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[Intervention Review]

Antibiotics for trachoma

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ABSTRACT

Background

Trachoma is the world's leading infectious cause of blindness. In 1997 the World Health Organization (WHO) launched an Alliance for the Global Elimination of Trachoma by the year 2020, based on the 'SAFE' strategy (surgery, antibiotics, facial cleanliness and environmental improvement).

Objectives

To assess the evidence supporting the antibiotic arm of the SAFE strategy by assessing the effects of antibiotics on both active trachoma (primary objective) and on *Chlamydia trachomatis* (*C. trachomatis*) infection of the conjunctiva (secondary objective).

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2010, Issue 11), MEDLINE (January 1950 to December 2010), EMBASE (January 1980 to December 2010), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com) (December 2010) and ClinicalTrials.gov (www.clinicaltrials.gov) (December 2010). We used the Science Citation Index to look for articles that cited the included studies. We searched the reference lists of identified articles and we contacted authors and experts for details of further relevant studies. There were no language or date restrictions in the search for trials. The electronic databases were last searched on 12 December 2010.

Selection criteria

We included randomised trials that satisfied either of two criteria: (a) trials in which topical or oral administration of an antibiotic was compared to placebo or no treatment in people or communities with trachoma, (b) trials in which a topical antibiotic was compared with an oral antibiotic in people or communities with trachoma. A subdivision of particular interest was trials in which topical tetracycline or chlortetracycline and oral azithromycin were compared with each other, or in which one of these treatments was compared with placebo or no treatment, as these are the two WHO recommended antibiotics. We considered individually randomised and cluster-randomised trials separately.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We contacted investigators for missing data. Where appropriate, the effect estimates from the individual studies (risk ratios) were pooled using a random-effects model.

Main results

A total of 14 trials randomised individuals with trachoma to oral antibiotic, topical antibiotic, both, or control (no treatment or placebo) and were eligible for inclusion in this review (n = 3587). Overall, the quality of the evidence provided from these trials was low. Nine of the trials compared antibiotic treatment to control. Most of the studies found a beneficial effect of treatment on active trachoma and ocular chlamydial infection at three and 12 months follow up. There was considerable clinical and statistical heterogeneity between trials, which meant that it was difficult to reliably estimate the size of the treatment effect. It is likely to be in the region of a 20% relative risk reduction. Seven of the 14 trials compared the effectiveness of oral and topical antibiotics. There was no consistent evidence as to whether oral or topical antibiotics were more effective, although one trial suggested that a single dose of oral azithromycin was significantly more effective than unsupervised use of topical tetracycline

A further eight trials assessed the effectiveness of community-based treatment. In five trials antibiotic treatment was compared to no (or delayed) treatment (57 communities), and in three trials oral antibiotic was compared to topical treatment (12 communities). The quality of the evidence provided by these trials was variable but at least one trial was considered to provide high quality evidence. There was evidence that community-based antibiotic treatment reduced the prevalence of active trachoma and ocular infection 12 months after single-dose treatment. There was some evidence that oral azithromycin was more effective than topical tetracycline as a community treatment. Data on adverse effects were not consistently reported however there were no reported serious adverse events associated with treatment with oral azithromycin or topical tetracycline; in one sample survey of 671 people treated with azithromycin between 10% and 15% experienced gastrointestinal adverse effects (nausea or vomiting, or both).

Authors' conclusions

Antibiotic treatment reduces the risk of active trachoma and ocular chlamydial infection in people infected with *C. trachomatis*, but we do not know for certain the size of the treatment effect in individuals. Mass antibiotic treatment with single-dose oral azithromycin reduces the prevalence of active trachoma and ocular infection in communities.

PLAIN LANGUAGE SUMMARY

Antibiotics reduce the prevalence of ocular infection with trachoma

Trachoma is common in people living in poor communities and is the most common infectious cause of vision loss. Repeated bouts of conjunctivitis (inflammation of the membranes of the eyes) caused by *Chlamydia* infection eventually lead to scarring and inward turning of the eyelid. The lashes rub on the cornea causing opacification and blindness. Antibiotics can be used to treat the *Chlamydia* infection and may be given as an ointment or by mouth. This review included 14 trials in 3587 people with ocular trachoma and eight community-based trials (67 communities). Antibiotic treatment reduce conjunctivitis caused by trachoma ('active trachoma') and ocular infection in individuals. Community-based trials provided evidence that azithromycin treatment reduces the prevalence of active trachoma and ocular *Chlamydia* infection.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotic versus control for trachoma

Patient or population: patients with trachoma
Settings: individuals
Intervention: antibiotic
Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	control	antibiotic				
Active trachoma Follow-up: 3 months	**Medium risk population**[1]		**RR 0.78** (0.69 to 0.89)	1961 (9 studies)	⊕⊕◯◯ **low**[2,3]	
	800 per 1000	**624 per 1000** (552 to 712)				
Ocular chlamydia trachomatis infection Follow-up: 3 months	**Medium risk population**[1]		**RR 0.81** (0.63 to 1.04)	297 (4 studies)	⊕⊕◯◯ **low**[4,5]	
	600 per 1000	**486 per 1000** (378 to 624)				
Active trachoma Follow-up: 12 months	**Medium risk population**[1]		**RR 0.74** (0.55 to 1)	1035 (4 studies)	⊕⊕◯◯ **low**[6,7,8]	
	750 per 1000	**555 per 1000** (413 to 750)				
Ocular chlamydial trachomatis infection Follow-up: 12 months	**Medium risk population**		**RR 0.25** (0.08 to 0.78)	129 (1 study)	⊕⊕◯◯ **low**[9]	
	190 per 1000	**48 per 1000** (15 to 148)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Median risk in control groups in included studies (rounded to nearest 10 per 1000)
[2] Serious limitations in design: None of the trials reported methods to conceal the allocation. Two trials only attempted to mask the assessment of active trachoma.
[3] Serious inconsistency: Risk ratios ranged from 0.40 to 1.02.
[4] Serious limitations in study design: None of the trials reported adequate allocation concealment. Three out of four trials masked outcome assessment.
[5] Serious imprecision: 95% confidence intervals include 1 (0.63 to 1.04)
[6] Serious limitations in design: None of the trials reported allocation concealment or masking of outcome assessment.
[7] Serious inconsistency: Risk ratios ranged from 0.50 to 1.05.
[8] No downgrading for imprecision: The pooled estimate of effect is imprecise (confidence intervals 0.55 to 1). However, we felt that this inconsistency probably arises due to limitation in study design and inconsistency and therefore did not additionally downgrade the quality of evidence on the basis of this criteria.
[9] Very serious limitations in study design: Only one small trial which did not report adequate methods of allocation concealment and did not mask outcome assessment.

BACKGROUND

Description of the condition

Trachoma is the world's leading infectious cause of blindness (Resnikoff 2004). Active trachoma affects an estimated 41 million people, the majority of them children (Mariotti 2009). About 1.3 million people are blind as a consequence of trachoma (Resnikoff 2004). It is a disease of poverty and is associated with poor water supplies and sanitation.

There are two phases of trachoma. In the first phase, most frequently seen in infancy and childhood, there are repeated attacks of conjunctivitis caused by the organism *Chlamydia trachomatis* (*C. trachomatis*). The conjunctivitis is characterised by the presence of follicles on the under surface of the upper eyelid and by vascular changes in active trachoma. Active trachoma is associated with discharge from the eyes and nose that is particularly noticeable on the faces of children, but the active stage may also be asymptomatic in children and adults. When symptomatic, symptoms may persist for months after the infection is cleared. *C. trachomatis* is transmitted from child to child and from child to mother and back to child through eye-finger-eye contacts, fomites and via eye-seeking flies.

Repeated conjunctival infections over a number of years lead to the second phase of disease, characterised by scarring and shortening of the upper eyelid. Ultimately, the lashes turn inwards to rub on the cornea, causing pain, corneal abrasions and secondary infection. Blindness results from corneal opacification. The blinding phase affects women more commonly than men and typically starts in adult life (Burton 2009). The treatment at this stage is surgery to reposition the eyelid margin.

Description of the intervention

Active trachoma has been treated with antibiotics since the 1950s and a variety of regimens have been used. The antibiotic can be applied directly to the conjunctiva (topical) or taken orally (systemic). Antibiotics applied topically are usually in the form of an ointment and a variable amount is squeezed onto the inner surface of the lower eyelid. This route gives a high concentration of the antibiotic to the conjunctiva but a low dose to the nasopharynx, which is also a reservoir for the organism. Ointments may cause stinging eyes and temporary blurred vision, and they are difficult to apply to small children.

Oral treatment gives a higher dose of antibiotic to sites of infection outside of the eye, but systemic antibiotics can have various adverse effects in the person taking them. Bacteria anywhere in the body may also develop antibiotic resistance. A full course of oral treatment has a higher compliance rate than a course of topical antibiotic.

Efforts in trachoma control have used various antibiotic treatment regimens and have also been aimed at different subgroups within a trachoma endemic area. Examples of subgroups are only those individuals with clinical signs of disease (detected actively or passively), and active cases together with family contacts or high-risk groups including school children. Because many individuals harbour infection without demonstrating physical signs, it has been suggested that trachoma control cannot be achieved by antibiotic treatment given only to subgroups of a trachoma endemic community (Bailey 1993; Kamiya 1956; Sutter 1983). This led to the concept of community-based interventions, where all residents of a community should receive treatment irrespective of disease status.

The desired primary endpoint of any intervention against the active disease is reduction of blindness but this could only be demonstrated 20 to 30 years after the start of the intervention. The usual surrogate outcome measure in trachoma intervention trials is clinically active disease. In some trials a secondary endpoint is laboratory evidence of ocular *C. trachomatis* infection.

Why it is important to do this review

International interest in trachoma was given a boost in 1997 when the WHO launched a new initiative for trachoma control, based on the 'SAFE' strategy. The components giving their name to the acronym are surgery, antibiotics, facial cleanliness and environmental improvement. Cochrane systematic reviews on surgery for trichiasis (Yorston 2006), face washing (Ejere 2004) and environmental sanitary interventions (Rabiu 2007) have also been completed.

The World Health Organization (WHO) recommended topical treatment is 1% tetracycline ointment to both eyes, either twice daily for six weeks or on five consecutive days each month for six months. Compliance with this treatment is poor due to the side effects of the ointment and the length of the treatment programme. The WHO recommended oral antibiotic is azithromycin, given as a single dose of one gram in adults and 20 mg/kg of body weight in children. Azithromycin has low plasma levels but high intracellular concentrations and a long half-life. It has been shown to be an effective treatment of genital chlamydial infections.

It is important to do this review to systematically evaluate the safety and effectiveness of these recommended treatment regimens.

OBJECTIVES

The aim of this review is to assess the evidence in relation to the antibiotic arm of the SAFE strategy by assessing the effects of antibiotics on both active trachoma (primary objective) and on *C. trachomatis* infection (secondary objective). In particular, when this review was first published in 2002, the aim was to investigate

the strength of evidence that antibiotics were more effective than placebo in reducing disease and to compare the effects of oral azithromycin with topical tetracycline.

These objectives were modified when the review was updated in 2010. It was decided to consider individually randomised and cluster-randomised trials separately as we felt that they were addressing different questions and were likely to be measuring different effects. The following two objectives were identified.

1. What is the effect of antibiotic treatment for individuals on active trachoma and ocular *C. trachomatis* infection?

2. What is the effect of community treatment with antibiotics on the prevalence of active trachoma and ocular *C. trachomatis* infection?

METHODS

Criteria for considering studies for this review

Types of studies

This review includes only randomised controlled trials (RCTs) of antibiotic treatment for active trachoma. Clinical and community-based trials were included in this review. In clinical trials the unit of randomisation was the individual with active trachoma and outcomes were reported at an individual level. In community-based trials the unit of randomisation was a community, in which some individuals had active trachoma, and outcomes may have been reported at an individual or a community level.

Types of participants

Participants in the trials were people who were usually resident in a trachoma endemic area.

Types of interventions

We included trials in which the interventions were:
1. topical or oral administration of an antibiotic at any dose or frequency compared to placebo or no treatment;
2. topical administration of an antibiotic at any dose or frequency compared to oral administration of an antibiotic at any dose or frequency.
We excluded studies if the antibiotic was combined with an environmental or educational intervention unless this component was used uniformly across the trial and only the antibiotic treatment varied in the different groups.

Types of outcome measures

We measured outcomes at three, 12 and 24 months after the start of treatment. Three months was the time at which the maximum effect on active trachoma was expected given that clinical signs take several months to resolve after the clearance of infection. We selected 12 months to represent the period during which recurrence of infection or relapse would be most likely to occur, and we selected 24 months to reflect the expected long-term result of one course of treatment. A course of treatment may be a single or multiple doses of an oral antibiotic or interrupted applications of a topical antibiotic applied over six weeks to several months.
In order to take into account the fact that studies may not have collected outcomes at those exact times, we defined the following ranges for each:

- three months, i.e. outcomes measured before six months;
- 12 months, i.e. outcomes measured between six months and 18 months;
- 24 months, i.e. outcomes measured after 18 months.

If more than one outcome measurement was available, then we selected the nearest measurement to three, 12 or 24 months.

Primary outcomes

The primary outcome for this review was active trachoma. There are five main trachoma grading scales (Dawson 1975b; Dawson 1981b; MacCallan 1936; Thylefors 1987; WHO 1962). All these scales, except for MacCallan, quantify the number of follicles and the degree of vascular engorgement of the under surface of the upper eyelid as seen with low magnification (usually x 2.5). The Dawson scales subdivide the follicular and papillary activity as F 0 to 3 and P 0 to 3. The Thylefors scale is a simplified version defining active trachoma by the grades TF (mild-moderate) and TI (intense). The MacCallan scale is not directly comparable with the other scales as scarring is included as an indicator of active disease. The four more recent scales are broadly comparable. A minor inconsistency between them is that Dawson's F1 is defined as five or fewer follicles in zones two and three, and F2 as "more than 5 follicles in zones 2 and 3 together, but less than 5 in zone 3"; whereas TF is five or more follicles in zones two and three. This means that the divisions between F1 and F2 and 'not TF' and TF do not quite coincide.
In this review we defined the absence of active trachoma as:

- not TF and not TI (Thylefors scale);
- (P0 or P1 or P2) AND (F0 or F1) (WHO and Dawson scales).

We defined active trachoma as TF, TI, or both, in the Thylefors scale; or any other grade for P or F in the WHO or Dawson scales.

Secondary outcomes

The secondary outcome was a positive test for *C. trachomatis* infection. A variety of tests have been used to demonstrate presence

of the pathogen. Historically, staining of conjunctival cells to show inclusion bodies was the first method of identifying infection. This was followed by culture of the organism, which was time consuming and lacking in sensitivity. The demonstration of antigen by various antibody staining methods followed, and finally identification of chlamydial DNA by various amplification methods. The tests, in order of increasing sensitivity, are:

1. culture by *C. trachomatis* isolation in eggs or tissue culture;
2. staining of conjunctival smears with giemsa or iodine;
3. direct fluorescent antibody cytology;
4. indirect enzyme immunoassay;
5. DNA hybridisation;
6. DNA amplification with the ligase chain reaction;
7. DNA amplification with the polymerase chain reaction.

We recorded adverse effects, if reported.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2010, Issue 11, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 12 December 2010), MEDLINE (January 1950 to December 2010), EMBASE (January 1980 to December 2010), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com) (December 2010) and ClinicalTrials.gov (www.clinicaltrials.gov) (December 2010). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 12 December 2010. See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), *m*RCT (Appendix 4) and ClinicalTrials.gov (Appendix 5).

Searching other resources

We used the Science Citation Index to search for articles that cited the included studies. We searched the reference lists of identified articles for any other potentially relevant studies. We also contacted experts in the field, either directly or through the membership of the WHO workshops, requesting information on unpublished trials.

Data collection and analysis

Selection of studies

For the first publication of this review, one author assessed the titles identified from the initial searches and selected all titles that made reference to treatment for trachoma. When the review was updated in 2005, and again in 2011, two authors screened the search results. The searches also found references to genital *C. trachomatis* infections and to laboratory tests on *C. trachomatis*. We excluded titles that clearly referred to either of these groups at the first viewing. Two authors independently obtained the full copies of all possibly relevant papers and assessed them according to the 'Criteria for considering studies for this review'. We assessed the trials meeting these criteria for quality.

Data extraction and management

Two authors independently extracted data. Discrepancies were resolved before entry into Review Manager 5 (RevMan 2008).

For the update of the review in 2011, JE checked the original data collection and entry. Appendix 6 summarises the changes that were made. For the new trials that were identified, two authors (JE, AWS) extracted data independently and resolved discrepancies by discussion. Data were entered by both authors onto two spreadsheets and cross-checked. Data were cut and pasted into RevMan from the spreadsheet (JE).

Assessment of risk of bias in included studies

This was a new feature for the update in 2011. We assessed the risk of bias using the Cochrane Collaboration's tool for assessing the risk of bias (Higgins 2008a).

We assessed the extent to which bias could have been introduced in the following aspects of study design and execution: sequence generation, allocation concealment, blinding (masking), incomplete outcome data and selective outcome reporting.

We did not assess sequence generation and allocation concealment for cluster-randomised studies but considered two additional criteria: recruitment bias and baseline imbalances (Higgins 2008b). Two authors (JE, AWS) independently assessed risk of bias, compared results and resolved discrepancies by discussion.

Measures of treatment effect

The primary outcome for the review was active trachoma and the secondary outcome was ocular *C. trachomatis* infection. Both of these are dichotomous (adverse) outcomes and our preferred effect measure was the risk ratio.

Unit of analysis issues

This review includes trials in which individuals were randomly allocated to treatment and trials in which communities were the unit of allocation (cluster-randomised trials). A correct analysis of cluster-randomised trials includes an adjustment for the fact that people within a cluster tend to be more similar to each other than to people from other clusters i.e. the observations are not independent. The effect of cluster-randomisation is to increase the size of standard errors and hence widen the confidence intervals compared with a study of the same size using individual participant randomisation (Donner 1982).

For the update in 2011, our preferred method of analysis of cluster-randomised studies was as follows: for those studies that reported the effect measure using an analysis that properly accounted for the cluster design, we planned to enter and pool data from different studies using the generic-inverse variance method in RevMan. However, we were aware that cluster-randomised trials are not always analysed and reported appropriately. For those studies that did not report such an effect measure we planned to perform an approximate analysis (Higgins 2008b) as follows:

- calculate a 'design effect' of 1 + (M - 1) ICC (where ICC = intra-cluster correlation coefficient and M = average cluster size);
- multiply the standard error of an analysis at the individual level by the square root of the design effect.

Estimates from the literature suggest that the ICC can vary from 0.05 to 0.2 (Katz 1988; West 1991). We planned sensitivity analyses using iCC estimates of 0.05. 0.1 and 0.2.

Dealing with missing data

The clinical need to change or discontinue antibiotic therapy (for an individual undergoing treatment for a single episode of infection of disease, or a community undergoing a single round of mass treatment) is likely to be rare. This reduces the potential problems associated with performing the analysis on an intention-to-treat basis. More serious problems may arise from losses to follow up and non-compliance. Some of the trials have been done in largely transient populations in which losses to follow up rapidly accumulate as people move on. Such losses were assumed to be independent of the outcome measures, therefore we did not exclude studies on this basis.

Assessment of heterogeneity

We assessed heterogeneity by considering clinical and study design differences between trials and by examining the forest plots. We also considered statistical measures of heterogeneity such as the χ^2 test and I^2 statistic.

Assessment of reporting biases

As less than 10 trials were included in the meta-analyses in this version of the review we did not assess publication bias. In future updates that include more trials, we will assess the possibility of small study effects, including publication bias, using a funnel plot (plotting the risk ratio along the x axis versus standard error along the y axis).

We did not judge the possibility of selective reporting of outcomes to be a problem in most of the included trials because the two main outcomes of this review, active trachoma and *C. trachomatis* infection, were usually reported.

We included all trials irrespective of the language of publication, however we cannot exclude the possibility that negative trials have been published in less accessible journals (see publication bias above).

We did not find any evidence of multiple (duplicate) reporting publication bias. Data from one of our included trials (ACT 1999 The Gambia) were published twice, with ocular *C. trachomatis* infection being the focus of one publication and active trachoma the focus of the other, but the relationship of the data was clear from the publications.

Data synthesis

In the original review, the review authors pooled outcomes from community-based trials in which non-affected and affected cases were treated with outcomes from individual-based trials in which only affected cases were treated. The original protocol planned but did not carry out a sensitivity analysis to determine the effect of using only data from cases that were active at baseline.

In the update, we considered these community-based and individually randomised trials separately as they are asking different questions and are likely to be estimating different treatment effects.

