea and/or chlamydia) by 25% (RR 0.75, 95%CI 0.5-1.1). Protection was a little higher among women with high compliance (RR 0.6, 0.3-1.0). Irritation symptoms were more common among women using N-9 (7.2 vs 4.3 per 100 woman-weeks), and three women from the placebo group and nine from the N-9 group withdrew due to irritation. Genital ulcers developed in 16 women in the N-9 group and 13 in the placebo group.

Rendon 1980 identified five infections with trichomonas in the N-9 group and four in the placebo group. Four cases of gonorrhoea occurred in the N-9 group and eight in the placebo group. One woman from each group reported side effects but none withdrew from the study. All differences were not significantly different.

Rosenberg 1987 reported a rate ratio for chlamydia of 0.67 (95%CI 0.42-1.07) favouring N-9 users and a rate ratio of 0.31 (0.16-0.8) for gonorrhoea in the parallel phase of their study. The rate ratio for candidiasis was 2.76 (0.96-7.98) among N-9 users.

Richardson 2001 reported adjusted relative risks for all STIs that did not reach statistical significance.

In meta-analysis of these results, the risks of gonorrhoea (relative risk [RR] 0.91, 95%CI 0.67-1.24), cervical infection (RR 1.01, 0.84-1.22), trichomoniasis (RR 0.84, 0.69-1.02), bacterial vaginosis (0.88, 0.74-1.04), chlamydia (RR 0.88, 0.77-1.01) and candidiasis (RR 0.97, 0.84-1.12) were not statistically significantly different in women receiving N-9 compared with placebo. Genital lesions were more common in the N-9 users (RR 1.17, 95%CI 1.02-1.35, p=0.02).

DISCUSSION

N-9 is a nonionic detergent that has been used for around 50 years as a spermicide. It has in vitro and some in vivo activities against STIs and HIV. It also protects macaques against intra vaginal challenge with simian immunodeficiency virus. Observational studies have suggested that N-9 may protect against STIs and HIV infection (Cook 1998). Trials have however been inconclusive, and some concern has been raised about the potential for increased rates of genital ulceration among N-9 users, particularly frequent users (Roddy 1998b).

Our systematic review and meta-analysis of the ten available high-quality randomised controlled trials shows that N-9 provides no protection against STIs. Furthermore, these trials suggest that N-9 use is associated with an increased risk of genital ulceration. Our review of N-9 and HIV infection showed that N-9 is associated with higher rates of HIV acquisition when compared with placebo, and that women using N-9 also have higher rates of genital ulceration.

It is notable that in the trials, relatively high rates of STI infection were measured despite high levels of reported male condom use and despite regular screening for, and treatment of, STIs. There was, therefore, sufficient power in these trials to detect an effect of N-9 on STI transmission, but no effect was seen. It seems reasonable to conclude that N-9 is unlikely to provide substantial (if any) protection among women using male condoms at lower rates and unable to access STI treatment, which is more typically the situation found in developing countries.

Most genital ulcers or lesions were observed on the vulva, away from the sites of highest concentration of N-9. The aetiology of these lesions is somewhat uncertain although some studies have indicated that N-9 causes imbalance in the normal vaginal flora leading to a higher incidence of Candida vaginitis, which may in turn lead to vaginitis. Direct erosive or hypersensitivity effects may also be important. Finally other STIs, such as reactivation of genital herpes, may play a role. That the lesions may not be entirely due to N-9 is suggested by the Van Damme trial, where the placebo group showed increasing rates of genital lesions with increasing frequency of use. However, the potentially dangerous role of N-9 and the role of these lesions in increasing risk of HIV acquisition, is shown in the same trial where genital lesion rates were higher among high N-9 users than among high placebo users and there was an association between lesions that breached the epithelium and HIV infection.

Therefore, there seems to be little if any role for N-9 as an STI prophylactic. As most of these trials were mainly done in high-risk female sex workers working in high STI prevalence areas and with high rates of partner change, it would be unwise to generalise the results to lower risk women using N-9 occasionally as a spermicide.

The STI and HIV/AIDS epidemics continue to grow and spread. Despite the known and demonstrated effectiveness of a variety of prevention and care strategies, we do need more strategies (WHO/UNAIDS 1997), especially those controlled by women (Elias 1996). As such, it is important that research into other potential microbicides continues apace and that large scale, high quality randomised controlled efficacy trials of other products start soon.

