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Antibiotics for trachoma (Review)

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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 1996, WHO launched the 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), *Chlamydia trachomatis* infection of the conjunctiva, antibiotic resistance, and adverse effects (secondary objectives).

Search methods

We searched relevant electronic databases and trials registers. The date of the last search was 4 January 2019.

Selection criteria

We included randomised controlled trials (RCTs) 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. We also included studies addressing different dosing strategies in the population.

Data collection and analysis

We used standard methods expected by Cochrane. We assessed the certainty of the evidence using the GRADE approach.

Main results

We identified 14 studies where individuals with trachoma were randomised and 12 cluster-randomised studies.

Any antibiotic versus control (individuals)

Nine studies (1961 participants) randomised individuals with trachoma to antibiotic or control (no treatment or placebo). All of these studies enrolled children and young people with active trachoma. The antibiotics used in these studies included topical (oxy)tetracycline (5 studies), doxycycline (2 studies), and sulfonamides (4 studies). Four studies had more than two study arms. In general these studies were poorly reported, and it was difficult to judge risk of bias.

These studies provided low-certainty evidence that people with active trachoma treated with antibiotics experienced a reduction in active trachoma at three months (risk ratio (RR) 0.78, 95% confidence interval (CI) 0.69 to 0.89; 1961 people; 9 RCTs; I^2 = 73%) and 12 months (RR 0.74, 95% CI 0.55 to 1.00; 1035 people; 4 RCTs; I^2 = 90%). Low-certainty evidence was available for ocular infection at three months (RR 0.81, 95% CI 0.63 to 1.04; 297 people; 4 RCTs; I^2 = 0%) and 12 months (RR 0.25, 95% CI 0.08 to 0.78; 129 people; 1 RCT). None of these studies assessed antimicrobial resistance. In those studies that reported harms, no serious adverse effects were reported (low-certainty evidence).

Oral versus topical antibiotics (individuals)

Eight studies (1583 participants) compared oral and topical antibiotics. Only one study included people older than 21 years of age. Oral antibiotics included azithromycin (5 studies), sulfonamides (2 studies), and doxycycline (1 study). Topical antibiotics included (oxy)tetracycline (6 studies), azithromycin (1 study), and sulfonamide (1 study). These studies were poorly reported, and it was difficult to judge risk of bias.

There was low-certainty evidence of little or no difference in effect between oral and topical antibiotics on active trachoma at three months (RR 0.97, 95% CI 0.81 to 1.16; 953 people; 6 RCTs; I^2 = 63%) and 12 months (RR 0.93, 95% CI 0.75 to 1.15; 886 people; 5 RCTs; I^2 = 56%). There was very low-certainty evidence for ocular infection at three or 12 months. Antimicrobial resistance was not assessed. In those studies that reported adverse effects, no serious adverse effects were reported; one study reported abdominal pain with azithromycin; one study reported a couple of cases of nausea with azithromycin; and one study reported three cases of reaction to sulfonamides (low-certainty evidence).

Oral azithromycin versus control (communities)

Four cluster-randomised studies compared antibiotic with no or delayed treatment. Data were available on active trachoma at 12 months from two studies but could not be pooled because of reporting differences. One study at low risk of bias found a reduced prevalence of active trachoma 12 months after a single dose of azithromycin in communities with a high prevalence of infection (RR 0.58, 95% CI 0.52 to 0.65; 1247 people). The other, lower quality, study in low-prevalence communities reported similar median prevalences of infection at 12 months: 9.3% in communities treated with azithromycin and 8.2% in untreated communities. We judged this moderate-certainty evidence for a reduction in active trachoma with treatment, downgrading one level for inconsistency between the two studies. Two studies reported ocular infection at 12 months and data could be pooled. There was a reduction in ocular infection (RR 0.36, 0.31 to 0.43; 2139 people) 12 months after mass treatment with a single dose compared with no treatment (moderate-certainty evidence). There was high-certainty evidence of an increased risk of resistance of *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli* to azithromycin, tetracycline, and clindamycin in communities treated with azithromycin, with approximately 5-fold risk ratios at 12 months. The evidence did not support increased resistance to penicillin or trimethoprim-sulfamethoxazole. None of the studies measured resistance to *C trachomatis*. No serious adverse events were reported. The main adverse effect noted for azithromycin (~10%) was abdominal pain, vomiting, and nausea.

Oral azithromycin versus topical tetracycline (communities)

Three cluster-randomised studies compared oral azithromycin with topical tetracycline. The evidence was inconsistent for active trachoma and ocular infection at three and 12 months (low-certainty evidence) and was not pooled due to considerable heterogeneity. Antimicrobial resistance and adverse effects were not reported.

Different dosing strategies

Six studies compared different strategies for dosing. There were: mass treatment at different dosing intervals; applying cessation or stopping rules to mass treatment; strategies to increase mass treatment coverage. There was no strong evidence to support any variation in the recommended annual mass treatment.

Authors' conclusions

Antibiotic treatment may reduce the risk of active trachoma and ocular infection in people infected with *C trachomatis*, compared to no treatment/placebo, but the size of the treatment effect in individuals is uncertain. Mass antibiotic treatment with single dose oral azithromycin reduces the prevalence of active trachoma and ocular infection in communities. There is no strong evidence to support

any variation in the recommended periodicity of annual mass treatment. There is evidence of an increased risk of antibiotic resistance at 12 months in communities treated with antibiotics.

PLAIN LANGUAGE SUMMARY

Antibiotics for trachoma

What is the aim of this review?

The aim of this Cochrane Review was to find out if antibiotics work for treating trachoma, either in individuals or communities. Cochrane researchers collected and analysed all relevant studies to answer this question and found 26 studies.

Key messages

The review shows that antibiotic treatment of people and communities with trachoma leads to less eye infection due to trachoma and less eye disease. Mass treatment of communities with antibiotics is associated with increased antimicrobial resistance.

What was studied in the review?

Trachoma is caused by a kind of bacterial infection of the outer eye which, if not treated, can lead to blindness. This germ is known as *Chlamydia trachomatis*, which thrives where water is scarce and hygiene is poor. Trachoma is the most common infectious cause of vision loss and usually affects people living in poor communities. Repeated bouts of conjunctivitis (inflammation of the membrane that covers the surface of the eyeball and inside of the eyelids) known as 'active trachoma' caused by this eye infection can lead to inward turning of the upper eyelid. The eyelashes rub the clear front part of the eye (cornea) leading to pain, scarring, and blindness.

The World Health Organization (WHO) has developed the SAFE strategy to eliminate trachoma.

• **S**urgery for inward-turning eyelids

• **A**ntibiotics to clear the eye infection

• **F**acial cleanliness to stop the eye infection being passed on

• **E**nvironmental improvement, in particular clean water and sanitation

This review considers the **A** part of the SAFE strategy**.** Antibiotics can be used to treat the eye infection and may be given as an ointment or by mouth. The two antibiotics commonly used for the treatment of trachoma are azithromycin (single dose by mouth) and tetracycline (ointment applied to the eye over several weeks).

What are the main results of the review?

Cochrane researchers found 26 relevant studies.

Fourteen studies enrolled people with trachoma. These studies took place in the following WHO regions (one study took place in two regions): African Region (three studies), Eastern Mediterranean Region (five studies), Region of the Americas (four studies), South-East Asian Region (one study), and Western Pacific Region (two studies). Most of the studies enrolled children and young people with active trachoma.

These studies showed that:

people with trachoma treated with antibiotics may have less active trachoma and eye infection at three and 12 months after treatment (low-certainty evidence);

there may be little or no difference in active trachoma between oral and topical antibiotics at three months and 12 months (low-certainty evidence) but there was only very low-certainty evidence on eye infection at three and 12 months;

there were no reports of serious adverse effects. The most common adverse effect reported was nausea with azithromycin.

Twelve studies enrolled communities in areas where trachoma is common and treated the whole community ('mass treatment'). These studies took place mainly in the African Region (10 studies), with one study in the Eastern Mediterranean Region (Egypt) and one study in the Western Pacific Region (Vietnam).

These studies showed that:

communities treated with azithromycin had less trachoma (active trachoma and eye infection) 12 months after a single dose treatment (moderate-certainty evidence);

there was no strong evidence to support changing from the currently recommended strategy of mass treatment of affected communities every year;

there was an increased risk of antimicrobial resistance in treated communities (high-certainty evidence).

How up-to-date is this review?

Cochrane researchers searched for studies that had been published up to 4 January 2019.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotic versus control for trachoma: individuals

Patient or population: people (any age) with active trachoma
Settings: people resident in a trachoma endemic area
Intervention: antibiotics, including (oxy)tetracycline, doxycycline, sulfonamides
Comparison: control (no treatment or placebo)

Outcomes	Follow-up	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
		Assumed risk	Corresponding risk			
		Control	Antibiotic			
Active trachoma Clinical assessment: active trachoma defined as TF, TI, or both	3 months	**Study population**		**RR 0.78** (0.69 to 0.89)	1961 (9 studies)	⊕⊕◯◯ **low**[1]
		800 per 1000	**624 per 1000** (552 to 712)			
	12 months	**Study population**		**RR 0.74** (0.55 to 1.00)	1035 (4 studies)	⊕⊕◯◯ **low**[2]
		750 per 1000	**555 per 1000** (413 to 750)			
Ocular *C trachomatis* infection Positive test for *C trachomatis* infection identified by culture, staining on conjunctival smears, or nucleic acid amplification methods	3 months	**Study population**		**RR 0.81** (0.63 to 1.04)	297 (4 studies)	⊕⊕◯◯ **low**[3]
		500 per 1000	**405 per 1000** (315 to 520)			
	12 months	**Study population**		**RR 0.25** (0.08 to 0.78)	129 (1 study)	⊕⊕◯◯ **low**[4]
		200 per 1000	**50 per 1000** (16 to 156)			

Antibiotic resistance Proportion of samples showing evidence of resistance to antibiotic	Any time point	None of the studies addressed this outcome.		
Adverse effects	Any time point	4 studies made no comment on adverse effects. 3 studies noted no untoward reactions (sulfonamides) or only trivial reactions (tetracycline, sulfonamide) 1 study of 155 students noted 3 adverse reactions to sulfonamide (severe purpura associated with marked thrombocytopenia, 2 cases of drug rash) 1 study of 122 children noted anorexia, nausea, vomiting, or diarrhoea in 3 children. 2 of these children were receiving doxycycline, and the disturbances lasted only a single day in each child, in spite of continuing medication	1961 (9 studies)	⊕⊕◯◯ **low**[5]

*The **assumed risk** is the median risk in control groups in the included studies (rounded to nearest 10 per 1000). 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; **TF:** trachomatous inflammation-follicular; **TI:** trachomatous inflammation-intense; **RR:** risk ratio

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for serious limitations in study design (methods of sequence generation, allocation concealment, and masking poorly reported; three studies at high risk of attrition bias) and one level for serious inconsistency (risk ratios ranged from 0.40 to 1.02 and I^2 = 73%).
[2]Downgraded one level for serious limitations in study design (methods of sequence generation, allocation concealment, and masking poorly reported; two studies at high risk of attrition bias) and one level for serious inconsistency: risk ratios ranged from 0.50 to 1.05 and I^2 = 90%). We did not additionally downgrade for imprecision, although the upper confidence interval was 1.00, as we felt that this imprecision probably reflects limitations in study design and inconsistency.
[3]Downgraded one level for serious limitations in study design (methods of sequence generation and allocation concealment poorly reported; two studies at high risk of attrition bias) and one level for serious imprecision (95% CI 0.63 to 1.04 include null effect 1).
[4]Downgraded two levels for very serious limitations in study design (only one small study with poorly reported methods of sequence generation and allocation concealment and which did not mask outcome assessment).

[5]Downgraded one level for very serious limitations in study design (methods of sequence generation, allocation concealment, and masking poorly reported; three studies at high risk of attrition bias) and one level for imprecision, as the studies were not large enough to assess rare adverse events.

BACKGROUND

Description of the condition

Trachoma is the world's leading infectious cause of blindness (WHO 2018). In 2015, there were an estimated 398,000 people blind due to trachoma (80% uncertainty intervals 114,000 to 851,000) (Flaxman 2017). Trachoma is a disease of poverty and is associated with poor water supplies and sanitation (Garn 2018). The age-standardised all-ages prevalence of blindness due to trachoma varies from 0% in most high-income countries to 0.23% (0.07% to 0.42%) in East sub-Saharan Africa and 0.19% (0.06% to 0.35%) in West sub-Saharan Africa (Flaxman 2017).

There are two phases of trachoma. In the first phase, most frequently seen in infancy and childhood, there are repeated rounds of conjunctivitis caused by the bacterium *Chlamydia trachomatis*. The conjunctivitis is characterised by the presence of follicles on the under surface of the upper eyelid and by vascular changes and is known as 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 thought to be 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 can 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. Treatment at this stage is surgery to reposition the eyelid margin. Blindness results from corneal opacification. The blinding phase affects women more commonly than men (Cromwell 2009), and typically starts in adult life (Burton 2009).

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). Topically applied antibiotics 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 cause various adverse effects in the person taking them. Bacteria anywhere in the body may also develop antibiotic resistance. As the currently recommended oral antibiotic regimen is a single, directly observed dose of azithromycin, as compared to six weeks of twice-daily topical tetracycline, oral treatment is likely to have 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); active cases together with family contacts; or high-risk groups including schoolchildren. Because many individuals harbour infection without demonstrating clinical signs, it has been suggested that trachoma elimination 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 active disease is reduction of blindness, but this can 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 1996 when the World Health Organization (WHO) launched a new initiative for trachoma control, based on the 'SAFE' strategy, and in 1998 the 51st World Health Assembly passed a resolution on "Global elimination of blinding trachoma" (WHA 1998). The components of the SAFE acronym are **S**urgery, **A**ntibiotics, **F**acial cleanliness, and **E**nvironmental improvement. Cochrane Reviews on surgery for trichiasis (Burton 2015), face washing (Ejere 2015), and environmental sanitary interventions have also been completed (Rabiu 2012).

The WHO recommends the following antibiotic treatment for trachoma: either topical treatment of 1% tetracycline ointment to both eyes, twice daily for six weeks, or azithromycin, given as a single oral dose of 1 g in adults and 20 mg/kg of body weight in children (Solomon 2006).

This review was important to systematically evaluate the safety and effectiveness of these recommended treatment regimens.

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), *Chlamydia trachomatis* infection of the

conjunctiva, antibiotic resistance, and adverse effects (secondary objectives).

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

- What is the effect of antibiotic treatment versus no treatment?
- What is the effect of oral versus topical antibiotic?
- What is the effect of oral azithromycin compared to topical tetracycline?

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

- What is the effect of mass administration of antibiotic compared to no treatment?
- What is the effect of mass administration of oral azithromycin versus topical tetracycline?
- What is the effect of annual versus different treatment frequencies?

(3) What are the adverse effects of antibiotic treatment?

- What are the adverse effects at the individual level?
- What is the effect of mass administration of oral azithromycin or topical tetracycline on resistance in (i) *C trachomatis* and (ii) other bacteria?

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. We included clinical and community-based trials. 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.

We also included studies addressing different dosing strategies in the population.

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 (Grassly 2008). We selected 12 months to represent the period during which recurrence of infection or relapse would most likely occur, and 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 these 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 in any of these follow-up ranges 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 1975a; Dawson 1981a; 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 (trachomatous inflammation-follicular) and TI (trachomatous inflammation-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 for this review 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 nucleic acid amplification methods. The tests, in order of increasing sensitivity, are:

- culture by *C trachomatis* isolation in eggs or tissue culture;
- staining of conjunctival smears with Giemsa or iodine;
- direct fluorescent antibody cytology;
- indirect enzyme immunoassay;
- nucleic acid test (NAT);
- nucleic acid amplification tests (NAAT).

For the current update we defined an additional secondary outcome: **resistance: proportion of samples showing evidence of resistance to antibiotic** in (i) *C trachomatis* and (ii) other bacteria. We considered any measure of resistance reported in the included studies. This included genotypic and phenotypic measures for all organisms and drug classes. We focused on the proportion of samples that were resistant, but also collected data, where available, on the proportion of isolates that were resistant.

Adverse effects

We recorded all adverse effects reported in the included studies.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for randomised controlled trials and controlled clinical trials. There were no restrictions on language or year of publication. The electronic databases were last searched on 4 January 2019.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 1) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 4 January 2019) (Appendix 1).
- MEDLINE Ovid (1946 to 4 January 2019) (Appendix 2).
- Embase Ovid (1980 to 4 January 2019) (Appendix 3).
- International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/editAdvancedSearch; searched 4 January 2019) (Appendix 4).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 4 January 2019) (Appendix 5).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 4 January 2019) (Appendix 6).

Searching other resources

We used the Science Citation Index to search for articles that cited the included studies. We searched the reference lists of included articles for any other potentially relevant studies. For previous versions of this review, we also contacted experts in the field, either directly or through the membership of the WHO workshops, requesting information on unpublished trials. We did not do this for the current update, however we did contact individual trialists for more information.

Data collection and analysis

Selection of studies

For the first publication of this review (Mabey 2005), one review author assessed the titles identified from the initial searches and selected all titles that made reference to treatment for trachoma. For subsequent updates (Evans 2011 and current update), two review 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 screening. Two review authors independently reviewed the full texts of all potentially relevant papers and assessed them according to the Criteria for considering studies for this review.

Data extraction and management

Two review authors independently extracted data. Any discrepancies were resolved before data were entered into Review Manager 5 (Review Manager 2008).

For the 2011 review update, JE checked the original data collection and entry. The changes that were made are summarised in Appendix 7. For the newly identified trials, two review authors (JE, AWS) independently extracted data, resolving any discrepancies by discussion. Data were entered by both review authors onto two spreadsheets and cross-checked. Data were cut and pasted into RevMan from the spreadsheet (JE). For the current update, the process was repeated by JE/EHE using updated Review Manager 5 (RevMan 5) software (Review Manager 2014).

Assessment of risk of bias in included studies

We assessed risk of bias using Cochrane's 'Risk of bias' assessment tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). 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 considered two additional criteria for cluster-randomised trials: recruitment bias and baseline imbalances (Higgins 2011). Two review authors (JE/AWS (2011), JE/EHE (2019)) independently assessed risk of bias, compared results, and resolved any discrepancies by discussion.

Measures of treatment effect

The primary outcome for the review was active trachoma, and the secondary outcomes were ocular *C trachomatis* infection and antibiotic resistance. 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).

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 5. However, we were aware that cluster-randomised trials are not always analysed and reported appropriately. We planned that for those studies that did not report such an effect measure, we would perform an approximate analysis (Higgins 2011), as follows:

- calculate a 'design effect' of 1 + (M − 1) ICC (where ICC = intracluster 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 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 updates we considered these community-based and individually randomised trials separately, as we believed that they were asking different questions and were likely to be estimating different treatment effects. The individually randomised studies address the question: what is the effect of antibiotic treatment on individuals? The cluster-randomised trials address the question: what is the effect of antibiotic treatment on communities? The effect of treatment in individuals in treated communities may be different because as well as the individual-level effect, there may be an additional impact via reduction in transmission. The following two objectives were identified.

Where appropriate, data were pooled using a random-effects model. We used a fixed-effect model if there were three or fewer trials. 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 in the Unit of analysis issues section, we considered the possible effect of assumptions about the size of the intracluster correlation coefficient (ICC) on the results.

'Summary of findings' table

'Summary of findings' tables were introduced in the current update following new Cochrane guidance. As such, these tables are post hoc, but as fewer than seven outcomes were specified in this review, and we focused on the key comparisons in individuals and communities, there were no significant judgements that may have been influenced by our knowledge of the data in the preparation of these tables. We graded the certainty of the evidence for the comparisons and outcomes included in the 'Summary of findings' tables using the GRADE approach (Schünemann 2017). We considered risk of bias in the studies contributing data, consistency of effects, precision of the effect estimate, directness of the evidence, and possibility of publication bias when grading the evidence. The initial assessment was done by JE, and this was checked by co-authors.

RESULTS

Description of studies

Results of the search

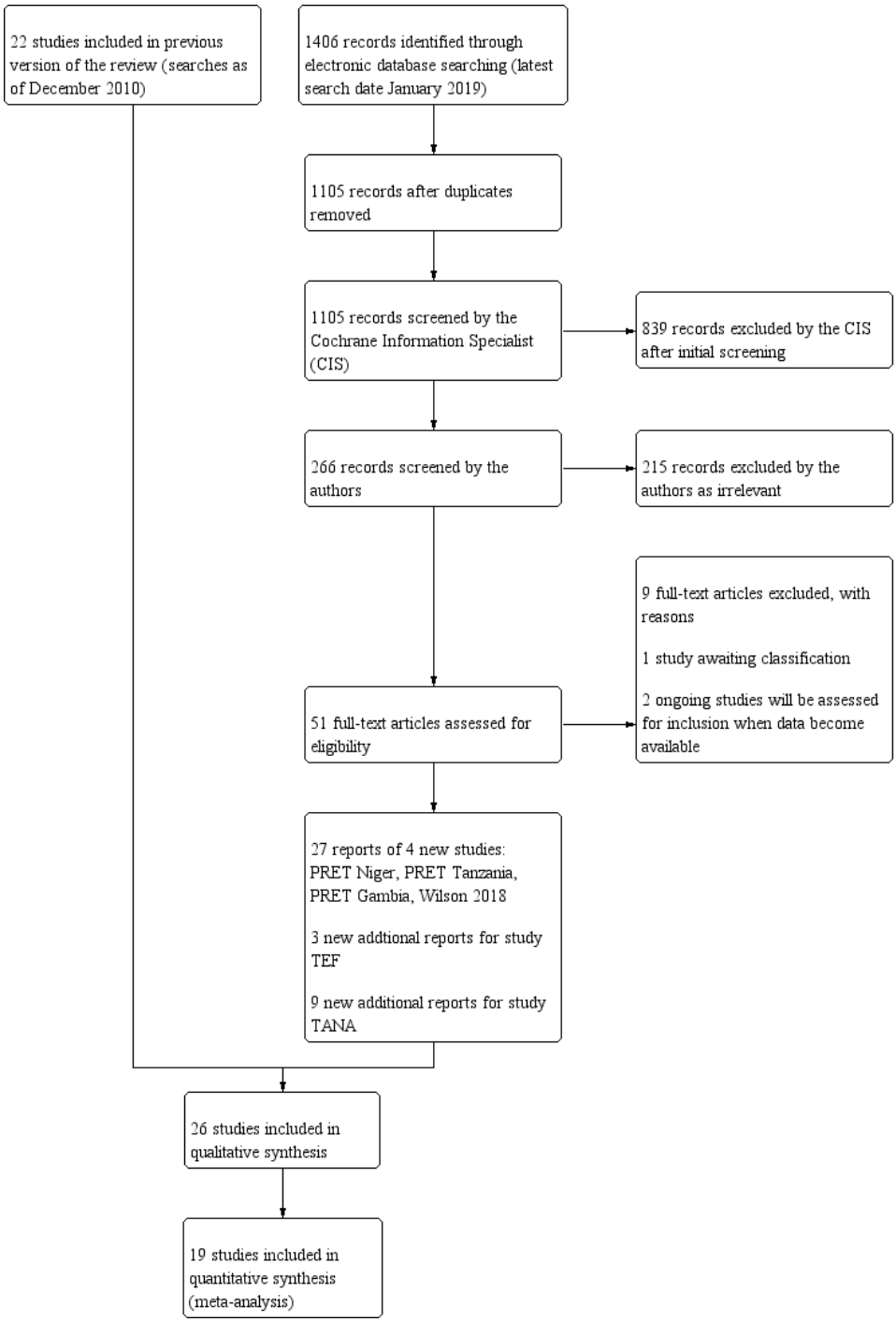
2011 version

The previous edition of this review published in 2011 included 22 studies. Fourteen of these studies were individually randomised, and a further eight were cluster-randomised.

2019 update

The searches run in January 2019 yielded a further 1406 records (Figure 1). After removal of 301 duplicates, the Cochrane Information Specialist screened the remaining 1105 records and removed 839 references that were not relevant to the scope of the review. We screened the remaining 266 references and obtained 51 full-text reports for further assessment. We identified 27 reports of four new cluster-randomised studies (PRET Niger; PRET Tanzania; PRET The Gambia; Wilson 2018). The searches identified three new reports for the TEF study and nine new reports for the TANA study. The total number of included studies was 26; see Characteristics of included studies for further details.

Figure 1. Study flow diagram.



We will assess two ongoing studies for potential inclusion when data become available (NCT03523156; SWIFT 2017), and one study by Last 2015 is awaiting classification.
We excluded nine reports of the following nine studies: Coulibaly 2013; MORDOR 2018; NCT00286026; NCT00347607; NCT00347776; NCT01178762; NCT01767506; NCT02211729; Schachterle 2014. The total number of excluded studies is 63; see Characteristics of excluded studies for further details.

Included studies

Individually randomised studies

Fourteen individually randomised studies are included in the review (Table 1).

Types of participants

These 14 studies took place in the following countries (according to WHO region) (one study, Cochereau 2007, was conducted in two regions).

African Region

- The Gambia (Bailey 1993; Bowman 2000)
- Guinea (Cochereau 2007)

Eastern Mediterranean Region

- Egypt (Attiah 1973; Dawson 1997)
- Iran (Darougar 1980)
- Pakistan (Cochereau 2007)
- Saudi Arabia (Tabbara 1996)

Region of the Americas

- USA (Dawson 1969 Sherman; Dawson 1969 Stewart; Foster 1966; Hoshiwara 1973)

South-East Asian Region

- India (Shukla 1966)

Western Pacific Region

- Australia (Peach 1986)
- Taiwan (Woolridge 1967)

The participants in these studies had active trachoma. The number of participants randomised ranged from 29, in Dawson 1969 Sherman, to 670, in Cochereau 2007. Almost all of the studies enrolled children and/or young people (21 years or younger) only, with the exception of Bailey 1993, which had a wider age range (9 months to 60 years). Not all studies reported the proportion of males and females, but in those that did there were approximately equal proportions. Participants in the studies in USA and Australia were from Indigenous communities (Native American and Aboriginal, respectively).