Where appropriate, data were pooled using a random-effects model. If there were three trials or less we used a fixed-effect model. In cases where there was substantial heterogeneity or inconsistency, that is the individual study estimates were different sides of the null line and/or confidence intervals did not overlap, with corresponding high levels of I^2 we did not pool the results.

Subgroup analysis and investigation of heterogeneity

We considered type of antibiotic (oral or topical) to be a potential source of clinical heterogeneity. This subgroup analysis was not specified explicitly but was implied in the objectives of the original protocol which were to consider oral and topical antibiotics separately, in particular oral azithromycin and topical tetracycline. A further subgroup analysis considered just those trials in which communities were randomised to oral azithromycin, topical tetracycline, or both, where the antibiotic was administered using regimens consistent with WHO guidelines current in 2010, compared either to each other, placebo or no treatment.

Sensitivity analysis

As set out above under 'unit of analysis issues', we considered the possible effect of assumptions about the size of the intra-class correlation coefficient (ICC) on the results.

RESULTS

Description of studies

The characteristics of the included studies and reasons for exclusion of studies are detailed in the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Results of the search

Details of the original searches for previous versions of this review are in Appendix 7. The electronic searches were updated in December 2010. After de-duplication, the search identified a total of 341 references. The Trials Search Co-ordinator scanned the search results and removed 251 references which were not relevant to the scope of the review. Two authors independently reviewed the remaining 90 references and three new studies were identified (Atik 2006; Lee 2007; TANA 2009). Three studies previously classified as excluded studies were considered to be eligible for inclusion (Bailey 1993; Chidambaram 2006; Resnikoff 1995). One new report with relevant data for ACT 1999 The Gambia was identified. Fourteen individually randomised studies were included in this review (Attiah 1973; Bailey 1993; Bowman 2000; Cochereau 2007; Darougar 1980; Dawson 1969 Sherman; Dawson 1969 Stewart; Dawson 1997; Foster 1966; Hoshiwara 1973; Peach 1986; Shukla 1966; Tabbara 1996; Woolridge 1967). The citations Dawson 1969 Sherman and Dawson 1969 Stewart refer to two arms of the same trial, which were conducted in different schools. As the results were reported separately in the paper, they have been treated as separate studies.

Eight community-based studies were included in this review (ACT 1999 Egypt; ACT 1999 Tanzania; ACT 1999 The Gambia; Atik 2006; Chidambaram 2006; Lee 2007; Resnikoff 1995; TANA 2009). The three ACT citations used the same protocol, which was applied in different countries and reported in the same article. Chidambaram 2006, Lee 2007 and TANA 2009 used communities with 'delayed treatment' as a comparator group. Although this had the disadvantage that baseline data were not available, it is an ethical solution to community randomisation.

Included studies

Types of participants

In individually randomised studies, all participants had active trachoma in at least one eye. The groups described were children aged six to 12 years in Egypt (Attiah 1973), people aged nine months and older in The Gambia (Bailey 1993), children aged six months to 10 years in The Gambia (Bowman 2000), children age one to 10 years in Pakistan and Guinea-Conakry (Cochereau 2007), preschool children in Iran (Darougar 1980), boarding school residents aged 12 to 21 years in USA (Dawson 1969 Sherman; Dawson 1969 Stewart), children aged two to 10 years in Egypt (Dawson 1997), boarding school residents aged eight to 20 years in USA (Foster 1966), boarding school residents aged seven to 13 years in USA (Hoshiwara 1973), children under 21 years in northern Australia (Peach 1986), school children aged five to 13 years in India (Shukla 1966), children aged seven to 14 years in Saudi Arabia (Tabbara 1996), primary school children in Taiwan (Woolridge 1967).

In the community-based studies, three studies (ACT 1999 Egypt; ACT 1999 Tanzania; ACT 1999 The Gambia) included all residents of the study villages irrespective of age or trachoma status. Chidambaram 2006 and TANA 2009 offered treatment to everyone over the age of one year but data were reported for children aged one to five and one to 10 years old respectively. The settings were Egypt, Ethiopia, Saudi Arabia, The Gambia and Tanzania. One study (Atik 2006) included all residents of study villages who were over the age of six months; the setting was Vietnam. In three studies, carried out in Ethiopia (Chidambaram 2006; Lee 2007) and Mali (Resnikoff 1995), only children aged one to five years were examined but all residents of treated villages were offered treatment.

Types of intervention

There were various treatment strategies applied over periods of three weeks to 12 months. Table 1 summarises the different treatment schedules for the individually randomised studies.

Eleven trials investigated oral antibiotics (Bowman 2000; Bailey 1993; Cochereau 2007; Darougar 1980; Dawson 1969 Sherman; Dawson 1969 Stewart; Dawson 1997; Foster 1966; Hoshiwara 1973; Shukla 1966; Tabbara 1996). Five trials used azithromycin 20 mg/kg (Bailey 1993; Bowman 2000; Cochereau 2007; Dawson 1997; Tabbara 1996). Other oral antibiotics included doxycycline (Darougar 1980; Hoshiwara 1973), trisulphapyrimidines (Dawson 1969 Sherman; Dawson 1969 Stewart), sulphamethoxypyridazine (Foster 1966) and sulphadimethoxine (Shukla 1966).

Almost all of the included individually-randomised trials had a treatment arm with topical antibiotics (the exception was Hoshiwara 1973.) Almost all of these trials of topical antibiotic used tetracycline or oxytetracycline. Most used 1% formulations. One trial used 0.25% (Attiah 1973) and in one trial people with 'severe disease' were given erythromycin 250 mg four times daily for two weeks in addition to topical tetracycline (Bailey 1993). A couple of trials did not report the dose (Bowman 2000; Peach 1986). Dawson 1997 used tetracycline 1% with polymyxin 10,000 units/g. Shukla 1966 used sulphafurazole 15%. There was considerable variation in the treatment schedules used. Topical treatment was applied one to four times daily, for one to seven days over a six week to 12 month period. Cochereau 2007 was the only trial to use topical azithromycin 1.5% on a two-day and three-day treatment schedule.

Some trials compared oral and topical treatments (Bailey 1993; Bowman 2000; Cochereau 2007; Darougar 1980; Dawson 1969 Sherman; Dawson 1969 Stewart; Dawson 1997; Foster 1966; Shukla 1966; Tabbara 1996). In three of these trials there was also an untreated control group (Darougar 1980; Foster 1966; Shukla 1966).

Table 2 summarises the treatments used in the cluster-randomised studies. The majority of the cluster-randomised trials investigated azithromycin 20 mg/kg and this was compared to tetracycline or oxytetracycline 1% (ACT 1999 Egypt; ACT 1999 Tanzania; ACT 1999 The Gambia; Atik 2006). One trial (Atik 2006) assessed the effect of targeted treatment (with azithromycin 20 mg/kg) on schoolchildren with active trachoma, aged five to 15 years, plus their family members within the selected clusters rather than mass treatment of the entire cluster. One trial compared oxytetracycline 1% against no treatment (Resnikoff 1995). Three trials compared azithromycin 20 mg/kg against no (delayed) treatment (Chidambaram 2006; Lee 2007; TANA 2009). Specific exclusion criteria were usually given for pregnant women who were given either oral erythromycin or topical tetracycline instead of azithromycin.

Types of outcome measures

Most trials used active trachoma as the main outcome measure, the exceptions being Lee 2007, Chidambaram 2006 and TANA 2009 which focused on ocular chlamydial infection. The trachoma grading scales used after 1962 do not have scarring as a feature of active trachoma and so the underlying principles in the grades are more or less equivalent in all of the studies, using only the presence of follicles and papillae for diagnosis of active disease.

The secondary outcome measure was presence of *C. trachomatis*. The laboratory tests used were culture in McCoy cells, one to five identifiable inclusions per 100 to 1000 cells, elementary bodies $\leq$ 200 or $\geq$ 200 on conjunctival smear immunofluorescence, polymerase chain reaction (PCR) and ligase chain reaction (LCR).

Follow up

Most studies reported outcomes at three months. Fewer trials reported outcomes at 12 months and only one trial reported outcomes at 24 months.

Excluded studies

See the 'Characteristics of excluded studies' table for information on excluded studies, including reasons for exclusion.

Risk of bias in included studies

See Figure 1 and Figure 2. There were 14 individually randomised trials included in this review and eight cluster-randomised trials. We did not assess sequence generation and allocation concealment for cluster-randomised studies but considered two additional criteria: recruitment bias and baseline imbalances (see other potential sources of bias).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

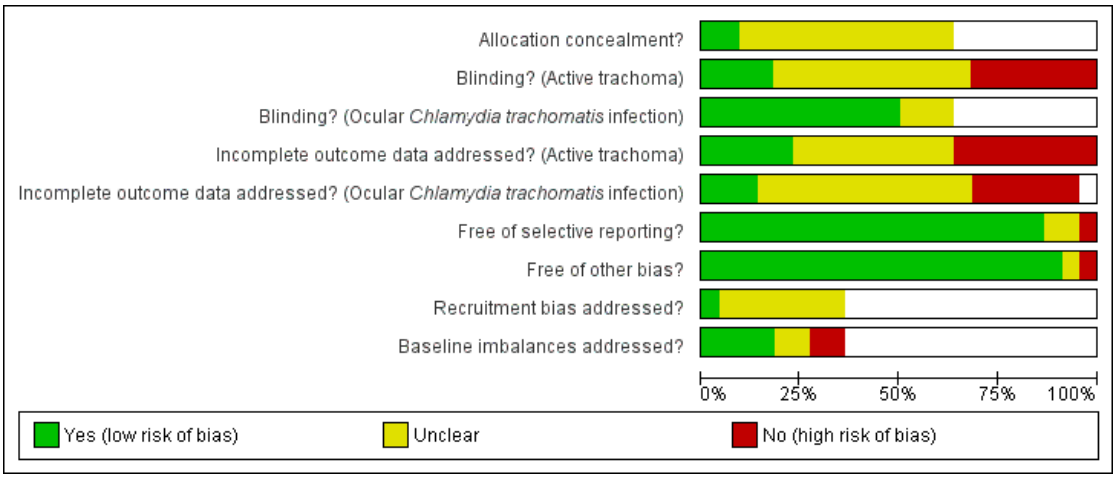
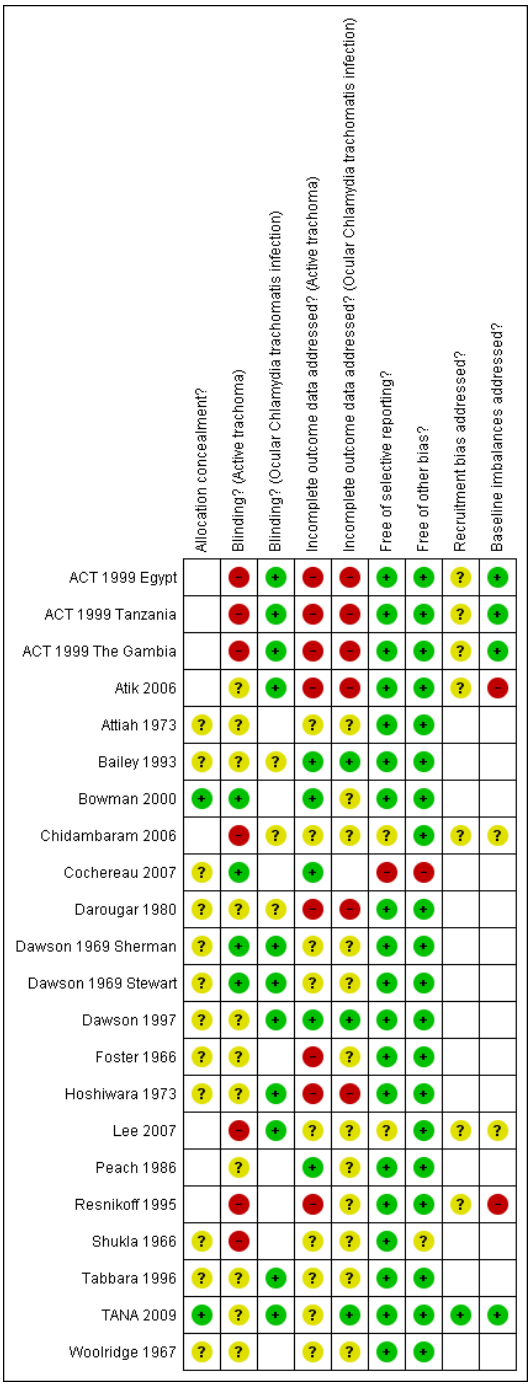


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Sequence generation and allocation concealment were poorly described, with only one trial (Bowman 2000) reporting adequate methods for both of these criteria. Dawson 1997 and Woolridge 1967 reported adequate sequence generation but not allocation concealment, which was likely to be a more important source of bias.

Blinding

Assessment of ocular *C. trachomatis* infection is relatively easy to mask as it is straightforward to anonymise laboratory samples. Eleven out of 14 studies that reported ocular chlamydial infection also reported masking the assessment of the laboratory samples. Clinical assessments of trachoma are more difficult to mask, especially in the cluster-randomised studies where one community received treatment and another did not, or in cases where the treatments differed for example oral versus topical antibiotic. Only five studies reported efforts to mask the assessment of active trachoma (Bailey 1993; Bowman 2000; Cochereau 2007; Dawson 1969 Sherman; Dawson 1969 Stewart).

Incomplete outcome data

Only three studies provided data suggesting that incomplete outcome data were unlikely to bias the results, that is they reported high follow-up rates which were equal between intervention groups (Bailey 1993; Dawson 1997; TANA 2009).

Selective reporting

There was little suggestion of selective outcome reporting. Table 3 and Table 4 show the outcome reporting grid. In most cases, where an outcome was not reported it was because the study follow up was not conducted at that time point or "Not mentioned but clinical judgement says unlikely to have been measured", which is unlikely to introduce bias. Three trials did not report active trachoma. For Chidambaram 2006 and TANA 2009, data on active trachoma were collected and not reported; the authors have supplied unpublished data on active trachoma for TANA 2009. For Lee 2007 the focus of the study was the presence of *C. trachomatis* DNA on flies and in the eyes of children, so it was plausible that a clinical assessment was not done. Nine trials (out of a total of 21 included studies) did not report ocular *C. trachomatis* infection but there was nothing in the reports of these studies to suggest that the data had been collected and not reported. In one trial Cochereau 2007 it was clear that data on ocular infection had been collected but not reported.

All studies (with the exception of Lee 2007) reported outcomes at three months. Thirteen (out of 21) trials reported outcomes at 12 months. Only one trial reported 24 months outcomes for both treatment and control groups (Atik 2006), although Chidambaram 2006 reported outcomes for the treated communities only at 24 months. Again, there was no suggestion from the published reports that the non-publication of outcomes at 12 or 24 months was related to study results (Table 3, Table 4).

Other potential sources of bias

Recruitment bias can occur when individuals are recruited to the trial after the clusters have been randomised as the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited (Higgins 2008b). None of the included studies discussed this issue.

When small numbers of clusters are randomised, there is a possibility of chance baseline imbalance between the randomised groups in terms of either the clusters or the individuals (Higgins 2008b). This was a particular problem with the cluster-randomised trials included in this review. Four of the trials randomised only two communities to treatment or control (ACT 1999 Egypt; ACT 1999 Tanzania; Atik 2006; Resnikoff 1995) and one trial randomised only six communities (three in each group) to treatment or control (Lee 2007). Only two studies were of a reasonable size (Chidambaram 2006: 15 communities; TANA 2009: 24 communities). In ACT 1999 The Gambia eight communities were pair matched.

Reporting of the baseline comparability of clusters or statistical adjustment for baseline characteristics (ACT 1999 Egypt; ACT 1999 Tanzania; Lee 2007) can help reduce concern about the effects of baseline imbalances, however it is difficult to interpret differences in treatment effect between only two communities because there may be some other unknown confounding factor that explains the difference in effect.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotic versus control for trachoma: individuals; **Summary of findings 2** Oral versus topical antibiotic for trachoma: individuals; **Summary of findings 3** Oral azithromycin compared to control for trachoma: communities; **Summary of findings 4** Oral azithromycin compared to topical tetracycline for trachoma: communities

What is the effect of antibiotic treatment of the individual on active trachoma and ocular *C. trachomatis* infection?

Antibiotic versus control (placebo)

Analysis 1.1 shows the effect of any antibiotic treatment on active trachoma at three months. Nine trials randomising 1961 people contributed to this analysis. There was considerable heterogeneity between trials (I^2 = 73%). The treatment effects observed in the different trials ranged from a risk ratio of 0.40 (95% CI 0.20 to 0.79) (Dawson 1969 Stewart) to a risk ratio of 1.02 (95% CI 0.83 to 1.25) (Darougar 1980). However, most of the trials suggested an apparent beneficial effect of treatment on active trachoma measured at three months follow up. The pooled risk ratio was 0.78 (95% CI 0.69 to 0.89).

Analysis 1.2 shows the effect of any antibiotic treatment on ocular *C. trachomatis* infection at three months. Fewer trials contributed to this analysis (four trials, n = 297). However, in contrast to the effect on active trachoma there was no evidence of any heterogeneity in treatment effect between trials (I^2 = 0). The treatment effect appeared to be of a similar order of effect as for active trachoma but did not achieve conventional levels of statistical significance (pooled risk ratio of 0.81, 95% CI 0.63 to 1.04).

Analysis 1.3 shows the effect of any antibiotic treatment on active trachoma at 12 months. Four trials randomising 1035 people contributed to this analysis. Again there was evidence of considerable heterogeneity between trials (I^2 = 90%). The treatment effects observed in the different trials ranged from a risk ratio of 0.50 (95% CI 0.41 to 0.62) (Shukla 1966) to a risk ratio of 1.05 (95% CI 0.88 to 1.24) (Foster 1966). However, three of the four trials showed a statistically significant beneficial effect of treatment on active trachoma measured at 12 months follow up. The pooled risk ratio was 0.74 (95% CI 0.55 to 1.00).

Analysis 1.4 shows the effect of any antibiotic treatment on *C. trachomatis* infection at 12 months. Only one trial provided data on ocular chlamydial infection at 12 months (Darougar 1980). The effect was strong with a risk ratio of 0.25. Although this was statistically significant the estimate of treatment effect was imprecise with a wide confidence interval (0.08 to 0.78), reflecting the small sample size of the trial.

One source of clinical heterogeneity in these trials was whether oral or topical antibiotic was used. One of the objectives of the review was to compare oral and topical treatment, in particular oral azithromycin and topical tetracycline.

Analysis 2.1 shows the results separately for the trials that considered oral antibiotic versus control and the trials that considered topical antibiotic versus control on active trachoma at three months. Although statistical heterogeneity was reduced by considering these trials separately, there remained substantial heterogeneity (I^2 of 60% and 68%). The pooled estimate of treatment effect for oral antibiotics on active trachoma at three months was 0.81 (95% CI 0.67 to 0.97) and for topical antibiotics was 0.82 (0.72 to 0.92). A similar picture was seen for active trachoma at 12 months (Analysis 2.3). There were not enough data to make a reliable comparison of the effects of oral and topical antibiotics versus control on *C. trachomatis* infection (Analysis 2.2; Analysis 2.4).

Subgroup analyses such as these can be misleading because there may be other reasons for differences between trials apart from the type of antibiotic used. Direct comparison of oral versus topical antibiotic within trials is a more reliable estimate of relative effect.

Oral versus topical antibiotic

Analysis 3.1 shows the effect of oral versus topical antibiotic on active trachoma at three months from within-trial comparisons (six trials, n = 953). There was considerable statistical heterogeneity (I^2 = 63%). The estimates of effect were spread across the null line with three trials reporting a beneficial effect of oral antibiotics and three trials reporting a beneficial effect of topical antibiotics. Three of the six trials (Darougar 1980; Dawson 1997; Foster 1966) had findings consistent with a hypothesis of no difference in effect. Similarly for active trachoma at 12 months (Analysis 3.3), *C. trachomatis* infection at three (Analysis 3.2) and 12 months (Analysis 3.4), there was no consistent evidence as to whether oral or topical antibiotics were more effective.

Examining the trials for clinical heterogeneity suggested that the interventions used in Bowman 2000 were different. In particular, this study focused on "practical operational conditions" which meant that the topical treatments were unsupervised. Excluding this trial from the analyses substantially reduced the observed inconsistency (I^2 = 0) with a pooled risk ratio for the remaining five included trials of 1.04 (95% CI 0.94 to 1.16). Similar improvements in consistency were seen when Bowman 2000 was excluded from the 12 months analyses (i^2 changed from 56% to 29%, pooled risk ratio 1.01 (95% CI 0.85 to 1.20).