AUTHORS' CONCLUSIONS

Implications for practice

There is good evidence that N-9 does not protect against sexually transmitted infections. There is good evidence that N-9 may be

harmful by increasing the rate of genital ulceration. As such, this product cannot be promoted for STI prevention.

Implications for research

There seems to be no justification for further research into the use of N-9 as prophylaxis against sexually transmitted infections, but other potential microbicides should undergo further study.

POTENTIAL CONFLICT OF INTEREST

Gita Ramjee was an investigator in one of the trials cited.

SOURCES OF SUPPORT

External sources of support

- HRP-UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Geneva SWITZERLAND
- California Health Care Foundation USA

Internal sources of support

- Adelaide University AUSTRALIA
- University of South Australia AUSTRALIA
- South African Medical Research Council SOUTH AFRICA

REFERENCES

References to studies included in this review

Barbone 1990 *{published data only}*

* Barbone F, Austin H, Louv WC, Alexander WJ. A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. *American Journal of Obstetrics and Gynaecology* 1990;**163**(2):51–514.

Kreiss 1992 *{published data only}*

* Kreiss J, Ngugi E, Holmes KK, Ndinya-Achola J, Waiyaki P, Roberts PL, Ruminjo I, Sajabi R, Kimata J, Fleming TR, Anzala A, Holton D, Plummer F. Efficacy of nonoxynol-9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. *JAMA* 1992;**268**(4):477–482.

Louv 1988 *{published data only}*

* Louv WC, Austin H, Alexander WJ, Stagno S, Cheeks J. A clinical trial of nonoxynol-9 for preventing gonococcal and chlamydial infection. *Journal of Infectious Diseases* 1988;**158**(3):518–523.

Niruthisard 1992 *{published data only}*

* Niruthisard S, Roddy RE, Chutivongse S. Use of nonoxynol-9 and reduction in rate of gonococcal and chlamydial cervical infections. *Lancet* 1992;**339**(8806):1371–1375.

Rendon 1980 *{published data only}*

* Rendon AL, Covarrubias J, McCarney KE, Marion-Landais G, Luna del Villar J. A controlled comparative study of phenylmercuric acetate, nonoxynol-9 and placebo vaginal suppositories as prophylactic agents against gonorrhoea. *Current Therapeutic Research* 1980; **27**:780–783.

Richardson 2001 *{published data only}*

Roddy 1998 *{published data only}*

* Roddy RE, Zekeng L, Ryan KA, Tamoufe U, Weir SS, Wong EL. A controlled trial of nonoxynol-9 film to reduce male to female transmission of sexualy transmitted diseases. *New England Journal of Medicine* 1998;**339**(8):504–510.

Roddy 2001 *{published data only}*

* Roddy RE, Zekeng L, Ryan KA, Tamoufe U, Tweedy KG. Nonoxynol-9 provides no prophylaxis for urogenital gonorrhoea and chlamydial infection: randomised controlled trial.

Rosenberg 1987 *{published data only}*

* Rosenberg MJ, Rojanapithayakorn W, Feldblum PJ, Higgins JE. Effect of the contraceptive sponge onchlamydial infection, gonorrhoea, and candidiasis. A comparative clinical trial. *JAMA* 1987;**257** (17):780–783.

Van Damme 2001 *{published data only}*

* Van Damme. Effectiveness on HIV-1 transmission of COL-1492, a nonoxynol-9 vaginal gel, among female sex workers.

References to studies excluded from this review

Cutler 1977

* Cutler JC, Singh B, Carpenter U, Nickens O, Scarola A, Sussman N, Wade M, Volkin L, Marsico A, Balinsky H. Vaginal contraceptives as prophylaxis against gonorrhoea and other sexually transmissible diseases. *Advanced Planned Parenthood* 1977;**12**:45–56.

Sacks 1990

* Sacks SL, Varner TL, Davies KS, Rekart ML, Stiver HG, DeLong ER, Sellers PW. Randomised, double-blind, placebo-controlled, patient initiated study of topical high- and low-dose interferon-alpha with nonoxynol-9 in the treatment of recurrent genital herpes. *Journal of Infectious Diseases* 1990;**161**(4):692–698.