Types of interventions

Table 2 summarises the comparisons addressed in these studies.
Nine studies compared antibiotic with a no-treatment or placebo arm. These antibiotics were:

- tetracycline or oxytetracycline applied topically (Attiah 1973; Darougar 1980; Woolridge 1967);
- oral tetracycline (Peach 1986);
- doxycycline (Hoshiwara 1973);
- sulfonamides (Dawson 1969 Sherman; Dawson 1969 Stewart; Foster 1966; Shukla 1966).

Four studies compared oral azithromycin with topical tetracycline (Bailey 1993; Bowman 2000; Dawson 1997; Tabbara 1996).
One study compared topical azithromycin with oral azithromycin (Cochereau 2007).
Azithromycin was usually given as a single dose of 20 mg/kg up to 1 g (for adults). Topical tetracycline was usually the 1% dose, although there was some variation in treatment schedules. In general, the application of topical tetracycline was supervised, or applied by personnel in the research team. The exceptions were Bailey 1993 and Bowman 2000, where the ointment was administered by carers and was not supervised.

Types of outcome measures

Reporting of the two main outcome measures for this review is presented in Table 3.
All studies provided data at around three months (range two to five months). Six studies had longer follow-up, ranging from six months (Bailey 1993; Bowman 2000), and 12 months (Darougar 1980; Dawson 1997; Foster 1966) to three years (Woolridge 1967).
All 14 individually randomised studies reported active trachoma at follow-up. A variety of classification schemes were used for active

trachoma. The majority of studies used one of the scales described in Types of outcome measures.

- MacCallan 1936 (Dawson 1969 Sherman; Dawson 1969 Stewart; Woolridge 1967)
- WHO 1962 (Attiah 1973; Shukla 1966)
- Dawson 1975 (Darougar 1980)
- Dawson 1981 (Bailey 1993; Tabbara 1996)
- Thylefors 1987 (Bowman 2000; Cochereau 2007; Dawson 1997)

Three studies used different classifications, but these were likely to have been based on a similar assessment (Foster 1966; Hoshiwara 1973; Peach 1986). 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.

Six of the 14 studies reported assessment of ocular infection (Bailey 1993; Cochereau 2007; Darougar 1980; Dawson 1997; Hoshiwara 1973; Tabbara 1996), but comparative data on ocular infection between intervention groups were not reported by Cochereau 2007.

None of the studies considered resistance as an outcome. Adverse effects were reported inconsistently.

Cluster-randomised studies

Twelve community-based studies are included in the review (Table 4).

Types of participants

These 12 studies took place in the following countries (according to WHO region).

African Region

- The Gambia (ACT 1999 The Gambia; PRET The Gambia)
- Ethiopia (TANA; TEF)
- Niger (NCT00618449; PRET Niger)
- Mali (Resnikoff 1995)
- Tanzania (ACT 1999 Tanzania; PRET Tanzania; Wilson 2018)

Eastern Mediterranean Region

- Egypt (ACT 1999 Egypt)

Western Pacific Region

- Vietnam (Atik 2006)

The inclusion criteria for communities were not always clearly specified in these studies, and varied where they were specified. Some studies randomly selected communities in specific regions (Atik 2006; TEF); some studies specified a cut-point in terms of prevalence of active trachoma between 5% and 20% (NCT00618449; PRET Niger; PRET Tanzania; PRET The Gambia); one study included communities that had not received azithromycin since 2009 with an estimated prevalence of active trachoma between 5% and less than 10% (Wilson 2018); and others used logistical considerations (TANA).

All the studies (except Atik 2006) evaluated some form of mass drug administration and therefore included everyone present in the communities. The evaluation of the outcome was often done on a random sample of children and adults, termed a "sentinel" sample. Where sex was reported, approximately 50% of the population were male.

Most studies were conducted in trachoma endemic areas with high levels of infection and clinical disease, particularly in children. The exceptions were Atik 2006, NCT00618449, and PRET The Gambia, where active trachoma and ocular infection were less than 20%.

Types of interventions

Table 5 summarises the comparisons addressed in the 12 cluster-randomised studies. Almost all of these studies evaluated mass drug administration with azithromycin at 20 mg/kg up to 1 g for adults. Resnikoff 1995 assessed topical tetracycline 1%. Atik 2006 only treated people with active trachoma and their household members.

Four studies compared antibiotic to no treatment, Resnikoff 1995, or delayed treatment (TANA; TEF; Wilson 2018).

Four studies compared azithromycin and topical tetracycline (ACT 1999 Egypt; ACT 1999 Tanzania; ACT 1999 The Gambia; Atik 2006).

Six studies compared different strategies for mass drug administration:

- NCT00618449 compared azithromycin twice (one month apart) with a single dose of azithromycin;
- the three PRET studies compared enhanced coverage (> 90%) with standard coverage (80% to 90%) (PRET Niger; PRET Tanzania; PRET The Gambia);
- three studies compared azithromycin twice a year for two or three years with azithromycin once a year for two or three years (PRET Niger; TANA; TEF), with only children being treated twice a year in PRET Niger;
- PRET Tanzania and PRET The Gambia compared azithromycin annually for three years with a cessation rule.

Specific exclusion criteria were usually given for pregnant women, children younger than six months, or people with macrolide al-

lergy. Other treatments offered included oral erythromycin or topical tetracycline.

Types of outcome measures

Table 6 summarises the reporting of the main outcome measures for this review in these cluster-randomised studies. Follow-up ranged from six months, in Resnikoff 1995, to 42 months, in TANA, with most studies reporting at least to 12 months. Most studies used the classification of trachoma as set out in Thylefors 1987, the exception being the ACT studies (ACT 1999 Egypt; ACT 1999 Tanzania; ACT 1999 The Gambia), which used Dawson 1981a. Almost all studies (except Resnikoff 1995) did some form of assessment of ocular infection using a variety of techniques, but most commonly polymerase chain reaction (PCR). Five studies assessed resistance (PRET Niger; PRET Tanzania; PRET The Gambia; TANA; TEF). None of the studies assessed resistance of *C trachomatis* to antibiotics, but a number of other bacteria were considered (*Streptococcus pneumoniae*, *Staphylococcus aureas*, *Escherichia coli*), as well as genetic determinants of macrolide resistance.

Excluded studies

We excluded 63 studies for the following reasons (Characteristics of excluded studies).

- Types of studies: not RCTs (33 studies).
- Types of participants: not people with trachoma or not conducted in a trachoma endemic area (4 studies).
- Types of interventions: not a relevant intervention or comparator (21 studies).
- Types of outcomes: eye outcomes not measured, or assessed effect of antibiotics on trichiasis only (4 studies).
- Other reason: study not done (1 study), trial report not found (1 study).

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

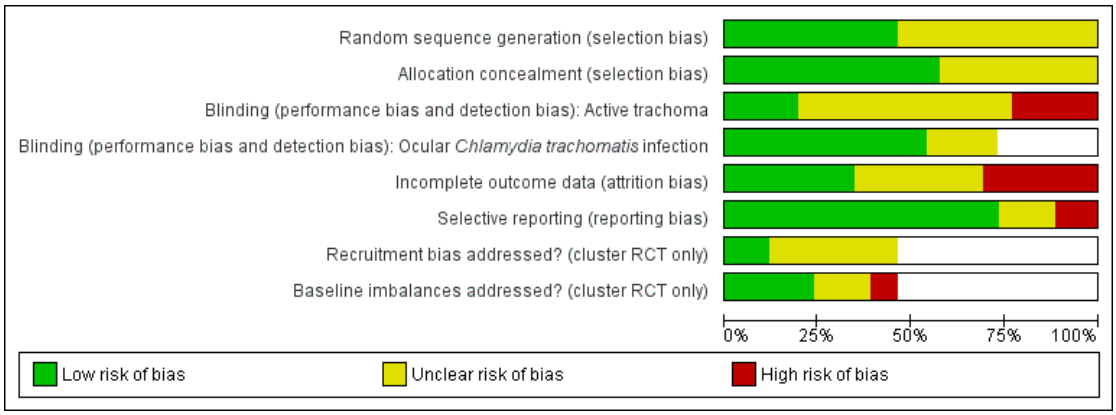
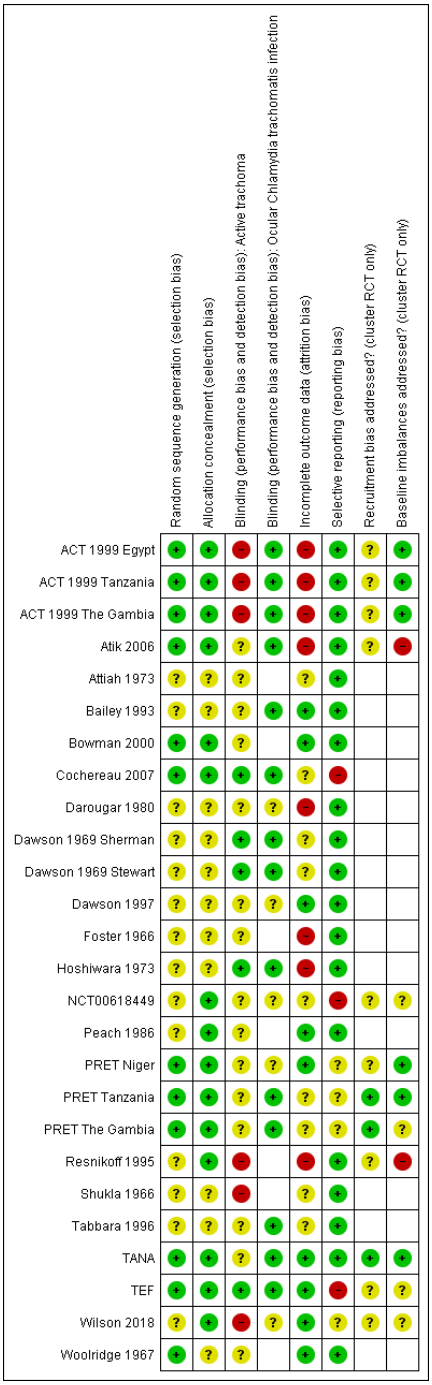


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Twelve studies described adequate methods of generating an unpredictable sequence, using either computer-generated sequences or random number tables. We considered that allocation concealment was not an issue for cluster-randomised trials, and graded all 12 cluster-randomised studies as at low risk of bias for this domain. Three of the individually randomised studies reported adequate methods of allocation concealment. The remaining studies reported insufficient detail to judge the risk of selection bias.

Blinding

We considered performance and detection bias together, but separated the two main outcomes (active trachoma and ocular infection) because we considered that masking would have a different impact on these two outcomes. We considered that the issues of performance and detection bias for antimicrobial resistance were likely to be similar to those for ocular infection, as antimicrobial resistance is also assessed using laboratory tests.

Individually randomised studies

Active trachoma

In most of the individually randomised studies the treatments were quite different, either comparisons with no treatment, or comparing oral and topical treatments. Only four studies used placebo treatments to mask the study arms: three studies compared active treatment to placebo (Dawson 1969 Sherman; Dawson 1969 Stewart; Hoshiwara 1973), and one study compared oral and topical azithromycin with equivalent placebo treatments in each arm (Cochereau 2007). We graded these studies as at low risk of bias for performance and detection bias for active trachoma. A number of studies mentioned masking, particularly of outcome assessors. Masking was not well described in general, and we marked these studies as having an unclear risk of bias for performance and detection bias for active trachoma, given that the interventions were so clearly different. We graded studies where masking was not mentioned as at high risk of bias (Shukla 1966).

Ocular infection

Fewer studies measured ocular infection. Where masking was described, these were graded in general as having low risk of bias. Two of the individually randomised studies did not describe masking of laboratory samples and so were graded as at unclear risk of bias (Darougar 1980; Dawson 1997).

Cluster-randomised studies

Active trachoma

All the comparisons in the cluster-randomised studies were obviously different, and none of the studies reported using placebos. We therefore graded these studies as at high risk of bias, unless they reported efforts to mask the assessment of trachoma and/or attempted to minimise knowledge of the other arms of the study, in which case we graded them as at unclear risk of bias.

Ocular infection (and antimicrobial resistance where assessed)

We graded the majority of studies that examined these outcomes as at low risk of bias, as efforts to mask the laboratory assessment were generally well described. Three studies described masking procedures in insufficient detail (NCT00618449; PRET Niger; Wilson 2018).

Incomplete outcome data

Only eight studies provided data suggesting that incomplete outcome data were unlikely to bias the results, that is they reported high follow-up rates (greater than 80%) that were reasonably equal between intervention groups (Bailey 1993; Bowman 2000; Dawson 1997; Peach 1986; PRET Niger; TANA; TEF; Woolridge 1967). We graded seven studies with high or unequal loss to follow-up as at high risk of attrition bias (ACT 1999 Egypt; ACT 1999 Tanzania; ACT 1999 The Gambia; Atik 2006; Foster 1966; Hoshiwara 1973; Resnikoff 1995). In another study, people were excluded because of inadequate treatment, and it was not clear to which group this applied (Darougar 1980); this study was also graded as at high risk of attrition bias. Attrition bias was difficult to judge for the remaining studies, which we graded as at unclear risk of bias.

Selective reporting

There was little suggestion of selective outcome reporting. Table 3 and Table 6 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, which is unlikely to introduce bias. TANA did not publish data on active trachoma, but this information was supplied by the authors. In two studies (Cochereau 2007; NCT00618449), it was clear that data on ocular infection had been collected but not reported.

Other potential sources of bias

Recruitment 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 2011). None of the included studies discussed this issue.

Baseline imbalances

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 2011). This was a problem with some of 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). Reporting of the baseline comparability of clusters or statistical adjustment for baseline characteristics can help reduce concern about the effects of baseline imbalances (ACT 1999 Egypt; ACT 1999 Tanzania), 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. In ACT 1999 The Gambia, eight communities were pair-matched. The more recent cluster-randomised studies were larger: PRET Niger (24 communities); PRET Tanzania (32 communities); PRET The Gambia (48 communities); TANA (48 communities); TEF (16 communities); Wilson 2018 (96 communities).

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

Comparison 1: Any antibiotic versus control (individuals)

Primary outcome: active trachoma

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% confidence interval (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). We judged this to be low-certainty evidence, downgrading for risk of bias and inconsistency (Summary of findings for the main comparison).

Analysis 1.2 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). We judged this to be low-certainty evidence, downgrading for serious limitations in study design and inconsistency (Summary of findings for the main comparison).

Subgroup analysis: oral antibiotics versus control compared with topical antibiotics versus control

Analysis 1.3 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, substantial heterogeneity remained (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 0.82 (95% CI 0.72 to 0.92). A similar picture was seen for active trachoma at 12 months (Analysis 1.4). 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.

Secondary outcome: *C trachomatis* infection

Analysis 1.5 shows the effect of any antibiotic treatment on ocular *C trachomatis* infection at three months. Fewer trials contributed to this analysis (4 trials, n = 297). However, in contrast to the effect on active trachoma, there was no evidence of 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). We judged this to be low-certainty evidence, downgrading for serious limitations in study design and imprecision (Summary of findings for the main comparison).

Analysis 1.6 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. We judged this to be low-certainty evidence, downgrading for very serious limitations in study design: one small study at risk of bias.

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

Subgroup analysis: oral antibiotics versus control compared with topical antibiotics versus control

Data were insufficient to make a reliable comparison of the effects of oral and topical antibiotics versus control on *C trachomatis* infection (Analysis 1.7; Analysis 1.8).

Secondary outcome: antimicrobial resistance

None of the studies assessed antimicrobial resistance.

Adverse effects

Table 7 summarises the information on adverse effects reported in the individually randomised studies. In 5 of the 14 individually randomised studies, there was no mention of adverse effects in the study report.

- In Bailey 1993 abdominal pain was reported more often in the azithromycin group (26% versus 16%, P = 0.09). Other effects: diarrhoea, vomiting, fever, headache, body pain, other similar between two study groups.
- Cochereau 2007 reported no treatment-related adverse events.
- Dawson 1969 Sherman and Dawson 1969 Stewart noted "No untoward reactions to sulfonamides".
- Dawson 1997 reported that azithromycin was well tolerated, and that only two children (of 125 treated) complained of nausea.
- Foster 1966 noted three adverse reactions to sulphamethoxypyridazine in 155 children given the drug.
- Hoshiwara 1973 reported "Anorexia, nausea, vomiting or diarrhoea..." in two children out of 49 receiving doxycycline.
- Tabbara 1996 reported no adverse effects in 31 people given azithromycin and 29 given tetracycline.
- Woolridge 1967 noted only trivial reactions.

Comparison 2: Oral versus topical antibiotics (individuals)

Primary outcome: active trachoma

Analysis 2.1 shows the effect of oral versus topical antibiotic on active trachoma at three months from within-trial comparisons (6 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 had findings consistent with no difference in effect (Darougar 1980; Dawson 1997; Foster 1966). We judged this to be moderate-certainty evidence, downgrading one level for serious limitations in study design and one level for inconsistency as the study estimates ranged from 0.65 to 1.37 (Summary of findings 2).

Analysis 2.2 shows the effect of oral versus topical antibiotic on active trachoma at 12 months from within-trial comparisons (5 trials, n = 886). There was considerable statistical heterogeneity (I^2 = 56%). The estimates of effect were spread across the null line, with three trials reporting a beneficial effect of oral antibiotics, and two trials reporting a beneficial effect of topical antibiotics. Three of the six trials had findings consistent with no difference in effect (Darougar 1980; Dawson 1997; Foster 1966). We judged this to be low-certainty evidence, downgrading one level for serious limitations in study design and one level for inconsistency as the study estimates ranged from 0.66 to 1.15 (Summary of findings 2).

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. A post hoc analysis excluding this trial from the analyses substantially reduced the observed inconsistency (I^2 = 0%) at three months, 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)). In the other trials, application of topical antibiotics was done by members of the research team or schoolteachers.

Secondary outcome: *C trachomatis* infection

Similarly for active trachoma at 12 months, there was no consistent evidence to support either oral or topical antibiotics being more effective for *C trachomatis* infection at three (Analysis 2.3) or 12 months (Analysis 2.4) (Summary of findings 2).

Secondary outcome: antimicrobial resistance

None of the studies assessed antimicrobial resistance.

Adverse effects

See Comparison 1 above.

Comparison 3: Oral azithromycin versus topical tetracycline (individuals)

Primary outcome: active trachoma

Analysis 3.1 and Analysis 3.2 show the specific comparison between oral azithromycin and topical tetracycline for active trachoma at three and 12 months. There was considerable heterogeneity in the results of these studies for active trachoma (Analysis 3.1). 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 that was not statistically significant (risk ratio 0.90, 95% CI 0.65 to 1.23).

We have not included data from Bailey 1993 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 trachoma 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 trachoma in the azithromycin group and 27/97 in the tetracycline/erythromycin group (risk ratio 0.78, 95% CI 0.47 to 1.28). Approximately 42% of each group were antigen positive. We have also not included data from Cochereau 2007 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 96.6% of the two-day group, three-day group, and oral treatment group 60 days after treatment.

Secondary outcome: *C trachomatis* infection

Analysis 3.3 and Analysis 3.4 show the specific comparison between oral azithromycin and topical tetracycline for *C trachomatis* infection at three and 12 months. Two studies reported this outcome at three months. The results of these studies differed: Dawson 1997 risk ratio 0.57, 95% CI 0.14 to 2.30, favouring azithromycin, and TANA risk ratio 1.30, 95% CI 0.41 to 4.11, favouring tetracycline. At 12 months there were only data from Dawson 1997, but with few events the effect estimate was imprecisely estimated (risk ratio 0.50, 95% 0.18 to 1.43).

Secondary outcome: antimicrobial resistance

None of the studies assessed antimicrobial resistance.

Adverse effects

See Comparison 1 above.

Comparison 4: Oral antibiotics versus control (communities)

Four cluster-randomised community-based trials compared antibiotic to no or delayed treatment: three studies of oral azithromycin (TANA; TEF; Wilson 2018) and one study of topical tetracycline (Resnikoff 1995).

Primary outcome: active trachoma

None of the studies followed up at three months.

Two studies published on active trachoma at 12 months (Resnikoff 1995; Wilson 2018) and one study provided unpublished data (TANA).

In TANA, 258/634 sentinel children aged 0 to 9 years in 12 communities treated with a single dose of azithromycin had active trachoma at 12 months compared with 429/613 children in communities where treatment was delayed to 12 months (risk ratio 0.58, 95% CI 0.52 to 0.65). The results of this study were reasonably robust to assumptions about the intracluster correlation coefficient (ICC): adjusting for an ICC of 0.2 gave a 95% CI of 0.41 to 0.83.

Wilson 2018 reported data as median community prevalence. At 12 months, the median community prevalence of active trachoma was 9.3% in communities given one single dose of azithromycin (range 0 to 38.9%) and 8.2% in communities that had not been treated (range 0 to 52.9%).

There are several potential reasons for the difference between TANA and Wilson 2018: (1) The prevalence of active trachoma in the population of Wilson 2018 was low (median 6%). In TANA disease prevalence was much higher: over 70% of children had active trachoma at baseline in the intervention groups; (2) We judged TANA largely at low risk of bias but Wilson 2018 was a mixture of unclear and high risk of bias. In particular, the authors reported that reported that people taking part in the 12-month follow-up were less likely to report exposure to a face-washing educational campaign and were less likely to live within 30 minutes of a water source; (3) the coverage of mass drug administration was lower in Wilson 2018 at 73% whereas in TANA it was over 80%.

In Resnikoff 1995 four villages were randomly allocated 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.

Secondary outcome: *C trachomatis* infection

TEF and TANA reported *C trachomatis* infection at 12 months (Analysis 4.2). In both 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 and 0.32 in TANA, I^2 = 97%). 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, both of the studies indicated a statistically significant beneficial effect of antibiotic treatment on *C trachomatis* infection. Again, we judged this to be moderate-certainty evidence, downgrading for inconsistency (Summary of findings 3).

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.

In TANA communities were treated at 12 months. However, at a later stage after four years of mass treatment, communities were randomised to continuation versus discontinuation of annual or biannual mass treatment. In the discontinuation arm, the mean prevalence of infection in children aged 0 to 9 years increased from 8.3% (95% CI 4.2% to 12.4%) at baseline (0 months) to 14.7% (95% CI 8.7% to 20.8%, P = 0.04) at 36 months. The prevalence of *C trachomatis* in communities randomised to continuation of mass treatment was 7.2% (95% CI 3.3% to 11.0%) at baseline and 6.6% (95% CI 1.1% to 12.0%, P = 0.64) at 36 months.

Wilson 2018 reported data as median community prevalence. At 12 months, the median community prevalence of ocular infection was 0% in communities given one single dose of azithromycin (range 0 to 14.3%) and 0% in communities that had not been treated (range 0 to 14.3%).

Secondary outcome: antimicrobial resistance

Five studies, all taking place in Africa, assessed antimicrobial resistance (Table 8) (PRET Niger; PRET Tanzania; PRET The Gambia; TANA; TEF). Three of these studies compared azithromycin with no azithromycin (PRET Tanzania; TANA; TEF). In PRET Tanzania azithromycin was given once a year for three years; in TANA azithromycin was given every three months for one year; and in TEF azithromycin was given twice a year for three years. Two studies compared different frequencies of azithromycin administration. PRET Niger compared azithromycin twice a year for two years to azithromycin once a year for two years. PRET The Gambia compared azithromycin once a year for three years to azithromycin once a year for one year. In all five studies antibiotic resistance was assessed in children, although the age ranges differed.

None of the studies assessed antibiotic resistance in *C trachomatis*. Three studies assessed *S pneumoniae* (PRET The Gambia; TANA; TEF); one study assessed *S aureus* (PRET The Gambia); and one study assessed *E coli* (PRET Tanzania). Carriage was nasopharyngeal, with the exception of *E coli*, which was gastrointestinal. Four studies assessed resistance to azithromycin. PRET Niger and TANA assessed genetic evidence of resistance to macrolides and azithromycin, respectively. Other antibiotics were also considered: erythromycin (PRET Tanzania), clindamycin (PRET The Gambia; TANA), tetracycline (TANA; TEF), penicillin (TANA; TEF), and trimethoprim-sulfamethoxazole (TMP-SMX) (TEF).

Maximum follow-up (after baseline mass drug administration (MDA) treatment) was six months (PRET Tanzania), 12 months (TANA), 24 months (PRET Niger), 30 months (PRET The Gambia), and 54 months (TEF).

Due to the heterogeneity of studies, outcomes, and reporting, we did not perform any meta-analysis of antimicrobial resistance outcomes.

Antibiotic resistance in *S pneumoniae*

Table 9 show the results of the studies investigating resistance to *S pneumoniae* (PRET The Gambia; TANA; TEF).

In PRET The Gambia azithromycin/macrolide resistance was assessed one month before, one month after, and six months after the third annual round of MDA in two communities. This was compared to antibiotic resistance 30 months after one round of MDA in six communities. There were few cases of resistance to azithromycin: no cases one month before the third round of azithromycin MDA; 5/417 (1.2%) one month after; and 3/343 (0.9%) six months after. In the comparator group there was one case of resistance in 400 children (0.3%) 30 months after one annual round of MDA. The risk ratio comparing intervention (six months after the third round of mass treatment) and control (30 months after one annual round of mass treatment) suggested an increased risk of resistance in the intervention communities (risk ratio 3.5, 95% CI 0.4 to 33.5). However, wide confidence intervals, due to the sparse data, were compatible with increased or decreased risk.