Analysis 4.1, Analysis 4.2, Analysis 4.3 and Analysis 4.4 show the specific comparison between oral azithromycin and topical tetracycline for active trachoma and *C. trachomatis* infection at three and 12 months. There was considerable heterogeneity in the results of these studies for active trachoma (Analysis 4.1). As before, excluding Bowman 2000 from the analyses substantially reduced the inconsistency (I^2 = 0) and the pooled risk ratio of the two remaining trials was 1.01 (95% CI 0.80 to 1.28). Only two trials reported data at 12 months. Bowman 2000 reported a beneficial effect of azithromycin compared to tetracycline (risk ratio 0.66, 95% CI 0.45 to 0.98). Dawson 1997 reported a smaller effect which was not statistically significant (risk ratio 0.90, 95% CI 0.65 to 1.23).

Data from Bailey 1993 have not been included in the graphical analyses because they compared oral antibiotic (single-dose azithromycin) with a combination of topical/oral antibiotic (topical tetracycline with oral erythromycin for severe cases). A total of 194 people with active disease were randomly allocated to treatment, 97 in each group. Approximately 60% of these people were antigen positive at baseline. At 26 weeks 21/97 had active disease in the azithromycin group and 27/97 in the tetracycline/erythromycin group (risk ratio 0.78 95% CI 0.47 to 1.28). Ap-

proximately 42% of each group was antigen positive. Data from Cochereau 2007 also have not been included in the meta-analyses because they compared oral azithromycin with two regimens of topical azithromycin and treated people accompanying the children to the treatment centre. They found that trachoma resolved in 93.0%, 96.3% and 9.6.6% of the two-day group, three-day group and oral treatment group 60 days after treatment.

What is the effect of community treatment with antibiotics on active trachoma and ocular C. trachomatis infection?

All the cluster-randomised community-based trials discussed in this section compared oral azithromycin to control or oral azithromycin to topical tetracycline.

Antibiotic versus control (placebo)

Four community-based trials compared azithromycin versus no treatment (Atik 2006; Chidambaram 2006; Lee 2007; TANA 2009). None of these trials reported outcomes at three months. Atik 2006 published data on active trachoma at 12 months and unpublished data were supplied for TANA 2009 (Analysis 5.1). The two trials reported very different results. Atik 2006 reported a non-significant increased risk of active trachoma in the community treated with azithromycin (risk ratio 1.14, 95% CI 0.67 to 1.94) whereas in TANA 2009, communities receiving mass treatment with azithromycin had a reduced prevalence of active trachoma in children 12 months after treatment (risk ratio 0.58, 95% CI 0.52, 0.65). It is difficult to explain the differences between the two studies, however, Atik 2006 only compared two communities compared to the 24 randomised in TANA 2009. Of the two studies TANA 2009 was judged to be at lower risk of bias (Figure 2).

These analyses do not take into account the cluster design of the studies. Data from TANA 2009 suggested an intra-cluster correlation coefficient (ICC) of approximately 0.06. Adjusting the results of TANA 2009 for this ICC gave a 95% CI 0.47 to 0.72. In fact the results of this study were reasonably robust to assumptions about the ICC; adjusting for an ICC of 0.2 gave a 95% CI of 0.41 to 0.83.

Atik 2006, Chidambaram 2006, Lee 2007 and TANA 2009 reported *C. trachomatis* infection at 12 months (Analysis 5.2). In all four studies communities treated with azithromycin were less likely to have *C. trachomatis* infection at 12 months compared to untreated communities. These studies gave different estimates of effect (0.61 in Atik 2006, 0.49 in Chidambaram 2006, 0.04 in Lee 2007 and 0.32 in TANA 2009). The pooled risk ratio was 0.35 (95% CI 0.21 to 0.60). Although it is likely that the size of the pooled effect estimate is unreliable, given the differences between the studies, all of the studies indicated a statistically significant beneficial effect of antibiotic treatment on *C. trachomatis* infection.

The conclusions did not change as a result of adjusting for the extra variation introduced by the cluster design of the studies. Adjusting for an ICC of 0.2 gave a confidence interval for the pooled risk ratio of 0.20 to 0.63.

Data from Resnikoff 1995 are not included in the forest plots as it was difficult to extract data in a suitable format. The study randomly allocated four villages in factorial fashion to treatment with 1% oxytetracycline or health education. Individuals treated with tetracycline experienced a higher cure rate than people who were not and communities treated with tetracycline experienced a lower incidence and prevalence of the disease.

Oral versus topical antibiotic

Only one study compared oral and topical community-based treatment for trachoma, the 'Azithromycin in Control of Trachoma' study (ACT). As this study took place in three different countries in Africa (Egypt, The Gambia and Tanzania), it is included in the analyses as three studies.

Even though all three studies had the same interventions and the one study protocol there was still considerable heterogeneity of effect. However, it must be remembered that in two locations only two communities were randomised to oral versus topical treatment (ACT 1999 Egypt; ACT 1999 Tanzania).

Analyses 6.1 to 6.4 show the effect of community-based treatment with azithromycin versus topical tetracycline (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4). In ACT 1999 Egypt and ACT 1999 The Gambia there was some evidence that azithromycin was more effective than topical tetracycline in reducing the risk of active trachoma and *C. trachomatis* infection at three and 12 months. However, these results were not very robust to assumptions about the ICC. Adjusting for an ICC of 0.05 resulted in confidence intervals including one for all the results. In ACT 1999 Tanzania, the findings were less consistent, with a risk ratio greater than one (favouring topical treatment) for active trachoma and *C. trachomatis* infection at 12 months and risk ratio less than one (favouring oral treatment) for *C. trachomatis* infection at three months.

Adverse effects

Table 5 summarises the information on adverse effects reported in the included studies. Data on adverse effects were sparsely reported. In 12 of the 22 included studies there was no mention of adverse effects in the study report. In TANA 2009 data on adverse effects were collected systematically: 96/671 individuals treated with azithromycin reported an adverse effect of treatment (14.3%, 95% CI 11.7% to 17.2%); 72 of these (10.7% 95% CI 8.5% to 13.3) were gastrointestinal (abdominal pain, vomiting, nausea, diarrhoea, constipation and related issues); no serious adverse events were recorded in this study. A specific analysis of childhood mortality suggested that azithromycin treatment reduced the rate of childhood mortality in these communities. The mortality rate for children aged one to nine years was 4.1 per 1000 person-years

(95% CI 3.0 to 5.7) in the treated communities compared to 8.3 per 1000 person-years (95% CI 5.3 to 13.1) in the untreated communities.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Oral versus topical antibiotic for trachoma

Patient or population: patients with trachoma
Settings: individuals
Intervention: oral antibiotic
Comparison: topical antibiotic

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk topical antibiotic	Corresponding risk oral antibiotic				
Active trachoma Follow-up: 3 months	**Medium risk population**[1] **578 per 1000**	**566 per 1000** (474 to 682)	**RR 0.98** (0.82 to 1.18)	953 (6 studies)	⊕⊕⊕◯ **moderate**[2]	Pooled RR excluding Bowman 2000 RR 1.04 (95% CI 0.94, 1.16). [3]
Ocular chlamydia trachomatis infection Follow-up: 3 months	See comment	See comment	Not estimable	298 (3 studies)	⊕◯◯◯ **very low**[4,5]	Darougar 1980 RR 6.05 (95% CI 0.78, 46.95) ; Dawson 1997 RR 0.57 (0.14, 2.30); Tabbara 1996 RR 1.30 (0.41,4.11)
Active trachoma Follow-up: 12 months	**Medium risk population**[1] **565 per 1000**	**525 per 1000** (424 to 650)	**RR 0.93** (0.75 to 1.15)	886 (5 studies)	⊕◯◯◯ **very low**[6,7]	Pooled RR excluding Bowman 2000 RR 1.01 (95% CI 0.85, 1.20). [3]

Ocular chlamydia trachomatis infection Follow-up: 12 months	See comment	See comment	Not estimable	220 (2 studies)	⊕○○○ **very low**	Darougar 1980 RR 2.59 (95% CI 0.28, 23.88); Dawson 1997 RR 0.50 (0.18, 1.43)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Median risk in control groups in included studies (rounded to nearest 10 per 1000)
[2] Serious limitations in design: none of the trials reported adequate methods for allocation concealment and masking of outcome assessment.
[3] In contrast to the other trials here Bowman 2000 aimed to compare azithromycin and tetracycline ' ' under practical operational conditions - i.e. without supervision of the administration of the ointment". The results of this study were quite different from the other trials and excluding it from the pooled estimated reduced the I2 value from 63% to 0% for 3 months follow-up and from 56% to 29% for 12 months follow-up.
[4] Serious limitations in design: no trial reported adequate allocation concealment. Two out of the three trials reported masking outcome assessment.
[5] Very serious inconsistency: Effect estimates ranged from 0.57 in favour of oral antibiotics to 6.05 in favour of topical antibiotics, although confidence intervals for all studies overlapped with each other. Only 8 events in total in the control groups of these three studies.
[6] Serious limitations in design: no trial reported adequate allocation concealment. One out of the two trials reported masking outcome assessment.
[7] Very serious inconsistency: One trial found in favour of oral antibiotics with a RR of 0.5, the other found in favour of topical antibiotics with a RR of 2.59. Neither trial was statistically significant and their confidence intervals overlapped.

Oral azithromycin compared to control for trachoma

Patient or population: patients with trachoma
Settings: communities
Intervention: oral azithromycin
Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	control	oral azithromycin				
Active trachoma Follow-up: 12 months	See comment	See comment	Not estimable	2764 (2 studies)	⊕⊕⊕◯ **moderate**[1,2]	Best estimate of effect is likely to come from TANA 2009 RR 0.58 (95% CI from individual analysis 0.52 to 0.65, 95% CI adjusted for clustering 0.47 to 0.72).[3]
Ocular chlamydia trachomatis infection Follow-up: 12 months	**Medium risk population**[4]		**RR 0.35** (0.21 to 0.60)[5]	4345 (4 studies)	⊕⊕⊕◯ **moderate**[1,6]	
	100 per 1000	**35 per 1000** (21 to 60)				
	High risk population[4]					
	500 per 1000	**175 per 1000** (105 to 300)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Trials were of variable quality but the majority of evidence was from TANA 2009 which was judged to be at low risk of bias so we did not downgrade for limitations in design.

[2] Serious inconsistency: TANA 2009 and Atik 2006 provided different estimates of effect. RR 0.58, (95% CI 0.67, 1.94) in TANA 2009 compared to RR 1.14, (0.67, 1.94) in Atik 2006.

[3] TANA 2009 randomised 24 communities and was judged to be at low risk of bias. Atik 2006 randomised 2 communities and was judged to be at a greater risk of bias. For that reason, we judge that the estimate of effect from TANA 2009 is likely to provide a better estimate of the true effect.

[4] Populations with medium (10%) prevalence and high (50%) prevalence of trachoma.

[5] These confidence intervals do not take into account the cluster design of the study. Adjusting for cluster design of the study did not affect the conclusions. Adjusting for an ICC of 0.2 gave a confidence interval for the pooled risk ratio of 0.20 to 0.63.

[6] Serious inconsistency: Estimates of effect in the four studies range from 0.04 to 0.61.

Oral azithromycin compared to topical tetracycline for trachoma

Patient or population: patients with trachoma
Settings: communities
Intervention: oral azithromycin
Comparison: topical tetracycline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	topical tetracycline	oral azithromycin				
Active trachoma Follow-up: 3 months	See comment	See comment	Not estimable	6002 (3 studies)	⊕⊕◯◯ **low**[1,2]	ACT 1999 Egypt: RR 0.52 (95% CI 0.43,0.64); ACT 1999 Tanzania RR 1.16 (1.00,1.36); ACT 1999 The Gambia RR 0.76 (0.50,1.15)
Ocular C. trachomatis infection Follow-up: 3 months	See comment	See comment	Not estimable	5773 (3 studies)	⊕⊕◯◯ **low**[1,2]	ACT 1999 Egypt: RR 0.22 (95% CI 0.11,0.44); ACT 1999 Tanzania RR 0.68 (0.49,0.95); ACT 1999 The Gambia RR 0.51 (0.37,0.70)
Active trachoma Follow-up: 12 months	See comment	See comment	Not estimable	5414 (3 studies)	⊕⊕◯◯ **low**[1,2]	ACT 1999 Egypt: RR 0.74 (95% CI 0.61,0.90); ACT 1999 Tanzania RR 1.19 (1.02,1.40); ACT 1999 The Gambia RR 0.55 (0.40,0.75)

Ocular C. trachomatis infection Follow-up: 12 months	See comment	See comment	Not estimable	5276 (3 studies)	⊕⊕◯◯ **low**[1,2]	ACT 1999 Egypt: RR 0.48 (95% CI 0.31,0.74); ACT 1999 Tanzania RR 1.01 (0.76,1.35); ACT 1999 The Gambia RR 0.62 (0.44,0.87)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Serious limitations in design: Three cluster-randomised trials, two of the trials only randomised two communities to oral/topical antibiotic. Assessment of trachoma was not masked but assessment of ocular infection was. Recruitment bias not addressed and problems with incomplete outcome data. Some attempt made to adjust for baseline imbalances.
[2] Serious inconsistency:

DISCUSSION

Summary of main results

Trials included in this review provide evidence that individuals with trachoma benefit from antibiotic treatment (Summary of findings for the main comparison). Antibiotic treatment reduces the risk of active trachoma and ocular *C. trachomatis* infection up to 12 months after treatment. The trials included in this review were clinically and statistically heterogeneous and most had serious limitations in their design. This makes it difficult to estimate the size of the effect; the current best guess would be an approximate 20% risk reduction. Overall the quality of the evidence is graded as low. Oral and topical treatments appeared to have similar effects if used as prescribed (Summary of findings 2). One trial (Bowman 2000) compared oral antibiotic and unsupervised topical treatment and found the oral antibiotic to be more effective "under practical operational conditions", which may have been due to poor compliance with the more complex topical treatment regimen.

Only three of the more recent trials in individuals used azithromycin, which is the currently recommended oral antibiotic treatment. None of these trials had a no treatment group. However, in the individually-randomised trials there was no evidence that azithromycin was less effective than topical tetracycline.

We identified four community-based trials comparing azithromycin versus no treatment. These trials were of variable quality and size, however there was one large, good quality trial conducted in Ethiopia (TANA 2009) that provided good evidence that community-based treatment with a single dose of azithromycin reduces the prevalence of active trachoma and ocular chlamydial infection in children up to 12 months after treatment (Summary of findings 3).

Only one trial compared oral versus topical community-based treatment (Summary of findings 4). This study was conducted in three countries in Africa and therefore is included as three separate studies in this review. Data from this study were inconsistent. In The Gambia and Egypt there was some evidence that oral azithromycin was more effective than topical tetracycline, particularly with regards to ocular infection. However, after adjustment for the cluster design of the study these findings were not statistically significant and were not replicated consistently in the Tanzanian arm of the study.

None of the included trials reported any serious adverse events associated with either of the currently used antibiotics, azithromycin and topical tetracycline. However, for many of the trials it was not clear whether data on adverse effects had been collected systematically. In the one trial that did report these data, between 10% and 15% of people experienced symptoms such as nausea and vomiting with azithromycin treatment.

Overall completeness and applicability of evidence

A strength of the evidence is that the included trials come from many different countries and populations. However, it is unfortunate that heterogeneity between trial results means that we cannot estimate with any confidence the size of the effect for treatment of trachoma with oral or topical antibiotics, although it is likely that both oral and topical treatments have a beneficial effect.

Almost all the trials in individuals were done in children and the generaliseability of these findings to adults is uncertain. In the community-based trials, data were reported for adults and children. With the small number of trials it was not possible to determine whether the effects are different in these groups but one study (TANA 2009) provided data on ocular infection after mass treatment in both children and adults. The observed risk ratio in children was 0.32 (95% CI 0.26 to 0.40) and in adults was 0.49 (0.33 to 0.71).

Evidence for community-based or mass treatment campaigns is sparse. It was not possible to determine who should be treated on the basis of available data, what the important factors are in planning treatment strategies and whether it is the whole community, all children under 10 years of age, all women and children or families of all children with active trachoma. There is some evidence that frequent treatment of children may be an effective strategy to reduce the community prevalence of infection (TANA 2009).

Azithromycin was given in the trials as a single, double or triple dose but it was not possible to determine whether there was any difference in effect. Where azithromycin is not donated, there is a major cost difference between topical tetracycline and oral azithromycin, but it was not possible to determine which is the more cost-effective strategy per extra case cured. Some populations in which trachoma is endemic are subject to migration and that may account in part for the low follow-up rates in the community trials; it may also have implications in determining the most effective treatment in those populations where new infected cases migrate into the community.

Our review does not directly address the evidence for the WHO guidelines. In part this is because we did not identify any trial data that directly tested the efficacy of the mass antibiotic administration schedules currently recommended. These are that where the baseline district-level prevalence of TF in one to nine year-old children is 10% or greater, mass antibiotic treatment should be undertaken annually for three years before a repeat district-level survey (Solomon 2006).

Quality of the evidence

The included trials were published from 1966 onwards and their quality was variable. The quality of evidence for most outcomes was low, particularly for the comparison antibiotics versus no treatment (Summary of findings for the main comparison). Reporting

of sequence generation and allocation concealment was not good and it was often difficult to assess the effect of incomplete data due to inadequate reporting. There was considerable heterogeneity of results. However, masking of outcome assessment was reported for laboratory analyses (less so for clinical assessments of active trachoma) and there was little evidence of selective outcome reporting. There was moderate quality evidence for the comparison of oral and topical antibiotics for the outcome active trachoma (Summary of findings 2).

The community-based trials were also of poor methodological quality with the exception of one study (TANA 2009) (Summary of findings 3; Summary of findings 4). The main problem with the included studies was that in most of the studies only two communities were randomly allocated to treatment (only two trials randomised sufficient number of clusters). Although adjustment for baseline characteristics can alleviate this problem to some extent, the interpretation of these studies is always problematic as it is difficult to exclude the alternative explanation that there is some characteristic that is different between the communities (apart from treatment of trachoma) and which may be the real cause of any observed differences in outcome. There was also little information on other potential sources of bias in cluster-randomised trials such as recruitment bias.

Three community-based trials (Chidambaram 2006; Lee 2007; TANA 2009) had a 'delayed treatment' design that involved randomly selecting clusters for treatment and comparing the prevalence of trachoma 12 months after treatment with a random selection of untreated clusters that are then enrolled in the treatment programme. This study design overcomes the ethical dilemma of surveying communities for trachoma and then withholding treatment for 12 months but has the disadvantage that baseline data on trachoma are not available in the control group.

Potential biases in the review process

This review has been substantially revised for the update. New methods, such as assessment of risk of bias and subgroup and sensitivity analyses, have been incorporated. A new protocol was not written. It is possible that the update could have been influenced by knowledge of the trial results.

Agreements and disagreements with other studies or reviews

This update, like previous versions of the Cochrane review of antibiotics for trachoma (Mabey 2002; Mabey 2005), found some evidence of benefit of treatment of individuals with clinical signs of active trachoma, but only limited evidence to support the use of oral azithromycin in preference to topical tetracycline. In contrast to those previous Cochrane reviews, we found some good quality evidence demonstrating the effectiveness of community-based treatment, with some limited evidence of greater benefit of mass treatment with azithromycin over mass treatment with topical tetracycline.

AUTHORS' CONCLUSIONS

Implications for practice

Whilst the data are not of sufficient quality to make firm conclusions, there is some evidence that people treated with either oral or topical antibiotics may experience a reduction in the risk of active trachoma (perhaps of the order of 20% relative risk reduction). It is likely that oral azithromycin and topical tetracycline have similar effects if used as prescribed.

Community-based trials show that mass administration of antibiotics reduces the prevalence of active trachoma and ocular infection with *C.trachomatis*. There were no trial data that directly tested the mass antibiotic administration schedules currently recommended by WHO.

Implications for research

The Alliance for the Global Elimination of Trachoma has endorsed the donation of azithromycin for the treatment of trachoma. This would be an ideal setting in which to conduct community-randomised trials, under operational conditions, comparing the effect of mass distribution of azithromycin to that of placebo or no treatment. Opportunities for ethically conducting such trials occur in countries and districts newly enrolling in trachoma control programmes. Inequities are bound to exist in some settings at start-up, when antibiotics and resources for their distribution are generally in limited supply. Allocating interventions randomly in these circumstances is reasonable, with roll-out of the intervention to areas initially randomised to 'control' in later treatment rounds. Such an approach has been used in several of the trials included in this review. Trials to determine optimal dosages and dosage intervals of azithromycin at various levels of endemicity, test the most appropriate thresholds for starting and stopping mass treatment, and to determine which subgroups will need to be treated at various stages of the pathway towards elimination are also required; where potential strategies to evaluate could be selected on the basis of recent mathematical modelling work. Cost effectiveness per extra case cured should be one of the outcome measures. The adverse effects of azithromycin and emergence of resistance are also areas that should be addressed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACT 1999 Egypt

Methods	Allocation: random within one matched pair. Unit of randomisation: village. Masking: participant - no, provider - no, outcome - no. Exclusions after randomisation: no. Losses to follow up: yes, temporary absence.
Participants	Country: Egypt. Number randomised: 2238. Age (ave.): all ages. Sex: not reported. Clinical grading: Dawson 1981. Lab tests: LCR. Inclusion criteria: all villagers present. Exclusion criteria: none, but alternative treatment for azithromycin-allocated women at childbearing age
Interventions	TREATMENT: azithromycin. Administration: oral. Dose: 20 mg/kg up to 1 g. Duration: once a week for 3 weeks. Women of childbearing age erythromycin for 14 days, 500 mg twice daily or 250 mg four times daily (amoxicillin in case of intolerance) COMPARISON: oxytetracycline. Administration: topical. Dose: 1%. Duration: once daily for 6 weeks.
Outcomes	Primary: active trachoma. Secondary: infection.
Notes	"Compliance was good for all groups, except the tetracycline treatment village in Egypt (table 2)." (page 633). From table 2, the percentage receiving at least 1 dose of azithromycin was 95% and the percentage receiving 28 applications of tetracycline was 59.5% Only one pair of villages randomised.