Additional references

Cook 1998

Cook RL, Rosenberg MJ. Do spermicides containing nonoxynol-9 prevent sexually transmitted infections?. *Sexually Transmitted Diseases* 1998;**25**(3):144–150.

De Zoysa 1996

De Zoysa I, Sweat M, Denison J. Faithful but fearful: reducing HIV transmission in stable relationships. *AIDS* 1996;**10**(Suppl):S197–203.

Elias 1996

Elias C, Coggins C. Female-controlled methods to prevent sexual transmission of HIV. *AIDS* 1996;**10**(Suppl):S43–51.

Fleming 1999

Fleming DT, Wasserheit JN. From epidemiological synergy to public health practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sexually Transmitted Infections* 1999;**75**:3–17.

Padian 1991

Padian NS, Shoboski SC, Jewell NP. Female-to-male transmission of human immunodeficiency virus. *JAMA* 1991;**266**:1664–1667.

Roddy 1998b

Roddy RE, Schulz KF, Cates W. Microbicides, meta-analysis, and the N-9 question. *Sexually Transmitted Diseases* 1998;**25**(3):151–153.

WHO 1995

World Health Organisation. An overview of selected curable sexually transmitted diseases. 1995:World Health Organisation, Geneva.

WHO/UNAIDS 1997

WHO/UNAIDS. Sexually transmitted diseases: policies and principles for prevention and care. 1997:WHO/UNAIDS, Geneva.

** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Barbone 1990**
Methods	Double blind RCT
Participants	818 women STI clinic attendees, USA
Interventions	150mg N-9 gel and identical placebo
Outcomes	Gonorrhoea and chlamydia
Notes	Same trial as that reported by Louv
Allocation concealment	A – Adequate

Study	**Kreiss 1992**
Methods	Unblinded RCT
Participants	116 female sex workers in Kenya
Interventions	1000mg N-9 sponge and placebo products
Outcomes	Gonorrhoea and chlamydia and genital lesions
Notes	All women received male condoms, STI treatment and condoms
Allocation concealment	D – Not used

Characteristics of included studies (*Continued*)

Study	**Louv 1988**
Methods	Double blind RCT
Participants	818 women STI clinic attendees, USA
Interventions	150mg N-9 gel and identical placebo
Outcomes	Trichomoniasis, bacterial vaginosis and candidiasis
Notes	Same trial as that reported by Barbone
Allocation concealment	A – Adequate

Study	**Niruthisard 1992**
Methods	Single blind RCT
Participants	343 female sex workers in Bangkok, Thailand
Interventions	70mg N-9 film and non-film lubricant
Outcomes	Gonorrhoea and chlamydia infection
Notes	
Allocation concealment	D – Not used

Study	**Rendon 1980**
Methods	Double blind RCT
Participants	53 women from an unspecified clinic in Mexico
Interventions	150mg N-9 suppository and placebo
Outcomes	Gonorrhoea and trichomoniasis
Notes	Low follow up (55%)
Allocation concealment	B – Unclear

Study	**Richardson 2001**
Methods	Double blind RCT
Participants	278 female sex workers in Kenya
Interventions	52.5mg N-9 gel and placebo
Outcomes	HIV, other STIs and genital lesions
Notes	All received male condoms, STI treatment and counselling
Allocation concealment	B – Unclear

Study	**Roddy 1998**
Methods	Double blind RCT
Participants	1170 female sex workers in Cameroon
Interventions	70mg N-9 film and placebo film
Outcomes	Gonorrhoea and chlamydia and genital lesions
Notes	All women received male condoms, STI treatment and HIV prevention messages
Allocation concealment	A – Adequate

Study	**Roddy 2001**
Methods	Unblinded RCT

Participants	1241 low risk non-sex working women (women with STI symptoms) in Cameroon
Interventions	100mg N-9 gel and non-users
Outcomes	Gonorrhoea and chlamydia infection (combined)
Notes	Comparison here is gel plus condoms vs condoms alone
Allocation concealment	D – Not used

Study	**Rosenberg 1987**
Methods	Unblinded RCT
Participants	307 female sex workes inBangkok, Thailand
Interventions	1000mg N-9 sponge and non-users
Outcomes	Gonorrhoea and chlamydia infection
Notes	
Allocation concealment	D – Not used

Study	**Van Damme 2001**
Methods	Triple blind RCT
Participants	765 female sex workers from various African and Asian countries
Interventions	52.5mg N-9 gel and placebo gel
Outcomes	Gonorrhoea and chlamydia infection and genital lesions
Notes	All women received male condoms, STI treatment and HIV prevention messages
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	**Reason for exclusion**
Cutler 1977	There is no report of adequate allocation concealment. The entry criteria and the analysis criteria were changed midway through the study
Sacks 1990	The trial used N-9 plus low dose interferon-alpha as the intervention. The STI under study was recurrent genital herpes.