TANA compared antibiotic resistance in 12 communities allocated to mass treatment with azithromycin every three months for 12 months, which was compared to antibiotic resistance in 12 communities that did not receive azithromycin for 12 months. At baseline in the intervention communities, on average 3.6% of children were carrying *S pneumoniae* resistant to azithromycin. At 12 months this had increased to 46.9%. The 12 untreated control communities were not assessed at baseline, but at 12 months had an average azithromycin-resistant *S pneumoniae* carriage risk of 9.2% (risk ratio 5.1, 95% CI 2.8 to 9.3). These analyses are based on the proportion of swabbed children who were classified as resistant. Similar findings were seen for analyses of the proportion of pneumococcal isolates that were classified as resistant (risk ratio 5.6, 95% CI 3.1 to 9.9). The confidence intervals around the effect estimate do not take into account the cluster design of the study. In the study report, confidence intervals were only provided for risk estimates by group and not for the risk ratio. Comparing

these with confidence intervals calculated ignoring the cluster design suggested that any design effect in this study would be less than 1.5. Repeating the risk ratio calculations assuming a conservative design effect of 2 suggests the lower confidence interval would be not less than 2.

Similar results were seen in TEF. A substantial proportion of children in eight communities treated with azithromycin twice a year for three years were carrying *S pneumoniae* resistant to azithromycin at follow-up visits: 28.2% at 24 months and 76.8% at 36 months. This proportion decreased after cessation of azithromycin and was 30.6% at 42 months and 20.8% at 54 months. Data from eight untreated control communities had a lower risk of resistance: 0.9% at 24 months and 0% at 36 months. Risk ratio was 34.0 (95% CI 4.7 to 244) at 24 months and 183.4 (95% CI 11.5 to 2922) at 36 months. Again, repeating analyses assuming a design effect of 2, the lower confidence intervals were always well above 1.

In TANA an increased risk of clindamycin resistance was seen in the intervention communities (risk ratio 4, 95% CI 1.4 to 11.7), but the prevalence of resistance was lower than in other studies: 13.3% in communities treated every three months compared to 3.3% in untreated communities. Similar results were seen for analyses of isolates of *S pneumoniae* infection.

Both TANA and TEF investigated penicillin resistance in *S pneumoniae*. There were very few cases (0 or 1 only) in both studies.

Both TANA and TEF investigated tetracycline resistance in *S pneumoniae*. In TANA 10% of children had tetracycline-resistant *S pneumoniae* at baseline; this increased to 28.4% in communities given mass treatment with azithromycin every three months. This was compared to 17.5% resistance in the non-treated communities at 12 months (risk ratio 1.6, 95% CI 1.01 to 2.6). An analysis with design effect of 2 reduced the lower confidence interval to below 1. Similar results were seen when the analyses were restricted to isolates of *S pneumoniae* infection. In TEF tetracycline resistance was seen in 36.5%, 68.7%, 57.2%, and 38.7% of samples at 24, 36, 42, and 54 months, respectively. This was compared to 18.9% and 15.7% resistance in the control group at 24 months and 36 months (risk ratio 1.9 (95% CI 1.2 to 3.0) and 4.3 (2.8 to 6.6), respectively). The lower confidence interval for the latter analysis remained above 1 with a design effect of 2.

TEF was the only study to look at TMP-SMX and found a similar order of magnitude of resistance in intervention (approximately 8%) and comparator groups (approximately 7% at 36 months) (risk ratio 1.1, 95% CI 0.5 to 2.8).

Antibiotic resistance in *S aureus*

Table 10 shows the results of the studies investigating resistance to *S aureus* (PRET The Gambia).

Only one study reported resistance to *S aureus* (PRET The Gambia). This study compared azithromycin once a year for three years with azithromycin once a year for one year.

Resistance to azithromycin rose from 8.9% one month before the third round of mass treatment to 34.1% one month after and dropped again to 7.3% six months later in two communities. This was higher than the prevalence of resistance in six comparator communities (1.6%) that had received 1 dose of azithromycin 30 months previously (risk ratio 4.6, 95% CI 1.9 to 11.0). A similar change over time was seen with clindamycin (5.8% one month before third round; 30.7% one month after third round; and 5.8% six months after third round), with a low risk in comparator communities (0.8% prevalence 30 months after baseline) risk ratio 7.3 (95% CI 2.2 to 24.3).

Antibiotic resistance in *E coli*

One study reported resistance to *E coli* (Table 11) (PRET Tanzania). In the four intervention communities, azithromycin resistance increased from 16.3% at baseline to 61.2% one month after mass treatment, thereafter decreasing to 42.1% at three months, and 31.3% at six months. In the four untreated communities, azithromycin resistance was lower: 20.8%, 18.7%, 15.9%, and 20.0% (risk ratio at six months 1.6, 95% CI 0.8 to 3.0). A similar pattern was seen for erythromycin. In the four intervention communities, erythromycin resistance varied from 26.0% at baseline to 76.0% at one month after mass treatment, to 54.9% at three months, and 38.6% at six months. In the four untreated communities, erythromycin resistance was lower: 22.9%, 28.4%, 23.8%, and 26.0% (risk ratio at six months 1.8, 95% CI 0.8 to 3.9).

Adverse effects

Table 12 summarises the information on adverse effects reported in the cluster-randomised studies. In TANA data on adverse effects due to azithromycin 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 96 people (75%) had gastrointestinal effects (abdominal pain, vomiting, nausea, diarrhoea, constipation, and related issues) (10.7% of total sample of 671 people, 95% CI 8.5% to 13.3%);
- 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 1 to 9 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.

- NCT00618449, PRET Tanzania, Tabbara 1996, TEF, and Wilson 2018 reported that there were no serious adverse events.

Notably, two other large cluster-randomised studies of azithromycin did not comment on adverse events (PRET Niger; PRET The

Gambia), but in PRET Niger "a data and safety monitoring committee met annually to review results and serious adverse events".

Comparison 5: Oral azithromycin versus topical tetracycline (communities)

Primary outcome: active trachoma

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 separate studies.

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

The effect of community-based treatment with azithromycin versus topical tetracycline on active trachoma is shown in Analysis 5.1 and Analysis 5.2. 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 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 1 for all the results. In ACT 1999 Tanzania, the findings were less consistent, with a risk ratio greater than 1 (favouring topical treatment) for active trachoma at three and 12 months. We judged this to be low-certainty evidence, downgrading for serious limitations in study design and inconsistency (Summary of findings 4).

One further study with a more complex design compared targeted azithromycin combined with surgery versus surgery alone. People with active trachoma in the control group received tetracycline, as did non-index cases in the intervention group (Atik 2006). The proportion of people with active trachoma at 12 months was 21/523 in the intervention group compared with 35/994 in the control (risk ratio 1.14, 95% CI 0.67 to 1.94). The figures for ocular infection were: 23/659 vs 68/1192 (risk ratio 0.61, 95% CI 0.39 to 0.97).

Secondary outcome: *C trachomatis* infection

The effect of community-based treatment with azithromycin versus topical tetracycline on active trachoma is shown in Analysis 5.3 and Analysis 5.4. At three months, azithromycin appeared to be more effective than topical tetracycline in reducing the risk of *C trachomatis* infection. However, these results were not very robust to assumptions about the ICC. Adjusting for an ICC of 0.05 resulted in confidence intervals including 1 for all the results. In ACT 1999 Tanzania, the findings were less consistent, with a risk ratio greater than 1 (favouring topical treatment) for *C trachomatis* infection at 12 months. We judged this to be low-certainty evidence, downgrading for serious limitations in study design and inconsistency (Summary of findings 4).

Secondary outcome: antimicrobial resistance

See Comparison 4 above.

Adverse effects

See Comparison 4 above.

Comparison 6: Annual versus different treatment frequencies

The included studies considered several different dosing strategies. These fall into three broad categories: applying mass treatment at different dosing intervals; applying cessation or stopping rules to mass treatment; and strategies to increase mass treatment coverage.

Mass administration of azithromycin at different dosing intervals

The WHO recommends annual treatment with antibiotics for communities where the prevalence of active trachoma in children aged 1 to 9 years is 10% or more (Solomon 2006; WHO 2014). Four studies compared different dosing intervals with azithromycin versus annual treatment with azithromycin. The different dosing intervals evaluated were as follows.

- Two doses of azithromycin (day 0 and day 30) compared with one dose (day 0) for one year (NCT00618449).
- Azithromycin (single dose) every three months for one year (children aged 1 to 10 years only) (TANA).
- Azithromycin (single dose) every six months for two years (TEF).
- Azithromycin (single dose) every six months for three years (children aged 0 to 12 years only) (PRET Niger).
- Azithromycin (single dose) every six months for three years (TANA).

Two doses of azithromycin (day 0 and day 30) compared with one dose (day 0) for one year

NCT00618449 compared two doses of azithromycin (day 0 and day 30) with a single dose of azithromycin (day 0) in 10 communities within the Maradi region of Niger with a high prevalence of clinical active trachoma in children aged 10 years and younger. This study is unpublished, but study results were available on the trials register (clinicaltrials.gov/ct2/show/results/NCT00618449). The results of this study were inconclusive. At one year, 19/679 (2.8%) participants in the two dose arm had *C trachomatis* infection compared with 12/668 (1.8%) in the single

dose arm (risk ratio 1.56, 95% CI 0.76 to 3.18). The investigators reported that "Prevalence of infection in communities was less than predicted, as was return of infection post-treatment, thus hypothesis could not be evaluated".

Azithromycin (single dose) every three months for 12 months

TANA evaluated the treatment of children aged 1 to 10 years every three months for one year in 12 communities in Ethiopia. Active trachoma was reported for the children-treated arm only. Table 13 shows results for *C trachomatis* infection. At 12 months there was a lower prevalence of infection in children age 1 to 10 years in the communities where children were treated every three months (3.6%) compared with the communities where everyone was offered 1 annual dose (14.6%). Similar prevalence of infection at 12 months was observed in the two groups in people age 11 years and above (8.2% versus 6.2%).

Azithromycin (single dose) every six months

Three studies compared azithromycin mass treatment every six months with annual treatment (PRET Niger; TANA; TEF). In PRET Niger, the treatment every six months was targeted at children aged 0 to 12 years only. PRET Niger and TANA reported active trachoma, and results were similar between communities treated every six months and communities treated annually.

- In PRET Niger, the prevalence of active trachoma at 36 months was 7.8% (95% CI 5.3% to 11.4%) in the communities where children were treated every six months and 8.0% (95% CI 5.0% to 11.6%) in the communities where everyone was treated annually.
- In TANA, the prevalence of active trachoma in children aged 0 to 9 years at 42 months was 35.0% (95% CI 23.9% to 46.1%) in communities treated every six months compared with 31.5% (95% CI 21.6% to 41.3%) in communities treated annually. The authors reported that they did not detect a difference at all other time points (12, 18, 24, 30, 36 months) in children aged 0 to 9 years nor in people aged 10 years or older.

All three studies reported results for *C trachomatis* (see Table 14). Overall, there was some evidence of lower prevalence of *C trachomatis* infection in communities treated every six months, but the differences were generally small and not statistically significant. These data were not pooled due to differences in follow-up and age groups considered and in reporting (mean community prevalences).

Annual mass drug administration compared to annual mass drug administration if evidence of trachoma in the community (*C trachomatis* infection or active trachoma)

In PRET Tanzania and PRET The Gambia, annual mass drug administration was also compared to annual mass drug administration if there was evidence of follicular trachoma or infection, that is the lack of infection was to be used as a stopping rule.
In PRET Tanzania the stopping rule was not applied because infection was observed in all communities after dosing.
In PRET The Gambia there was no evidence of any difference according to stopping rule on active trachoma (rate ratio 1.17, 95% CI 0.65 to 1.53) or *C trachomatis* infection (rate ratio 0.78, 95% CI 0.14 to 4.49) at 36 months, but with wide confidence intervals, indicating considerable uncertainty in the effect estimate. The rate ratios quoted here compare communities allocated to stopping rule, that is that received only one round of mass drug treatment, with communities that received three rounds of mass drug treatment, with confidence intervals adjusted for cluster design. Communities in the stopping-rule arms only received treatment if there were observed cases of infection or disease in the community in the previous six months, and this rule was implemented for all communities, hence they received only one round of mass drug treatment.

Strategies to improve the coverage of mass treatment with azithromycin

In the three PRET studies (PRET Niger; PRET Tanzania; PRET The Gambia), annual mass drug administration with single dose azithromycin and a standard coverage of 80% to 90% was compared to annual mass drug administration of azithromycin with enhanced coverage of 90% or more. All three studies found little evidence of a benefit of the additional effort to increase the coverage of mass treatment.

- In PRET Niger, the prevalence of *C trachomatis* infection at 36 months was 7.1% (95% CI 2.7% to 11.4%) in the enhanced-coverage communities compared with 4.6% (95% CI 0% to 9.5%) in the standard-coverage communities.
- In PRET Tanzania at 36 months (one year after the third mass drug administration), there was no evidence of any difference in the prevalence of *C trachomatis* infection according to coverage of mass drug administration. The prevalence of infection was 4.0% in the standard-coverage communities and 5.4% in the enhanced-coverage communities. The authors reported an adjusted difference of 1.4% (95% CI −1.0% to 3.8%).
- In PRET The Gambia, there was no evidence for an effect of enhanced coverage on *C trachomatis* infection (rate ratio 1.03, 95% CI 0.18 to 5.89) or active trachoma (rate ratio 1.15, 95% CI 0.74 to 1.79), but with wide confidence intervals, indicating considerable uncertainty in the effect estimate.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Oral versus topical antibiotic for trachoma: individuals

Patient or population: people (any age) with active trachoma
Settings: people resident in a trachoma endemic area
Intervention: oral antibiotic, including azithromycin, doxycycline, sulfamethoxypyridazine, and sulfadimethoxine
Comparison: topical antibiotic, including tetracycline and sulfafurazole

Outcomes	Follow-up	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Topical antibiotic	Oral antibiotic				
Active trachoma Clinical assessment: active trachoma defined as TF, TI, or both	3 months	**Study population**		**RR 0.97** (0.81 to 1.16)	953 (6 studies)	⊕⊕◯◯ **low**[1]	
		600 per 1000	**582 per 1000** (486 to 696)				
	12 months	**Study population**		**RR 0.93** (0.75 to 1.15)	886 (5 studies)	⊕⊕◯◯ **low**[2]	
		500 per 1000	**465 per 1000** (375 to 575)				
Ocular *C trachomatis* infection Positive test for *C trachomatis* infection identified by culture, staining on conjunctival smears, or nucleic acid amplification methods	3 months	See comment	See comment	Not estimable	298 (3 studies)	⊕◯◯◯ **very low**[3]	No pooled estimate due to high heterogeneity: 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)

	12 months	See comment	See comment	Not estimable	220 (2 studies)	⊕◯◯◯ **very low**[4]	Darougar 1980 RR 2.59 (95% CI 0.28, 23.88); Dawson 1997 RR 0.50 (0.18, 1.43)
Antibiotic resistance Proportion of samples showing evidence of resistance to antibiotic	Any time point	None of the studies addressed this outcome.					
Adverse effects	Any time point	3 studies made no comment on adverse effects. 1 study of 155 students noted 3 adverse reactions to sulfonamide (severe purpura associated with marked thrombocytopenia, 2 cases of drug rash) 1 study of 194 people reported abdominal pain more often in azithromycin group (26% versus 16%, P = 0.09). Other effects: diarrhoea, vomiting, fever, headache, body pain were similar between 2 study groups. 1 study of 60 people reported no serious adverse reactions and that both azithromycin and tetracycline were well tolerated. 1 study of 168 children noted that azithromycin was well tolerated and that only 2 children (of 125 treated) complained of nausea			1583 (8 studies)	⊕⊕◯◯ **low**[5]	

*The **assumed risk** is the median risk in control groups in the included studies (rounded to nearest 10 per 1000). 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; **TF:** trachomatous inflammation-follicular; **TI:** trachomatous inflammation-intense; **RR:** risk ratio

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for serious limitations in study design (only one study reported adequate methods for allocation concealment and masking of outcome assessment) and one level for inconsistency (study estimates ranged from 0.65 to 1.37 and I^2 = 63%).

[2]Downgraded one level for serious limitations in study design (only one study reported adequate methods for allocation concealment and masking of outcome assessment) and one level for inconsistency (study estimates ranged from 0.66 to 1.15 and I^2 = 56%).

[3]Downgraded one level for serious limitations in study design (methods of sequence generation and allocation concealment poorly reported, one study at high risk of attrition bias) and two levels for very serious inconsistency (see comment column in table).

[4]Downgraded one level for serious limitations in study design (methods of sequence generation and allocation concealment poorly reported, one study at high risk of attrition bias); one level for serious inconsistency (see comment column in table); and one level for imprecision (only 16 events in total).

[5]Downgraded one level for serious limitations in study design (none of the trials reported adequate methods of allocation concealment and masking of outcome assessment, and adverse effects were not consistently considered and reported) and one level for imprecision (individual studies were underpowered to assess rare effects).

Oral azithromycin compared to control for trachoma: communities

Patient or population: people (any age) with active trachoma
Settings: communities in a trachoma endemic area
Intervention: oral azithromycin
Comparison: control (no treatment)

Outcomes	Follow-up	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
		Assumed risk	Corresponding risk			
		Control	Oral azithromycin			
Active trachoma Clinical assessment: active trachoma defined as TF, TI, or both	3 months	None of the studies addressed this outcome.				
	12 months	**Medium-risk population**		**RR 0.58** (0.52 to 0.65)	1247 (1 study)	⊕⊕⊕◯ **moderate**[1]
		100 per 1000	**58 per 1000** (52 to 65)			
		High-risk population				
		300 per 1000	**174 per 1000** (156 to 195)			
Ocular *C trachomatis* infection Follow-up: 3 months Positive test for *C trachomatis* infection identified by culture, staining on conjunctival smears, or nucleic acid amplification methods	3 months	None of the studies addressed this outcome.				

	12 months	**Medium-risk population**		**RR 0.36**	2139	⊕⊕⊕◯ **moderate**[2]
		100 per 1000	**36 per 1000** (31 to 43)			
		High-risk population				
		300 per 1000	**108 per 1000** (93 to 129)			
Antibiotic resistance Proportion of samples showing evidence of resistance to antibiotic	Any time point	There was evidence of an increased risk of resistance of *S pneumoniae*, *S aureus*, and *E coli* to azithromycin, tetracycline, and clindamycin with risk ratios in the order of 5 at 12 months. No evidence to support increased resistance to penicillin or trimethoprim/sulfamethoxazole			1354 (4 studies)	⊕⊕⊕⊕ **high**
Adverse effects	Any time point	No serious adverse events reported. Azithromycin associated with reduced mortality in children. Main adverse effect of azithromycin (in approximately 10% of the population) was abdominal pain, vomiting, and nausea			3069 (2 studies)	⊕⊕⊕⊕ **high**

*The **assumed risk** (medium/high risk) were based on prevalence estimates used as the basis for recommendations as set out in WHO 2010. 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; **TF:** trachomatous inflammation-follicular; **TI:** trachomatous inflammation-intense; **RR:** risk ratio

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for serious inconsistency.
[2]Downgraded one level for serious inconsistency: I^2 = 79%. However, both study estimates were in the same direction 0.32 (0.26 , 0.40) and 0.49 (0.36 , 0.68).

Oral azithromycin compared to topical tetracycline for trachoma: communities

Patient or population: people (any age) with active trachoma
Settings: communities in a trachoma endemic area
Intervention: oral azithromycin
Comparison: topical tetracycline

Outcomes	Follow-up	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Topical tetracycline	Oral azithromycin				
Active trachoma Clinical assessment: active trachoma defined as TF, TI, or both	3 months	See comment		Not estimable	6002 (3 studies)	⊕⊕◯◯ **low**[1]	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)
	12 months	See comment		Not estimable	5414 (3 studies)	⊕⊕◯◯ **low**[1]	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* Positive test for *C trachomatis* infection identified by culture, staining on conjunctival smears, or nu-	3 months	See comment		Not estimable	5773 (3 studies)	⊕⊕◯◯ **low**[1]	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.

cleic acid amplification methods						37, 0.70)
	12 months	See comment	Not estimable	5276 (3 studies)	⊕⊕◯◯ **low**[1]	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)
Antibiotic resistance Proportion of samples showing evidence of resistance to antibiotic	Any time point	None of the studies addressed this outcome.				
Adverse effects	Any time point	No comment on adverse effects in study reports		6002 (3 studies)	-	

CI: confidence interval; **TF:** trachomatous inflammation-follicular; **TI:** trachomatous inflammation-intense; **RR:** risk ratio

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for serious limitations in study design (three cluster-randomised trials, two of which 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) and one level for serious inconsistency (results were different in the different studies - see comment column in table).

DISCUSSION

Summary of main results

The 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. We judged the certainty of the evidence to be low. Oral and topical treatments appeared to have similar effects if used as prescribed (Summary of findings 2). One study 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 (Bowman 2000).

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 providing moderate-certainty 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) (TANA).

Only one trial compared oral versus topical community-based treatment (Summary of findings 4). This study was conducted in three countries in Africa and was therefore 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.

The included studies considered several different dosing strategies. These fall into three broad categories: applying mass treatment at different dosing intervals; applying cessation or stopping rules to mass treatment; and strategies to increase mass treatment coverage. There was no strong evidence to support any variation in the recommended annual mass treatment.

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 collect and report these data systematically, between 10% and 15% of people experienced symptoms such as nausea and vomiting with azithromycin treatment.

Results from five cluster-randomised trials of mass treatment with azithromycin provided high-certainty evidence of an increased risk of resistance of *S pneumoniae*,*S aureus*, and *E coli* to azithromycin, tetracycline, and clindamycin with risk ratios in the order of 5 at 12 months. There was no evidence to support increased resistance to penicillin or trimethoprim-sulfamethoxazole (TMP-SMX).

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 meant that we could not 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.

The epidemiology of trachoma has changed over time as programmes have implemented the SAFE strategy. In March 2019, the number of people living in areas where the prevalence of trachomatous inflammation-follicular (TF) in children aged 1 to 9 years was $\geq$ 5% was 142.2 million, down from 1517 million in 2002 (WER 2019). The majority of people living in trachoma endemic areas are in sub-Saharan Africa. Many of the more recent trials included in this review took place in countries in the African Region. The level of endemicity was relatively high in most of these studies, and the extent to which they are applicable in settings with lower endemicity is unclear.

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

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, which 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.

Quality of the evidence

The included trials were published from 1966 onwards, and their quality was variable. The certainty of evidence for most outcomes was low, particularly for the comparison of 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-certainty evidence for the comparison of oral versus topical antibiotics for the outcome active trachoma (Summary of findings 2).

The community-based trials were also of variable methodological quality (Summary of findings 3; Summary of findings 4). In some cluster-randomised studies, only two communities were randomly allocated to treatment. Although adjustment for baseline characteristics can alleviate this problem to some extent, the interpretation of these studies remains problematic. As well as being underpowered, 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.

Four community-based trials 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, which are then enrolled in the treatment programme (Resnikoff 1995; TANA; TEF; Wilson 2018). 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, and inclusion of antimicrobial resistance as an outcome, 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.

We found the classification Atik 2006 problematic. In the last edition of this review we included this trial in the comparison "azithromycin versus no treatment" but on re-evaluation for the current edition we considered the trial to be "azithromycin versus tetracycline". Although the study was described as azithromycin versus no azithromycin in fact people with active trachoma in the control group received tetracycline. The change in classification of this study did not affect the conclusions of this review.

In the current 2019 update we included studies that compared different treatment strategies. We added in the additional question to our objectives: "What is the effect of annual versus different treatment frequencies?". We did not repeat the searches for this additional question. There may be studies that were not included in previous editions of the review (for example Schemann 2007), that would have been eligible for the current update. We do not anticipate that we will have missed many relevant studies as searches were screened from 2010 onwards.

Agreements and disagreements with other studies or reviews

We identified a number of non-randomised studies providing data on antimicrobial resistance. Their results are summarised in Table 15. Overall, the non-randomised studies provided inconsistent evidence on resistance, with some evidence of increased resistance to azithromycin for *S pneumoniae.* Three studies considered resistance in *C trachomatis* after mass treatment and suggest little evidence of resistance to azithromycin.

A recent systematic review of community-level interventions in reducing the prevalence of active trachoma (published as an abstract only) identified a similar number of trials as the current review and came to similar conclusions, that is that mass drug administration reduces active trachoma and ocular chlamydia infection (Bobba 2018). Diab 2018 concluded that azithromycin eye drops twice daily for three days may be as efficient as oral azithromycin in treating active trachoma. This was largely based on the findings of a non-randomised study, but the authors did identify the one trial on this topic identified in the current review (Cochereau 2007). We agree that the trial identified similar rates of cure over 60 days, but suggest that confirmatory studies are needed to assess longer-term follow-up.

A recent systematic review of resistance following mass azithromycin distribution drew similar conclusions to the current review (O'Brien 2019), that is that the available evidence suggests that macrolide resistance to azithromycin is increased after mass azithromycin distribution, particularly for *S pneumoniae.*

AUTHORS' CONCLUSIONS

Implications for practice

Oral or topical antibiotic treatment reduces the risk of active trachoma and ocular chlamydial infection in people who have active trachoma, but the size of the treatment effect in individuals is uncertain. It is likely that oral azithromycin and topical tetracycline have similar effects if used as prescribed. Mass antibiotic treatment with single dose oral azithromycin reduces the prevalence of active

trachoma and ocular infection in communities. There is evidence of an increased risk of antibiotic resistance in communities treated with antibiotics.