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Active trachoma	High risk	The treatments were quite different - oral versus topical. No measures were reported

		to mask study participants and personnel from knowledge of which intervention a participant received
Blinding? Ocular Chlamydia trachomatis infection	Low risk	"Laboratory staff were not aware of the clinical and treatment status of study participants" and "Identification numbers for laboratory samples differed from those used on the ocular examination forms to conceal village and treatment status from the laboratory staff" (page 632)
Incomplete outcome data addressed? Active trachoma	High risk	"Some individuals or families could not be reached at scheduled treatment times (they worked out of town, had moved away on a temporary or permanent basis, or were working in the fields when the teams were present). There were some refusals at all sites." Egypt: "little movement was documented" (page 633) From table 6 (page 633): 92% of azithromycin group and 86% of tetracycline group had assessment of active trachoma at baseline. At one year, 87% of azithromycin group and 75% of tetracycline group had data on active trachoma
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	High risk	From table 4 (page 632): 81% of azithromycin group and 58% of tetracycline group had assessment of ocular infection after treatment. At one year, 80% of azithromycin group and 69% of tetracycline group had data on ocular infection
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	
Recruitment bias addressed?	Unclear risk	Recruitment bias was not specifically addressed in the report however the following statement was made "At all study sites we attempted to treat every individual present in each village" (Schachter page 631) The following data were available in the report which suggests that recruitment bias may have been a possibility A=Azithromycin group T= tetracycline group, numbers expressed as %

ACT 1999 Egypt (*Continued*)

		of pre-study census Pre-study census: A: 1179 T: 1212 At time of treatment: A: 1139 (97%) T: 1099 (91%) Baseline clinical trachoma status: A: 1080 (92%) T: 1044 (86%) Compliance (at least 1 dose azithromycin or 28 applications of tetracycline) A: 95% T:60%
Baseline imbalances addressed?	Low risk	"In each of the endemic areas, pairs of villages were matched on the basis of an initial rapid assessment of the trachoma rate among children aged between 1 and 10 years. One member of each village pair was randomly assigned mass treatment with oral azithromycin, with the other receiving the topical tetracycline regimen; in each village we generated a random number for each and took the number closest to one to be assigned azithromycin". (Schachter page 631). However, note in Egypt only 2 clusters were randomised Baseline comparability of clusters not reported in Schachter but "[...], we have done multivariate analyses, which adjust for clustering of individual within households and for co-variates that may affect an individuals' risk of being infected with chlamydia (LCR positive) at 1 year. The assumption underlying these models is that after adjustment for covariates there are no village characteristics, other than treatment type, that affect the risk of positivity at 1 year after treatment" (Schachter page 632)

ACT 1999 Tanzania

Methods	Allocation: random within one matched pair. Unit of randomisation: village. Masking: participant - no, provider - no, outcome - no. Exclusions after randomisation: none Losses to follow up: yes, temporary absence.

ACT 1999 Tanzania (*Continued*)

Participants	Country: Tanzania. Number randomised: 3261. Age (ave.): all ages. Sex: not reported. Clinical grading: Dawson 1981. Lab tests: LCR. Inclusion criteria: all villagers present. Exclusion criteria: none, but alternative treatment for azithromycin-allocated women at childbearing age
Interventions	TREATMENT: azithromycin. Administration: oral. Dose: 20 mg/kg up to 1 g. Duration: once a week for 3 weeks. Women of childbearing age erythromycin for 14 days, 500 mg twice daily or 250 mg four times daily (amoxicillin in case of intolerance) COMPARISON: oxytetracycline. Administration: topical. Dose: 1%. Duration: once daily for 6 weeks.
Outcomes	Primary: active trachoma. Secondary: infection.
Notes	Only one pair of villages randomly allocated to treatment. High population movement.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Active trachoma	High risk	The treatments were quite different - oral versus topical. No measures were reported to mask study participants and personnel from knowledge of which intervention a participant received
Blinding? Ocular Chlamydia trachomatis infection	Low risk	"Laboratory staff were not aware of the clinical and treatment status of study participants" and "Identification numbers for laboratory samples differed from those used on the ocular examination forms to conceal village and treatment status from the laboratory staff" (page 632)
Incomplete outcome data addressed? Active trachoma	High risk	Some individuals or families could not be reached at scheduled treatment times (they worked out of town, had moved away on a temporary or permanent basis, or were

		working in the fields when the teams were present). There were some refusals at all sites (page 633) From table 6 (page 633): 78% of azithromycin group and 88% of tetracycline group had assessment of active trachoma at baseline. At one year, 60% of azithromycin group and 77% of tetracycline group had data on active trachoma
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	High risk	From table 4 (page 632): 58% of azithromycin group and 78% of tetracycline group had assessment of ocular infection after treatment. At one year, 45% of azithromycin group and 61% of tetracycline group had data on ocular infection
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	
Recruitment bias addressed?	Unclear risk	Recruitment bias was not specifically addressed in the report however the following statement was made "At all study sites we attempted to treat every individual present in each village" (Schachter page 631) The following data were available in the report which suggests that recruitment bias may have been a possibility A=Azithromycin group T= tetracycline group, numbers expressed as % of pre-study census Pre-study census: A: 2167 T: 1179 At time of treatment: A: 2161 (100%) T: 1100 (93%) Baseline clinical trachoma status: A: 1696 (78%) T: 1036 (88%) Compliance (at least 1 dose azithromycin or 28 applications of tetracycline) A: 89% T: 90%
Baseline imbalances addressed?	Low risk	Baseline comparability of clusters not reported in Schachter but "[...], we have done multivariate analyses, which adjust for clustering of individual within households and for co-variates that may affect an individuals' risk of being infected with chlamydia (LCR positive) at 1 year. The assumption underlying these models is that after ad-

ACT 1999 Tanzania (*Continued*)

		justment for covariates there are no village characteristics, other than treatment type, that affect the risk of positivity at 1 year after treatment." (Schachter page 632)

ACT 1999 The Gambia

Methods	Allocation: random within four matched pairs. Unit of randomisation: village. Masking: participant - no, provider - no, outcome - no. Exclusions after randomisation: no. Losses to follow up: yes, temporary absence.
Participants	Country: The Gambia. Number randomised: 1753. Age (ave.): all ages. Sex: not reported. Clinical grading: Dawson 1981. Lab tests: LCR. Inclusion criteria: all villagers present. Exclusion criteria: none, but alternative treatment for azithromycin-allocated women at childbearing age
Interventions	TREATMENT: azithromycin. Administration: oral. Dose: 20 mg/kg up to 1 g. Duration: once a week for 3 weeks. Women of childbearing age erythromycin for 14 days, 500 mg twice daily or 250 mg four times daily (amoxicillin in case of intolerance) COMPARISON: oxytetracycline. Administration: topical. Dose: 1%. Duration: once daily for 6 weeks.
Outcomes	Primary: active trachoma. Secondary: infection.
Notes	Very high migration rate.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Active trachoma	High risk	The treatments were quite different - oral versus topical. No measures were reported to mask study participants and personnel

		from knowledge of which intervention a participant received
Blinding? Ocular Chlamydia trachomatis infection	Low risk	"Laboratory staff were not aware of the clinical and treatment status of study participants" and "Identification numbers for laboratory samples differed from those used on the ocular examination forms to conceal village and treatment status from the laboratory staff" (Schachter page 632)
Incomplete outcome data addressed? Active trachoma	High risk	All clusters completed the trial in theory although one cluster allocated to azithromycin had very poor follow-up (0% at 12 months). Some individuals or families could not be reached at scheduled treatment times (they worked out of town, had moved away on a temporary or permanent basis, or were working in the fields when the teams were present). There were some refusals at all sites (Schachter page 633) From table 6 (Schachter page 633): 91% of azithromycin group and 82% of tetracycline group had assessment of active trachoma at baseline. At one year, 65% of azithromycin group and 50% of tetracycline group had data on active trachoma
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	High risk	From table 4 (Schachter page 632): 61% of azithromycin group and 54% of tetracycline group had assessment of ocular infection after treatment. At one year, 47% of azithromycin group and 36% of tetracycline group had data on ocular infection Fraser-Hurt: Individual factors statistically associated with attendance at none or only one of the three post-treatment surveys were increasing age (P = 0.02), Wolof ethnicity (P < 0.001), absence of active trachoma at baseline (P = 0.001), and noncompliance with treatment (P = 0.06)
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	

ACT 1999 The Gambia (*Continued*)

Recruitment bias addressed?	Unclear risk	"All residents who were present at the pre-treatment survey were eligible for participation in the trial." (Fraser-Hurt) "At all study sites we attempted to treat every individual present in each village" (Schachter page 631)
Baseline imbalances addressed?	Low risk	"In each of the endemic areas, pairs of villages were matched on the basis of an initial rapid assessment of the trachoma rate among children aged between 1 and 10 years. One member of each village pair was randomly assigned mass treatment with oral azithromycin, with the other receiving the topical tetracycline regimen; in each village we generated a random number for each and took the number closest to one to be assigned azithromycin" (Schachter page 631). "The villages were matched in pairs of similar size, and azithromycin and tetracycline were allocated randomly within these pairs. " (Fraser-Hurt page 633). Baseline comparability of clusters reported (Fraser-Hurt table 1 page 635). There were some baseline imbalances but these were controlled for in the analysis: "Point estimates of the odds ratio for the comparison of azithromycin with tetracycline, adjusted for age, latrine ownership and, where appropriate, trachoma status at baseline, were obtained using logistic regression with individual records." (Fraser-Hurt page 634) Baseline comparability of clusters not reported in Schachter but "[...], we have done multivariate analyses, which adjust for clustering of individual within households and for co-variates that may affect an individuals' risk of being infected with chlamydia (LCR positive) at 1 year. The assumption underlying these models is that after adjustment for covariates there are no village characteristics, other than treatment type, that affect the risk of positivity at 1 year after treatment." (Schachter page 632)

Atik 2006

Methods	Allocation: random allocation of surgery or surgery plus antibiotics Unit of randomisation: commune. Masking: participant - no, provider - no, outcome - unclear. Exclusions after randomisation: no. Losses to follow up: unclear.
Participants	Country: Vietnam. Number randomised: 2 communes randomised; 1851 people enrolled in the study Age: 6 months and older. Sex: approximately 60% female. Clinical grading: Thylefors 1987. Lab tests:Amplicor-PCR (polymerase chain reaction) assay (Roche Diagnostics, Branchburg, NJ) of conjunctival samples Inclusion criteria: all ages 6 months and older. Exclusion criteria: none, but pregnant women received erythromycin
Interventions	Azithromycin 20 mg/kg for children; 1 g for adults. Pregnant women received erythromycin All commune residents older than 6 months were included in the study. There were 2 components to the assessment and intervention. The first component involved examination of all schoolchildren aged 5 through 15 years; children who had active trachoma defined as follicular inflammation, intense inflammation, or both were considered index cases. The second component included examination of the remaining individuals either at a central commune or village site Index cases and their household members were treated with a single oral dose of azithromycin at baseline and 12 months. Non-index cases and non-household members who had active trachoma (follicular inflammation, intense inflammation, or both) received topical tetracycline In the control community trachomatous trichiasis cases were identified and informed of the availability of surgery. All patients who had active trachoma (follicular inflammation, intense inflammation, or both) received topical tetracycline
Outcomes	Active trachoma and *C. trachomatis* infection.
Notes	Only two communes compared.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Active trachoma	Unclear risk	The interventions were not masked but the communes were "geographically isolated from one another" (page 1489). It was not clear if the participants were aware of the existence of other potential interventions

		"At each time point of the study, all participants were examined by an ophthalmologist and graded for trachoma in a masked fashion using a modified grading scale" (page 1489) However, the extent to which the ophthalmologist might be aware of what treatment the community had received was not discussed
Blinding? Ocular Chlamydia trachomatis infection	Low risk	"Samples were labelled with date and a unique identification number to maintain confidentiality and to process samples in a masked fashion" (page 1489)
Incomplete outcome data addressed? Active trachoma	High risk	Both clusters completed the trial. Response rates were not reported explicitly The following gives the total population and the percentage graded for trachoma at baseline, 6 months, 12 months and 24 months (from table 1 and figure 2) Azithromycin community: total = 659: 100%; 86%;79%;56%. Untreated community: total=1192; 100%; 89%; 83%; 72%.
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	High risk	The following gives the total population and the percentage graded for ocular infection at baseline, 6 months, 12 months and 24 months (from table 1 and figure 2) Azithromycin community: total = 659: 98%;79%;100%;52%. Untreated community: total=1192; 95%; 76%; 100%; 71%. A response rate of 100% at one year is unusual and might suggest that some of the people assessed at one year were not present at census. it is also surprising that both communities had 100% follow-up at the same time point
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	
Recruitment bias addressed?	Unclear risk	"selected communes were geographically isolated from one another" (page 1489) and "All commune residents older than 6

		months were included in the study" (page 1489) however no information on response rates were given so it is not clear how many of the residents actually took part in the study
Baseline imbalances addressed?	High risk	Only two clusters included in the trial so no pair-matching. Baseline comparability of clusters was reported with respect to sex and trachoma only (table 1 page 1491). There was a higher baseline prevalence of active trachoma in people aged > 15 in the control cluster (10.6% versus 3.6% P < 0. 001) and higher baseline prevalence of active trachoma in children 5-15 years in the intervention cluster (9.2% versus 4.7% P = 0.033). Statistical adjustment was made for sex, age, and having at least one person with chlamydial infection in the household

Attiah 1973

Methods	Allocation: stratified random. Unit of randomisation: individual. Masking: participant - no, provider - yes, outcome - yes. Exclusions after randomisation: no. Losses to follow-up: 0. Unusual study design: follow up right after treatment termination, over two weeks
Participants	Country: Egypt Number randomised: 228. Age (ave.): 6 to 12 years. Sex: not reported. Clinical grading: WHO. Lab tests: none. Inclusion criteria: active trachoma or 'undetermined case'. Exclusion criteria: none.
Interventions	TREATMENT 1: tetracycline derivative GS2989. Administration: topical. Dose: 0.25%. duration: once every school day for 11 weeks. TREATMENT 2: terramycin. Administration: topical. Dose: not reported. Duration: once every school day for 11 weeks.

	COMPARISON: no treatment. Administration: not applicable. Dose: not applicable. Duration: not applicable.
Outcomes	Primary: active trachoma. Secondary: - Adverse effects: n.a.
Notes	Treatment irregular, although intended for every school day. One village - no description of why it was chosen. Only school children. 228 subjects divided into 11 clinical groups, each of which randomised into three intervention groups. Unclear why 10 weeks and 6 days was felt to be the optimal duration of therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Not reported
Blinding? Active trachoma	Unclear risk	"the principle of double blindness ensured in the experiment" (page 11) "The examiner had no knowledge of the treatment assignment to the groups or of the randomisation process used in the trial" (page 12) "After three months treatment, the results were checked using WHO criteria without investigators knowing what treatment applied" (page 16) However, the report gave no indication as to how the groups were masked and whether the control group received any placebo treatment
Incomplete outcome data addressed? Active trachoma	Unclear risk	Reported 100% follow up. This is unusual and could indicate that children who were not followed-up were not reported. However, 100% may be feasible in a school situation. We have left this as "unclear" because we cannot tell which of the two options apply
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	No data on ocular infection reported.
Free of selective reporting?	Low risk	Clinical examination only and no suggestion that any assessment of ocular infection made

Attiah 1973 (*Continued*)

Free of other bias?	Low risk	

Bailey 1993

Methods	Allocation: not reported. Unit of randomisation: unclear "randomisation was by room, all active cases within a room receiving the same treatment" (page 454) Masking: participant - no, provider - no, outcome - unclear. Exclusions after randomisation: none. Losses to follow up: none.
Participants	Country: The Gambia. Number randomised: 194. Age: 9 months to 60 years. Sex: 51% male. Clinical grading: Dawson 1981. Lab tests: IDEIA amplified enzyme-linked immunosorbent assay (Dako) for genus-specific lypopolysaccharide antigen Inclusion criteria: active trachoma. Exclusion criteria: pregnant or lactating.
Interventions	Oral azithromycin single-dose 20 mg/kg. Topical tetracycline 1% eye ointment twice daily for six weeks. Those with 'severe disease' also received oral erythromycin stearate 250 mg four times daily for two weeks
Outcomes	"resolution of disease".
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	No information on how the sequence was generated or allocated "Randomisation was by room, all active cases within a room receiving the same treatment" (page 454)
Blinding? Active trachoma	Unclear risk	No placebos used for either tablets or ointment. "Subjects were examined [...] by a trained observer (RLB) unaware of treatment allocation" (page 454)

Bailey 1993 (*Continued*)

Blinding? Ocular Chlamydia trachomatis infection	Unclear risk	No specific information on this but as clinical examinations masked it is likely that the laboratory analyses were as well
Incomplete outcome data addressed? Active trachoma	Low risk	Of 194 subjects randomised, 194 examined at 4 weeks, 194 examined at 8 weeks, 191 examined at 16 weeks, and 193 examined at 26 weeks (one subject had died by that point)
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Low risk	Of 194 subjects randomised, 194 examined at 4 weeks, 194 examined at 8 weeks, 191 examined at 16 weeks, and 193 examined at 26 weeks (one subject had died by that point)
Free of selective reporting?	Low risk	Both outcomes - infection and clinical disease - reported
Free of other bias?	Low risk	

Bowman 2000

Methods	Allocation: randomisation by block. Unit of randomisation: individual. Masking: participant - no, provider - no, outcome - yes. Exclusions after randomisation: no. Losses to follow up: numbers recorded.
Participants	Country: The Gambia. Number randomised: 314. Age: 6 months to 10 years. Sex: Boys 50%. Clinical grading: simplified WHO scale 1987. No lab tests.
Interventions	TREATMENT: single-dose azithromycin 20 mg/kg. COMPARISON: topical tetracycline applied once by a nurse in front of the care-giver and then twice daily by care-giver for 6 weeks
Outcomes	Primary: active trachoma. No secondary outcome.
Notes	Trial aim to compare treatments under operational and not best possible conditions

Bowman 2000 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	"Codes in numbered sealed envelopes were used by the nurse administering treatment to allocate treatment to the subject. The clinical assessors had no knowledge of the randomisation sequence or of the treatment received by previous subjects. Similarly the nurse had no knowledge of the block randomisation procedure and did not examine the children but administered treatment according to the allocation in the envelope." (page 4075).
Blinding? Active trachoma	Low risk	Interventions were different - oral dose of azithromycin syrup versus topical tetracycline -so not possible to prevent knowledge to caregivers and participants. However, eyes were graded by "a clinical assessor blind to the treatment allocation." (page 4075). "Patients were aware of their treatments, and therefore inadvertent unmasking of the clinical assessors at follow-up by the patients was possible. There were no reports of the occurring, however, and the similar cure rate ratios for both clinical and photographic outcome suggest that unmasking and bias were not a significant problem." (page 4077)
Incomplete outcome data addressed? Active trachoma	Low risk	Figure 1 (page 4076). Analysis was not by intention to treat as 4 participants received the wrong allocation and were analysed according to their received treatment not according to their random allocation. However as this number was low it is unlikely to have biased the outcome Of 154 children who received tetracycline 15 (10%) were not followed at 6 months; of 160 who received azithromycin 11 (7%) missed follow up. No reason was given for loss to follow up but as this was low and not substantially different between the groups it is unlikely to have caused bias

Bowman 2000 (*Continued*)

Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	Not enough information provided
Free of selective reporting?	Low risk	This study reported one of the primary outcomes for this review - active trachoma. There was no indication that the other outcome *C. trachomatis* infection was collected but not reported.
Free of other bias?	Low risk	