ANALYSES

Comparison 01. N-9 vs placebo

Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Gonorrhoea	6	3017	Relative Risk (Fixed) 95% CI	0.97 [0.85, 1.11]
02 Chlamydia	5	2955	Relative Risk (Fixed) 95% CI	0.88 [0.77, 1.01]
03 Cervical infection	2	1584	Relative Risk (Fixed) 95% CI	1.01 [0.84, 1.22]
04 Trichomoniasis	3	1101	Relative Risk (Fixed) 95% CI	0.84 [0.69, 1.02]
05 Bacterial vaginosis	1	770	Relative Risk (Fixed) 95% CI	0.88 [0.74, 1.04]
06 Candidiasis	3	1360	Relative Risk (Fixed) 95% CI	0.97 [0.84, 1.12]
07 Genital lesions	4	2138	Relative Risk (Fixed) 95% CI	1.17 [1.02, 1.35]

INDEX TERMS

Medical Subject Headings (MeSH)

Nonoxynol [*therapeutic use]; Randomized Controlled Trials; Sexually Transmitted Diseases [*prevention & control]; Spermatocidal Agents [*therapeutic use]

MeSH check words

Female; Humans; Male

COVER SHEET

Title	Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men
Authors	Wilkinson D, Ramjee G, Tholandi M, Rutherford G
Contribution of author(s)	DW developed the protocol, extracted data and wrote the first draft of the review. GR developed the protocol and contributed to the review. MT did the search, extracted data and contributed to the review. GWR developed the protocol and contributed to the review.
Issue protocol first published	/
Review first published	/
Date of most recent amendment	10 September 2002
Date of most recent SUBSTANTIVE amendment	14 October 2001
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Prof David Wilkinson Pro Vice Chancellor and Vice President Division of Health Sciences University of South Australia 15 Bishop Street Skye South Australia 5072 AUSTRALIA E-mail: david.wilkinson@unisa.edu.au Tel: +61 8 8302 2029 Fax: +61 8 8647 6164+61 8 8302 2030
DOI	10.1002/14651858.CD003939
Cochrane Library number	CD003939

Editorial group Cochrane Sexually Transmitted Diseases Group

Editorial group code HM-STD

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 N-9 vs placebo, Outcome 01 Gonorrhoea

Review: Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men

Comparison: 01 N-9 vs placebo

Outcome: 01 Gonorrhoea

Study	N-9 n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Louv 1988	64/388	74/388		21.8	0.86 [0.64, 1.17]
Rendon 1980	4/24	8/29		2.1	0.60 [0.21, 1.76]
Richardson 2001	34/139	21/139		6.2	1.62 [0.99, 2.64]
Roddy 1998	114/441	111/435		32.9	1.01 [0.81, 1.27]
Rosenberg 1987	7/149	31/163		8.7	0.25 [0.11, 0.54]
Van Damme 2001	106/356	97/366		28.2	1.12 [0.89, 1.42]
Total (95% CI)	1497	1520		100.0	0.97 [0.85, 1.11]

Total events: 329 (N-9), 342 (Placebo)

Test for heterogeneity chi-square=18.63 df=5 p=0.002 I^2 =73.2%

Test for overall effect z=0.39 p=0.7

Analysis 01.02. Comparison 01 N-9 vs placebo, Outcome 02 Chlamydia

Review: Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men

Comparison: 01 N-9 vs placebo

Outcome: 02 Chlamydia

Study	N-9 n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Louv 1988	98/382	125/388		36.8	0.80 [0.64, 1.00]
Richardson 2001	18/139	11/139		3.3	1.64 [0.80, 3.34]
Roddy 1998	79/451	81/420		24.9	0.91 [0.69, 1.20]
Rosenberg 1987	29/149	49/163		13.9	0.65 [0.43, 0.97]
Van Damme 2001	72/353	73/371		21.1	1.04 [0.77, 1.39]
Total (95% CI)	1474	1481		100.0	0.88 [0.77, 1.01]
Total events: 296 (N-9), 339 (Placebo)					
Test for heterogeneity chi-square=7.19 df=4 p=0.13 I^2 =44.4%					
Test for overall effect z=1.80 p=0.07					