The evidence provided in this review supports the current "A" strategy as set out by the World Health Organization (WHO) (Solomon 2006; WHO 2014), and does not provide convincing evidence for any alternate regimen.

This review is largely based on studies conducted in areas of relatively high endemicity. It does not provide evidence as to the role of mass administration of antibiotics as communities approach elimination of trachoma as a public health problem.

Implications for research

The WHO Alliance for the Global Elimination of Trachoma endorsed the donation of azithromycin for the treatment of trachoma, and as of July 2019, over 850 million doses donated by Pfizer Inc. had been distributed via the International Trachoma Initiative (ITI) since 1999. Locations that have not yet started azithromycin mass drug administration would enable community-randomised trials to be conducted under operational conditions. Inequities are bound to exist in some settings at start-up, when resources for antibiotic 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 are required to determine optimal dosage intervals of azithromycin at various levels of endemicity, test the most appropriate thresholds for starting and stopping mass treatment, determine minimum treatment coverage requirements, and to determine which subgroups could be treated at various stages of the pathway towards elimination. 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 and persistence 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	**Unit of randomisation:** community (1 matched pair). **Masking:** • participant - no, • provider - no, • outcome - no. **Exclusions after randomisation:** no. **Losses to follow-up:** yes, temporary absence.
Participants	**Country:** Egypt. **Endemicity:** "trachoma endemic". Percentage prevalence of active trachoma in study villages was 20% for all ages. **Number of communities randomised:** 2. **Number of people randomised:** 2238. **Age**: all ages. **Sex:** not reported. **Clinical grading:** Dawson 1981b. **Laboratory tests:** LCR. **Inclusion criteria:** all villagers present. **Exclusion criteria:** none, but alternative treatment for azithromycin-allocated women at childbearing age
Interventions	**Intervention:** 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 4 times daily (amoxicillin in case of intolerance) **Comparator:** oxytetracycline. • Administration: topical. • Dose: 1%. • Duration: once daily for 6 weeks, trained village assistants were responsible for administration.
Outcomes	**Primary:** active trachoma. **Secondary:** ocular *C trachomatis* infection. **Adverse effects:** not reported. **Follow-up:** 12 to 14 months.
Notes	**Study name:** Azithromycin in Control of Trachoma. **Date study conducted:** not reported. **Funding source:** Quote: "This project was supported by a grant from the National Institute of Allergy and Infectious Disease (PO1 A135682), and by Pfizer Labs (New York, NY), the Edna McConnell Clark Foundation (New York, NY) and Abbott Laboratories (Abbott Park, IL)."

	Conflict of interest: not reported. **Trial registration ID:** not reported.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "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"
Allocation concealment (selection bias)	Low risk	Judgement comment: cluster-randomised controlled trial, so not applicable
Blinding (performance bias and detection bias) Active trachoma	High risk	Judgement comment: 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 (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "Laboratory staff were not aware of the clinical and treatment status of study participants" Quote: "Identification numbers for laboratory samples differed from those used on the ocular examination forms to conceal village and treatment status from the laboratory staff"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "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." Quote: "little movement was documented" Quote: "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% Judgement comment: different follow-up in intervention and control, and follow-up in control group less than 80%. From Table 6: 92% of azithromycin group and 86% of tetracycline group had assessment of active trachoma at baseline. At 1 year, 87% of azithromycin group and 75% of tetracycline group had data on active trachoma
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.
Recruitment bias addressed? (cluster RCT only)	Unclear risk	Judgement comment: 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 suggest that compliance was very different in the 2 groups. This is almost certainly related to the number of doses, but may indicate that recruitment bias is a possibility A = azithromycin group; T = tetracycline group, numbers expressed as % 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? (cluster RCT only)	Low risk	Quote: "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

ACT 1999 Egypt (*Continued*)

		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	**Unit of randomisation:** community (1 matched pair). **Masking:** • participant - no, • provider - no, • outcome - no. **Exclusions after randomisation:** none. **Losses to follow-up:** yes, temporary absence.
Participants	**Country:** Tanzania. **Endemicity:** "trachoma endemic". Percentage prevalence of active trachoma in study villages was 31% for all ages. **Number of communities randomised:** 2. **Number of people randomised:** 3261. **Age**: all ages. **Sex**: not reported. **Clinical grading:** Dawson 1981b. **Laboratory tests**: LCR. **Inclusion criteria:** all villagers present. **Exclusion criteria:** none, but alternative treatment for azithromycin-allocated women at childbearing age
Interventions	**Intervention:** azithromycin. • Administration: oral. • Dose: 20 mg/kg up to 1 g. • Duration: once a week for 3 weeks. Women of childbearing age were given erythromycin for 14 days, 500 mg twice daily or 250 mg 4 times daily (amoxicillin in case of intolerance) **Comparator**: oxytetracycline (tetracycline). • Administration: topical (supervised). • Dose: 1%. • Duration: once daily for 6 weeks, trained village assistants were responsible for

	administration.
Outcomes	**Primary:** active trachoma. **Secondary:** ocular *C trachomatis* infection. **Adverse effects:** none. **Follow-up:** 12 to 14 months.
Notes	**Study name:** Azithromycin in Control of Trachoma. **Date study conducted:** not reported. **Funding source:** Quote: "Financial support for the trial was received from Pfizer Ltd, the Edna McConnell Clark Foundation, and the National Institutes of Health; the data analysis was supported by the Freiwillige Akademische Gesellschaft and the L. & Th. La Roche Stiftung." **Conflict of interest:** none declared. **Trial registration ID:** not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "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"
Allocation concealment (selection bias)	Low risk	Quote: "The villages were matched in pairs of similar size, and azithromycin and tetracycline were allocated randomly within these pairs." Judgement comment: allocation concealment unlikely to have been an issue with this design
Blinding (performance bias and detection bias) 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 (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	"Laboratory staff were not aware of the clinical and treatment status of study participants" and "Identification numbers for lab-

		oratory 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 (attrition bias) All outcomes	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 1 year, 60% of azithromycin group and 77% of tetracycline group had data on active trachoma
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.
Recruitment bias addressed? (cluster RCT only)	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 suggest 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? (cluster RCT only)	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 as-

ACT 1999 Tanzania (*Continued*)

		sumption 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 The Gambia

Methods	**Unit of randomisation:** community. **Masking**: • participant - no, • provider - no, • outcome - no. **Exclusions after randomisation:** no. **Losses to follow-up:** yes, temporary absence.
Participants	**Country:** The Gambia. **Endemicity:** "trachoma endemic". Percentage prevalence of active trachoma in study villages was 16% for all ages and 36% for children less than 10 years. **Number of communities randomised:** 8 (pair-matched). **Number of people randomised:** 1753. **Age**: all ages. **Sex**: not reported. **Clinical grading**: Dawson 1981b. **Laboratory tests**: LCR. **Inclusion criteria:** all villagers present. **Exclusion criteria:** none, but alternative treatment for azithromycin-allocated women at childbearing age
Interventions	**Intervention:** azithromycin. • Administration: oral. • Dose: 20 mg/kg up to 1 g. • Duration: 3 weeks. • Treatment frequency: once a week, "Compliance was determined by trained volunteers who recorded the ingestion of tablets or application of ointment." Women of childbearing age erythromycin for 14 days, 500 mg twice daily or 250 mg 4 times daily (amoxicillin in case of intolerance) **Comparator:** oxytetracycline. • Administration: topical. • Dose: 1%. • Duration: 6 weeks. • Treatment frequency: once daily, "Compliance was determined by trained volunteers who recorded the ingestion of tablets or application of ointment."
Outcomes	**Primary:** active trachoma. **Secondary:** ocular *C trachomatis* infection. **Adverse effects:** none. **Follow-up:** 12 months

Notes	**Study name:** Azithromycin in Control of Trachoma. **Date study conducted:** July 1994 to October 1994. **Funding source:** Quote: "Financial support for the trial was received from Pfizer Ltd, the Edna McConnell Clark Foundation, and the National Institutes of Health; the data analysis was supported by the Freiwillige Akademische Gesellschaft and the L. & Th. La Roche Stiftung." **Conflict of interest:** Quote: "none declared". **Trial registration ID:** not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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"
Allocation concealment (selection bias)	Low risk	Quote: "The villages were matched in pairs of similar size, and azithromycin and tetracycline were allocated randomly within these pairs." Judgement comment: allocation concealment unlikely to have been an issue with this design
Blinding (performance bias and detection bias) 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 (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "Laboratory staff were not aware of the clinical and treatment status of study participants" Quote: "Identification numbers for laboratory samples differed from those used on the ocular examination forms to conceal village and treatment status from the laboratory staff"

Incomplete outcome data (attrition bias) All outcomes	High risk	All clusters completed the trial in theory, although 1 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 1 year, 65% of azithromycin group and 50% of tetracycline group had data on active trachoma
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.
Recruitment bias addressed? (cluster RCT only)	Unclear risk	Quote: "All residents who were present at the pre-treatment survey were eligible for participation in the trial." (Fraser-Hurt) Quote: "At all study sites we attempted to treat every individual present in each village" (Schachter page 631)
Baseline imbalances addressed? (cluster RCT only)	Low risk	Quote: "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 esti-

		mates 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	**Unit of randomisation:** community (1 matched pair). **Masking:** • participant - no, • provider - no, • outcome - unclear. **Exclusions after randomisation:** no. **Losses to follow-up:** unclear.
Participants	**Country:** Vietnam. **Endemicity:** Quote: "All 8 communes had approximately a 20% prevalence rate of active trachoma based on rapid assessment." **Number of communities randomised:** 2 (8 included in study, 2 relevant to this review) . **Number of people randomised:** 1851. **Age:** 6 months and older. **Sex:** approximately 60% female. **Clinical grading**: Thylefors 1987. **Laboratory tests:** Amplicor-PCR 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	**Intervention:** azithromycin. • Administration: oral • Dose: 20 mg/kg for children; 1 g for adults. Pregnant women received erythromycin. • Duration: baseline and 12 months. All schoolchildren aged 5 through 15 years were examined; children who had active

	trachoma defined as follicular inflammation, intense inflammation, or both were considered index cases. Index cases and their household members were treated with azithromycin. Non-index cases and non-household members who had active trachoma (follicular inflammation, intense inflammation, or both) received topical tetracycline **Comparator:** no azithromycin. People with trachomatous trichiasis were identified and informed of the availability of surgery. People with active trachoma (follicular inflammation, intense inflammation, or both) received topical tetracycline
Outcomes	**Primary:** active trachoma and *C trachomatis* infection. **Secondary:** none. **Adverse effects:** none. **Follow-up:** 24 months.
Notes	**Study name:** none. **Date study conducted:** November 2000 to November 2003. **Funding source:** Quote: "This work was supported by International Trachoma Initiative grant ITI 01-040 (Dr Dean) and Public Health Service grant EY/AI12219 (Dr Dean), from the National Institutes of Health." **Conflict of interest:** Quote: "Financial Disclosures: None reported." **Trial registration ID:** ACTRN012606000360516 (www.anzctr.org.au/)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Three of 8 communes in Thanh Hoa Province were randomly chosen using a random number list." Quote: "The assignment of the communes to the various treatments was performed randomly."
Allocation concealment (selection bias)	Low risk	Quote: "Three of 8 communes in Thanh Hoa Province were randomly chosen using a random number list." Quote: "The assignment of the communes to the various treatments was performed randomly." Judgement comment: allocation concealment unlikely to have been an issue with this design
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "the 3 randomly selected communes were geographically isolated from one another" Judgement comment: it was not clear if the participants were aware of the existence of other potential interventions

		Quote: "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" Judgement comment: the extent to which the ophthalmologist might be aware of what treatment the community had received was not discussed
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "Samples were labelled with date and a unique identification number to maintain confidentiality and to process samples in a masked fashion"
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: both clusters completed the trial. Attrition was high and unequal between the 2 groups. Response rates were not reported explicitly. The total population and the percentage graded for trachoma at baseline, 6 months, 12 months, and 24 months are as follows (from Table 1 and Figure 2) Azithromycin community: total = 659: 100%; 86%; 79%; 56%. Untreated community: total = 1192; 100%; 89%; 83%; 72%.
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.
Recruitment bias addressed? (cluster RCT only)	Unclear risk	Quote: "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 unclear how many of the residents actually took part in the study
Baseline imbalances addressed? (cluster RCT only)	High risk	Only 2 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 years in the control cluster (10.6% versus 3.6%, $P < 0.001$) and a higher baseline prevalence of active trachoma in children 5 to 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 1 person with chlamydial infection in the household

Attiah 1973

Methods	**Unit of randomisation:** individual. **Masking:** • participant - no, • provider - yes, • outcome - yes. **Exclusions after randomisation:** no. **Losses to follow-up:** none. **Unusual study design:** random allocation stratified by disease severity (clinical signs, 11 strata)
Participants	**Country:** Egypt. **Number of people randomised**: 228. **Age**: 6 to 12 years. **Sex**: not reported. **Clinical grading:** WHO 1962. **Laboratory tests**: none. **Inclusion criteria:** active trachoma or "undetermined case". **Exclusion criteria:** none.
Interventions	**Intervention 1:** tetracycline derivative GS2989. • Administration: topical. • Dose: 0.25%. • Duration: once every school day for 11 weeks, administered by trained public health nurse. **Intervention 2:** oxytetracycline (Terramycin). • Administration: topical. • Dose: not reported. • Duration: once every school day for 11 weeks, administered by trained public health nurse. **Comparator:**: no treatment. • Administration: not applicable. • Dose: not applicable. • Duration: not applicable.
Outcomes	**Primary:** active trachoma. **Secondary:** none. **Adverse effects:** not reported. **Follow-up:** 3 months.

Notes	**Study name:** none. **Date study conducted:** February to May 1965. **Funding source:** Quote: "We are grateful to Dr Ali Gaber, Medical Director, of Pfizer Egypt, who kindly supplied the study with the GS-2989." **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "the principle of double blindness ensured in the experiment" Quote: "The examiner had no knowledge of the treatment assignment to the groups or of the randomisation process used in the trial" Quote: "After three months treatment, the results were checked using WHO criteria without investigators knowing what treatment applied" Judgement comment: the report gave no indication as to how the groups were masked and whether the control group received any placebo treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 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 2 options apply
Selective reporting (reporting bias)	Low risk	Clinical examination only and no suggestion that any assessment of ocular infection made

Bailey 1993

Methods	**Unit of randomisation:** Quote: "randomisation was by room, all active cases within a room receiving the same treatment" **Masking:** • participant - no, • provider - no, • outcome - unclear. **Exclusions after randomisation:** none. **Losses to follow-up:** none.
Participants	**Country:** The Gambia. **Number of communities randomised:** not reported. **Number of people randomised:** 194. **Age:** 9 months to 60 years. **Sex:** 51% male. **Clinical grading:** Dawson 1981a. **Laboratory tests:** IDEIA amplified enzyme-linked immunosorbent assay (Dako) for genus-specific lypopolysaccharide antigen **Inclusion criteria:** active trachoma. **Exclusion criteria:** pregnant or lactating.
Interventions	**Intervention:** azithromycin. • Administration: oral. • Dose: 20 mg/kg. • Duration: single dose. **Comparator:** tetracycline.* • Administration: topical. • Dose: 1% eye ointment. • Duration: twice daily for 6 weeks, applied by patient's mother. *Those with 'severe disease' also received oral erythromycin stearate 250 mg 4 times daily for 2 weeks
Outcomes	**Primary and secondary:** "resolution of disease" clinical signs and antigen positivity **Adverse effects:** standard interview 3 days after treatment including questions about gastrointestinal symptoms in the preceding 3 days and open questions about general health **Follow-up:** 26 weeks.
Notes	**Study name:** none. **Date study conducted:** ocular survey done in May 1992 followed by treatment and follow-up for 26 weeks **Funding source:** Quote: "This project was supported by a grant from the Edna McConnell Clark Foundation, New York, USA." **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement

Bailey 1993 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was by room, all active cases within a room receiving the same treatment" Judgement comment: unclear how the random allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomisation was by room, all active cases within a room receiving the same treatment" Judgement comment: unclear how allocation was concealed.
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "Subjects were examined [...] by a trained observer (RLB) unaware of treatment allocation" Judgement comment: unclear how this masking was maintained as no placebos used for either tablets or ointment
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	No specific information on this, but as the investigators attempted to mask the clinical examinations, it is likely that the laboratory analyses were masked as well, and this would have been easier to do
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 194 participants randomised, 194 examined at 4 weeks; 194 examined at 8 weeks; 191 examined at 16 weeks; and 193 examined at 26 weeks (1 participant had died by that point)
Selective reporting (reporting bias)	Low risk	Both outcomes (infection and clinical disease) were reported

Bowman 2000

Methods	**Unit of randomisation:** individual. **Masking:** • participant - no, • provider - no, • outcome - yes. **Exclusions after randomisation:** no. **Losses to follow-up:** numbers recorded. **Unusual study design:** trial aimed to compare treatments under operational and not best-possible conditions
Participants	**Country:** The Gambia. **Number of people randomised:** 314.

Bowman 2000 (*Continued*)

	Age: 6 months to 10 years. **Sex:** 50% male. **Clinical grading:** Thylefors 1987. **Laboratory tests:** none. **Inclusion criteria:** clinical signs of active trachoma in at least 1 eye. **Exclusion criteria:** not reported.
Interventions	**Intervention**: azithromycin. • Administration: oral. • Dose: 20 mg/kg. • Duration: single dose. **Comparator:** tetracycline. • Administration: topical. • Dose: not reported. • Duration: applied once by a nurse in front of the caregiver, and then twice daily by caregiver for 6 weeks.
Outcomes	**Primary:** active trachoma. **Secondary:** none. **Adverse effects:** not reported. **Follow-up:** 6 months.
Notes	**Study name:** none. **Date study conducted:** recruitment April and May 1998, follow-up 6 months later. **Funding source:** Quote: "Supported by Sight Savers International (GJJ, RJCB). The azithromycin was donated by Pfizer." **Conflict of interest:** Quote: "Commercial relationships policy: N." **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects with clinical signs of active trachoma in at least one eye were randomized, using a block design" Judgment comment: although method of generating sequence was not clearly reported, inclusion of term 'block design' suggests that an unpredictable sequence was generated
Allocation concealment (selection bias)	Low risk	Quote: "Treatment 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 knowl-

		edge of the block randomisation procedure and did not examine the children but administered treatment according to the allocation in the envelope."
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "...graded by a clinical assessor blind to the treatment allocation." Quote: "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." Judgement comment: interventions were different - oral dose of azithromycin syrup versus topical tetracycline - so it was not possible to prevent knowledge to caregivers and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: analysis was not by intention-to-treat, as 4 participants received the wrong allocation and were analysed according to their received treatment, not per 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 groups it is unlikely to have caused bias
Selective reporting (reporting bias)	Low risk	This study reported one of the primary outcomes for this review: active trachoma. There was no indication that the other outcome for this review, *C trachomatis* infection, was collected but not reported.

Cochereau 2007

Methods	**Unit of randomisation**: individual. **Masking**: • participant - yes, • provider - yes, • outcome - yes. **Exclusions after randomisation**: 1 person in eye drop group did not receive allocated treatment. **Losses to follow-up**: generally low (less than 5%), some imbalance between groups. Protocol deviations mean that per-protocol analysis included 80% to 90% of randomly allocated population
Participants	**Country**: Guinea-Conakry (community) and Pakistan (boys schools only) **Number of people randomised:** 670. **Age:** 1 to 10 years. **Sex:** 50% male. **Clinical grading:** Thylefors 1987. **Laboratory tests:** conjunctival swab analysed using PCR. **Inclusion criteria:** active trachoma (TF+TI0 or TF+TI+ on simplified World Health Organization (WHO) scale) **Exclusion criteria:** Quote: "trichiasis or corneal opacity; fibrosis with palpebral deformation; ocular abnormality; ocular infection; organic amblyopia; hypersensitivity to the investigational product; immunosuppressive conditions; systemic steroids, or ophthalmic systemic antibiotics, or topical treatments, or systemic non-steroidal anti-inflammatory drugs prior to the study."
Interventions	**Intervention 1:** azithromycin (eye drops 2 days) and placebo paediatric suspension (n = 224) • Administration: topical. • Dose: 1.5% eye drops. • Duration: twice daily for 2 days, administered by a member of the research team. **Intervention 2:** azithromycin (eye drops 3 days) and placebo paediatric suspension (n = 225) • Administration: topical. • Dose: 1.5% eye drops. • Duration: twice daily for 3 days administered by a member of the research team. **Comparator:** azithromycin (oral) and placebo eye drops (n = 221). • Administration: oral. • Dose: 20 mg/kg. • Duration: single dose administered by a member of the research team.
Outcomes	**Primary:** clinical cure in children with clinically active trachoma. **Secondary:** ocular infection, tolerance. **Adverse effects:** yes. **Follow-up:** 2 months.
Notes	**Study name:** none. **Date study conducted:** January to May 2004. **Funding source:** Quote: "This clinical trial was sponsored by Laboratoires Thea, Clermont-Ferrand, France."

	Conflict of interest: Quote: "IC, PG, AG, TA, TB and PYR have no financial interest in Laboratoires Thea and the product Azyter. PP and LD are employees of Laboratoires Thea." **Trial registration ID:** not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation list used random permuted blocks of six (SAS v 8.2)."
Allocation concealment (selection bias)	Low risk	Quote: "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." Judgement comment: as placebo controlled, it is likely that allocation was concealed
Blinding (performance bias and detection bias) Active trachoma	Low risk	Quote: "We used a double-dummy design with placebo eye drops and placebo paediatric suspension"
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "We used a double-dummy design with placebo eye drops and placebo paediatric suspension"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up data reported as follows (Figure 1, page 669). Some participants may have more than 1 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 ITT analysis (222, 99.1%) • number available for per-protocol 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) • participant request (1) • adverse event (1) • family member illness (1) • number available for ITT analysis (220, 97.8%) • number available for per-protocol 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) • participant request (1) • adverse event (1) • family member illness (1) • number available for ITT analysis (214, 96.8%) • number available for per-protocol analysis (179, 81.0%) Judgement comment: some imbalance in per-protocol analysis, which was main way outcomes were reported, however the impact of this is unclear. Last observation carried forward for missing data
Selective reporting (reporting bias)	High risk	Quote: "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. " Judgement comment: 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"

Darougar 1980

Methods	**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). 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. Some data available only in graphical form
Participants	**Country:** Iran. **Number of people randomised:** 147. **Age**: pre-school (average 6 years). **Sex:** 38% male. **Clinical grading:** modification of Dawson 1975a. **Laboratory tests:** culture (Darougar 1970). **Inclusion criteria:** active trachoma, residence in study village. **Exclusion criteria:** none.
Interventions	**Intervention 1:** oxytetracycline. • Administration: topical. • Dose: 1%. • Duration: twice daily for 7 consecutive days, every month for 12 months, administered by field technician. **Intervention 2:** doxycycline. • Administration: oral. • Dose: 5 mg/kg. • Duration: single dose, every month for 12 months, administered by field technician. **Comparator:** vitamin pills. • Administration: oral. • Dose: not reported. • Duration: 1 dose per month for 12 months, administered by field technician.
Outcomes	**Primary:** active trachoma. **Secondary:** culture (McCoy cells). **Adverse effects:** not reported. **Follow-up:** 4 and 12 months.
Notes	**Study name:** none. **Date study conducted:** not reported. **Funding source:** Quote: "The research project was partially supported by grants from the Dulverton Trust, the Wellcome Foundation, the Order of St John, and an anonymous donor." **Conflict of interest:** not reported. **Trial registration ID:** none.

Darougar 1980 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients with active trachoma were divided into 3 groups according to a randomisation schedule stratified for age, sex, intensity of trachoma, and the number of children with active trachoma in each family." Judgement comment: unclear how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Judgement comment: no information about allocation concealment, although the study is described as "double-blind"
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Judgement comment: no information about allocation concealment, although the study is described as "double-blind". Treatments are different - topical versus oral antibiotics versus vitamin tablets - so the participants will not have been masked.
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Unclear risk	Judgement comment: no information about allocation concealment, although the study is described as "double-blind". Treatments are different - topical versus oral antibiotics versus vitamin tablets - so the participants will not have been masked
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: 147 participants included; 18 excluded because of inadequate treatment or follow-up; it was not reported to which groups these 18 participants had originally been allocated
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.

Dawson 1969 Sherman

Methods	**Unit of randomisation:** individual. **Masking:** • participant - yes, • provider - yes, • outcome - yes. **Exclusions after randomisation:** no. **Losses to follow-up:** not reported. **Unusual study design:** 2 similar studies with few participants each. Numbers need to be read from figures, some not very clear
Participants	**Country:** USA (Native American). **Number of people randomised:** 29. **Age**: 12 to 21 years. **Sex:** not reported. **Clinical grading:** MacCallan 1936. **Laboratory tests:** IFAT on conjunctival smears. **Inclusion criteria:** active disease, boarding at Sherman Institute. **Exclusion criteria:** none.
Interventions	**Intervention:** trisulphapyrimidines. • Administration: oral. • Dose: 3 daily doses to total 3.5 g/day. • Duration: 21 consecutive days. **Comparator:** lactose-placebo. • Administration: oral. • Dose: not reported. • Duration: 21 consecutive days.
Outcomes	**Primary:** active trachoma. **Secondary:** positive IFAT. **Adverse events:** reported. **Follow-up:** 20 weeks.
Notes	**Study name:** none. **Date of study conducted:** September 1967 to April 1968. **Funding source:** Quote: "Supported by a grant (NB 00604) from the National Institutes of Health, US Public Health Service and by a Research Career Development Award to CRD" **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: unclear how the allocation sequence was generated

Dawson 1969 Sherman (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "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" Judgement comment: this statement suggests that allocation was concealed, however it does not tell us who allocated the treatment
Blinding (performance bias and detection bias) Active trachoma	Low risk	Quote: "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"
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "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"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 29 children took part; all (100%) were followed up. Theoretically they could have recruited more and had some lost to follow-up that 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 2 possibilities, we have assigned a judgement of unclear risk
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.