Chidambaram 2006

Methods	Longitudinal cohort study conducted March 2003 to March 2005 in the Gurage Zone of Ethiopia. Eight randomly selected villages were assessed for ocular chlamydial infection. Twelve months after treatment, an additional 2 untreated villages were randomly selected from each of the original 8 peasant associations
Participants	All residents aged 1 year or older.
Interventions	Single-dose oral azithromycin (1 g in adults/20 mg/kg in children) directly observed treatment. Pregnant women, children younger than 1 year, and those allergic to macrolides were offered a 6-week course of topical 1% tetracycline ointment (applied twice daily to both eyes, not directly observed)
Outcomes	Presence of ocular chlamydial infection in children aged 1 to 5. A random sample of adults were tested at 18 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Active trachoma	High risk	Unclear whether this outcome was collected.
Blinding? Ocular Chlamydia trachomatis infection	Unclear risk	Masking not reported.
Incomplete outcome data addressed? Active trachoma	Unclear risk	Not applicable - prevalence surveys in selected communities at 12 months
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	Not applicable - prevalence surveys in selected communities at 12 months

Chidambaram 2006 (*Continued*)

Free of selective reporting?	Unclear risk	Only ocular infection reported - data on active trachoma were collected but not reported
Free of other bias?	Low risk	
Recruitment bias addressed?	Unclear risk	No information on recruitment bias in the report.
Baseline imbalances addressed?	Unclear risk	Difficult to assess as no data reported and study design is such that information on baseline infection status in control villages not available

Cochereau 2007

Methods	Allocation: randomisation by block. Unit of randomisation: individual. Masking: participant - yes, provider - yes, outcome - yes. Exclusions after randomisation: yes. Losses to follow up: numbers recorded
Participants	Country: Guinea-Conakry (comunity) and Pakistan (boys schools only) Number randomised: 670 Age: 1-10 years. Sex: 49.8% male Clinical grading: simplified WHO scale 1987. No lab tests.
Interventions	Azithromycin 1.5% eye drops 2x daily for 2 days (n=224) and 2x daily for 3 days (n=225) compared to oral azithromycin 20 mg/kg single dose (n=221)
Outcomes	% clinical cure in children with clinically active trachoma 2 months after treatment
Notes	In Pakistan only children from boys schools recruited. Last observation carried forward for missing data.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	"The randomisation list used random permuted blocks of six (SAS v 8.2). Within each village, patient numbers were allocated in ascending order using the next

		available number. Study drugs were identified by patient number using the randomisation list. (*Randomisation procedures and treatments p668).*
Blinding? Active trachoma	Low risk	"We used a double-dummy design with placebo eye drops and placebo paediatric suspension" (*Randomisation procedures and treatments p668).*
Incomplete outcome data addressed? Active trachoma	Low risk	Follow-up data reported as follows (figure 1, page 669). Some patients may have more than one reason for not being followed up 2-day eye drops group (n=224): · Did not receive allocated treatment (lost to follow-up) (1) · moved to another region (2) · probably did not fit inclusion criteria (22) · use of other medications (1) · non-compliance (2) · no follow-up at 2 months (1) · number available for analysis (199, 88.8%) 3-day eye drops group (n=225): · moved to another region (9) · probably did not fit inclusion criteria (23) · use of other medications (1) · non-compliance (1) · no follow-up at 2 months (7) · patient request (1) · adverse event (1) · family member illness (1) · number available for analysis (190, 84.4%) Oral azithromycin (n=221) · moved to another region (9) · probably did not fit inclusion criteria (33) · non-compliance (2) · no follow-up at 2 months (4) · patient request (1) · adverse event (1) · family member illness (1) · number available for analysis (179, 81.0%)

Free of selective reporting?	High risk	"A conjunctival swabbing was taken on days 0, 30 and 60 under strictly sterile conditions and analyzed for *Chlamydia trachomatis* using a polymerase chain reaction. " *Study assessments p668.* The PCR used (name of product used if a commercial assay, or details of method if an in-house assay) are not specified, and no data on PCR positivity are provided, other than the statement "Positivity to *Chlamydia* was not confirmed to be a prognostic factor by the stepwise logistic regression analysis." (*First paragraph, page 669).*
Free of other bias?	High risk	"In order to limit the confounding factors for assessing the outcome of the initial trachoma episode, reinfection risks were strictly controlled. Person coming to the investigation centre with the affected children were to be treated with oral azithromcin. Soap was provided and villagers were informed about well-known environmental risk factors for trachoma" (*Randomisation procedures and treatments p668).* However, no information was provided on the numbers of people offered and accepting this treatment and the potential efficacy of this additional intervention. Any imbalance between the two groups in the extent to which this was taken up

Darougar 1980

Methods	Allocation: randomisation schedule, stratification by age, sex, trachoma intensity, diseased children in family. Unit of randomisation: individual. Masking: participant - no, provider - no, outcome: unclear. Exclusions after randomisation: yes, poor compliers. Losses to follow up: not given by group. Unusual study design: family-based treatment (family members treated but not analysed)
Participants	Country: Iran. Number randomised: 147. Age (ave.): pre-school (5.5 years). Sex: 38% male.

Darougar 1980 (*Continued*)

	Clinical grading: Darougar 1980, 1981. Lab tests: culture (Darougar 1970). Inclusion criteria: active trachoma, residence in study village. Exclusion criteria: none
Interventions	TREATMENT 1: oxytetracycline. Administration: topical. Dose: 1%. Duration: twice daily for 7 consecutive days every month for 12 months TREATMENT 2: doxycycline. Administration: oral. Dose: 5 mg/kg. Duration: one dose per month for 12 months. COMPARISON: vitamin pills Administration: oral. Dose: not reported. Duration: 1 dose per month for 12 months.
Outcomes	Primary: active trachoma. Secondary: culture (McCoy cells). Adverse effects: n.a.
Notes	Some data only in graphical form. Data on whole conjunctiva and upper conjunctiva given. Patients with "active trachoma in their whole conjunctiva" were included. Patients with active disease may have been excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	No information about allocation concealment although the study is described as "double-blind" (abstract page 291)
Blinding? Active trachoma	Unclear risk	No information about the masking although study is described as "double blind" (see above). Treatments are different - topical versus oral antibiotics versus vitamin tablets - so the participants will not have been masked.
Blinding? Ocular Chlamydia trachomatis infection	Unclear risk	See above.
Incomplete outcome data addressed? Active trachoma	High risk	147 patients included; 18 excluded because of inadequate treatment or follow-up; it was not reported to which groups these 18 patients were originally allocated

Darougar 1980 (*Continued*)

Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	High risk	See above.
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	

Dawson 1969 Sherman

Methods	Allocation: random. Unit of randomisation: individual. Masking: participant: yes, provider: yes, outcome: yes. Exclusions after randomisation: no. Losses to follow up: - Unusual study design: two similar studies with few participants each
Participants	Country: USA. Number randomised: 29. Age (ave.): 12 to 21 years. Sex: not reported. Clinical grading: MacCallan 1936 Lab tests: IFAT on conjunctival smears. Inclusion criteria: active disease, boarding at Sherman Institute. Exclusion criteria: none
Interventions	TREATMENT: trisulphapyrimidines. Administration: oral. Dose: 3 daily doses to total 3.5 g/day Duration: 21 consecutive days COMPARISON: lactose-placebo. Administration: oral. Dose: not reported. Duration: 3 daily for 3 consecutive weeks.
Outcomes	Primary: active trachoma. Secondary: positive IFAT (1 - 5 identifiable inclusions per 100 - 1000 cells)
Notes	Participants from Indian reservations. Numbers need to be read from figures, some not very clear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Dawson 1969 Sherman (*Continued*)

Allocation concealment?	Unclear risk	"At each school, a full-time nurse personally administered all drugs and placebos. All materials were coded, and the identify of drug or placebo remained unknown to subjects, nurse, and physicians throughout the trials until all examination results had been recorded" (page 582). This statement suggests that allocation was concealed however it does not tell us who allocated the treatment
Blinding? Active trachoma	Low risk	"At each school, a full-time nurse personally administered all drugs and placebos. All materials were coded, and the identify of drug or placebo remained unknown to subjects, nurse, and physicians throughout the trials until all examination results had been recorded" (page 582)
Blinding? Ocular Chlamydia trachomatis infection	Low risk	The statement above implies that all outcome assessments were masked including laboratory analyses
Incomplete outcome data addressed? Active trachoma	Unclear risk	36 children took part in one school, 29 in the other. All (100%) were followed up. Theoretically they could have recruited more and had some lost to follow-up which they did not report but it is also possible that in a boarding school environment loss to follow-up would be nil. As we cannot distinguish between these two possibilities we have put unclear
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	See above
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	

Dawson 1969 Stewart

Methods	Allocation: random. Unit of randomisation: individual. Masking: participant - yes, provider - yes, outcome - yes. Exclusions after randomisation: no Losses to follow up: - Unusual study design: two similar studies with few participants each
Participants	Country: USA. Number randomised: 36. Age (ave.): 12 to 21 years. Sex: not reported. Clinical grading: Dawson 1966. Lab tests: IFAT on conjunctival smears. Inclusion criteria: active disease, boarding at Stewart School. Exclusion criteria: none.
Interventions	TREATMENT: trisulphapyrimidines. Administration: oral. Dose: 3.5 g/day. Duration: 3 daily during 3 consecutive weeks. COMPARISON: lactose-placebo. Administration: oral. Dose: not reported. Duration: 3 daily for 3 consecutive weeks.
Outcomes	Primary: active trachoma. Secondary: positive IFAT (1 - 5 identifiable inclusions per 100 - 1000 cells)
Notes	Participants from Indian reservations. Numbers need to be read from figures, some not very clear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	"At each school, a full-time nurse personally administered all drugs and placebos. All materials were coded, and the identify of drug or placebo remained unknown to subjects, nurse, and physicians throughout the trials until all examination results had been recorded" (page 582). This statement suggests that allocation was concealed however it does not tell us who allocated the treatment

Dawson 1969 Stewart (*Continued*)

Blinding? Active trachoma	Low risk	"At each school, a full-time nurse personally administered all drugs and placebos. All materials were coded, and the identify of drug or placebo remained unknown to subjects, nurse, and physicians throughout the trials until all examination results had been recorded" (page 582)
Blinding? Ocular Chlamydia trachomatis infection	Low risk	The statement above implies that all outcome assessments were masked including laboratory analyses
Incomplete outcome data addressed? Active trachoma	Unclear risk	36 children took part in one school, 29 in the other. All (100%) were followed up. Theoretically they could have recruited more and had some lost to follow up which they did not report but it is also possible that in a boarding school environment loss to follow up would be nil. As we cannot distinguish between these two possibilities we have put unclear
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	See above.
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	

Dawson 1997

Methods	Allocation: random. Unit of randomisation: blocks of eight. Masking: participant: for azithromycin, provider: no, outcome: yes. Exclusions after randomisation: no. Losses to follow up: absence in village/not found. Unusual study design: oral placebo for different azithromycin regimens, no placebo for topical treatment
Participants	Country: Egypt. Number randomised: 168. Age (ave.): 2 to 10 years (4). Sex: 59.5% male. Clinical grading: Thylefors 1987.

	Lab tests: Thylefors 1987; Dawson 1981. Inclusion criteria: active trachoma, two to 10 years, resident in a study village. Exclusion criteria: missing baseline record.
Interventions	TREATMENT: azithromycin. Administration: oral. Dose: 20 mg/kg Duration: single dose; or single dose weekly for 3 weeks; or single dose monthly for six months COMPARISON: Oxytetracycline/polymyxin + oral placebo. Administration: topical. Dose: oxytetracycline 1%/polymyxin 10,000 units/g. Duration: once daily for 5 consecutive days every 28 days for 6 times
Outcomes	Primary: active trachoma. Secondary: elementary bodies ≤ 200 or > 200 on conjunctival smears. Adverse effects: -
Notes	Epidemic of purulent conjunctivitis at 8/12 years; cut-off for positivity not justified. Three azithromycin regimens analysed together.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	"This clinical trial was double-masked, placebo-controlled, and randomized" (page 364). However, no information about allocation concealment given. Treatment groups were different, for example, no ointment placebo and different dosing schedules for oral antibiotic
Blinding? Active trachoma	Unclear risk	"Ophthalmologists experienced in the diagnosis of trachoma performed all examinations and were masked as to the treatment used" (page 365). However, no details of the masking were given and theoretically, as the treatments were different, the examiners could have been unmasked by their patients
Blinding? Ocular Chlamydia trachomatis infection	Low risk	Assessment of conjunctival specimens will have been easier to mask
Incomplete outcome data addressed? Active trachoma	Low risk	Follow-up rates at 12 months were good from 91% to 98%. Ointment group 42/43, one oral dose 39/40, 3 oral doses 39/43, 6 oral doses 39/42. The groups with larger

Dawson 1997 (*Continued*)

		number of oral doses had lower follow-up rates but these were only 4 and 3 children respectively "In most cases, children were lost to follow-up at specific examinations because they and their family were not in the village or because the child could not be found on the day of the examination." (page 365).
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Low risk	See above.
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	

Foster 1966

Methods	Allocation: random. Unit of randomisation: individuals. Masking: participant: no, provider: no, outcome: yes. Exclusions after randomisation: not reported. Losses to follow-up: yes.
Participants	Country: USA. Number randomised: approx. 305. Age (ave.): 8 to 20 years. Sex: not reported. Clinical grading: Thygeson 1960. Lab tests: - Inclusion criteria: active trachoma, studying in a study school. Exclusion criteria: none.
Interventions	TREATMENT 1: sulphamethoxypyridazine. Administration: oral. Dose: 0.5 g. Duration: once daily for 5 consecutive days every week for 3 weeks TREATMENT 2: tetracycline. Administration: topical. Dose: 1%. Duration: 3 times daily on 5 consecutive days every week for 6 weeks COMPARISON: no treatment.

Foster 1966 (*Continued*)

Outcomes	Primary: active trachoma. Secondary: none. Adverse effects: not recorded.	
Notes	Participants boarding.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Not reported.
Blinding? Active trachoma	Unclear risk	The treatments were different so the students will have known which treatment they received (oral versus topical antibiotic) Clinical outcome: "The examiner had no knowledge of the earlier findings or of the nature of the treatment of the students being examined, and the order of the examinations was randomised" (page 452). Potential for the examiners being told by students which treatment they received
Incomplete outcome data addressed? Active trachoma	High risk	A total of 457 active cases were identified but only results reported for 325 (71%) "For the purpose of analysis, only the 325 students who were examined on all three occasions are included in Tables 3,4 and 5. " (page 452 and 453)
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	No data on ocular infection reported.
Free of selective reporting?	Low risk	Only clinical outcomes recorded but no indication of any assessment of ocular infection
Free of other bias?	Low risk	

Hoshiwara 1973

Methods	Allocation: random. Unit of randomisation: individual. Masking: participant - yes, provider - yes, outcome - yes. Exclusions after randomisation: no. Losses to follow up: poor compliance, lack of sample.
Participants	Country: USA. Number randomised: 120. Age (ave.): 7 to 13 years (9.9). Sex: not reported. Clinical grading: Dawson 1969. Lab tests: IFAT on scrapings of upper tarsal conjunctival epithelium Inclusion criteria: active disease, boarding at study school. Exclusion criteria: none
Interventions	TREATMENT: doxycycline. Administration: oral. Dose: 2.5-4.0 mg/kg. Duration: once daily for 5 consecutive days every week up to 28 doses in 40 days COMPARISON: placebo. Administration: oral. Duration: once daily for 5 consecutive days every week up to 28 doses in 40 days
Outcomes	Primary: active trachoma. Secondary: TRIC-positive immunofluorescent inclusions. Adverse effects: anorexia, nausea, vomiting or diarrhoea.
Notes	Participants boarding. Placebo with 'strong beneficial effect'.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Although the drugs were identical appearance and taste and coded A/B (see below) it was not clear how they were allocated, for example, whether they were sequentially numbered
Blinding? Active trachoma	Unclear risk	"Doxycycline capsules (50 mg) and a placebo of identical appearance and taste were used. Medications were coded as Drug A or Drug B, and the identity remained unknown to subjects, physicians and nursing personnel until the results of all examina-

		tion had been recorded." (page 221) However, since there was a marked improvement in the doxycycline-treated group and the drugs were only labelled A or B, the identity of the active drugs may well have been obvious well before the end of the trial
Blinding? Ocular Chlamydia trachomatis infection	Low risk	"Doxycycline capsules (50 mg) and a placebo of identical appearance and taste were used. Medications were coded as Drug A or Drug B, and the identity remained unknown to subjects, physicians and nursing personnel until the results of all examination had been recorded." (page 221) Laboratory analyses will have been easier to mask effectively,
Incomplete outcome data addressed? Active trachoma	High risk	120 students randomised and 103 (86%) followed up: 54 placebo and 49 active treatment. However, not clear what the original random allocations were "The others had to be eliminated because of definite gaps in intake of medication, because serum levels or drug could not be documented, or because they were unavailable for one or more follow-up examinations" (page 222)
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	High risk	See above.
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	

Lee 2007

Methods	Allocation: random. Unit of randomisation: village. Masking: participant - no, provider - no, outcome - no (active trachoma), yes (*C.trachomatis* infection). Exclusions after randomisation: no. Losses to follow up: no information.
Participants	Country: Ethiopia. Number randomised: 3 villages in each group; 170 children examined in treated villages and 185 in control villages. Age: 1 to 5 years. Sex: not reported. Clinical grading: Dawson 1981. Lab tests: Amplicor polymerase chain reaction (PCR; Roche Diagnostics, Branchburg, NJ) Inclusion criteria: Exclusion criteria:
Interventions	TREATMENT: azithromycin "mass treatment" so presumably whole community treated not just the children. Administration: oral. Dose: not stated. Duration: two doses per year. COMPARISON: no treatment.
Outcomes	Primary: ocular chlamydial infection.
Notes	3 villages randomly selected for treatment as part of national control programme. 3 villages randomly selected out of villages not yet enrolled in national programme for examination as controls

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Active trachoma	High risk	In treated villages children were given oral antibiotic. In control villages, treatment was planned for a later date. So children would have known whether or not they had been treated and probably the person conducting the clinical examinations would also have known which villages had been treated
Blinding? Ocular Chlamydia trachomatis infection	Low risk	"All samples were processed in a masked manner" (page 129). "Samples and controls were labelled with random numbers for processing by masked

		laboratory personnel." (page 130)
Incomplete outcome data addressed? Active trachoma	Unclear risk	Study design - random selection of 3 treated villages and 3 as yet untreated villages in a trachoma control program for survey - meant that all clusters by definition completed the trial No information on numbers of children in villages and percentage seen in survey given so difficult to tell
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	See above.
Free of selective reporting?	Unclear risk	Both microbiological and clinical outcomes collected but only microbiological outcomes reported. However, this appeared to be the main purpose of the trial so it is not clear that this was selective outcome reporting as such
Free of other bias?	Low risk	
Recruitment bias addressed?	Unclear risk	"All children 1-5 years of age were identified through the census and requested to come to a central location with a guardian." (page 129) No information given on response rates to this request for participation
Baseline imbalances addressed?	Unclear risk	Stratified or pair-matched randomisation of clusters was not employed. No baseline characteristics other than prevalence of infection (1) in the conjunctivae of children and (2) in flies caught from children's eyes were reported

Peach 1986

Methods	Allocation: stratified randomisation. Unit of randomisation: community but analysed as individuals Masking: participant - no, provider - no, outcome: no. Exclusions after randomisation: no. Losses to follow up: yes.
Participants	Country: Australia. Number randomised: 641. Age: children 5 to 14 years (plus 5% under 5 and 5% over 14). Sex: not reported. Grading: local version with at least one follicle or some papillary hypertrophy being positive. No lab tests.
Interventions	TREATMENT: oily tetracycline daily for 5 days once a month for 3 months COMPARISON: no treatment.
Outcomes	Primary: active trachoma.
Notes	One arm of a larger trial with components face washing and face washing plus antibiotics

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Active trachoma	Unclear risk	Topical antibiotics versus observation. Communities will have known which treatment group "The trachoma workers did not know what treatment program, if any, had been allocated to a particular community and communities were visited in the same order in which they had initially been screened." (page 76)
Incomplete outcome data addressed? Active trachoma	Low risk	No information on the clusters. "Children lost to follow-up were assumed to have follicles and were included in the analysis on that basis" (page 76) 22/211 (10%) were lost to follow-up in control communities. 34/374 (9%) lost to follow-up in treated communities. These were not large losses to follow up and the assumption that they all have active trachoma is a conservative one which is why we have put yes here

Peach 1986 (*Continued*)

Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	No data on ocular infection reported.
Free of selective reporting?	Low risk	Only clinical outcomes reported but no indication of any collection of data on microbiological outcomes
Free of other bias?	Low risk	