Analysis 01.03. Comparison 01 N-9 vs placebo, Outcome 03 Cervical infection

Review: Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men

Comparison: 01 N-9 vs placebo

Outcome: 03 Cervical infection

Study	N-9 n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Niruthisard 1992	57/186	61/157		39.8	0.79 [0.59, 1.06]
Roddy 2001	116/622	100/619		60.2	1.15 [0.91, 1.47]
Total (95% CI)	808	776		100.0	1.01 [0.84, 1.22]
Total events: 173 (N-9), 161 (Placebo)					
Test for heterogeneity chi-square=3.91 df=1 p=0.05 I^2 =74.4%					
Test for overall effect z=0.09 p=0.9					

Analysis 01.04. Comparison 01 N-9 vs placebo, Outcome 04 Trichomoniasis

Review: Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men

Comparison: 01 N-9 vs placebo

Outcome: 04 Trichomoniasis

Study	N-9 n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Barbone 1990	79/382	92/388		57.8	0.87 [0.67, 1.14]
Rendon 1980	5/24	4/29		2.3	1.51 [0.46, 5.01]
Richardson 2001	48/139	63/139		39.9	0.76 [0.57, 1.02]
Total (95% CI)	545	556		100.0	0.84 [0.69, 1.02]

Total events: 132 (N-9), 159 (Placebo)

Test for heterogeneity chi-square=1.43 df=2 p=0.49 I^2 =0.0%

Test for overall effect z=1.72 p=0.09

Analysis 01.05. Comparison 01 N-9 vs placebo, Outcome 05 Bacterial vaginosis

Review: Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men

Comparison: 01 N-9 vs placebo

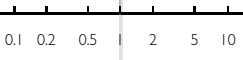
Outcome: 05 Bacterial vaginosis

Study	N-9 n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Barbone 1990	147/382	170/388		100.0	0.88 [0.74, 1.04]
Total (95% CI)	382	388		100.0	0.88 [0.74, 1.04]

Total events: 147 (N-9), 170 (Placebo)

Test for heterogeneity: not applicable

Test for overall effect z=1.50 p=0.1



Analysis 01.06. Comparison 01 N-9 vs placebo, Outcome 06 Candidiasis

Review: Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men

Comparison: 01 N-9 vs placebo

Outcome: 06 Candidiasis

Study	N-9 n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Barbone 1990	100/382	98/388		48.1	1.04 [0.82, 1.32]
Richardson 2001	85/139	101/139		50.0	0.84 [0.71, 0.99]
Rosenberg 1987	10/149	4/163		1.9	2.73 [0.88, 8.53]
Total (95% CI)	670	690		100.0	0.97 [0.84, 1.12]
Total events: 195 (N-9), 203 (Placebo)					
Test for heterogeneity chi-square=6.28 df=2 p=0.04 I^2 =68.1%					
Test for overall effect z=0.39 p=0.7					

Analysis 01.07. Comparison 01 N-9 vs placebo, Outcome 07 Genital lesions

Review: Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men

Comparison: 01 N-9 vs placebo

Outcome: 07 Genital lesions

Study	N-9 n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Niruthisard 1992	16/186	13/157		5.5	1.04 [0.52, 2.09]
Richardson 2001	21/139	22/139		8.6	0.95 [0.55, 1.65]
Roddy 1998	129/370	107/382		41.1	1.24 [1.01, 1.54]
Van Damme 2001	132/376	117/389		44.9	1.17 [0.95, 1.43]
Total (95% CI)	1071	1067		100.0	1.17 [1.02, 1.35]
Total events: 298 (N-9), 259 (Placebo)					
Test for heterogeneity chi-square=0.96 df=3 p=0.81 I^2 =0.0%					
Test for overall effect z=2.24 p=0.02