Dawson 1969 Stewart

Methods	**Unit of randomisation:** individual. **Masking:** • participant - yes, • provider - yes, • outcome - yes. **Exclusions after randomisation:** no. **Losses to follow-up:** not reported. **Unusual study design:** 2 similar studies with few participants each. Numbers need to be read from figures, some not very clear
Participants	**Country:** USA (Native American). **Number of people randomised:** 36. **Age**: 12 to 21 years. **Sex:** not reported. **Clinical grading:** MacCallan 1936. **Laboratory tests:** IFAT on conjunctival smears. **Inclusion criteria:** active disease, boarding at Stewart School. **Exclusion criteria:** none.
Interventions	**Intervention:** trisulphapyrimidines. • Administration: oral. • Dose: 3.5 g/day. • Duration: 21 consecutive days. **Comparator:** lactose-placebo. • Administration: oral. • Dose: not reported. • Duration: 21 consecutive days.
Outcomes	**Primary:** active trachoma. **Secondary:** positive IFAT. **Adverse events:** reported. **Follow-up:** 20 weeks.
Notes	**Study name:** none. **Date study conducted:** September 1967 to March 1968. **Funding source:** Quote: "Supported by a grant (NB 00604) from the National Institutes of Health, US Public Health Service and by a Research Career Development Award to CRD" **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: unclear how the allocation sequence was generated

Dawson 1969 Stewart (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "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" Judgement comment: this statement suggests that allocation was concealed, however it does not tell us who allocated the treatment
Blinding (performance bias and detection bias) Active trachoma	Low risk	Quote: "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"
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "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"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 36 children took part; all (100%) were followed up. Theoretically they could have recruited more and had some lost to follow-up that 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 2 possibilities, we have assigned a judgement of unclear risk
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.

Dawson 1997

Methods	**Unit of randomisation:** individual. **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. Epidemic of purulent conjunctivitis at 8/12 years; cut-off for positivity not justified. 3 azithromycin regimens analysed together.
Participants	**Country:** Egypt. **Number of people randomised:** 168. **Age**: 2 to 10 years (average age 4 years). **Sex:** 60% male. **Clinical grading:** Thylefors 1987. **Laboratory tests:** Thylefors 1987; Dawson 1981b. **Inclusion criteria:** active trachoma, 2 to 10 years, resident in a study village. **Exclusion criteria:** missing baseline record.
Interventions	**Intervention:** azithromycin. • Administration: oral. • Dose: 20 mg/kg. • Duration: single dose; or single dose weekly for 3 weeks; or single dose monthly for 6 months. **Comparator:** oxytetracycline/polymyxin + oral placebo. • Administration: topical. • Dose: oxytetracycline 1%/polymyxin 10,000 units/gram. • Duration: once daily for 5 consecutive days every 28 days for 6 times, applied by trained medical personnel.
Outcomes	**Primary:** active trachoma. **Secondary:** elementary bodies ≤ 200 or > 200 on conjunctival smears. **Adverse effects:** reported in Discussion only. **Follow-up:** 12 months.
Notes	**Study name:** none. **Date of study conducted:** February 1992 to February 1993. **Funding source:** not reported. **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement

Dawson 1997 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "A total of 168 children were randomized to one of the four treatment groups in blocks of eight" Judgement comment: not enough information to judge whether the sequence was unpredictable
Allocation concealment (selection bias)	Unclear risk	Quote: "This clinical trial was double-masked, placebo-controlled, and randomized" Judgement comment: no information about allocation concealment given. Treatment groups were different, e.g. no ointment placebo, and different dosing schedules for oral antibiotic
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "Ophthalmologists experienced in the diagnosis of trachoma performed all examinations and were masked as to the treatment used" Judgement comment: no details of the masking were given, and as the treatments were different, the examiners could theoretically have been unmasked by their patients
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Unclear risk	Judgement comment: no details of the masking were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "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." Judgement comment: follow-up rates at 12 months were good from 91% to 98%. Ointment group 42/43, 1 oral dose 39/40, 3 oral doses 39/43, 6 oral doses 39/42. The groups with a larger number of oral doses had lower follow-up rates, but these were only 4 and 3 children, respectively
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.

Foster 1966

Methods	**Unit of randomisation:** individuals. **Masking:** • participant: no, • provider: no, • outcome: yes. **Exclusions after randomisation:** not reported. **Losses to follow-up:** yes.
Participants	**Country:** USA (Native American). **Number of people randomised:** 457. **Age**: 8 to 20 years. **Sex:** not reported. **Clinical grading:** Thygeson 1960. **Laboratory tests:** none. **Inclusion criteria:** active trachoma, studying in a study school. **Exclusion criteria:** none.
Interventions	**Intervention: 1:** sulfamethoxypyridazine (n = 112 analysed). • Administration: oral. • Dose: 0.5 g. • Duration: once daily for 5 consecutive days every week for 3 weeks. **Intervention: 2:** tetracycline (n = 106 analysed). • Administration: topical. • Dose: 1%. • Duration: 3 times daily on 5 consecutive days every week for 6 weeks. **Comparator:** no treatment (n = 107 analysed).
Outcomes	**Primary:** active trachoma. **Secondary:** none. **Adverse effects:** not recorded. **Follow-up:** 3 and 12 months.
Notes	**Study name:** none. **Date study conducted:** September 1963 to September 1964. **Funding source:** Quote: "This work was supported in part by grants from Research to Prevent Blindness, Inc., and from the National Institute of health (B604)" **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The active cases were assigned at random to one of three treatment groups" Judgement comment: not enough information.

Foster 1966 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Judgement comment: not enough information. Allocation concealment not reported
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "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" Judgement comment: the treatments were different, so the students will have known which treatment they received (oral versus topical antibiotic)
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "For the purpose of analysis, only the 325 students who were examined on all three occasions are included in Tables 3,4 and 5." Judgement comment: a total of 457 active cases were identified, but results reported for only 325 (71%) who had complete follow-up. No information on follow-up by group
Selective reporting (reporting bias)	Low risk	Judgement comment: only clinical outcomes recorded, but no indication of any assessment of ocular infection

Hoshiwara 1973

Methods	**Unit of randomisation:** individual. **Masking:** • participant - yes, • provider - yes, • outcome - yes. **Exclusions after randomisation:** no. **Losses to follow-up:** poor compliance, lack of sample. Placebo with "strong beneficial effect"
Participants	**Country:** USA. **Number of people randomised:** 120. **Age**: 7 to 13 years (average 10 years). **Sex:** not reported. **Clinical grading:** Dawson 1969. **Laboratory tests:** IFAT on scrapings of upper tarsal conjunctival epithelium. **Inclusion criteria:** active disease, boarding at study school. **Exclusion criteria:** none.

Hoshiwara 1973 (*Continued*)

Interventions	**Intervention:** doxycycline. • Administration: oral. • Dose: 2.5 to 4.0 mg/kg. • Duration: once daily for 5 consecutive days every week up to 28 doses in 40 days. **Comparator:** placebo. • Administration: oral. • Dose: not applicable. • 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. **Follow-up:** 5 months.
Notes	**Study name:** none. **Date study conducted:** October 1971 to April 1972. **Funding source:** Quote: "This investigation was supported by National Institutes of Health grant EY 00186 and the Burroughs Welcome Fund. Doxycycline capsules were supplied as Vibramycin and a placebo was supplied through Barabar Liebovityz MD and doxycycline hyclate was supplied as Vibramycin hyclate through Kenneth Munnelly PhD Pfizer Inc. Brooklyn NY." **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Students with signs of active trachoma were randomly assigned placebo or drug" Judgement comment: not enough information on sequence allocation
Allocation concealment (selection bias)	Unclear risk	Judgement comment: although the drugs were identical in appearance and taste and coded A/B (see below), it was not clear how they were allocated, e.g. whether they were sequentially numbered
Blinding (performance bias and detection bias) Active trachoma	Low risk	Quote: "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."

Hoshiwara 1973 (*Continued*)

Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "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." Judgement comment: laboratory analyses will have been easier to mask effectively
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: 120 students randomised and 103 (86%) followed up: 54 placebo and 49 active treatment. However, it is not clear what the original random allocations were Quote: "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."
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.

NCT00618449

Methods	**Unit of randomisation:** village. **Masking:** • participant - no, • provider - no, • outcome - no (active trachoma), yes (*C trachomatis* infection). **Exclusions after randomisation:** not reported. **Losses to follow-up:** not reported. **Notes:** study is unpublished, but results available on clinicaltrials.gov/ct2/show/results/NCT00618449. Investigators comment: "Prevalence of infection in communities was less than predicted, as was return of infection post-treatment, thus hypothesis could not be evaluated"
Participants	**Country:** Niger. **Endemicity:** Quote: "high prevalence of clinically active trachoma amongst children<= age 10." but "Prevalence of infection in communities was less than predicted". Actual prevalence not reported. **Number of communities randomised:** 10. **Number of people randomised:** not reported. **Age:** average age 18 to 19 years. **Sex:** 52% female. **Clinical grading:** method not specified.

	Laboratory tests: nucleic acid amplification test. **Inclusion criteria:** people living in selected villages, unclear how villages were selected but have high prevalence of clinically active trachoma > 15% in children in the village. **Exclusion criteria:** history of allergy to ANY macrolide antibiotic; severe nausea or diarrhoea after the first dose of azithromycin; inability to tolerate oral therapy; pre-existing serious illness
Interventions	**Intervention:** azithromycin (2 doses) (n = 679 people). • Administration: oral. • Dose: 20 mg/kg up to 1 g. • Duration: Day 0 and Day 30. **Comparator:** azithromycin (single dose) (n = 668 people). • Administration: oral. • Dose: 20 mg/kg up to 1 g. • Duration: Day 0.
Outcomes	**Primary:** infection with *C trachomatis* diagnosed by use of nucleic acid amplification tests. **Adverse effects:** serious (death, life-threatening, inpatient hospitalisation, ongoing or significant incapacity or interferes substantially with normal life functions, birth defects) **Follow-up:** 1 month and 1 year post-treatment.
Notes	**Study name:** Impact of Two Alternative Dosing Strategies for Trachoma Control in Niger **Date study conducted:** January 2008 to May 2009. **Funding source:** not reported. **Conflict of interest:** not reported. **Trial registration ID:** NCT00618449.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: not reported.
Allocation concealment (selection bias)	Low risk	Judgement comment: not reported, but cluster-RCT.
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Not reported
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

NCT00618449 (*Continued*)

Selective reporting (reporting bias)	High risk	Judgement comment: study unpublished, but results reported on ClinicalTrials.gov. Active trachoma not reported
Recruitment bias addressed? (cluster RCT only)	Unclear risk	Not reported
Baseline imbalances addressed? (cluster RCT only)	Unclear risk	Not reported

Peach 1986

Methods	**Unit of randomisation:** community, but analysed as individuals. **Masking:** • participant - no, • provider - no, • outcome: no. **Exclusions after randomisation:** no. **Losses to follow-up:** yes. **Note:** 1 arm of a larger trial with components face washing and face washing plus antibiotics. Communities randomly allocated, but trial was analysed and reported as if it was individually randomised, so no information provided on clusters. We have considered it as analysed, i.e. grouped it with the individually randomised studies
Participants	**Country:** Australia (Aboriginal children). **Number of people randomised:** 641. **Age:** children 5 to 14 years (plus 5% under 5 and 5% over 14). **Sex:** not reported. **Clinical grading:** local version with at least 1 follicle or some papillary hypertrophy being positive. **Laboratory tests:** none. **Inclusion criteria:** follicular trachoma. **Exclusion criteria:** none.
Interventions	**Intervention:** oily tetracycline. • Administration: topical. • Dose: daily for 5 days once a month. • Duration: 3 months. **Comparator:** no treatment.
Outcomes	**Primary:** active trachoma. **Secondary:** none. **Adverse events:** not reported. **Follow-up:** 3 months.
Notes	**Study name:** none. **Date study conducted:** not reported. **Funding source:** not reported.

Peach 1986 (*Continued*)

	Conflict of interest: not reported. **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Accordingly, whole communities were randomly allocated to one of thre treatment groups or to the fourth (non-treatment) group" Judgement comment: generation of the allocation sequence not described
Allocation concealment (selection bias)	Low risk	Quote: "Accordingly, whole communities were randomly allocated to one of thre treatment groups or to the fourth (non-treatment) group" Judgement comment: allocation concealment not described.
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "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." Judgement comment: topical antibiotics versus observation. Communities will have known which treatment group they were allocated to
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Children lost to follow-up were assumed to have follicles and were included in the analysis on that basis" Judgement comment: 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 assigned a judgement of low risk
Selective reporting (reporting bias)	Low risk	Judgement comment: only clinical outcomes reported, but no indication of any collection of data on microbiological outcomes

PRET Niger

Methods	**Unit of randomisation:** community (grappe, government health unit). **Masking:** • participant - no, • provider - no, • outcome - no. **Exclusions after randomisation:** none. **Losses to follow-up:** none. **Notes:** 2x2 factorial design, random sample of 100 sentinel children and 40 people aged 15 years or older were followed up in each community, mesoendemic region
Participants	**Country:** Niger. **Endemicity:** selected on the basis of at least 10% prevalence of active trachoma. Reported prevalence of trachomatous inflammation in children 0 to 5 years was 28%. **Number of communities randomised:** 24. **Number of people randomised:** 12,991. **Age:** sentinel children were aged 0 to 5. **Sex:** approximately 52% female. **Clinical grading:** Thylefors 1987. **Laboratory tests:** Amplicor PCR. **Inclusion criteria:** Communities: • Population between 250 and 600 at the most recent government census. • Prevalence of 10% or more of active trachoma in children aged 0 to 60 months.
Interventions	All intervention groups received azithromycin, as follows. • Administration: oral. • Dose: 20 mg/kg, up to 1 g in suspension (children) or tablets (adults, or children able to swallow tablets). • Quote: "Children under 6 months of age and those known to be allergic to macrolides were offered tetracycline ointment (1%) to be applied to both eyes two times per day for 6 weeks." **Intervention 1:** azithromycin (standard coverage 80% to 90%) (n = 12 communities, people analysed = 1016 children at baseline, 772 children at 36 months) • Duration: single dose at 4 time points (i.e. annually): 0, 12, 24, and 36 months. • Quote: "(azithromycin)... was distributed during a single day, aiming for a coverage target of 80% or greater of children and adults." **Intervention 2:** azithromycin (enhanced coverage > 90%) (n = 12 communities, people analysed = 1196 children at baseline, 906 children at 36 months) • Duration: single dose at 4 time points (i.e. annually): 0, 12, 24, and 36 months. • Quote: "...communities received up to three follow-up visits to achieve coverage of 90% or greater of children and adults." **Intervention 3:** azithromycin (annual all ages) (n = 24 communities). • Duration: single dose at 4 time points (i.e. annually): 0, 12, 24, and 36 months. • Quote: "In annually treated communities, study participants aged ≥6 months received a directly observed dose of oral azithromycin". **Intervention 4:** azithromycin (twice yearly MDA in children 0 to 12 years) (n = 24 communities) • Duration: single dose at 7 time points (i.e. twice yearly): 0, 6, 12, 18, 24, 30, and 36 months.

	• Quote: "only study participants aged 6 months to 12 years were offered treatment."
Outcomes	(from trial register entry) **Primary:** • Community prevalence of trachoma and ocular *C trachomatis* infection at 5 years. **Secondary:** • Community costs of mass treatment (5 years). • Community costs of incident infection (5 years). • Macrolide resistance in pneumococcus (3 years). • Anthropometry in children 5 years old or younger (1 to 3 years after baseline). • Prevalence of anaemia in children 5 years old or younger (1 to 3 years after baseline). • Rates of health clinic visits overall, for infectious diseases, diarrhoea, malaria, respiratory disease, and antibiotics (1, 2, and 3 years after baseline). • Mortality in children (over study period). • Mortality in adults (over study period). **Adverse events: not reported.** **Follow-up:** every 6 months for 3 years. Quote: "a random sample of 100 children aged 0-5 years per community (or all children if a given community had fewer than 100 children) was selected from the most recent census for examination." Quote: for comparison of annual versus bi-annual "In both arms, childhood examinations and swabs were biannual, while adult swabs were at baseline, 6, 12, and 36 months by design"
Notes	**Study name:** Partnership for the Rapid Elimination of Trachoma. **Date study conducted:** May 2010 to August 2013. **Funding source:** Quote: "This trial was funded by the Bill & Melinda Gates Foundation" **Conflict of interest:** Quote: "All authors: No reported conflicts." **Trial registration ID:** NCT00792922.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Communities were randomised by stratified block randomisation within each CSI by high or low trachoma prevalence in children. Within a given CSI, communities above the median trachoma prevalence were considered to be 'high', and those below the median were considered to be 'low'. The random allocation sequence was generated by TCP using R V.2.12 (R Foundation for Statistical Computing, Vienna, Austria; http://www. r- project. org)."

PRET Niger (*Continued*)

Allocation concealment (selection bias)	Low risk	Judgement comment: not discussed, but as this was a cluster-RCT unlikely to have created selection bias
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Judgement comment: not discussed.
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Unclear risk	Judgement comment: not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: all clusters followed up. Similar numbers of children sampled in each cluster
Selective reporting (reporting bias)	Unclear risk	Judgement comment: some mismatch between the trial registry outcomes and what was actually reported, but unclear whether this will affect the conclusions of this review
Recruitment bias addressed? (cluster RCT only)	Unclear risk	Judgement comment: not discussed.
Baseline imbalances addressed? (cluster RCT only)	Low risk	Judgement comment: communities appeared to be balanced with respect to age, sex, and prevalence of trachoma. Random allocation was stratified by trachoma prevalence

PRET Tanzania

Methods	**Unit of randomisation:** community (geographically distinct subvillages, averaging 1500 people) **Masking:** • participant - no, • provider - no, • outcome - no. **Exclusions after randomisation:** none. **Losses to follow-up:** none. **Notes:** 2x2 factorial trial. Mesonendemic communities - prevalence of trachoma >= 20%. Quote: "The studies define communities as the smallest population unit for which health services are organized and trachoma control programs are implemented."
Participants	**Country:** Tanzania. **Endemicity:** prevalence of active trachoma in children aged less than 5 years was approximately 30% **Number of communities randomised:** 32.

PRET Tanzania (*Continued*)

	Number of people randomised: not reported. **Age:** all ages treated, sentinel children followed up aged 0 to 5. **Sex:** % female ranged from 48% to 50% in 4 arms of the study (in sentinel children at baseline assessment). **Clinical grading:** Thylefors 1987. **Laboratory tests:** Amplicor PCR. **Inclusion criteria:** Communities: • Less than 5000 people with an estimated active trachoma prevalence of between 20% and 50% for mesoendemic communities and less than 20% for hypoendemic communities. Sentinel children: • Aged 5 years or less at the time of census. • Resided in an eligible community (defined as either living in the community since birth, or moved in with parents or guardians). • Had no ocular condition that precluded trachoma grading or prevented obtaining an ocular specimen. • Had an identifiable guardian capable of providing consent to participate.
Interventions	All intervention groups received azithromycin, as follows. • Administration: oral. • Dose: 20 mg/kg, up to 1 g in suspension (children) or tablets (adults, or children able to swallow tablets). Children below 6 months were given topical tetracycline. **Intervention 1:** azithromycin (standard coverage 80% to 90%) (n = 16 communities, people analysed = not reported) • Duration: single dose at 4 time points (i.e. annually): 0, 12, 24, and 36 months. • Quote: "For 80-90.0% coverage, CDDs (Community Drug Distributors) provide mass treatment in the community for 2 days, with additional follow-up allowed to achieve at least 80% coverage. Treatment is available at a central site the first day, with follow-up to individual homes the second day and, if needed, subsequent days". **Intervention 2:** azithromycin (enhanced coverage > 90%) (n = 16 communities, people analysed = not reported) • Duration: single dose at 4 time points (i.e. annually): 0, 12, 24, and 36 months. • Quote: "To reach >90.0% coverage, treatment is available at a central site for 1 to 2 days with household follow-up for 5 to 7 days as necessary to achieve > 90% coverage." **Intervention 3:** azithromycin (annual MDA for 3 years) (n = 8 communities). • Duration: single dose at 4 time points (i.e. annually): 0, 12, 24, and 36 months. • Quote: "In annually treated communities, study participants aged ≥6 months received a directly observed dose of oral azithromycin". **Intervention 4:** azithromycin (MDA cessation rule) (n = 8 communities). • Duration: single dose at 0 months and thereafter only if infection prevalence was greater than 0% at 6- or 18-month visit. • MDA to be stopped early if prevalence of ocular *C trachomatis* was less than 5%.
Outcomes	Outcome measures as recorded in trials register entry (clinicaltrials.gov/show/NCT00792922, accessed 14 May 2014) **Primary outcome measure:** • Community prevalence of trachoma and ocular *C trachomatis* infection at 5 years.

PRET Tanzania (*Continued*)

	Secondary outcome measures: • Community costs of mass treatment (5 years). • Community costs of incident infection (5 years). **Follow-up:** every 6 months for 3 years.
Notes	**Study name:** Partnership for the Rapid Elimination of Trachoma. **Date study conducted:** February 2010 and September 2011. **Funding source:** Bill and Melinda Gates Foundation. **Conflict of interest:** Authors reported no conflict of interest. **Trial registration ID:** NCT00792922.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "In each study site, communities were randomly allocated by the study statistician in a 1:1:1:1 ratio to trial arms using the 2X2 factorial design". Quote: "A constrained randomization was used to reduce the likelihood of a bad randomization outcome by balancing on estimated (pre-study) trachoma prevalence and geographic location of villages as covariates19 and to assign a sufficient number of communities to each of the 2X2 cells in the factorial design (Table 1). A SAS macro was developed (Version 9.0, SAS Institute, Cary, NC) for this purpose."
Allocation concealment (selection bias)	Low risk	Judgement comment: cluster-RCT, so not applicable.
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "Only the study statistician and mass treatment team were aware of the community assignment; survey teams and census teams were masked". Quote: "The survey team was masked to the allocation of the communities into the two arms. Team members were not shown allocation schemes and surveys did not occur in order of treatment allocation. It was theoretically possible that survey personnel may have been unmasked once the cessation rule took effect, but cessation did not occur in the study."

Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "The survey team was masked to the allocation of the communities into the two arms. Team members were not shown allocation schemes and surveys did not occur in order of treatment allocation. It was theoretically possible that survey personnel may have been unmasked once the cessation rule took effect, but cessation did not occur in the study." Quote: "The laboratory at Johns Hopkins University which processed the specimens for infection was also masked to treatment allocation. The specimen labels did not reveal treatment allocation, and all infection data were managed by the study statistician and study data managers who had no access to the study teams. Community members were not told their laboratory results because all members of the community were eligible to receive the intervention. Therefore, infection outcome in this trial was double masked"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on numbers examined in each community.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes reported; secondary outcomes not yet reported Unclear why results for only 16 communities reported, but planned study design included 48 communities Results for comparison of coverage not yet reported.
Recruitment bias addressed? (cluster RCT only)	Low risk	Not mentioned but probably unlikely.
Baseline imbalances addressed? (cluster RCT only)	Low risk	Yes. Allocation constrained and baseline characteristics reported

PRET The Gambia

Methods	**Unit of randomisation:** community (Census Enumeration Area, quote: "several small villages, be equivalent to a medium sized village, or be part of a large village and have populations averaging 600-800 persons.") **Masking:** • participant - yes, • provider - yes, • outcome: yes. **Exclusions after randomisation:** none. **Losses to follow-up:** none. **Notes:** Quote: "The studies define communities as the smallest population unit for which health services are organized and trachoma control programs are implemented."
Participants	**Country:** The Gambia. **Endemicity:** prevalence of active trachoma in children 5 years or younger was 6.5% **Number of communities randomised:** 48 communities. **Number of people randomised:** random sample of 100 sentinel children followed up. **Age:** sentinel children were aged 0 to 5. **Sex:** approximately 50% female. **Clinical grading:** Thylefors 1987. **Laboratory tests:** Amplicor PCR. Eligible communities had a trachoma prevalence estimated to be greater than 5% To participate as a sentinel child, the child was: • aged 5 years or less at the time of census; • resided in an eligible community (defined as either living in the community since birth, or moved in with parents or guardians); • had no ocular condition that precluded trachoma grading or prevented obtaining an ocular specimen; • had an identifiable guardian capable of providing consent to participate.
Interventions	2x2 factorial design • Annual MDA with "standard coverage" 80% to 90% (n = 24 communities) versus "enhanced coverage" > 90% (n = 24 communities). • Annual MDA for 3 years (n = 24 communities) versus annual MDA for 3 years only if evidence of follicular trachoma or infection ("graduation") (n = 24 communities). **Intervention:** community treatment with single dose azithromycin 20 mg/kg, up to 1 g in a single dose of either suspension (children) or tablets (adults, or children able to swallow tablets). Pregnant women and children below 6 months of age were given topical tetracycline **Intervention:** oily tetracycline daily for 5 days once a month for 3 months • Administration: oral. • Dose: oily tetracycline daily for 5 days once a month. • Duration: 3 months.
Outcomes	Outcome measures as recorded in trials register entry (clinicaltrials.gov/show/NCT00792922, accessed 14 May 2014) **Primary outcome measure:** • Community prevalence of trachoma and ocular *C trachomatis* infection at 5 years. **Secondary outcome measures:** • Community costs of mass treatment (5 years).