Resnikoff 1995

Methods	Allocation: random. Unit of randomisation: village. Masking: participant - no, provider - no, outcome - no. Exclusions after randomisation: no information. Losses to follow-up: no information.
Participants	Country: Mali. Number randomised: 4 villages randomly allocated to four different interventions. 2 villages only eligible for inclusion in this review. Age: 1 to 5 years. Sex: not reported. Clinical grading: Thylefors 1987. Lab tests: none. Inclusion criteria: all inhabitants. Exclusion criteria: none.
Interventions	TREATMENT: 1% oxytetracycline eye drop solution (Innolyre). 1 drop 4 times daily for 7 days a month for 6 months. Directly supervised by village workers COMPARISON: no treatment.
Outcomes	Primary: active trachoma.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Active trachoma	High risk	This was not reported so we have assumed that it did not happen as treatment was compared to no treatment. The study was described as "open controlled clinical trial" (page 103)

Incomplete outcome data addressed? Active trachoma	High risk	"At the initial examination, 1810 subjects were enrolled and examined" (page 104). Of these, 424 were from the community treated with topical antibiotics (village 2) and 476 were from the control community (village 4) (table 2 page 109) "A total of 347 subjects with active trachoma were included in the clinical trial. Two hundred and sixty five (76%) of these subjects were successfully followed for 6 months and were included in the analysis of the results." (page 105) However, the distribution of these cases by village is not reported. Using figure 1 (page 109) we can estimate that there were 89 cases of active trachoma in treatment community and 90 cases in control community. The "cure rate" in treatment village was 82% (estimated 73 people cured) and 36% in control community (estimated 33 people cured). No information was given on possible reasons for loss to follow up
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	No data on ocular infection reported.
Free of selective reporting?	Low risk	Only clinical outcomes reported but no indication that microbiological data collected
Free of other bias?	Low risk	
Recruitment bias addressed?	Unclear risk	"With the permission of administrative and traditional authorities, all inhabitants of these four villages were surveyed" (page 102). No other information on recruitment in particular no indication as to response rates of the survey in the villages concerned
Baseline imbalances addressed?	High risk	"Four villages, matched for size and epidemiological, economic and social conditions, were included in the study. All villages were situated the same distance from the health centre and each village possessed a school and was equipped with boreholes. " (page 102) (NB: two of these villages concerned health education and data from

Resnikoff 1995 (*Continued*)

		these not included in this review) "The age and sex distribution was identical in all four villages" (page 103). Table 2 (page 109) shows the sex distribution (46% male in treatment community and 51% male in control community). No data on age distribution Baseline prevalence of active trachoma (figure 1, page 109) just over 20% in treatment community and just under 20% in control community

Shukla 1966

Methods	Type of trial: clinical. Allocation: random. Unit of randomisation: individual. Masking: participant - no, provider - no, outcome: - unclear. Exclusions after randomisation: no. Losses to follow up: none. Unusual study design: four-armed trial with factorial design
Participants	Country: India. Number randomised: 349. Age (ave.): 5 to 13 years. Sex: not reported. Clinical grading: WHO 1962. Lab tests: none. Inclusion criteria: active trachoma, schooling at a study school. Exclusion criteria: none.
Interventions	TREATMENT 1: sulphafurazole + sulphadimethoxine. Administration: topical + oral. Dose: 15%/100 mg/kg. Duration: twice daily for 5 consecutive days every month for 5 months/bi-weekly for 5 months TREATMENT 2: sulphadimethoxine. Administration: oral. Dose: 100 mg/kg. Duration: biweekly or weekly dose for 5 months. TREATMENT 3: sulphafurazole. Administration: topical. Dose: 15%. Duration: twice daily for 5 consecutive days every month for 5 months COMPARISON: no treatment.

Shukla 1966 (*Continued*)

Outcomes	Primary: active trachoma. Secondary: -
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	No information given .
Blinding? Active trachoma	High risk	No information given and treatments different in the different groups so study unlikely to have been blinded. However, study is described as "double-blind study"
Incomplete outcome data addressed? Active trachoma	Unclear risk	Apparently 100% follow up with exception of one group B1 at five months where 35/41 seen
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	No data on ocular infection reported.
Free of selective reporting?	Low risk	Only clinical outcomes reported but no indication that microbiological data collected
Free of other bias?	Unclear risk	Report too brief to assess.

Tabbara 1996

Methods	Type of trial: clinical. Allocation: random. Unit of randomisation: individual. Masking: participant - no, provider - no, outcome - yes. Exclusions after randomisation: no. Losses to follow up: absence.
Participants	Country: Saudi Arabia. Number randomised: 64. Age (ave.): 6 to 14 years (11.1). Sex: not reported. Clinical grading: Dawson 1981. Lab tests: conjunctival scrapings for inclusion bodies/cells/organisms/mucus; IFAT for free elementary bodies Inclusion criteria: active trachoma, schooling in study village.

Tabbara 1996 (*Continued*)

	Exclusion criteria: none.
Interventions	TREATMENT: azithromycin. Administration: oral. Dose: 20 mg/kg. Duration: 1 dose. COMPARISON: tetracycline. Administration: topical. Dose: 1%. Duration: twice daily for 5 consecutive days per week over 6 weeks
Outcomes	Primary: active trachoma. Secondary: intraepithelial cell inclusion bodies, free elementary bodies. Adverse effects: none.
Notes	Case definition not clear (probable diagnosis of trachoma based on cytology, definitive diagnosis of trachoma based on microscopical assessment of scrapings)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Not reported.
Blinding? Active trachoma	Unclear risk	Study was described as "single-masked" (page 843). Patients were aware of therapy because oral versus topical treatment "The examiner was unaware of the treatment allocation at the time of the examination" (page 843) No information on whether the masking was effective - for example, did the patients tell the examiners which treatment they had received?
Blinding? Ocular Chlamydia trachomatis infection	Low risk	"Conjunctival scrapings were obtained from each patient before initiation of therapy" "The slides were coded and masked to the reader" (page 843)
Incomplete outcome data addressed? Active trachoma	Unclear risk	It was not clear how many randomised to treatment/control but reported percentages suggest that it was 32 in each group 8 weeks: treatment 2/32 (6.3%) and control 5/32 (15.6%) lost to follow up 12 weeks: treatment 1/32 (3.1%) and control 3/32 (9.4%) lost to follow up 24 weeks: treatment 2/32 (6.3%) and control 6/32 (18.8%) lost to follow up

		Higher loss to follow up in control group but actual numbers not very large. No indication as to reason for not being seen. We have put "unclear" here because not sure what the effect of these missing data will be
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	See above.
Free of selective reporting?	Low risk	Both outcomes of relevance to this review reported.
Free of other bias?	Low risk	

TANA 2009

Methods	Cluster-randomised trial. 72 subkebeles (government defined units) randomised to treatment or delayed treatment. Six treatment groups of 12 subkebeles each
Participants	People resident in these communities. Different members of the population were treated according to the treatment schedule being tested (see interventions below)
Interventions	(1) Children aged 1-10 were offered oral azithromycin 4 times per year. Height based dosing equivalent to roughly 20 mg/Kg. Treatment directly observed. Children younger than 1 year were offered a 6-week course of topical tetracycline 1% (not directly observed). Children and adults aged 11 years and above were assessed for ocular chlamydial infection at 12 months (2) Treatment was delayed and delivered at 12 months. Children and adults aged 11 years and above were assessed for ocular chlamydial infection at 12 months (3) Annual mass treatment. All individuals aged 1 year and older were offered oral azithromycin as for (1). Women self-reporting as pregnant or children under 1 year offered topical tetracycline (4) Biannual mass treatment as for (3). [Treatment groups (5) and (6) refer to evaluation of benefits of added Intensive latrine construction and are outwith the remit of this review).] The following information about the overall study aims was obtained from the trial registration information on ClinicalTrials.gov *"The proposed study is a group-randomized trial to determine the frequency and treatment target of community-wide mass antibiotic treatment to eliminate trachoma. We will also study the impact of community-wide antibiotic distribution on antibiotic-resistance in pneumococcus. Communities in Goncha Siso Enese district of East Gojam Zone, Ethiopia will be randomly assigned to different treatment schemes and monitored to study the following research questions:* *Specific Aim 1. To determine whether biannual mass treatments is more likely to eliminate ocular chlamydia from hyper-endemic communities than annual mass treatments.* *Specific Aim 2. To determine whether children form a core group for the transmission of trachoma.* *Specific Aim 3. To determine whether latrine construction prevents the return of infection*

	into a community after mass treatment. *Specific Aim 4. To determine the effect of mass azithromycin treatments on antibiotic resistance in pneumococcus and the reduction in mortality."* As at April 2010, there are two publications available from this study. House et al addresses study aim 2 but has a slightly different emphasis - *"Assessment of herd protection against trachoma due to repeated mass antibiotic distributions: a cluster-randomised trial"*. Porco et al address part of aim 4 looking at mortality in Ethiopian children. *"Effect of Mass Distribution of Azithromycin for Trachoma Control on Overall Mortality in Ethiopian Children"*.
Outcomes	The following information about outcomes was obtained from the trial registration information on ClinicalTrials.gov *"Primary Outcome Measures:* • *The average prevalence of ocular chlamydia infection in communities in an arm as determined by pooled NAAT (Nucleic Acid Amplification Test)(at 42 months for Aim 1, at 12 months for Aim 2, post-treatment relative to pre-treatment for Aim 3) [Time Frame: 42 months] [Designated as safety issue: No]* *Secondary Outcome Measures:* • *Clinical active trachoma in community, as determined by the WHO simplified grading system [Time Frame: 42 months] [Designated as safety issue: No]* • *Childhood (>= 1 year of age) mortality, analyzed as 1-5, 6-10 years of age, and total [Time Frame: 42 months] [Designated as safety issue: No]* • *Macrolide resistance in pneumococcus (% resistance over time, clustered by randomization unit) [Time Frame: 42 months] [Designated as safety issue: No]"*
Notes	ClnicalTrials.gov identifier: NCT00322972 TANA: Trachoma Amelioration in Northern Amhara

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	"The 72 subkebeles were randomly assigned to one of six groups of 12 subkebeles each, forming three separate trachoma-specific comparisons (generation by KJR with RANDOM() and SORT() in Excel [version 2003], implementation by BA, concealed until assignment)." (*House et al Lancet 2009, page 1112).*
Blinding? Active trachoma	Unclear risk	"Censuses for all study communities were undertaken by trained health-care personnel who were blinded to study group and to the prevalence of ocular chlamydial infection".*House et al Lancet 2009, page 1112.* However, no mention of masking of clinical observers.

Blinding? Ocular Chlamydia trachomatis infection	Low risk	"Laboratory personnel were blinded to individual, community, and treatment-group identifications. Since dilution effects and underestimation due to pooling could theoretically occur, all communities had to be processed in an identical way, and complete masking of laboratory personnel had to be maintained." (*House et al Lancet 2009, page 1114).*
Incomplete outcome data addressed? Active trachoma	Unclear risk	Data not reported.
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Low risk	Random sample selected for measurement of ocular infection. 637/720 (88%) children seen in "children-treated" group, 618/720 (86%) children seen in control group (delayed treatment) and 600/720 (83%) children seen in mass treatment group. Equivalent measures for children>=11 and adults: 561/720 (78%); 550/720 (76%); 599/720 (83%)
Free of selective reporting?	Low risk	Currently data available for aim 2 of original study. Outcomes reported match those specified at trial registration
Free of other bias?	Low risk	
Recruitment bias addressed?	Low risk	No information reported however we believe that this is unlikely because in all arms treatment was offered at the same time as assessment
Baseline imbalances addressed?	Low risk	Pre-treatment age, sex, ocular and clinical infection in children reported at baseline for treated communities and 12 months for untreated communities. No major imbalances reported. (*House et al 2009. Table 1)* .

Woolridge 1967

Methods	Allocation: random. Unit of randomisation: individual. Masking: participant: no, provider: no, outcome: yes. Exclusions after randomisation: unclear. Losses to follow up: unclear. Unusual study design: combined vaccine and therapy trial. Review considers groups with placebo-vaccine
Participants	Country: Taiwan. Number randomised: 322. Age (ave.): primary school age. Sex: not reported. Clinical grading: Modified McCallan classification. Lab tests: none. Inclusion criteria: active trachoma. Exclusion criteria: none.
Interventions	TREATMENT: tetracycline. Administration: topical. Dose: 1%. Duration: twice daily for 6 consecutive days per week for 6 weeks COMPARISON: no treatment.
Outcomes	Primary: active trachoma. Secondary: none. Adverse effects: not assessed.
Notes	Only trachoma-positives included, but table does not show this. Numbers for analysis calculated from percentages given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Not reported.
Blinding? Active trachoma	Unclear risk	"The ophthalmologists making the eye examinations at no time knew to which vaccine or treatment group the subject belonged nor what his previous diagnosis had been" (page 1578) "Placebo therapy was not employed" (page 1578). No discussion as to whether the ophthalmologists might have been unmasked because the patients knew their treatment

Woolridge 1967 (*Continued*)

		group
Incomplete outcome data addressed? Active trachoma	Unclear risk	No information on completeness of follow up.
Incomplete outcome data addressed? Ocular Chlamydia trachomatis infection	Unclear risk	Data on ocular infection not reported.
Free of selective reporting?	Low risk	Active trachoma only reported but no indication any data collected on *C. trachomatis* infection.
Free of other bias?	Low risk	

ITT - intention to treat
mg/kg - milligrams per kilogram of body weight
LCR - ligase chain reaction
PCR - polymerase chain reaction
Ave. - average

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdou 2007	Prevalence study only.
Assaad 1968	Concealment of allocation: C (twice randomisation among two groups)
Astle 2006	Prevalence study only.
Babbar 1982	No comparison group receiving placebo or no treatment.
Biebesheimer 2009	No comparator villages.
Bietti 1967	Review only.
Broman 2006	Not randomised controlled trial.
Cerulli 1983	No evidence of randomisation.
Chumbley 1988	No comparison group receiving placebo or no treatment.
Daghfous 1974	No evidence of randomisation.

(*Continued*)

Daghfous 1985	No comparison group receiving placebo or no treatment. No evidence of randomisation.
Darougar 1980a	No comparison group receiving placebo or no treatment.
Darougar 1981	No comparison group.
Dawson 1967a	Allocation concealment inadequate (alternation).
Dawson 1967b	Allocation concealment inadequate (alternation).
Dawson 1968	No evidence of randomisation.
Dawson 1971	Allocation concealment inadequate (alternation).
Dawson 1972a	No evidence of randomisation.
Dawson 1972b	No evidence of randomisation.
Dawson 1974a	No evidence of randomisation.
Dawson 1974b	Allocation concealment inadequate.
Dawson 1975a	Allocation concealment inadequate.
Dawson 1981a	No proper control group (previously treated children who did not receive treatment during actual trial)
Dawson 1982	No comparison group receiving placebo or no treatment.
Edwards 2006	Health education intervention.
Gower 2006	Not randomised controlled trial.
Gupta 1966	No evidence of randomisation.
Gupta 1968	No comparison group receiving placebo or no treatment.
Guzey 2000	Inclusion criteria of participants non-specific. They had bilateral trachoma or showed symptoms (not described)
Hasan 1976	No comparison group receiving placebo or no treatment.
Humet 1989	No eye outcome.
Isenberg 2002	Study not carried out in a trachoma endemic area.
Ji 1986	No trial report.

(*Continued*)

Kamiya 1956	Lack of comparison villages.
Khandekar 2006	Prevalence study.
Lakew 2009	No comparator villages
Litricin 1968	No comparison group.
Mesfin 2006	Prevalence study
Mohan 1982	No evidence of randomisation.
Nabli 1988	No comparison group.
Ngondi 2006a	Prevalence study.
Ngondi 2006b	No antibiotic/no antibiotic comparison.
Nisbet 1979	Placebo invalid.
Obikili 1988	No comparison group.
Putschky 2006	No eye outcome.
Reinhards 1959	No comparison group.
Resnikoff 1994	No comparison group.
Schemann 2007	Comparison of different treatment targeting strategies therefore does not meet inclusion criteria for review
Tabbara 1988	Randomisation was by eye and not patient. It was not possible to determine the individual patient outcome
Toufic 1968	Report of control campaigns not trials.
Wadia 1980	No comparison group.
Werner 1977	No comparison group. No evidence of randomisation.
West 2006	Test efficacy of insecticide.
Whitcher 1974	No evidence of randomisation.
Zhang 2006	No appropriate control group.

DATA AND ANALYSES

Comparison 1. Any antibiotic versus control (individuals)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active trachoma at three months	9	1961	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.69, 0.89]
2 Ocular *C.trachomatis* infection at three months	4	297	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.04]
3 Active trachoma at 12 months	4	1035	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.55, 1.00]
4 Ocular *C. trachomatis* infection at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 2. Subgroup analysis: oral and topical antibiotics versus control (individuals)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active trachoma at three months	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Oral antibiotic	6	599	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.97]
1.2 Topical antibiotic	6	1478	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.72, 0.92]
2 Ocular *C. trachomatis* infection at three months	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Oral antibiotic	4	259	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.11]
2.2 Topical antibiotic	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.37]
3 Active trachoma at 12 months	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Oral antibiotic	3	429	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.00]
3.2 Topical antibiotic	4	724	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.71, 0.88]
4 Ocular *C. trachomatis* infection at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Oral antibiotic	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.10, 1.23]
4.2 Topical antibiotic	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.04]

Comparison 3. Oral versus topical antibiotics (individuals)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active trachoma at three months	6	953	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.18]
2 Ocular *C. trachomatis* infection at three months	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Active trachoma at 12 months	5	886	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.15]

4 Ocular *C. trachomatis* infection at 12 months	2	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Oral azithromycin versus topical tetracycline (individuals)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active trachoma at three months	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Ocular *C. trachomatis* infection at three months	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Active trachoma at 12 months	2	447	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.59, 0.99]
4 Ocular *C. trachomatis* infection at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Oral azithromycin versus control (communities)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active trachoma at 12 months	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Ocular *C. trachomatis* infection at 12 months	4	4345	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.21, 0.60]

Comparison 6. Oral azithromycin versus topical tetracycline (communities)

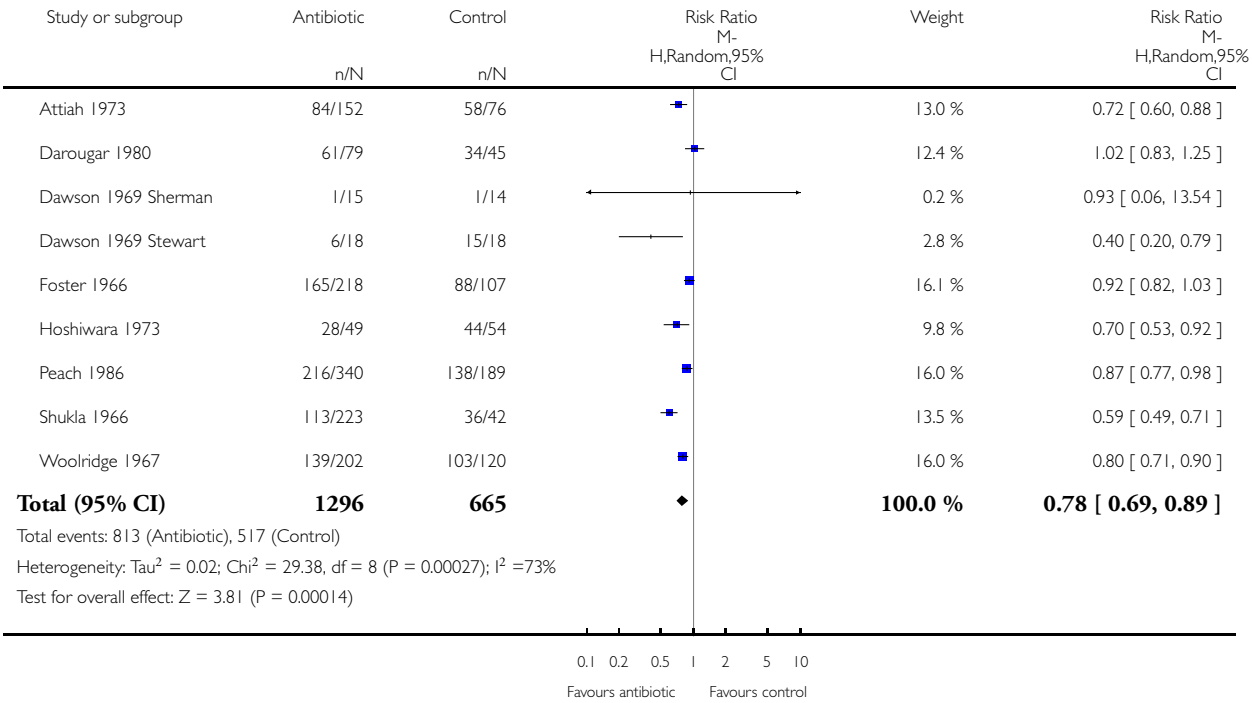
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active trachoma at 3 months	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Ocular *C. trachomatis* infection at 3 months	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Active trachoma at 12 months	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Ocular *C. trachomatis* infection at 12 months	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Any antibiotic versus control (individuals), Outcome 1 Active trachoma at three months.