	• Community costs of incident infection (5 years). • Mortality in children aged 1 to 5 years (over study period). • Cause-specific mortality in children aged 1 to 5 years (over study period). • Mortality in adults in the study area (over study period). • Cause-specific mortality in adults in the study area (over study period). • Morbidity among children aged 1 to 5 years as assessed by height for age, weight for age, weight for height, body mass index, and Hackett spleen size (30 months after baseline). • Serotype distribution, antibiotic sensitivity profile, and MLST type of *Streptococcus pneumoniae* carried in the nasopharynx of study children (30 months after baseline). **Follow-up:** every 6 months for 3 years.
Notes	**Study name:** Partnership for the Rapid Elimination of Trachoma. **Date study conducted:** 2008 to 2011. **Funding source:** Bill and Melinda Gates Foundation. **Conflict of interest:** authors reported no conflict of interest. **Trial registration ID:** NCT00792922.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "All 102 EAs in the 4 districts were randomly assigned by the study statistician to one of the four study arms: 1) Standard-SR; 2) Standard-36; 3) Enhanced-SR; 4) Enhanced-36 under the restriction that all EAs that represented segments of the same village were in the same randomization group and would receive the same combination of delivery strategies. The restriction process also aimed for balance of strategy by district and overall. From these EAs a random selection of 48 'study EAs' for sampling was made such that 12 study EAs per arm and per district were selected (three EAs per arm per district) and such that each large settlement was represented by only one of its segment EAs selected at random."
Allocation concealment (selection bias)	Low risk	Judgement comment: cluster-randomised study so not applicable
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "Only the study statistician and mass treatment team were aware of the community assignment; survey teams and census teams were masked".

		Quote: "The participants and census, examination and treatment teams were unaware of which EAs were allocated to which coverage arm." Quote: "The survey teams did not have access to the coverage assignment of the communities. The NEHP treatment team were not part of the survey and were unaware of treatment allocation on the first day they treated an EA. Laboratory personnel were masked to EA, coverage and treatment allocation. At time points after six months, concealment of stopping rule allocations from participants and treatment teams was not possible due to the design of the intervention."
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "Only the study statistician and mass treatment team were aware of the community assignment; survey teams and census teams were masked" Judgement comment: the participants and census, examination, and treatment teams were unaware of which enumeration areas (EA) were allocated to which coverage arm Quote: "The survey teams did not have access to the coverage assignment of the communities. The NEHP treatment team were not part of the survey and were unaware of treatment allocation on the first day they treated an EA. Laboratory personnel were masked to EA, coverage and treatment allocation. At time points after six months, concealment of stopping rule allocations from participants and treatment teams was not possible due to the design of the intervention."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No communities withdrew from the study. Quote: "A total of 5036 children aged 0-5 years were examined in The Gambia with only 3 missing values for clinical sign data. " No loss to follow-up of EAs . However, no data on attrition or exclusions at child level. Raw data only available for a breakdown at district level, and not by intervention group (where only percentages are provided, even in the supplementary tables)

PRET The Gambia (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Primary outcomes reported. Secondary outcomes not reported as yet
Recruitment bias addressed? (cluster RCT only)	Low risk	Not mentioned but unlikely.
Baseline imbalances addressed? (cluster RCT only)	Unclear risk	Quote: "A comparison of baseline characteristics of each group of communities showed no imbalances in population size, percentage of households with no latrine, percentage more than 30 minutes from water, or average education of head of household (Table 1). The baseline prevalence of TF and of infection with Ct was low and did not differ by study arm or allocation (Table 2)."

Resnikoff 1995

Methods	**Unit of randomisation:** village. **Masking:** • participant - no, • provider - no, • outcome - no. **Exclusions after randomisation:** no information. **Losses to follow-up:** no information. **Notes:** 2x2 factorial design with health education intervention.
Participants	**Country:** Mali. **Endemicity:** prevalence of active trachoma ranged from 15% to 22%. **Number of communities randomised:** 4 villages randomly allocated to 4 different interventions. 2 villages only eligible for inclusion in this review **Number of people randomised:** 1810. **Age:** 1 to 5 years. **Sex:** not reported. **Clinical grading:** Thylefors 1987. **Laboratory tests:** none. **Inclusion criteria:** all inhabitants. **Exclusion criteria:** none.
Interventions	**Intervention:** 1% oxytetracycline eye drop solution (Innolyre). • Administration: topical. • Dose: 1 drop 4 times daily for 7 days a month, directly supervised by village workers. • Duration: 6 months. **Comparator:** no treatment.

Outcomes	**Primary:** active trachoma (cure and incidence of new cases). **Secondary outcomes:** none. **Follow-up:** 3 and 6 months.
Notes	**Study name:** none. **Date study conducted**: March to September 1994. **Funding source:** not reported. **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Four types of treatment were defined, then attributed by randomization" Judgement comment: not enough information.
Allocation concealment (selection bias)	Low risk	Not reported, but as cluster-RCT not likely to be a problem.
Blinding (performance bias and detection bias) Active trachoma	High risk	This was not reported, so we have assumed that it did not occur, as treatment was compared to no treatment. The study was described as "open controlled clinical trial" (page 103)
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "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) Quote: "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) Judgement comment: 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

Resnikoff 1995 (*Continued*)

		(estimated 33 people cured). No information was given on possible reasons for loss to follow-up
Selective reporting (reporting bias)	Low risk	Only clinical outcomes reported, but no indication that microbiological data collected
Recruitment bias addressed? (cluster RCT only)	Unclear risk	Quote: "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? (cluster RCT only)	High risk	Quote: "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: 2 of these villages concerned health education; data from these not included in this review) Quote: "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	**Unit of randomisation:** individual. **Masking:** • participant - no, • provider - no, • outcome - unclear. **Exclusions after randomisation:** no. **Losses to follow-up:** none. **Notes:** 4-armed trial with factorial design.
Participants	**Country:** India. **Number of people randomised**: 349.

Shukla 1966 (*Continued*)

	Age: 5 to 13 years. **Sex:** not reported. **Clinical grading:** WHO 1962. **Laboratory tests:** none. **Inclusion criteria:** active trachoma, schooling at a study school. **Exclusion criteria:** none.
Interventions	**Intervention 1:** sulfafurazole + sulfadimethoxine. • 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. **Intervention 2:** sulfadimethoxine. • Administration: oral. • Dose: 100 mg/kg. • Duration: bi-weekly or weekly dose for 5 months. **Intervention 3:** sulfafurazole. • Administration: topical. • Dose: 15%. • Duration: twice daily for 5 consecutive days every month for 5 months. **Comparator:** no treatment.
Outcomes	**Primary:** active trachoma. **Secondary:** none. **Adverse events:** not reported. **Follow-up:** 5 months.
Notes	**Study name:** none. **Date study conducted:** October 1963 (recruitment). **Funding source:** Quote: "We are grateful to the Indian Council of Medical Research for adequate facilities and to Dr. B. Hegde, of Roche Products Lid., for the liberal supply of Gantrisin drops and Madribon tablets." **Conflict of interest:** not reported. **Trial registration ID:** none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The cases were randomly divided into four more or less identical groups" Judgement comment: not enough information to judge.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not mentioned. Judgement comment: not enough information to judge.

Shukla 1966 (*Continued*)

Blinding (performance bias and detection bias) Active trachoma	High risk	Judgement comment: no information given, and treatments different in the various groups, so study unlikely to have been masked. However, study is described as "double-blind study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: apparently 100% follow-up with exception of 1 group B1 at 5 months where 35/41 seen
Selective reporting (reporting bias)	Low risk	Judgement comment: only clinical outcomes reported, but no indication that microbiological data collected

Tabbara 1996

Methods	**Unit of randomisation:** individual. **Masking:** • participant - no, • provider - no, • outcome - yes. **Exclusions after randomisation:** no. **Losses to follow-up:** 8/64. **Notes**: case definition not clear (probable diagnosis of trachoma based on cytology, definitive diagnosis of trachoma based on microscopical assessment of scrapings)
Participants	**Country:** Saudi Arabia. **Number of people randomised:** 64. **Age:** 6 to 14 years (average 11 years). **Sex:** not reported. **Clinical grading:** Dawson 1981b. **Laboratory tests:** conjunctival scrapings for inclusion bodies/cells/organisms/mucus; IFAT for free elementary bodies **Inclusion criteria:** active trachoma, schooling in study village. **Exclusion criteria:** none.
Interventions	**Intervention:** azithromycin. • Administration: oral. • Dose: 20 mg/kg. • Duration: single dose. **Comparator:** tetracycline. • Administration: topical. • Dose: 1%. • Duration: twice daily for 5 consecutive days per week over 6 weeks, administered by teacher.

Tabbara 1996 (*Continued*)

Outcomes	**Primary:** active trachoma. **Secondary:** intraepithelial cell inclusion bodies, free elementary bodies. **Adverse events:** none. **Follow-up:** 4, 8, 12, and 24 weeks.
Notes	**Study name:** none. **Date study conducted:** not reported. **Funding source:** not reported. **Conflict of interest:** Quote: "The authors have no proprietary interest in any of the materials used in this study." **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were assigned randomly ..." Judgement comment: not enough information to judge.
Allocation concealment (selection bias)	Unclear risk	Not reported. Judgement comment: not enough information to judge.
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "The examiner was unaware of the treatment allocation at the time of the examination" Judgement comment: study was described as "single-masked". Patients were aware of therapy because oral versus topical treatment. No information on whether the masking was effective - e.g. did the patients tell the examiners which treatment they had received?
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "Conjunctival scrapings were obtained from each patient before initiation of therapy" Quote: "The slides were coded and masked to the reader"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: it was not clear how many people were 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

Tabbara 1996 (*Continued*)

		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 assigned a judgement of unclear risk because the effect of these missing data is uncertain
Selective reporting (reporting bias)	Low risk	Both outcomes of relevance to this review were reported.

TANA

Methods	**Unit of randomisation:** community (subkebeles, government-defined units). **Masking:** • participant - no, • provider - no, • outcome - yes. **Exclusions after randomisation:** none. **Losses to follow-up:** no communities lost to follow-up. **Notes:** study had 6 treatment arms, but 4 of these (12 communities in each) relevant to this review. The other 2 treatment groups evaluated intensive latrine construction and are beyond the remit of this review
Participants	**Country:** Ethiopia. **Endemicity:** prevalence of active trachoma in children aged 0 to 9 years was approximately 70% **Number of communities randomised:** 48. **Number of people randomised:** 66,404. **Age:** 32% aged 0 to 9 years **Sex:** 48% female **Clinical grading:** Thylefors 1987. **Laboratory tests:** Amplicor PCR assay (Roche Diagnostics, Branchburg, NJ, USA) **Inclusion criteria:** people resident in these communities. Different members of the population were treated according to the treatment schedule being tested (see interventions below). **Exclusion criteria:** none.
Interventions	All intervention groups received azithromycin, as follows. • Administration: oral. • Dose: adults 1 g, children 20 mg/kg, directly observed, unless contraindicated by allergy or pregnancy. • Duration: single dose. • Children younger than 1 year and pregnant women were offered a 6-week course of topical tetracycline 1% (not directly observed).

	Intervention 1: annual treatment of people 1 year and above (12 subkebeles, 15,902 people) • Duration: 3 years. **Intervention 2:** twice-yearly treatment of people 1 year and above (12 subkebeles, 17, 288 people) • Duration 3.5 years. **Intervention 3:** quarterly treatment of children age 1 to 10 years (12 subkebeles, 14, 716 people) • Duration: 1 year. **Intervention 4:** delayed treatment group (12 subkebeles, 18,498 people). • Duration: 1 year. In a follow-up study, communities were randomised to continuation or discontinuation of yearly or twice-yearly treatment
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 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]. **Secondary outcome measures:** • Clinical active trachoma in community, as determined by the WHO simplified grading system [Time Frame: 42 months]. • Childhood (>= 1 year of age) mortality, analysed as 1 to 5, 6 to 10 years of age, and total [Time Frame: 42 months]. • Macrolide resistance in pneumococcus (% resistance over time, clustered by randomisation unit) [Time Frame: 42 months].
Notes	**Study name:** Trachoma Amelioration in Northern Amhara (TANA). Follow-up study name: Tripartite International Research for the Elimination of Trachoma (TIRET) **Date study conducted:** May 2006 to November 2009. **Funding source:** Quote: "The National Institutes of Health (NEI U10 EY016214, NEI K12EX017269, NEI K23 EYO19881-01, and NCRR/OD UCSF-CTSI Grant Number KL2 RR024130) was the main supporter of this trial. We thank the International Trachoma Initiative for their generous donation of azithromycin, the Bernard Osher Foundation, That Man May See, the Harper Inglis Trust, the Bodri Foundation, the South Asia Research Fund, and Research to Prevent Blindness" **Conflict of interest:** Quote: "We declare that we have no conflicts of interest" **Trial registration ID:** NCT00322972. Follow-up study: NCT01202331.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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)."
Allocation concealment (selection bias)	Low risk	Quote: "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)."
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "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" Judgement comment: no mention of masking of clinical observers
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "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."
Incomplete outcome data (attrition bias) All outcomes	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 years and adults: 561/720 (78%); 550/720 (76%); 599/720 (83%)
Selective reporting (reporting bias)	Low risk	Data on active trachoma not reported but supplied by author.
Recruitment bias addressed? (cluster RCT only)	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

TANA (*Continued*)

Baseline imbalances addressed? (cluster RCT only)	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

TEF

Methods	**Unit of randomisation:** community. **Masking:** • participant - no, • provider - no, • outcome - no (active trachoma), yes (*C trachomatis* infection). **Exclusions after randomisation:** no. **Losses to follow-up:** numbers recorded.
Participants	**Country:** Ethiopia. **Endemicity:** mean prevalence of ocular infection in children aged 1 to 5 years was 43% **Number of communities randomised:** 16. **Number of people randomised:** 5410. **Age**: not reported. **Sex:** not reported. **Clinical grading:** Thylefors 1987. **Laboratory tests:** Amplicor PCR (Roche Diagnostics, Branchburg, NJ). **Inclusion criteria:** everyone 1 year and older. **Exclusion criteria:** none. Pregnant women and children younger than 1 year were offered 6-week course of topical 1% tetracycline (applied twice daily to both eyes and not directly observed)
Interventions	All intervention groups received azithromycin as follows. • Administration: oral. • Dose: 1 g in adults, 20 mg/kg in children. • Duration: single dose, directly observed. 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) **Intervention 1:** annual treatment people age 1 year and above (8 communities) **Intervention 2:** twice-yearly treatment people age 1 year and above (8 communities) **Intervention 3:** single treatment people age 1 year and above. **Comparator:** delayed treatment.
Outcomes	On trials register, as follows. • **Primary:** the prevalence of ocular chlamydia infection in a village as determined by PCR. • **Secondary:** clinical active trachoma, as determined by the WHO simplified grading system, by village. Presence of ocular chlamydial infection in children aged 1 to 5. A random sample of adults was tested at 18 months

TEF (*Continued*)

	Follow-up: 2, 6, 12, 18, and 24 months after treatment.
Notes	**Study name:** Trachoma Elimination Follow-up. **Date study conducted:** March 2003 to April 2005 (from clinical trials registration) **Funding source**: Quote: "This work was supported by the International Trachoma Initiative, the Bernard Osher Foundation, That Man May See, the Peierls Foundation, the Bodri Foundation, the Harper Inglis Trust, the South Asia Research Fund, Research to Prevent Blindness, and grants U10 EY016214 and R21 AI 55752 from the National Institutes of Health." **Conflict of interest:** none reported. **Trial registration ID:** NCT00221364.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eight villages were randomly assigned to receive annual treatments and 8 to receive biannual treatments (generation by the RAND command in Excel by T.M. L., implementation including enrollment and assignment of participants by M.M.)"
Allocation concealment (selection bias)	Low risk	Not reported, but not an issue in cluster-RCTs.
Blinding (performance bias and detection bias) Active trachoma	Low risk	Quote: "Fieldworkers who performed antibiotic distributions and clinical assessments were aware of treatment schedules. Laboratory personnel were masked to individual, village, and treatment group identifications."
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Low risk	Quote: "Fieldworkers who performed antibiotic distributions and clinical assessments were aware of treatment schedules. Laboratory personnel were masked to individual, village, and treatment group identifications."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All communities completed the study. 84% of children completed survey in annual treatment group compared to 78% in bi-annual treatment group. Most common reasons for non-participation were: absence from village, moved to another village, and death

TEF (*Continued*)

Selective reporting (reporting bias)	High risk	Secondary outcome on active trachoma not reported.
Recruitment bias addressed? (cluster RCT only)	Unclear risk	Quote: "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 rates of response to this request for participation
Baseline imbalances addressed? (cluster RCT only)	Unclear risk	Annually treatment arm villages had a higher average prevalence of ocular infection (43%) compared to bi-annually treated villages (32%), but differences not statistically significant

Wilson 2018

Methods	**Unit of randomisation:** communities (subvillage balozis). **Masking:** • participant - no, • provider - no, • outcome - no. **Exclusions after randomisation**: none. **Losses to follow-up:** no communities lost to follow-up, follow-up could not be assessed for individuals, as random samples of children were assessed at baseline and follow-up. **Notes:** 96 communities randomised, unclear how many people in the communities, but 20 children per community assessed
Participants	**Country:** Tanzania. **Endemicity:** prevalence of active trachoma was approximately 5% in children aged 1 to 9 years. **Number of communities randomised:** 96. **Number of people randomised:** unclear, approximately 1600 children aged 1 to 9 years assessed for trachoma. **Age**: 1 to 9 years. **Sex:** 48% male. **Clinical grading:** Thylefors 1987. **Laboratory tests:** swab specimen of right eye, *C trachomatis* diagnosed by use of nucleic acid amplification test. **Inclusion criteria:** • Communities: not been treated with azithromycin since 2009 and were predicted from prior prevalence surveys to have TF between 5% and 9.9%. • People: mass treatment, but only children aged 1 to 9 years with parental consent were assessed for trachoma. **Exclusion criteria:** • Pregnant women and infants under the age of 6 months were instead offered tetracycline eye ointment for daily use for up to 6 weeks.

Wilson 2018 (*Continued*)

Interventions	**Intervention:** azithromycin. • Administration: oral. • Dose: 20 mg/kg up to 1 g. • Duration: single dose. **Comparator:** no treatment.
Outcomes	**Primary:** not stated. **Secondary:** not stated. **Outcomes assessed:** clinical trachoma, ocular infection, antibody response. **Adverse effects:** yes. **Follow-up:** 12 months.
Notes	**Study name:** none. **Date study conducted:** October to December 2012. **Funding source:** Quote: "Funding for this project was provided by the Bill and Melinda Gates Foundation (project OPP1022543)." **Conflict of interest:** Quote: "The authors report no conflict of interest. The authors alone are responsible for the writing and content of this article." **Trial registration ID:** none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Balozis were randomly assigned to the intervention and control arms." Judgement: not enough information to make a judgement.
Allocation concealment (selection bias)	Low risk	Cluster-RCT.
Blinding (performance bias and detection bias) Active trachoma	High risk	Judgement comment: masking not reported and interventions different
Blinding (performance bias and detection bias) Ocular Chlamydia trachomatis infection	Unclear risk	Judgement comment: masking not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: similar numbers of children seen at baseline and 12 months in both arms
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to protocol, trial does not appear to be registered.

Recruitment bias addressed? (cluster RCT only)	Unclear risk	Judgement comment: difficult to assess with the information available.
Baseline imbalances addressed? (cluster RCT only)	Unclear risk	Judgement comment: clusters appeared to be similar except with respect to distance from water source - more communities in the no-treatment arm were less than 30 minutes from a water source (39% versus 35% in the treatment arm), and median percentage with active trachoma was higher in the no-treatment arm (6.0% versus 4. 3% in the treatment arm), however difference was not statistically significant

Woolridge 1967

Methods	**Unit of randomisation:** individual. **Masking:** • participant - no, • provider - no, • outcome - yes. **Exclusions after randomisation**: unclear. **Losses to follow-up:** unclear. **Notes:** combined vaccine and therapy trial.
Participants	**Country:** Taiwan. **Number of people randomised:** 322. **Age**: primary school age. **Sex:** not reported. **Clinical grading:** Modified McCallan classification. **Laboratory tests:** none. **Inclusion criteria:** active trachoma. **Exclusion criteria:** none.
Interventions	**Intervention:** tetracycline. • Administration: topical. • Dose: 1%. • Duration: twice daily for 6 consecutive days per week for 6 weeks. **Comparator:** no treatment.
Outcomes	**Primary:** active trachoma. **Secondary:** none. **Adverse effects:** not assessed. **Follow-up:** 3 years.
Notes	**Study name:** none. **Date study conducted:** February 1962 to October 1964. **Funding source:** Quote: "This study was supported in part by a United States Public

Woolridge 1967 (*Continued*)

	Health Service Research Grant" **Conflict of interest:** not reported. **Trial registration ID:** none.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Those that received treatment were chosen by random number"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Active trachoma	Unclear risk	Quote: "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" Quote: "Placebo therapy was not employed" (page 1578). No discussion as to whether the ophthalmologists might have been unmasked because the participants knew their treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	No information on completeness of follow-up.
Selective reporting (reporting bias)	Low risk	Active trachoma only reported, but no indication that any data were collected on *C trachomatis* infection.

IFAT: immunofluorescent antibody test
ITT: intention-to-treat

LCR: ligase chain reaction
MDA: mass drug administration
MLST: multilocus sequence typing
PCR: polymerase chain reaction
RCT: randomised controlled trial
TRIC: trachoma inclusion conjunctivitis
WHO: World Health Organization

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

Study	Reason for exclusion
Abdou 2007	Not a randomised controlled trial. Prevalence study only
Assaad 1968	Not a randomised controlled trial (quasi-randomised)
Astle 2006	Not a randomised controlled trial. Prevalence study only
Babbar 1982	Not a randomised controlled trial. No comparator group
Biebesheimer 2009	Not a randomised controlled trial. No comparator group
Bietti 1967	Not a randomised controlled trial (review)
Broman 2006	Not a randomised controlled trial
Cerulli 1983	Not a randomised controlled trial (no evidence of randomisation)
Chumbley 1988	Not a randomised controlled trial
Coulibaly 2013	Not a relevant intervention or comparator. Co-administered treatment for onchocerciasis, difficult to distinguish effects of azithromycin
Daghfous 1974	Not a randomised controlled trial (no evidence of randomisation)
Daghfous 1985	Not a randomised controlled trial (no evidence of randomisation)
Darougar 1980b	Not a relevant intervention or comparator. Topical therapy only
Darougar 1981	Not a relevant intervention or comparator. Topical therapy only
Dawson 1967a	Not a randomised controlled trial (quasi-randomised)
Dawson 1967b	Not a randomised controlled trial (quasi-randomised)
Dawson 1968	Not a randomised controlled trial (no evidence of randomisation)
Dawson 1971	Not a randomised controlled trial (quasi-randomised)
Dawson 1972a	Not a randomised controlled trial (no evidence of randomisation)
Dawson 1972b	Not a randomised controlled trial (no evidence of randomisation)
Dawson 1974a	Not a randomised controlled trial (no evidence of randomisation)
Dawson 1974b	Not a randomised controlled trial (quasi-randomised)

(*Continued*)

Dawson 1975b	Not a randomised controlled trial (quasi-randomised)
Dawson 1981b	Not a relevant intervention or comparator. Topical therapy only
Dawson 1982	Not a randomised controlled trial (children were matched by severity, age, and sex)
Edwards 2006	Not a relevant intervention or comparator. Health education intervention
Gower 2006	Not randomised controlled trial
Gupta 1966	Not a randomised controlled trial (no evidence of randomisation)
Gupta 1968	Not a relevant intervention or comparator. 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	Not a relevant intervention or comparator. No comparison group receiving placebo or no treatment
Humet 1989	No eye outcome measured
Isenberg 2002	Study not carried out in a trachoma endemic area.
Ji 1986	No trial report
Kamiya 1956	Not a relevant intervention or comparator. Lack of comparison villages
Khandekar 2006	Not a randomised controlled trial
Litricin 1968	Not a relevant intervention or comparator. No comparison group
Mesfin 2006	Not a randomised controlled trial
Mohan 1982	Not a randomised controlled trial
MORDOR 2018	Trial of azithromycin to reduce childhood mortality; participants did not have trachoma
Nabli 1988	Not a relevant intervention or comparator. No comparison group
NCT00286026	Study was not conducted because the prevalence of infection in the screened population was too low
NCT00347607	Not a relevant intervention or comparator. Trial of different approaches to surveillance
NCT00347776	Randomised controlled trial evaluating effect of antibiotic treatment on recurrence of trichiasis
NCT01178762	Not a randomised controlled trial
NCT01767506	Not a relevant intervention or comparator. Additional benefit of treating newcomers

(*Continued*)

NCT02211729	Trial of azithromycin as an adjunct to seasonal malaria chemoprevention, participants did not have trachoma
Ngondi 2006a	Not a randomised controlled trial
Ngondi 2006b	Not a relevant intervention or comparator. No antibiotic/no antibiotic comparison
Nisbet 1979	Not a relevant intervention or comparator. No comparator group
Obikili 1988	Not a relevant intervention or comparator. No comparator group
Putschky 2006	No eye outcome measured.
Reinhards 1959	Not a relevant intervention or comparator. No comparison group
Resnikoff 1994	Not a relevant intervention or comparator. No comparison group
Schachterle 2014	Not a randomised controlled trial
Schemann 2007	Not a relevant intervention or comparator. Comparison of different treatment targeting strategies, therefore does not meet inclusion criteria of review
Tabbara 1988	Randomisation was by eye and not patient. It was not possible to determine the individual patient outcome
Toufic 1968	Not a randomised controlled trial
Wadia 1980	Not a relevant intervention or comparator. No comparison group
Werner 1977	Not a randomised controlled trial
West 2006	Test efficacy of insecticide
Whitcher 1974	Not a randomised controlled trial
Zhang 2006	Not a relevant intervention or comparator. No appropriate control group

Characteristics of studies awaiting assessment *[ordered by study ID]*

Last 2015

Methods	Cluster-randomised controlled trial
Participants	1714 children aged 1 to 9 years
Interventions	Single versus 2 doses (Day 1 and Day 7) of oral azithromycin
Outcomes	Active trachoma and ocular infection

Notes	Published as abstract only

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

NCT03523156

Trial name or title	Trachoma Elimination Study by Focused Antibiotic (TESFA)
Methods	Cluster-randomised controlled trial
Participants	Country: Ethiopia 19,200
Interventions	• Azithromycin targeted treatment: community-wide MDA followed by 2 rounds targeted to children age 6 months to 9 years 1 to 2 weeks apart. • Azithromycin mass treatment: annual community-wide MDA.
Outcomes	(From ClinicalTrials.gov) "Primary Outcome Measures • Prevalence of *Chlamydia trachomatis* (CT) infection [Time Frame: Month 12]The community-level prevalence of CT infection in children aged 6 months to 9 years will be compared between study arms. Secondary Outcome Measures : • Change in prevalence of trachomatous inflammation-follicular (TF) [Time Frame: Baseline, Week 4, Month 12, Month 24]The prevalence of trachomatous inflammation-follicular (TF) among all household members will be noted at each visit and compared between study arms. • Change in prevalence of trachomatous inflammation-intense (TI) [Time Frame: Baseline, Week 4, Month 12, Month 24]The prevalence of trachomatous inflammation-intense (TI) among all household members will be noted at each visit and compared between study arms • Change in *Chlamydia trachomatis* (CT) infection in children [Time Frame: Baseline, Month 12, Month 24]The change in prevalence of *Chlamydia trachomatis* (CT) infections in children ages 6 months to 9 years will be compared between study arms. Analysis will be conducted which will include all three of these time-points to compare infection prevalence between the comparison arms • Prevalence of *Chlamydia trachomatis* (CT) infection among adults [Time Frame: Month 12]The prevalence of Chlamydia trachomatis (CT) infection among adults will be compared between study arms. • Cost [Time Frame: Month 24]The cost of the enhanced intervention will be compared to the cost of the standard-of-care intervention. • Cost-effectiveness [Time Frame: Month 24]The cost-effectiveness of the enhanced intervention will be compared to the cost of the standard-of-care intervention. The incremental cost effectiveness analysis ratio approach will be used. Effectiveness is defined as the percent CT reduction from baseline to 24 months and the outcome of this analysis will be the cost per percent of CT infection reduction. • Correlation between Chlamydial Infection and trachomatous inflammation-follicular (TF) and trachomatous inflammation-intense (TI) [Time Frame: Baseline, Week 4, Month 12, Month 24]We will conduct cluster level analysis using cluster level Ct and clinical data including TF and TI. • Cluster-level Chlamydial load [Time Frame: Baseline, Week 4, Month 12, Month 24]Infectious load for all individual specimens from 6 months to 9 year-old children who test positive for CT will be measured for chlamydia load. Chlamydial load will be noted at each visit and compared between study arms."

NCT03523156 (*Continued*)

Starting date	December 2018 Estimated study completion date: December 2020
Contact information	Contact: Kelly Callahan, MPH ecallah@emory.edu
Notes	clinicaltrials.gov/ct2/show/NCT03523156

SWIFT 2017

Trial name or title	Sanitation, Water, and Instruction in Face-washing for Trachoma (SWIFT)
Methods	Cluster-randomised controlled trial
Participants	Country: Ethiopia 220,000
Interventions	TAITU-A substudy • Targeted antibiotic treatment. • Mass antibiotics. TAITU-B • Targeted antibiotic treatment. • Delayed antibiotics. Targeted antibiotic treatment: communities will receive targeted antibiotic treatments for children testing positive for ocular chlamydia at 3, 6, 9, and 12 months after baseline testing. After testing for ocular chlamydia at 12 months, any children testing positive at this time point will receive antibiotic treatments at 15, 18, 21, and 24 months. Children 6 months and up will be offered azithromycin 20 mg/kg; those under 6 months will be offered tetracycline Delayed mass antibiotics: Delayed mass antibiotic treatment: Communities will receive no mass azithromycin treatment during the study period. Communities in this treatment group have previously received at least 8 rounds of mass azithromycin treatment. These clusters will be enrolled in an antibiotics treatment program (azithromycin or tetracycline) after the completion of the study Mass antibiotics: Mass antibiotic treatment: Communities will receive mass azithromycin treatment of all individuals aged 6 months and up (20 mg/kg for children, 1 g for adults); those younger than 6 months, pregnant, or allergic to macrolide antibiotics will be offered a 2-week course of tetracycline
Outcomes	(From ClinicalTrials.gov) "Primary Outcome Measures • Village-specific ocular chlamydia among 0-5 children over time (first trial: WUHA) [Time Frame: 12, 24, 36 months]Multiple time points will be used in a mixed effects regression model of the village-specific ocular chlamydia prevalences over time in 0-5 year olds as assessed by PCR. • Ocular chlamydia among 8-12 year olds (second trial: TAITU-A) [Time Frame: 24 months]Cluster-specific prevalence of ocular chlamydia among individuals aged 8-12 years, compared between the targeted azithromycin arm and the mass azithromycin arm. • Incident ocular chlamydia in 0-5 year-olds (third trial: TAITU-B) [Time Frame: 24 months]Incidence of new ocular chlamydia infection in 0-5 year-olds, compared between the targeted azithromycin arm and the delayed mass azithromycin arm. • Trial-based cost-effectiveness of intervention (intervention costs per percent of chlamydia reduction) [Time Frame: 24 months for TAITU, 36 months for WUHA]The short term analysis is designed to provide

SWIFT 2017 (*Continued*)

	insight into whether each intervention (WASH or targeted antibiotics) is effective for our primary trial outcome of reducing ocular chlamydial infection in children. The time horizon of these analyses will be the duration of each trial. Secondary Outcome Measures • Quantitative PCR chlamydia load [Time Frame: 12, 24, 36 months] • Follicular trachoma scores; age-stratified (0-5, 6-9, 10 and up for WUHA; 0-5, 8-12 for TAITU) [Time Frame: 12, 24, 36 months] • Inflammatory trachoma scores; age-stratified (0-5, 6-9, 10 and up for WUHA; 0-5, 8-12 for TAITU) [Time Frame: 12, 24, 36 months] • Ocular chlamydia; age-stratified (0-5, 6-9, 10 and up for WUHA; 0-5, 8-12 for TAITU) [Time Frame: 12, 24, 36 months] • Nasopharyngeal pneumococcal macrolide resistance [Time Frame: 12, 24, 36 months]Using standard microbiological techniques, the lab will process the swabs using media selective for Streptococcus pneumoniae, and then test for antibiotic resistance. Nasopharyngeal macrolide resistance in age 0-5 will be modeled at the village level, using treatment arm as a covariate. • Proportion of the population with clean faces at the village level [Time Frame: 12, 24, 36 months] • Childhood growth (height) [Time Frame: 12, 24, 36 months] • Childhood growth (weight) [Time Frame: 12, 24, 36 months] • Soil-transmitted helminth prevalence [Time Frame: 12, 24, 36 months] • Soil-transmitted helminth density [Time Frame: 12, 24, 36 months] • Prevalence of chlamydia and other antigen positivity from serological tests [Time Frame: 12, 24, and 36 months] • Prevalence of stool-based antigen (diarrheal pathogens, soil transmitted helminths) positivity from serological tests [Time Frame: 12, 24, and 36 months]”
Starting date	November 2015 Estimated study completion date: July 2019
Contact information	Contact: Dionna M Fry, MPH; dionna.fry@ucsf.edu Contact: Jeremy D Keenan, MD, MPH; jeremy.keenan@ucsf.edu
Notes	clinicaltrials.gov/ct2/show/NCT02754583

MDA: mass drug administration
PCR: polymerase chain reaction

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 3 months	9	1961	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.69, 0.89]
2 Active trachoma at 12 months	4	1035	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.55, 1.00]
3 Active trachoma at 3 months (subgroup analysis)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Oral antibiotic	6	599	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.97]
3.2 Topical antibiotic	6	1478	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.72, 0.92]
4 Active trachoma at 12 months (subgroup analysis)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Oral antibiotic	3	429	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.00]
4.2 Topical antibiotic	4	724	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.71, 0.88]
5 Ocular *C trachomatis* infection at 3 months	4	297	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.04]
6 Ocular *C trachomatis* infection at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7 Ocular *C trachomatis* infection at 3 months (subgroup analysis)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Oral antibiotic	4	259	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.11]
7.2 Topical antibiotic	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.37]
8 Ocular *C trachomatis* infection at 12 months (subgroup analysis)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Oral antibiotic	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.10, 1.23]
8.2 Topical antibiotic	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.04]

Comparison 2. Oral versus topical antibiotics (individuals)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active trachoma at 3 months	6	953	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.16]
2 Active trachoma at 12 months	5	886	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.15]
3 Ocular *C trachomatis* infection at 3 months	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Ocular *C trachomatis* infection at 12 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Oral azithromycin versus topical tetracycline (individuals)

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, Fixed, 95% CI)	Totals not selected
2 Active trachoma at 12 months	2	447	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.59, 0.99]
3 Ocular *C trachomatis* infection at 3 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Ocular *C trachomatis* infection at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. 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	1	1247	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.52, 0.65]
2 Ocular *C trachomatis* infection at 12 months	2	2139	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.31, 0.43]

Comparison 5. 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 Active trachoma at 12 months	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Ocular *C trachomatis* infection at 3 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 3 months.

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 1 Active trachoma at 3 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
Attiah 1973 (1)	84/152	58/76		13.0 %	0.72 [0.60, 0.88]
Darougar 1980 (2)	61/79	34/45		12.4 %	1.02 [0.83, 1.25]
Dawson 1969 Sherman (3)	1/15	1/14		0.2 %	0.93 [0.06, 13.54]
Dawson 1969 Stewart (4)	6/18	15/18		2.8 %	0.40 [0.20, 0.79]
Foster 1966 (5)	165/218	88/107		16.1 %	0.92 [0.82, 1.03]
Hoshiwara 1973 (6)	28/49	44/54		9.8 %	0.70 [0.53, 0.92]
Peach 1986 (7)	216/340	138/189		16.0 %	0.87 [0.77, 0.98]
Shukla 1966 (8)	113/223	36/42		13.5 %	0.59 [0.49, 0.71]
Woolridge 1967 (9)	139/202	103/120		16.0 %	0.80 [0.71, 0.90]
Total (95% CI)	**1296**	**665**		**100.0 %**	**0.78 [0.69, 0.89]**
Total events: 813 (Antibiotic), 517 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 29.38$, df = 8 (P = 0.00027); $I^2 = 73\%$					
Test for overall effect: Z = 3.81 (P = 0.00014)					
Test for subgroup differences: Not applicable					

(1) Antibiotic: topical tetracycline derivative GS2989 or topical oxytetracycline (terramycin). Control: no treatment

(2) Antibiotic: topical oxytetracycline or oral doxycycline. Control: vitamin pills

(3) Antibiotic: oral trisulphapyrimidines. Control: lactose-placebo.

(4) Antibiotic: oral trisulphapyrimidines. Control: lactose-placebo.

(5) Antibiotic: oral sulphamethoxypyridazine or topical tetracycline. Control: no treatment.

(6) Antibiotic: oral doxycycline. Control: placebo.

(7) Antibiotic: topical tetracycline. Control: no treatment.

(8) Antibiotic: topical sulphafurazole and/or oral sulphadimethoxine. Control: no treatment.

(9) Antibiotic: topical tetracycline. Control: no treatment.

Analysis 1.2. Comparison 1 Any antibiotic versus control (individuals), Outcome 2 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 2 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 (1)	43/82	33/47		22.7 %	0.75 [0.57, 0.99]
Foster 1966 (2)	145/218	68/107		25.9 %	1.05 [0.88, 1.24]
Shukla 1966 (3)	91/217	35/42		24.9 %	0.50 [0.41, 0.62]
Woolridge 1967 (4)	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)

Test for subgroup differences: Not applicable

(1) Antibiotic: topical oxytetracycline or oral doxycycline. Control: vitamin pills

(2) Antibiotic: oral sulphamethoxypyridazine or topical tetracycline. Control: no treatment.

(3) Antibiotic: topical sulphafurazole and/or oral sulphadimethoxine. Control: no treatment.

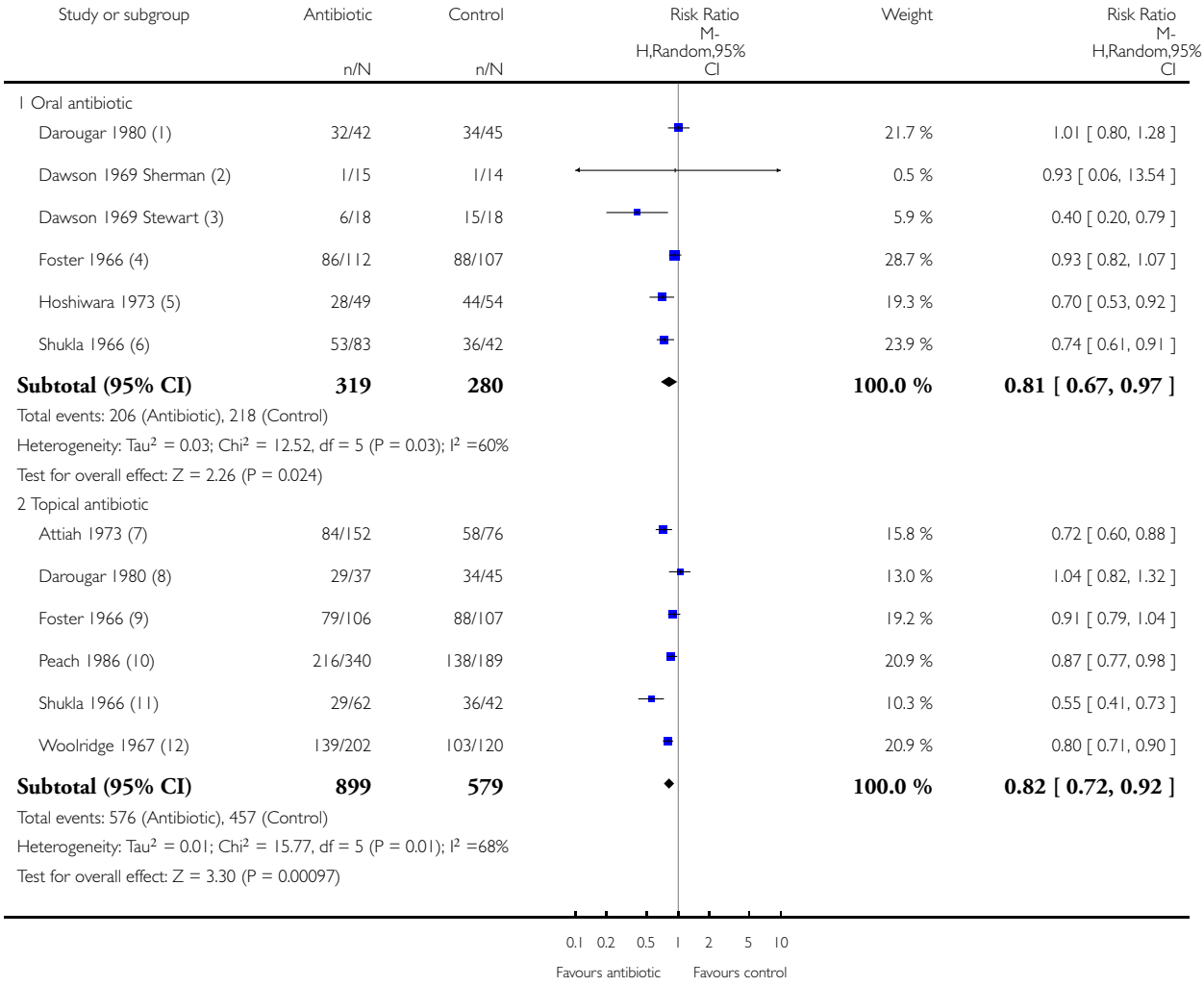
(4) Antibiotic: topical tetracycline. Control: no treatment.

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

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 3 Active trachoma at 3 months (subgroup analysis)



(1) Antibiotic: oral doxycycline. Control: vitamin pills

(2) Antibiotic: oral trisulphapyrimidines. Control: lactose-placebo.

(3) Antibiotic: oral trisulphapyrimidines. Control: lactose-placebo.

(4) Antibiotic: oral sulphamethoxypyridazine. Control: no treatment.

(5) Antibiotic: oral doxycycline. Control: placebo.

(6) Antibiotic: oral sulphadimethoxine. Control: no treatment.

(7) Antibiotic: topical tetracycline derivative GS2989 or topical oxytetracycline (terramycin). Control: no treatment

(8) Antibiotic: topical oxytetracycline. Control: vitamin pills

(9) Antibiotic: topical tetracycline. Control: no treatment.

(10) Antibiotic: topical tetracycline. Control: no treatment.

(11) Antibiotic: topical sulphafurazole. Control: no treatment.

(12) Antibiotic: topical tetracycline. Control: no treatment.

Analysis 1.4. Comparison 1 Any antibiotic versus control (individuals), Outcome 4 Active trachoma at 12 months (subgroup analysis).

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 4 Active trachoma at 12 months (subgroup analysis)

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]

(*Continued* . . .)

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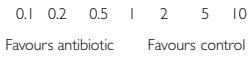
Study or subgroup	Antibiotic n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Foster 1966	65/106	68/107		26.2 %	0.96 [0.78, 1.19]
Shukla 1966	35/62	35/42		16.2 %	0.68 [0.52, 0.88]
Woolridge 1967	121/202	95/120		46.2 %	0.76 [0.65, 0.88]
Subtotal (95% CI)	**408**	**316**		**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)					



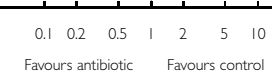
Analysis 1.5. Comparison 1 Any antibiotic versus control (individuals), Outcome 5 Ocular *C trachomatis* infection at 3 months.

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 5 Ocular *C trachomatis* infection at 3 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 (1)	8/82	7/47		7.1 %	0.66 [0.25, 1.69]
Dawson 1969 Sherman (2)	7/15	10/14		15.9 %	0.65 [0.35, 1.23]
Dawson 1969 Stewart (3)	11/18	14/18		32.4 %	0.79 [0.50, 1.22]
Hoshiwara 1973 (4)	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)					
Test for subgroup differences: Not applicable					



(1) Antibiotic: topical oxytetracycline or oral doxycycline. Control: vitamin pills

(2) Antibiotic: oral trisulphapyrimidines. Control: lactose-placebo.

(3) Antibiotic: oral trisulphapyrimidines. Control: lactose-placebo.

(4) Antibiotic: oral doxycycline. Control: placebo.

Analysis 1.6. Comparison 1 Any antibiotic versus control (individuals), Outcome 6 Ocular *C trachomatis* infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 6 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 (1)	4/82	9/47			0.25 [0.08, 0.78]

(1) Antibiotic: topical oxytetracycline or oral doxycycline. Control: vitamin pills

Analysis 1.7. Comparison 1 Any antibiotic versus control (individuals), Outcome 7 Ocular *C trachomatis* infection at 3 months (subgroup analysis).

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 7 Ocular *C trachomatis* infection at 3 months (subgroup analysis)

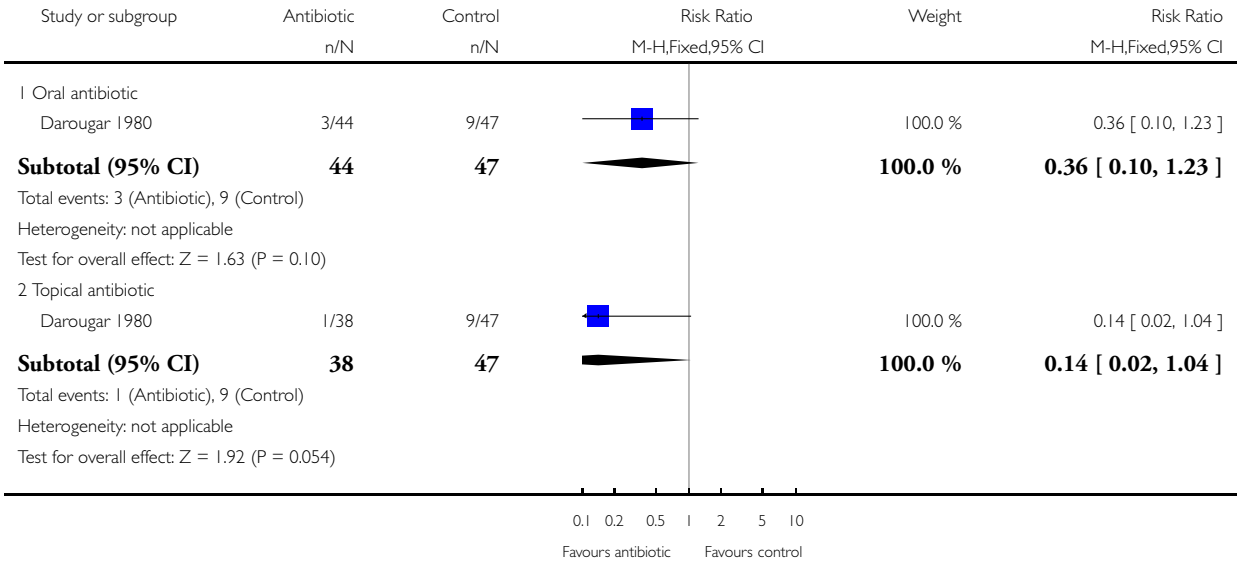
Study or subgroup	Antibiotic n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oral antibiotic					
Darougar 1980	7/44	7/47		11.5 %	1.07 [0.41, 2.80]
Dawson 1969 Sherman	7/15	10/14		17.6 %	0.65 [0.35, 1.23]
Dawson 1969 Stewart	11/18	14/18		23.8 %	0.79 [0.50, 1.22]
Hoshiwara 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 1.8. Comparison 1 Any antibiotic versus control (individuals), Outcome 8 Ocular *C trachomatis* infection at 12 months (subgroup analysis).

Review: Antibiotics for trachoma

Comparison: 1 Any antibiotic versus control (individuals)

Outcome: 8 Ocular *C trachomatis* infection at 12 months (subgroup analysis)



Analysis 2.1. Comparison 2 Oral versus topical antibiotics (individuals), Outcome 1 Active trachoma at 3 months.

Review: Antibiotics for trachoma

Comparison: 2 Oral versus topical antibiotics (individuals)

Outcome: 1 Active trachoma at 3 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 (1)	48/152	68/139		16.4 %	0.65 [0.48, 0.86]
Darougar 1980 (2)	32/42	29/37		19.0 %	0.97 [0.77, 1.23]
Dawson 1997 (3)	76/118	28/42		18.3 %	0.97 [0.75, 1.24]
Foster 1966 (4)	86/112	79/106		24.0 %	1.03 [0.89, 1.20]
Shukla 1966 (5)	53/83	29/62		15.4 %	1.37 [1.00, 1.86]
Tabbara 1996 (6)	13/31	12/29		6.8 %	1.01 [0.56, 1.85]
Total (95% CI)	**538**	**415**		**100.0 %**	**0.97 [0.81, 1.16]**

Total events: 308 (Oral antibiotic), 245 (Topical antibiotic)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 13.21$, df = 5 (P = 0.02); $I^2 = 62\%$

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable

(1) Oral antibiotic: azithromycin. Topical antibiotic: tetracycline.

(2) Oral antibiotic: doxycycline. Topical antibiotic: oxytetracycline.

(3) Oral antibiotic: azithromycin. Topical antibiotic: oxytetracycline/polymyxin and oral placebo.

(4) Oral antibiotic: sulphamethoxypyridazine. Topical antibiotic: tetracycline.

(5) Oral antibiotic: sulphadimethoxine. Topical antibiotic: sulphafurazole.

(6) Oral antibiotic: azithromycin. Topical antibiotic: tetracycline.

Analysis 2.2. Comparison 2 Oral versus topical antibiotics (individuals), Outcome 2 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 2 Oral versus topical antibiotics (individuals)

Outcome: 2 Active trachoma at 12 months

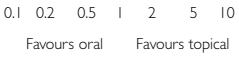
Study or subgroup	Oral antibiotic n/N	Topical antibiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bowman 2000 (1)	32/149	45/139		16.4 %	0.66 [0.45, 0.98]
Darougar 1980 (2)	24/44	19/38		15.2 %	1.09 [0.72, 1.66]
Dawson 1997 (3)	60/117	24/42		20.3 %	0.90 [0.65, 1.23]
Foster 1966 (4)	80/112	65/106		28.3 %	1.16 [0.96, 1.41]
Shukla 1966 (5)	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)

Test for subgroup differences: Not applicable



(1) Oral antibiotic: azithromycin. Topical antibiotic: tetracycline.