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 1 Active trachoma at three months



Analysis 1.2. Comparison 1 Any antibiotic versus control (individuals), Outcome 2 Ocular C.trachomatis infection at three months.

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

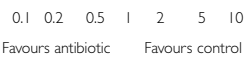
Outcome: 2 Ocular *C.trachomatis* infection at three months

Study or subgroup	Antibiotic n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Darougar 1980	8/82	7/47		7.1 %	0.66 [0.25, 1.69]
Dawson 1969 Sherman	7/15	10/14		15.9 %	0.65 [0.35, 1.23]
Dawson 1969 Stewart	11/18	14/18		32.4 %	0.79 [0.50, 1.22]
Hoshiwara 1973	24/49	29/54		44.6 %	0.91 [0.62, 1.33]
Total (95% CI)	**164**	**133**		**100.0 %**	**0.81 [0.63, 1.04]**

Total events: 50 (Antibiotic), 60 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.03$, df = 3 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 1.68 (P = 0.093)



Analysis 1.3. Comparison 1 Any antibiotic versus control (individuals), Outcome 3 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 3 Active trachoma at 12 months

Study or subgroup	Antibiotic n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Darougar 1980	43/82	33/47		22.7 %	0.75 [0.57, 0.99]
Foster 1966	145/218	68/107		25.9 %	1.05 [0.88, 1.24]
Shukla 1966	91/217	35/42		24.9 %	0.50 [0.41, 0.62]
Woolridge 1967	121/202	95/120		26.5 %	0.76 [0.65, 0.88]
Total (95% CI)	**719**	**316**		**100.0 %**	**0.74 [0.55, 1.00]**
Total events: 400 (Antibiotic), 231 (Control)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 29.16$, df = 3 (P<0.00001); I^2 =90%					
Test for overall effect: Z = 1.96 (P = 0.050)					

Analysis 1.4. Comparison 1 Any antibiotic versus control (individuals), Outcome 4 Ocular C. trachomatis infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 4 Ocular *C. trachomatis* infection at 12 months

Study or subgroup	Antibiotic n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Darougar 1980	4/82	9/47			0.25 [0.08, 0.78]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 4 (Antibiotic), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

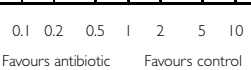
Analysis 2.1. Comparison 2 Subgroup analysis: oral and topical antibiotics versus control (individuals), Outcome 1 Active trachoma at three months.

Review: Antibiotics for trachoma

Comparison: 2 Subgroup analysis: oral and topical antibiotics versus control (individuals)

Outcome: 1 Active trachoma at three months

Study or subgroup	Antibiotic n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Oral antibiotic					
Darougar 1980	32/42	34/45		21.7 %	1.01 [0.80, 1.28]
Dawson 1969 Sherman	1/15	1/14		0.5 %	0.93 [0.06, 13.54]
Dawson 1969 Stewart	6/18	15/18		5.9 %	0.40 [0.20, 0.79]
Foster 1966	86/112	88/107		28.7 %	0.93 [0.82, 1.07]
Hoshiwara 1973	28/49	44/54		19.3 %	0.70 [0.53, 0.92]
Shukla 1966	53/83	36/42		23.9 %	0.74 [0.61, 0.91]
Subtotal (95% CI)	**319**	**280**		**100.0 %**	**0.81 [0.67, 0.97]**
Total events: 206 (Antibiotic), 218 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 12.52, df = 5 (P = 0.03); I^2 =60%					
Test for overall effect: Z = 2.26 (P = 0.024)					
2 Topical antibiotic					
Attiah 1973	84/152	58/76		15.8 %	0.72 [0.60, 0.88]
Darougar 1980	29/37	34/45		13.0 %	1.04 [0.82, 1.32]
Foster 1966	79/106	88/107		19.2 %	0.91 [0.79, 1.04]
Peach 1986	216/340	138/189		20.9 %	0.87 [0.77, 0.98]
Shukla 1966	29/62	36/42		10.3 %	0.55 [0.41, 0.73]
Woolridge 1967	139/202	103/120		20.9 %	0.80 [0.71, 0.90]
Subtotal (95% CI)	**899**	**579**		**100.0 %**	**0.82 [0.72, 0.92]**
Total events: 576 (Antibiotic), 457 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 15.77, df = 5 (P = 0.01); I^2 =68%					
Test for overall effect: Z = 3.30 (P = 0.00097)					



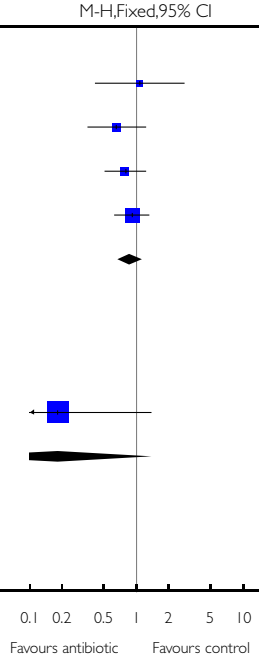
Analysis 2.2. Comparison 2 Subgroup analysis: oral and topical antibiotics versus control (individuals), Outcome 2 Ocular C. trachomatis infection at three months.

Review: Antibiotics for trachoma

Comparison: 2 Subgroup analysis: oral and topical antibiotics versus control (individuals)

Outcome: 2 Ocular *C. trachomatis* infection at three months

Study or subgroup	Antibiotic n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oral antibiotic					
Darougar 1980	7/44	7/47		11.5 %	1.07 [0.41, 2.80]
Dawson 1969 Sherman	7/15	10/14		17.6 %	0.65 [0.35, 1.23]
Dawson 1969 Stewart	11/18	14/18		23.8 %	0.79 [0.50, 1.22]
Hoshiwara 1973	24/49	29/54		47.0 %	0.91 [0.62, 1.33]
Subtotal (95% CI)	**126**	**133**		**100.0 %**	**0.85 [0.66, 1.11]**
Total events: 49 (Antibiotic), 60 (Control)					
Heterogeneity: Chi^2 = 1.14, df = 3 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 1.17 (P = 0.24)					
2 Topical antibiotic					
Darougar 1980	1/38	7/47		100.0 %	0.18 [0.02, 1.37]
Subtotal (95% CI)	**38**	**47**		**100.0 %**	**0.18 [0.02, 1.37]**
Total events: 1 (Antibiotic), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.66 (P = 0.098)					



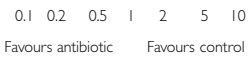
Analysis 2.3. Comparison 2 Subgroup analysis: oral and topical antibiotics versus control (individuals), Outcome 3 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 2 Subgroup analysis: oral and topical antibiotics versus control (individuals)

Outcome: 3 Active trachoma at 12 months

Study or subgroup	Antibiotic n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oral antibiotic					
Darougar 1980	24/44	33/47		21.7 %	0.78 [0.56, 1.08]
Foster 1966	80/112	68/107		47.4 %	1.12 [0.93, 1.35]
Shukla 1966	36/77	35/42		30.9 %	0.56 [0.43, 0.74]
Subtotal (95% CI)	**233**	**196**		**100.0 %**	**0.87 [0.76, 1.00]**
Total events: 140 (Antibiotic), 136 (Control)					
Heterogeneity: Chi^2 = 17.63, df = 2 (P = 0.00015); I^2 =89%					
Test for overall effect: Z = 1.90 (P = 0.057)					
2 Topical antibiotic					
Darougar 1980	19/38	33/47		11.4 %	0.71 [0.49, 1.03]
Foster 1966	65/106	68/107		26.2 %	0.96 [0.78, 1.19]
Shukla 1966	35/62	35/42		16.2 %	0.68 [0.52, 0.88]
Woolridge 1967	121/202	95/120		46.2 %	0.76 [0.65, 0.88]
Subtotal (95% CI)	**408**	**316**		**100.0 %**	**0.79 [0.71, 0.88]**
Total events: 240 (Antibiotic), 231 (Control)					
Heterogeneity: Chi^2 = 5.58, df = 3 (P = 0.13); I^2 =46%					
Test for overall effect: Z = 4.33 (P = 0.000015)					

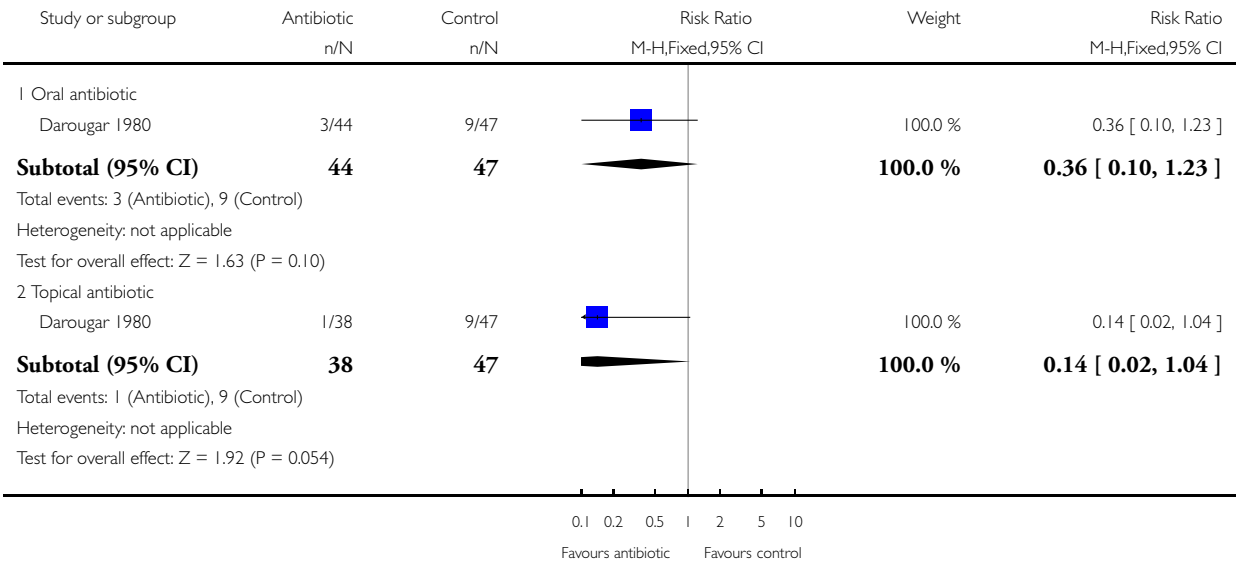


Analysis 2.4. Comparison 2 Subgroup analysis: oral and topical antibiotics versus control (individuals), Outcome 4 Ocular C. trachomatis infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 2 Subgroup analysis: oral and topical antibiotics versus control (individuals)

Outcome: 4 Ocular *C. trachomatis* infection at 12 months



Analysis 3.1. Comparison 3 Oral versus topical antibiotics (individuals), Outcome 1 Active trachoma at three months.

Review: Antibiotics for trachoma

Comparison: 3 Oral versus topical antibiotics (individuals)

Outcome: 1 Active trachoma at three months

Study or subgroup	Oral antibiotic n/N	Topical antibiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bowman 2000	48/152	68/139		16.4 %	0.65 [0.48, 0.86]
Darougar 1980	32/42	29/37		18.9 %	0.97 [0.77, 1.23]
Dawson 1997	76/118	28/42		18.2 %	0.97 [0.75, 1.24]
Foster 1966	86/112	79/106		23.8 %	1.03 [0.89, 1.20]
Shukla 1966	53/83	29/62		15.3 %	1.37 [1.00, 1.86]
Tabbara 1996	15/31	12/29		7.4 %	1.17 [0.66, 2.06]
Total (95% CI)	**538**	**415**		**100.0 %**	**0.98 [0.82, 1.18]**

Total events: 310 (Oral antibiotic), 245 (Topical antibiotic)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 13.48$, df = 5 (P = 0.02); $I^2 = 63\%$

Test for overall effect: Z = 0.18 (P = 0.85)

Analysis 3.2. Comparison 3 Oral versus topical antibiotics (individuals), Outcome 2 Ocular C. trachomatis infection at three months.

Review: Antibiotics for trachoma

Comparison: 3 Oral versus topical antibiotics (individuals)

Outcome: 2 Ocular *C. trachomatis* infection at three months

Study or subgroup	Oral antibiotic n/N	Topical antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Darougar 1980	7/44	1/38		6.05 [0.78, 46.95]
Dawson 1997	5/119	3/41		0.57 [0.14, 2.30]
Tabbara 1996	6/30	4/26		1.30 [0.41, 4.11]

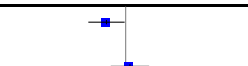
Analysis 3.3. Comparison 3 Oral versus topical antibiotics (individuals), Outcome 3 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 3 Oral versus topical antibiotics (individuals)

Outcome: 3 Active trachoma at 12 months

Study or subgroup	Oral antibiotic n/N	Topical antibiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bowman 2000	32/149	45/139		16.4 %	0.66 [0.45, 0.98]
Darougar 1980	24/44	19/38		15.2 %	1.09 [0.72, 1.66]
Dawson 1997	60/117	24/42		20.3 %	0.90 [0.65, 1.23]
Foster 1966	80/112	65/106		28.3 %	1.16 [0.96, 1.41]
Shukla 1966	36/77	35/62		19.8 %	0.83 [0.60, 1.14]
Total (95% CI)	**499**	**387**		**100.0 %**	**0.93 [0.75, 1.15]**
Total events: 232 (Oral antibiotic), 188 (Topical antibiotic)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 9.13, df = 4 (P = 0.06); I^2 =56%					
Test for overall effect: Z = 0.65 (P = 0.52)					



Analysis 3.4. Comparison 3 Oral versus topical antibiotics (individuals), Outcome 4 Ocular C. trachomatis infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 3 Oral versus topical antibiotics (individuals)

Outcome: 4 Ocular *C. trachomatis* infection at 12 months

Study or subgroup	Oral antibiotic n/N	Topical antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Darougar 1980	3/44	1/38		2.59 [0.28, 23.88]
Dawson 1997	8/105	5/33		0.50 [0.18, 1.43]

Analysis 4.1. Comparison 4 Oral azithromycin versus topical tetracycline (individuals), Outcome 1 Active trachoma at three months.

Review: Antibiotics for trachoma

Comparison: 4 Oral azithromycin versus topical tetracycline (individuals)

Outcome: 1 Active trachoma at three months

Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Bowman 2000	48/152	68/139		0.65 [0.48, 0.86]
Dawson 1997	76/118	28/42		0.97 [0.75, 1.24]
Tabbara 1996	15/31	12/29		1.17 [0.66, 2.06]

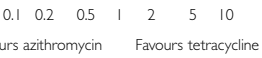
Analysis 4.2. Comparison 4 Oral azithromycin versus topical tetracycline (individuals), Outcome 2 Ocular *C. trachomatis* infection at three months.

Review: Antibiotics for trachoma

Comparison: 4 Oral azithromycin versus topical tetracycline (individuals)

Outcome: 2 Ocular *C. trachomatis* infection at three months

Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Dawson 1997	5/119	3/41		0.57 [0.14, 2.30]
Tabbara 1996	6/30	4/26		1.30 [0.41, 4.11]



Analysis 4.3. Comparison 4 Oral azithromycin versus topical tetracycline (individuals), Outcome 3 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 4 Oral azithromycin versus topical tetracycline (individuals)

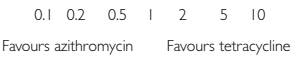
Outcome: 3 Active trachoma at 12 months

Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bowman 2000	32/149	45/139		56.9 %	0.66 [0.45, 0.98]
Dawson 1997	60/117	24/42		43.1 %	0.90 [0.65, 1.23]
Total (95% CI)	**266**	**181**		**100.0 %**	**0.76 [0.59, 0.99]**

Total events: 92 (Oral azithromycin), 69 (Topical tetracycline)

Heterogeneity: Chi^2 = 1.50, df = 1 (P = 0.22); I^2 =33%

Test for overall effect: Z = 2.07 (P = 0.038)



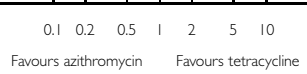
Analysis 4.4. Comparison 4 Oral azithromycin versus topical tetracycline (individuals), Outcome 4 Ocular C. trachomatis infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 4 Oral azithromycin versus topical tetracycline (individuals)

Outcome: 4 Ocular *C. trachomatis* infection at 12 months

Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dawson 1997	8/105	5/33		0.50 [0.18, 1.43]



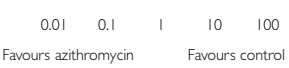
Analysis 5.1. Comparison 5 Oral azithromycin versus control (communities), Outcome 1 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 5 Oral azithromycin versus control (communities)

Outcome: 1 Active trachoma at 12 months

Study or subgroup	Oral azithromycin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Atik 2006	21/523	35/994		1.14 [0.67, 1.94]
TANA 2009	258/634	429/613		0.58 [0.52, 0.65]



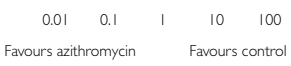
Analysis 5.2. Comparison 5 Oral azithromycin versus control (communities), Outcome 2 Ocular C. trachomatis infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 5 Oral azithromycin versus control (communities)

Outcome: 2 Ocular *C. trachomatis* infection at 12 months

Study or subgroup	Oral azithromycin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Atik 2006	23/659	68/1192		27.1 %	0.61 [0.39, 0.97]
Chidambaram 2006	51/513	82/408		30.3 %	0.49 [0.36, 0.68]
Lee 2007	2/170	56/185		10.2 %	0.04 [0.01, 0.16]
TANA 2009	88/600	282/618		32.4 %	0.32 [0.26, 0.40]
Total (95% CI)	**1942**	**2403**		**100.0 %**	**0.35 [0.21, 0.60]**
Total events: 164 (Oral azithromycin), 488 (Control)					
Heterogeneity: Tau^2 = 0.22; Chi^2 = 19.95, df = 3 (P = 0.00017); I^2 =85%					
Test for overall effect: Z = 3.85 (P = 0.00012)					



Analysis 6.1. Comparison 6 Oral azithromycin versus topical tetracycline (communities), Outcome 1 Active trachoma at 3 months.

Review: Antibiotics for trachoma

Comparison: 6 Oral azithromycin versus topical tetracycline (communities)

Outcome: 1 Active trachoma at 3 months

Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACT 1999 Egypt	141/1050	199/775		0.52 [0.43, 0.64]
ACT 1999 Tanzania	343/1535	200/1042		1.16 [1.00, 1.36]
ACT 1999 The Gambia	38/818	48/782		0.76 [0.50, 1.15]

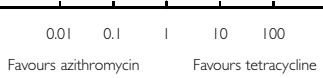
Analysis 6.2. Comparison 6 Oral azithromycin versus topical tetracycline (communities), Outcome 2 Ocular C. trachomatis infection at 3 months.

Review: Antibiotics for trachoma

Comparison: 6 Oral azithromycin versus topical tetracycline (communities)

Outcome: 2 Ocular *C. trachomatis* infection at 3 months

Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACT 1999 Egypt	10/1026	34/756		0.22 [0.11, 0.44]
ACT 1999 Tanzania	64/1510	64/1028		0.68 [0.49, 0.95]
ACT 1999 The Gambia	52/749	96/704		0.51 [0.37, 0.70]



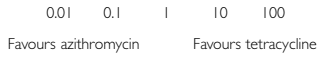
Analysis 6.3. Comparison 6 Oral azithromycin versus topical tetracycline (communities), Outcome 3 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 6 Oral azithromycin versus topical tetracycline (communities)

Outcome: 3 Active trachoma at 12 months

Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACT 1999 Egypt	149/1031	178/910		0.74 [0.61, 0.90]
ACT 1999 Tanzania	333/1351	191/925		1.19 [1.02, 1.40]
ACT 1999 The Gambia	58/675	82/522		0.55 [0.40, 0.75]



Analysis 6.4. Comparison 6 Oral azithromycin versus topical tetracycline (communities), Outcome 4 Ocular C. trachomatis infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 6 Oral azithromycin versus topical tetracycline (communities)

Outcome: 4 Ocular *C. trachomatis* infection at 12 months

Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
ACT 1999 Egypt	30/1013	56/901		0.48 [0.31, 0.74]
ACT 1999 Tanzania	108/1327	73/909		1.01 [0.76, 1.35]
ACT 1999 The Gambia	53/636	66/490		0.62 [0.44, 0.87]

ADDITIONAL TABLES

Table 1. Antibiotics: trial in individuals

	Study	Oral antibiotic	Oral antibiotic dose	Oral antibiotic schedule	Oral antibiotic comments	Topical antibiotic	Topical antibiotic dose	Topical antibiotic schedule	Topical antibiotic comments
1	Attiah 1973					Tetracycline	0.25%	1x daily for 11 weeks	School days only
2	Bailey 1993	Azithromycin	20 mg/kg	single dose	Not given to pregnant or lactating women	Tetracycline	1%	2x daily for six weeks	People with "severe disease" were also given erythromycin 250mg 4x daily for two weeks
3	Bowman 2000*	Azithromycin	20 mg/kg	single dose		Tetracycline	not reported	2x daily for six weeks	Unsupervised administration
4	Cochereau 2007	Azithromycin	20 mg/Kg	single dose	Persons accompanying children enrolled in the trial were treated with oral azithromycin; soap and health education provided	Azithromycin	1.5%	2x daily for 2 days and 3 days	Persons accompanying children enrolled in the trial were treated with oral azithromycin; soap and health education provided
5	Darougar 1980	Doxycycline	5 mg/kg	1x monthly for 12 months		Oxytetracycline	1%	2x daily for 7 days, every month for 12 months	consecutive days
6& 7	Dawson 1969 (Sherman and	Trisulphapyrimidines	3.5 g	3x daily for 21 days	3 daily doses to total 3.5g/day	Oxytetracycline	1%	1 drop 4x daily for 7 days, every months for	consecutive days

Table 1. Antibiotics: trial in individuals (*Continued*)

	Sterwart)							6 months	
8	Dawson 1997*	Azithromycin	20 mg/kg	single dose; single dose weekly for 3 weeks; single dose monthly for six months	three different dosing schedules	Oxytetracycline/ polymyxin	1% / 10, 000 units per g	1x daily for 5 days, every month for 6 months	
9	Foster 1966	Sulphamethoxypyridazine	500 mg/ day	1x daily for 5 days, every week for 3 weeks.		Tetracycline	1%	3x daily for 5 days, every week for 6 weeks	
10	Hoshiwara 1973	Doxycycline	2.5-4.0 mg/kg	1x daily for 5 days, every week up to 28 doses in 40 days.					
11	Peach 1986					Tetracycline	not reported	daily for 5 days, every month for 3 months	
12	Shukla 1966	Sulphadimethoxine	100 mg/kg	2x weekly or 1x weekly, for 5 months		Sulphafurazole	15%	2x daily for 5 days, every month for 5 months	
13	Tabbara* 1996	Azithromycin	20 mg/kg	single dose		Tetracycline	1%	2x daily for 5 days, every week for 6 weeks	
14	Woolridge 1967					Tetracycline	1%	2x daily for 6 days, every week for 6 weeks	

* No untreated or placebo control group

Table 2. Antibiotics: trials in communities

	Study	Oral antibiotic	Oral antibiotic dose	Oral antibiotic schedule	Oral antibiotic comments	Topical antibiotic	Topical antibiotic dose	Topical antibiotic schedule	Topical antibiotic comments
1,2& 3	ACT (Egypt, Tanzania and The Gambia)	Azithromycin	20 mg/kg up to 1g	once a week for three weeks	Pregnant women given erythromycin	oxytetracycline	1%	once daily for 6 weeks	
4	Atik 2006	Azithromycin	20 mg/kg for children; 1g for adults	single dose	Children with active trachoma and household members treated; Pregnant women given erythromycin	tetracycline	not reported	not reported	People with active trachoma treated
5	Chidambaram 2006	Azithromycin	20 mg/kg for children; 1g for adults directly observed treatment.	single dose	Pregnant women, children younger than 1 year, and those allergic to macrolides were offered a 6-week course of topical 1% tetracycline ointment (applied twice daily to both eyes, not directly observed)				
6	Lee 2007	Azithromycin	not reported	not reported	"Biannual mass azithromycin treatment of all				

Table 2. Antibiotics: trials in communities (*Continued*)

					individuals" aged 1 year or more				
7	Resnikoff 1995					oxytetracycline	1%	1 drop 4x/day	7 consecutive days per month for six months
8	TANA 2009	Azithromycin	Height-based dosing to roughly 20 mg/kg	single dose	Women self-reporting as pregnant and children aged less than 1 year offered topical tetracycline				

Table 3. Outcome reporting: trials in individuals

Study		3 months	3 months	12 months	12 months	24 months	24 months
		Active trachoma	Ocular infection	Active trachoma	Ocular infection	Active trachoma	Ocular infection
1	Attiah 1973	√	H [1]	H[2]	H[2]	H[2]	H[2]
2	Bailey 1993	√	√	√ (26 weeks)	√ (26 weeks)	H[2]	H[2]
3	Bowman 2000	√	H[3]	√	H[3]	H[2]	H[2]
4	Cochereau 2007	√	E	H[2]	H[2]	H[2]	H[2]
5	Darougar 1980	√	√	√	√	H[2]	H[2]
6	Dawson 1969 Sherman	√	H[2]	H[2]	H[2]	H[2]	H[2]
7	Dawson 1969 Stewart	√	H[2]	H[2]	H[2]	H[2]	H[2]
8	Dawson 1997	√	√	√	√	H[2]	H[2]

Table 3. Outcome reporting: trials in individuals (*Continued*)

9	Foster 1966	√	H [1]	√	H [1]	H[2]	H[2]
10	Hoshiwara 1973	√	√	H[2]	H[2]	H[2]	H[2]
11	Peach 1986	√	H [1]	H[2]	H[2]	H[2]	H[2]
12	Shukla 1966	√	√	H[2]	H[2]	H[2]	H[2]
13	Tabbara 1996	√	√	H[2]	H[2]	H[2]	H[2]
14	Woolridge 1967	√	H [1]	√	H [1]	H[2]	H[2]

ORBIT CLASSIFICATION (Kirkham 2010)
E: Clear that the outcome was measured but not necessarily analysed.
H: Outcome not mentioned but clinical judgement says unlikely to have been measured.
1. No mention of collection of laboratory samples in the paper.
2. No evidence of any data collection at this time point.
3. Study conducted on low budget therefore may not have been able to afford to collect lab specimens

Table 4. Outcome reporting: trials in communities

	Study	3 months	3 months	12 months	12 months	24 months	24 months
		Active trachoma	Ocular infection	Active trachoma	Ocular infection	Active trachoma	Ocular infection
1	ACT 1999 Egypt	√	√	√	√	H[2]	H[2]
2	ACT 1999 Tanzania	√	√	√	√	H[2]	H[2]
3	ACT 1999 The Gambia	√	√	√	√	H[2]	H[2]
4	Atik 2006	√	√	√	√	√	√
5	Chidambaram 2006	Request to authors for information	√ (treatment group only)	Request to authors for information	√		√ (treatment group only and control group treated at 12 months)
6	Lee 2007	H[3]	H[3]	H[4]	√	H[2]	H[2]

Table 4. Outcome reporting: trials in communities (*Continued*)

7	Resnikoff 1995	√	H [1]	√	H [1]	H[2]	H[2]
8	TANA 2009	Request to authors for information	F	Request to authors for information	√	H[5]	H[5]

ORBIT CLASSIFICATION (Kirkham 2010)
F: Clear that outcome was measured but not necessarily analysed.
H: Outcome not mentioned but clinical judgement says unlikely to have been measured.
1. No mention of collection of laboratory samples in the paper.
2. No suggestion that study went on longer than 12 months.
3. Only 12 month examination appeared to have been conducted**.**
4. Paper did not report any clinical examination whilst this is unusual the focus of the study was "chlamydia on flies and children" so it is possible that only laboratory samples were collected.
5. Control group treated at 12 months

Table 5. Adverse effects

	Study	Antibiotic (number treated)	Report
1, 2 & 3	ACT 1999 (Egypt/Tanzania/The Gambia)	Azithromycin (approx 3800) Tetracycline (approx 2400)	No comment on adverse effects in report
4	Atik 2006	Azithromycin and tetracycline (numbers treated difficult to work out exactly but probably in the order of 100)	No comment on adverse effects in report
5	Attiah 1973	Oxytetracycline (77) Tetracycline derivative GS2989 (75)	No comment on adverse effects in report
6	Bailey 1993	Azithromycin (97) Topical tetracycline with oral erythromycin in severe cases (97)	Table 2 on page 454 reports adverse effects. Abdominal pain reported more often in azithromycin group (26% versus 16%, P = 0.09). Other effects: diarrhoea, vomiting, fever, headache, body pain, other similar between two study groups "There were no serious adverse reactions and both treatments were well tolerated. All symptoms resolved spontaneously and none required treatment. " One study subject died, probably due to malaria. He had received topical tetracycline
7	Bowman 2000	Azithromycin (160) Tetracycline (154)	No comment on adverse effects in report

Table 5. Adverse effects (*Continued*)

8	Chidambaram 2006	Azithromycin (approx 500 children)	No comment on adverse effects in report
9	Cochereau 2007	Azithromycin topical 2-day regimen (222) 3-day (220 and oral azithromycin (214)	"Ocular adverse events were reported in 10.8%, 8.9% and 13.1% of patients in the 2-day, 3-day and oral treatment groups respectively. Systemic adverse events were reported in 2.6%, 10. 2% and 9.0% of patients. None of the adveres events were treatment-related events. On epatient (3-day group) had a serious unrelated adverse events (death due to head injury)." Page 670
10	Darougar 1980	Doxycycline (44) Oxytetracycline (38)	No comment on adverse effects in report
11 & 12	Dawson 1969 (Sherman/Stewart)	Trisulfapyrimidines (33)	"No untoward reactions to sulfonamides were noted" (page 587)
13	Dawson 1997	Oxytetracycline/polymyxin (43) Azithromycin (125)	"In this trial, azithromycin was well tolerated and only two children (of 125 treated) complained of nausea" (page 367)
14	Foster 1966	Sulfamethoxypyridazine (112) Tetracycline (106)	"3/155 students who received sulfamethoxypyridazine had adverse reactions to the drug. One girl developed a severe purpura associated with marked thrombocytopenia. She recovered following withdrawal of the drug and administration of corticosteroids. Two cases of diagnosed drug rash necessitated discontinuance of the drug. The nephrotic syndrome developed in one boy three months after completion of sulphonamide therapy, but the relationship of this development to therapy was not determined. No reactions or rashes occurred in the other two treatment groups" (page 453) (note: Table 3/table 4 report 112 children treated with sulphamethoxypyridazine)
15	Hoshiwara 1973	Doxycycline (49)	"Anorexia, nausea, vomiting or diarrhea occurred in three children between the 15th and 25th days of medication. Two of these children were re-

Table 5. Adverse effects (*Continued*)

			ceiving doxycycline, and the disturbances lasted only a single day in each child, in spite of continuing medication. Between day 21 and 28 of medication, transient macular rashes and one-day illness with low-grade fever and anorexia occurred in four children. Two of them had received drug, and two placebo. It is likely that an intercurrent, unrelated illness was responsible. Gross enamel dysplasia or tooth discoloration was not observed on examination 20 weeks after the end of medication." (page 222)
16	Lee 2007	Azithromycin (8 villages treated, number individuals treated not reported)	No comment on adverse effects in report
17	Peach 1986	Tetracycline (932)	No comment on adverse effects in report
18	Resnikoff 1995	Oxytetracycline (346)	No comment on adverse effects in report
19	Shukla 1966	Sulphafurazole (140) Sulphadimethoxine (161)	No comment on adverse effects in report
20	Tabbara 1996	Azithromycin (31) Tetracycline (29)	"No adverse effects were noted" (page 844) and "The safety of a single oral dose of azithromycin has been demonstrated in this study. Similar to other clinical studies, no adverse effects developed in any of the patients in the azithromycin group" (page 845)
21	TANA 2009	Azithromycin (over 16,000 people treated at baseline)	"We recorded no reported serious adverse events attributed to study medication. 96 deaths were recorded in subkebeles in the children-treated group and 126 deaths recorded in those in the control group. At 12 months a survey was undertaken to assess adverse effects in the treated population (n= 671, 96 side-effects reported). [..] 56 (11.3%) patients reported abdominal pain, vomiting, and nausea, whereas diarrhoea, constipation and related issues accounted for 16 (2.4%) of complaints.

Table 5. Adverse effects (*Continued*)

			Four (0.6%) patients reported haemorrhoid or other as side effects" (House et al page 1115). "In a trachoma-endemic area, mass distribution of oral azithromycin was associated with reduced mortality in children" (Porco et al, conclusion of abstract)
22	Woolridge 1967	Tetracycline (726) Sulfonamide (526)	"No more than trivial reactions were observed in any of these three studies, to vaccine, to oil adjuvant , to eye ointment or to sulfa drug." (page 1581)

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Trachoma
#2 MeSH descriptor Chlamydia trachomatis
#3 trachoma* or tracoma*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Anti-Bacterial Agents
#6 antibiotic*
#7 MeSH descriptor Azithromycin
#8 azithrom*cin*
#9 MeSH descriptor Tetracycline
#10 tetracycline*
#11 MeSH descriptor Chlortetracycline
#12 chlortetracycline*
#13 MeSH descriptor Macrolides
#14 macrolide*
#15 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16 (#4 AND #15)

Appendix 2. MEDLINE search strategy

1 randomized controlled trial.pt.
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/

10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp trachoma/
14 trac?oma$.tw.
15 exp chlamydia trachomatis/
16 or/13-15 (14120)
17 exp antibacterial agents/
18 antibiotic$.tw.
19 exp azithromycin/
20 azithrom?cin$.tw.
21 exp tetracycline/
22 tetracycline$.tw.
23 exp chlortetracycline/
24 chlortetracycline$.tw.
25 exp macrolides/
26 macrolide$.tw.
27 or/17-26
28 16 and 27
29 12 and 28
The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE search strategy

1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin$ adj3 trial$).tw.
14 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15 exp placebo/
16 placebo$.tw.
17 random$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control$ or prospectiv$ or volunteer$).tw.

29 or/25-28
30 29 not 10
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp trachoma/
34 trac?oma$.tw.
35 exp chlamydia trachomatis/
36 or/33-35
37 exp antibiotic agent/
38 antibiotic$.tw.
39 exp azithromycin/
40 azithrom?cin$.tw.
41 exp tetracycline/
42 tetracycline$.tw.
43 exp chlortetracycline/
44 chlortetracycline$.tw.
45 exp macrolide/
46 macrolide$.tw.
47 or/37-46
48 36 and 47
49 32 and 48

Appendix 4. *meta*Register of Controlled Trials search strategy

trachoma and antibiotics

Appendix 5. ClinicalTrials.gov search strategy

Trachoma AND Antibiotics

Appendix 6. Changes made to data in the 2011 update of the review

			Current review				Original review				
			Treatment		Control		Treatment		Control		Comments
Comparison		Study	n	N	n	N	n	N	n	N	
1.1	Active trachoma at 3 months	Peach 1986	216	340	138	189	284	408	182	233	Missing data counted twice in original review
1.3	Active trachoma	Woolridge 1967	121	202	95	120	149	202	100	120	Error in data extraction in original review

(*Continued*)

	at 12 months										
2.1	Active trachoma at 3 months	Peach 1986	216	340	138	189	284	408	182	233	Missing data counted twice in original review
2.3	Active trachoma at 12 months	Woolridge 1967	121	202	95	120	149	202	100	120	Error in data extraction in original review
3.1	Active trachoma at 3 months	Bowman 2000	48	152	68	139	56	158	83	156	People with missing data counted as having trachoma in original review
3.1	Active trachoma at 3 months	Shukla 1966	53	83	29	62	53	83	34	42	Error in data extraction in original review
3.1	Active trachoma at 3 months	Tabbara 1996	15	31	12	29	15	32	12	32	In the original review, people who were not followed up were included in the denominator. This makes the assumption that people who were not followed up had inactive trachoma
3.2	Chlamydia trachomatis infection at 3 months	Tabbara 1996	6	30	4	26					Not included in previous review
3.3	Active trachoma at 12 months	Bowman 2000	32	149	45	139					Not included in previous review

(*Continued*)

3.4	Chlamydia trachomatis infection at 12 months	Dawson 1997	8	105	5	33	7	105	5	33	Error in data extraction in original review
5.1	Active trachoma at 12 months	Atik 2006	21	523	35	994					Not included in previous review
5.2	Chlamydia trachomatis infection at 12 months	Atik 2006	23	659	68	1192					Not included in previous review
5.2	Chlamydia trachomatis infection at 12 months	Lee 2007	2	170	56	185					Not included in previous review
		ACT study	Data for the ACT trial in the original review was not exactly the same as the published data and included unpublished outcomes. The original review authors had access to individual patient data which was not available to the current authors. In the absence of access to the original data, we felt it was unwise to make any changes to the data included in the review.								

Appendix 7. Results of searches for previous versions of the review

The original electronic searches identified 566 reports of studies, of which 51 reported antibiotic treatment trials for trachoma. A total of 15 studies (8678 participants) met the inclusion criteria. Ten trials compared antibiotic to placebo or no treatment (Attiah 1973; Darougar 1980b; Dawson 1969i; Dawson 1969ii; Foster 1966; Hoshiwara 1973; Peach 1986; Shukla 1966; Tabbara 1988; Woolridge 1967). One trial (Tabbara 1988) was later excluded as it was not possible to identify patient outcomes as both eyes of the same patient were in some instances used in the randomisation and the results were reported as eyes not patients. The citations Dawson 1969i and Dawson 1969ii refer to two arms of the same trial, which were conducted in different schools; as the results are reported separately in the paper they have been treated as separate studies. Some of the above studies reported the comparison of topical against oral antibiotics. A further six trials compared topical tetracycline to oral azithromycin (Bowman 2000; Dawson 1997; Schachter 1999i; Schachter 1999ii; Schachter 1999iii; Tabbara 1996). The three Schachter 1999 citations used the same protocol but applied in different countries and reported in the same article. Schachter 1999i refers to results from Egypt, Schachter 1999ii from The Gambia and Schachter 1999iii from Tanzania. One further trial was excluded as an oral antibiotic, erythromycin, was used in conjunction with topical tetracycline in severe cases of trachoma, the comparison being oral azithromycin (Bailey 1993b).

The electronic searches were updated in 2005 and 206 new reports of studies were identified from the electronic searches. Hard copies of two reports were obtained for further scrutiny. One study was excluded as the trial did not take place in a trachoma endemic region (Isenberg 2002) and the other study by Humet 1989 was excluded as it did not assess the treatment of ocular *Chlamydia trachomatis*.

WHAT'S NEW

Last assessed as up-to-date: 11 December 2010.

Date	Event	Description
18 February 2011	New search has been performed	Issue 3 2011: Electronic searches updated and 6 new trials included. Risk of bias assessed for all studies and summary of findings tables added
9 February 2011	New citation required and conclusions have changed	Issue 3 2011: Review substantively updated. New authorship.

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 1, 2002

Date	Event	Description
31 March 2008	Amended	Converted to new review format.
1 February 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Original version of the review: Denise Mabey (DM) screened the search results, graded selected trials, extracted some data and wrote the review. DM was the guarantor for the review. Nicole Fraser-Hurt (NF) graded selected trials, extracted the data and contributed to writing the review.Chistine Powell screened the search results and worked on the update of the review.

Major update of review and change of authors 2011: JE and AWS screened search results, assessed the risk of bias of all included studies, extracted data from new included trials and substantially rewrote the text of the review.

The Cochrane Eyes and Vision Group editorial team developed the search strategies and undertook the electronic searches.

DECLARATIONS OF INTEREST

The Edna McConnell Clark Foundation supported DM and NF for one half day a week over a 10 month period to undertake the original review. SightSavers International part funded JE's salary to update the review. AWS is a member of the International Trachoma Initiative (ITI)'s Trachoma Expert Committee and has received research support from both ITI and Pfizer, the manufacturers of azithromycin.

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Internal sources

- No sources of support supplied

External sources

- The Edna McConnell Clark Foundation, USA.
- Christian Blind Mission, Germany.
- Sightsavers International, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In 2011 this review was substantially revised. The major change was that we considered separately the individually-randomised and cluster-randomised trials, and the Cochrane Collaboration's tool for assessing risk of bias was implemented. The greater detail required in Revman 5 format has meant that we have completed some aspects of the methods - such as assessment of heterogeneity - for this update which were not discussed in detail in the original protocol.

NOTES

This review was first published as Mabey D, Fraser-Hurt N. Antibiotics for trachoma. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD001860. DOI: 10.1002/14651858.CD001860.pub2. The 2011 updated version has been written by a new review team.

INDEX TERMS

Medical Subject Headings (MeSH)

*Chlamydia trachomatis; Administration, Oral; Administration, Topical; Anti-Bacterial Agents [administration & dosage; *therapeutic use]; Azithromycin [administration & dosage]; Randomized Controlled Trials as Topic; Tetracycline [administration & dosage]; Trachoma [*drug therapy]

MeSH check words

Humans