(2) Oral antibiotic: doxycycline. Topical antibiotic: oxytetracycline.

(3) Oral antibiotic: azithromycin. Topical antibiotic: oxytetracycline/polymyxin and oral placebo.

(4) Oral antibiotic: sulphamethoxypyridazine. Topical antibiotic: tetracycline.

(5) Oral antibiotic: sulphadimethoxine. Topical antibiotic: sulphafurazole.

Analysis 2.3. Comparison 2 Oral versus topical antibiotics (individuals), Outcome 3 Ocular *C trachomatis* infection at 3 months.

Review: Antibiotics for trachoma

Comparison: 2 Oral versus topical antibiotics (individuals)

Outcome: 3 Ocular *C trachomatis* infection at 3 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 (1)	7/44	1/38		6.05 [0.78, 46.95]
Dawson 1997 (2)	5/119	3/41		0.57 [0.14, 2.30]
Tabbara 1996 (3)	6/30	4/26		1.30 [0.41, 4.11]

(1) Oral antibiotic: doxycycline. Topical antibiotic: oxytetracycline.

(2) Oral antibiotic: azithromycin. Topical antibiotic: oxytetracycline/polymyxin and oral placebo.

(3) Oral antibiotic: azithromycin. Topical antibiotic: tetracycline.

Analysis 2.4. Comparison 2 Oral versus topical antibiotics (individuals), Outcome 4 Ocular *C trachomatis* infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 2 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 (1)	3/44	1/38		2.59 [0.28, 23.88]
Dawson 1997 (2)	8/105	5/33		0.50 [0.18, 1.43]

(1) Oral antibiotic: doxycycline. Topical antibiotic: oxytetracycline.

(2) Oral antibiotic: azithromycin. Topical antibiotic: oxytetracycline/polymyxin and oral placebo.

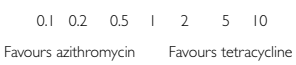
Analysis 3.1. Comparison 3 Oral azithromycin versus topical tetracycline (individuals), Outcome 1 Active trachoma at 3 months.

Review: Antibiotics for trachoma

Comparison: 3 Oral azithromycin versus topical tetracycline (individuals)

Outcome: 1 Active trachoma at 3 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 3.2. Comparison 3 Oral azithromycin versus topical tetracycline (individuals), Outcome 2 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 3 Oral azithromycin versus topical tetracycline (individuals)

Outcome: 2 Active trachoma at 12 months

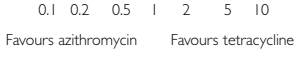
Study or subgroup	Oral azithromycin n/N	Topical tetracycline n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bowman 2000	32/149	45/139		56.9 %	0.66 [0.45, 0.98]
Dawson 1997	60/117	24/42		43.1 %	0.90 [0.65, 1.23]
Total (95% CI)	**266**	**181**		**100.0 %**	**0.76 [0.59, 0.99]**

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)

Test for subgroup differences: Not applicable



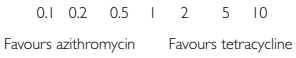
Analysis 3.3. Comparison 3 Oral azithromycin versus topical tetracycline (individuals), Outcome 3 Ocular *C trachomatis* infection at 3 months.

Review: Antibiotics for trachoma

Comparison: 3 Oral azithromycin versus topical tetracycline (individuals)

Outcome: 3 Ocular *C trachomatis* infection at 3 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	5/119	3/41		0.57 [0.14, 2.30]
Tabbara 1996	6/30	4/26		1.30 [0.41, 4.11]



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

Review: Antibiotics for trachoma

Comparison: 3 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 4.1. Comparison 4 Oral azithromycin versus control (communities), Outcome 1 Active trachoma at 12 months.

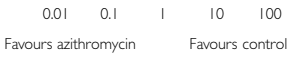
Review: Antibiotics for trachoma

Comparison: 4 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,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
TANA	258/634	429/613		100.0 %	0.58 [0.52, 0.65]
Total (95% CI)	**634**	**613**		**100.0 %**	**0.58 [0.52, 0.65]**

Total events: 258 (Oral azithromycin), 429 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 9.90 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4 Oral azithromycin versus control (communities), Outcome 2 Ocular *C trachomatis* infection at 12 months.

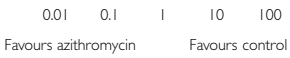
Review: Antibiotics for trachoma

Comparison: 4 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,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
TANA	88/600	282/618		75.3 %	0.32 [0.26, 0.40]
TEF	51/513	82/408		24.7 %	0.49 [0.36, 0.68]
Total (95% CI)	**1113**	**1026**		**100.0 %**	**0.36 [0.31, 0.43]**

Total events: 139 (Oral azithromycin), 364 (Control)
Heterogeneity: Chi^2 = 4.76, df = 1 (P = 0.03); I^2 =79%
Test for overall effect: Z = 11.23 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 5.1. Comparison 5 Oral azithromycin versus topical tetracycline (communities), Outcome 1 Active trachoma at 3 months.

Review: Antibiotics for trachoma

Comparison: 5 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 5.2. Comparison 5 Oral azithromycin versus topical tetracycline (communities), Outcome 2 Active trachoma at 12 months.

Review: Antibiotics for trachoma

Comparison: 5 Oral azithromycin versus topical tetracycline (communities)

Outcome: 2 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 5.3. Comparison 5 Oral azithromycin versus topical tetracycline (communities), Outcome 3 Ocular *C trachomatis* infection at 3 months.

Review: Antibiotics for trachoma

Comparison: 5 Oral azithromycin versus topical tetracycline (communities)

Outcome: 3 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]

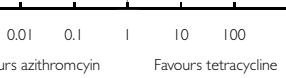
Analysis 5.4. Comparison 5 Oral azithromycin versus topical tetracycline (communities), Outcome 4 Ocular *C trachomatis* infection at 12 months.

Review: Antibiotics for trachoma

Comparison: 5 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. Individually randomised studies: participants

	Study	Country	Inclusion criteria	Number of people randomised	Age	Sex % male
1	Attiah 1973	Egypt	Active trachoma or "undetermined case"	228	6 to 12 years	Not reported
2	Bailey 1993	The Gambia	Active trachoma	194	9 months to 60 years	51%
3	Bowman 2000	The Gambia	Active trachoma	314	6 months to 10 years	50%
4	Cochereau 2007	Guinea and Pakistan	Active trachoma	670	1 to 10 years	50%
5	Darougar 1980	Iran	Active trachoma	147	Pre-school	38%
6	Dawson 1969 Sherman*	USA (Indian reservation)	Active trachoma	29	12 to 21 years	Not reported
7	Dawson 1969 Stewart*	USA (Indian reservation)	Active trachoma	36	12 to 21 years	Not reported
8	Dawson 1997	Egypt	Active trachoma	168	2 to 10 years	60%
9	Foster 1966	USA (Indian boarding school)	Active trachoma	457	8 to 20 years	Not reported
10	Hoshiwara 1973	USA (Indian boarding school)	Active trachoma	120	7 to 13 years	Not reported
11	Peach 1986	Australia (Aboriginal children)	Follicular trachoma	641	5 to 14 years	Not reported
12	Shukla 1966	India	Active trachoma	349	5 to 13 years	Not reported
13	Tabbara 1996	Saudi Arabia	Active trachoma	64	6 to 14 years	Not reported
14	Woolridge 1967	Taiwan	Active trachoma	322	Primary school age	Not reported

*Dawson 1969 Sherman and Dawson 1969 Stewart were reported in the same paper.

Table 2. Individually randomised studies: comparisons

Comparison	Intervention				Comparator			
	Antibiotic	Dose	Duration	Frequency	Intervention	Dose	Duration	Frequency
Studies with a no-treatment, placebo, or inactive treatment comparator group								
Attiah 1973*	tetracycline derivative GS2989 (topical)	0.25%	once every school day for 11 weeks	once	no treatment	-	-	-
Darougar 1980**	oxytetracycline (topical)	1%	twice daily for 7 consecutive days	every month for 12 months	vitamin pills	not reported	single dose	every month for 12 months
Woolridge 1967	tetracycline (topical)	1%	twice daily for 6 consecutive days	every week for 6 weeks	no treatment	-	-	-
Peach 1986	tetracycline (oral)	not reported	daily for 5 days	once a month for 3 months	no treatment	-	-	-
Hoshiwara 1973	doxycycline	2.5 to 4.0 mg/kg	once daily for 5 consecutive days	every week up to 28 doses in 40 days	placebo	-	once daily for 5 consecutive days	every week up to 28 doses in 40 days
Shukla 1966***	Sulfafurazole (topical) + sulfadimethoxine (oral)	15%/100 mg/kg	twice daily for 5 consecutive days every month for 5 months/bi-weekly for 5 months	twice daily for 5 consecutive days every month for 5 months/bi-weekly for 5 months	no treatment	-	-	-
Dawson 1969 Sherman; Dawson 1969 Stewart	trisulfapyrimidines (oral)	3.5 g/day (in 3 doses)	21 consecutive days	once	placebo	-	21 consecutive days	-
Oral versus topical antibiotic								

Table 2. Individually randomised studies: comparisons (*Continued*)

Bailey 1993	azithromycin (oral)	20 mg/kg	single dose	once	tetracycline (topical)	1%	twice daily for 6 weeks	once
Dawson 1997	azithromycin (oral)	20 mg/kg	single dose	once or weekly for 3 weeks or monthly for 6 months	oxytetracycline/ polymyxin + oral placebo	oxytetracycline 1%/ polymyxin 10,000 units/gram	once daily for 5 consecutive days	every 28 days for 6 months
Tabbara 1996; Bowman 2000	azithromycin (oral)	20 mg/kg	single dose	once	tetracycline (topical)	1%	twice daily for 5 consecutive days	every week for 6 weeks
Foster 1966	sulfamethoxypyridazine (oral)	0.5 g	once daily for 5 consecutive days	every week for 3 weeks	tetracycline (topical)	1%	3 times daily on 5 consecutive days	-
Cochereau 2007****	azithromycin (topical)	1.5%	twice daily for 2 days	-	azithromycin (oral)	20 mg/kg	single dose	-

*Also compared to oxytetracycline (Terramycin) once every school day for 11 weeks.
**Also compared to doxycycline (oral) 5 mg/kg single dose every month for 12 months.
***Also compared to sulfadimethoxine (oral) 100 mg/kg bi-weekly or weekly dose for 5 months and sulfafurazole (topical) 15% twice daily for 5 consecutive days, every month for 5 months.
****Also compared to azithromycin (topical) 1.5% twice daily for 3 days.

Table 3. Individually randomised studies: outcomes

	Study	Active trachoma			Ocular infection		
		Classification scheme	3 months	12 months	Laboratory assessments	3 months	12 months
1	Attiah 1973	WHO 1962	√	*No follow-up*	*No laboratory tests*	-	-
2	Bailey 1993	Dawson 1981	√	√ (26 weeks)	IDEIA amplified enzyme-linked immunosorbent assay (Dako) for genus-specific lypopolysaccharide antigen	√	√ (26 weeks)

Table 3. Individually randomised studies: outcomes (*Continued*)

3	Bowman 2000	Thylefors 1987	√	√ (6 months)	*No laboratory tests*	-	-
4	Cochereau 2007	Thylefors 1987	√ (2 months)	*No follow-up*	Conjunctival swab analysed using PCR	**Data not reported**	*No follow-up*
5	Darougar 1980	Modification of Dawson 1975	√ (4 months)	√	Conjunctival swabs followed by culture in irradiated McCoy cells	√ (4 months)	√
6	Dawson 1969 Sherman	MacCallan 1936	√ (20 weeks)	*No follow-up*	*No laboratory tests*	-	-
7	Dawson 1969 Stewart	MacCallan 1936	√ (20 weeks)	*No follow-up*	*No laboratory tests*	-	-
8	Dawson 1997	Thylefors 1987	√	√	Conjunctival specimens; slides stained with direct fluorescent antibody for chlamydial elementary bodies	√	√
9	Foster 1966	Thygeson 1960	√	√	*No laboratory tests*	-	-
10	Hoshiwara 1973	Dawson 1969	√ (5 months)	*No follow-up*	IFAT on scrapings of upper tarsal conjunctival epithelium	√ (5 months)	*No follow-up*
11	Peach 1986	At least 1 follicle or some papillary hypertrophy	√	*No follow-up*	*No laboratory tests*	-	-
12	Shukla 1966	WHO 1962	√ (5 months)	*No follow-up*	*No laboratory tests*	-	-
13	Tabbara 1996	Dawson 1981	√	*No follow-up*	Conjunctival scrapings for inclusion bodies/ cells/organisms/	√	*No follow-up*

Table 3. Individually randomised studies: outcomes (*Continued*)

					mucus; IFAT for free elementary bodies		
14	Woolridge 1967*	Modified McCallan classification	√	√	*No laboratory tests*	-	-

IFAT: immunofluorescence antibody test
PCR: polymerase chain reaction
*Followed up to three years.

Table 4. Cluster-randomised studies: participants

	Study	Country	Inclusion criteria: communities	Inclusion criteria: people	Number of communities randomised	Number of people randomised	Age	Sex % male	Endemicity	
									Children	Adults
1	ACT 1999 Egypt	Egypt	trachoma endemic areas	everyone present in community	2	2238	all ages	not reported	-	All ages: no active trachoma (64%); mild follicular inflammatory (F1, P1, P2) (16%); follicular trachoma (F2, F3) (14%); severe inflammatory trachoma (P3) (6%) Prevalence of ocular infection (LCR-positive) (36%)
2	ACT 1999	Tanzania	trachoma en-	everyone present in	2	3261	all ages	not reported	-	All ages: no active

Table 4. Cluster-randomised studies: participants (*Continued*)

	Tanzania		demic areas	community						trachoma (47%) ; mild follicular inflammatory (F1, P1, P2) (22%); follicular trachoma (F2, F3) (15%) ; severe inflammatory trachoma (P3) (16%) Prevalence of ocular infection (LCR-positive) (19%)
3	ACT 1999 The Gambia	The Gambia	trachoma endemic areas	everyone present in community	8 (pair-matched)	1753	all ages	not reported	Prevalence of active trachoma among 0 to 9 year olds (36%)	No active trachoma (57%) ; mild follicular inflammatory (F1, P1, P2) (27%) ; follicular trachoma (F2, F3) (9%); severe inflammatory trachoma (P3) (7%) Prevalence of ocular infection (LCR-positive) (36%)

Table 4. Cluster-randomised studies: participants (*Continued*)

4	Atik 2006	Vietnam	randomly selected from Thanh Hoa Province	everyone present in community older than 6 months was assessed for trachoma and people with trachoma and their household members treated	2	1851	6 months or older	~40%	Prevalence of active trachoma: 5 to 15 years (6%) less than 5 years (2%) Prevalence of *C trachomatis* infection: 5 to 15 years (16%) less than 5 years (17%)	Prevalence of active trachoma: 15 years and above (8%) Prevalence of *C trachomatis* infection: 15 years and above (8%)
5	NCT00618	Niger	> 15% prevalence of active trachoma in children	everyone present in community	not reported	1347	average age 18 to 19 years	48%	-	Prevalence of *C trachomatis* infection (all ages) (7%)
6	PRET Niger	Niger	population between 250 and 600 and prevalence of 10% or more of active trachoma in children aged 0 to 60 months	everyone present in community	24	12,991	all ages; sentinel children aged 0 to 5 years	48%	Prevalence of ocular *C trachomatis* infection in children aged 5 years or younger (approximately 20%) Prevalence of TF in children aged 5 years or younger (25% to 30%)	Prevalence of TF in people aged 15 years or older (approximately 1%)

Table 4. Cluster-randomised studies: participants (*Continued*)

7	PRET Tanzania	Tanzania	less than 5000 people with an estimated active trachoma prevalence of between 20% and 50% for mesoendemic communities and less than 20% for hypoendemic communities	everyone present in the community	32	not reported	all ages; sentinel children aged 0 to 5 years	50% to 52%	Prevalence of *C trachomatis* infection in children aged less than 5 years ranged from 18% to 25%. Prevalence of TF in children aged less than 5 years was 30%.	Prevalence of *C trachomatis* infection (all ages) (6%) Prevalence of TF (all ages) (12%)
8	PRET The Gambia	The Gambia	trachoma prevalence greater than 5%	everyone present in the community	48		all ages; sentinel children 5 years or less	~50%	Prevalence of *C trachomatis* infection in children aged 5 years or younger was 1%. Prevalence of TF in children aged 5 years or younger was 6%.	-
9	Resnikoff 1995	Mali	unclear	everyone present in the community	4 (2 with interventions relevant to this review)		all ages	not reported	-	Prevalence of active trachoma ranged from 15% to 22% (all ages)

Table 4. Cluster-randomised studies: participants (*Continued*)

10	TANA	Ethiopia	all subkebeles (geographical unit with approximately 1400 people) in the study region that were less than a 3-hour walk from the farthest point that could be reached with a 4-wheel drive vehicle	everyone present in the community	48	66,404	all ages; sentinel group of children and adults	~51%	Prevalence of *C trachomatis* infection in children aged less than 10 years ranged from 8% to 62% (mean approximately 40%)	Prevalence of *C trachomatis* infection in people aged 10 years or older ranged from 2% to 28% (mean approximately 15%). Prevalence of active trachoma (all ages) was between 69% and 77%
11	TEF	Ethiopia	random sample of peasant associations (standardised administrative unit)	everyone present in the community	16	5410	all ages; sentinel groups of children aged 1 to 5 years	not reported	Prevalence of *C trachomatis* infection in children aged 1 to 5 years ranged from 31% to 65% (mean approximately 43%)	-
12	Wilson 2018	Tanzania	not been treated with azithromycin since 2009 and were predicted	not clearly stated but assumed to be everyone in community apart from preg-	96	not reported	6 months or older, only sample of 20 children aged 1 to 9 years as-	48% (in children assessed)	Prevalence of C*trachomati* infection in children aged 1 to	.-

Table 4. Cluster-randomised studies: participants (*Continued*)

			from prior prevalence surveys to have TF between 5 and 9.9%	nant women and children under 6 months			sessed		9 years ranged from 0 to 33%, median 0%. Prevalence of TF in children aged 1 to 9 years ranged from 0 to 62%, median 5%	

LCR: ligase chain reaction
TF: trachomatous inflammation-follicular

Table 5. Cluster-randomised studies: comparisons

	Intervention		Comparator	
Comparison	**Antibiotic***	**Frequency**	**Antibiotic***	**Frequency**
Studies with a no-treatment or delayed-treatment comparator group				
Resnikoff 1995	tetracycline **	every month for 6 months	no treatment	-
TEF	azithromycin	once only; annually for 3 years; twice a year for 3 years	delayed treatment	-
TANA	azithromycin	every 3 months for 3 years	delayed treatment	-
Wilson 2018	azithromycin	once only	delayed treatment	-
Studies of azithromycin versus tetracycline				
ACT 1999 Egypt; ACT 1999 Tanzania; ACT 1999 The Gambia***	azithromycin	once a week for 3 weeks	tetracycline	once daily for 6 weeks
Atik 2006****	azithromycin	single dose at baseline and 12 months. Non-index cases received	All patients with active trachoma received topical tetracycline and surgery of-	-

Table 5. Cluster-randomised studies: comparisons (*Continued*)

		tetracycline, and surgery offered where appropriate	fered where appropriate	
Studies of different frequencies of azithromycin				
NCT00618449	azithromycin	for 1 month (Day 0 and Day 30)	azithromycin	Day 0
PRET Niger; PRET Tanzania; PRET The Gambia	azithromycin	annually for 3 years (enhanced coverage)	azithromycin	annually for 3 years (standard coverage)
PRET Niger;***** TANA; TEF	azithromycin	twice a year for 3 years	azithromycin	annually for 3 years
PRET Tanzania; PRET The Gambia	azithromycin	annually for 3 years	azithromycin	cessation rule

*Azithromycin was given as a single oral dose at 20 mg/kg up to 1 g (adults); tetracycline was given topically 1%.
**One drop four times daily for seven days.
***Once a week for three weeks.
****Treatment of people with active trachoma and their household members only.
*****Only children were treated twice yearly.

Table 6. Cluster-randomised studies: outcomes

	Study	Follow-up	Active trachoma	Ocular infection	Resistance	Adverse effects
1	ACT 1999 Egypt	12 to 14 months	Dawson 1981	Conjunctival swabs assessed using LCR.	*Not studied*	*Not reported*
2	ACT 1999 Tanzania	12 to 14 months	Dawson 1981	Conjunctival swabs assessed using LCR.	*Not studied*	*Not reported*
3	ACT 1999 The Gambia	12 months	Dawson 1981	Conjunctival swabs assessed using LCR.	*Not studied*	*Not reported*
4	Atik 2006	24 months	Thylefors 1987	Conjuctival samples analysed using polymerase chain reaction (Amplicor-PCR)	*Not studied*	*Not reported*
5	NCT00618449	12 months	Not specified	Conjunctival swabs assessed using nucleic acid amplification test	*Not studied*	Reported (no adverse events)

Table 6. Cluster-randomised studies: outcomes (*Continued*)

6	PRET Niger	36 months	Thylefors 1987	Conjuctival samples analysed using polymerase chain reaction (Amplicor-PCR)	lytA+ ermB-/mefA/E- ermB+/mefA/E- ermB-/mefA/E+ ermB+/mefA/E+	*Not reported*
7	PRET Tanzania	36 months	Thylefors 1987	Conjuctival samples analysed using polymerase chain reaction (Amplicor-PCR)	*E coli*	Reported (no serious adverse events)
8	PRET The Gambia	36 months	Thylefors 1987	Conjuctival samples analysed using polymerase chain reaction (Amplicor-PCR)	*S pneumoniae* *S aureus*	*Not reported*
9	Resnikoff 1995	6 months	Thylefors 1987	*No laboratory tests*	*Not studied*	*Not reported*
10	TANA	42 months	Thylefors 1987	Conjuctival samples analysed using polymerase chain reaction	*S pneumoniae* mefA+/ermB2 mefA+/ermB+	Reported
11	TEF	24 months	Thylefors 1987	Conjuctival samples analysed using polymerase chain reaction (Amplicor-PCR)	*S pneumoniae*	Reported (no serious adverse events)
12	Wilson 2018	12 months	Thylefors 1986	Conjuctival samples analysed using polymerase chain reaction	*Not studied*	Reported (no serious adverse events)

LCR: ligase chain reaction
PCR: polymerase chain reaction

Table 7. Adverse effects: individually randomised studies

	Study	Antibiotic (number of people treated)	Report
1	Attiah 1973	Oxytetracycline (77) Tetracycline derivative GS2989 (75)	No comment on adverse effects in report

Table 7. Adverse effects: individually randomised studies (*Continued*)

2	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 study groups "There were no serious adverse reactions and both treatments were well tolerated. All symptoms resolved spontaneously and none required treatment." 1 study participant died, probably due to malaria. He had received topical tetracycline
3	Bowman 2000	Azithromycin (160) Tetracycline (154)	No comment on adverse effects in report
4	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 adverse events were treatment-related events. One patient (3-day group) had a serious unrelated adverse events (death due to head injury)." (page 670)
5	Darougar 1980	Doxycycline (44) Oxytetracycline (38)	No comment on adverse effects in report
6 & 7	Dawson 1969 Sherman Dawson 1969 Stewart	Trisulfapyrimidines (33)	"No untoward reactions to sulfonamides were noted" (page 587)
8	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)
9	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 necessi-

Table 7. Adverse effects: individually randomised studies (*Continued*)

			tated 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 sulfamethoxypyridazine)
10	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 receiving 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)
11	Peach 1986	Tetracycline (932)	No comment on adverse effects in report
12	Shukla 1966	Sulfafurazole (140) Sulfadimethoxine (161)	No comment on adverse effects in report
13	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)
14	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)

Table 8. Studies reporting antibiotic resistance: characteristics

Studies*	Country	Intervention	Comparator	Age of participants	Bacteria or genetic determinant	Carriage body reservoir	Sample type	Antibiotic	Follow-up
PRET Niger	Niger (Matameye district in the Zinder region)	AZ twice a year for 2 years	AZ once a year for 2 years	6 months to 12 years	lytA+ ermB-/ mefA/E- ermB+/ mefA/E- ermB-/ mefA/E+ ermB+/ mefA/E+	Nasopharynx	Nasopharyngeal swab	Macrolide resistance	Baseline and 24 months
PRET Tanzania	Tanzania (Kongwa district)	AZ once a year for 3 years	No AZ	Less than 3 years	*E coli*	Gastrointestinal	Rectal swab	AZ Erythromycin	Baseline, 1, 3, and 6 months
PRET The Gambia	The Gambia	AZ once a year for 3 years	AZ once a year for 1 year	Less than 15 years	*S pneumoniae* *S aureus*	Nasopharynx	Nasopharyngeal swab	AZ Clindamycin	Intervention group: 1 month before and 1 month and 6 months after 3rd annual round of MDA Comparator group: 30 months after 1 annual round of MDA
TANA	Ethiopia (Goncho Siso Enese woreda district, Amhara zone)	AZ every 3 months for 12 months	No AZ (control communities treated at 12 months)	1 to 10 years	*S pneumoniae* mefA+/ ermB2 mefA+/ ermB+	Nasopharynx	Nasopharyngeal swab	AZ Clindamycin Penicillin Tetracycline	Baseline and 12 months
TEF	Ethiopia (Goro district of the Gurage zone of	AZ twice a year for 3 years	No AZ	1 to 5 years	*S pneumoniae*	Nasopharynx	Nasopharyngeal swab	AZ Tetracycline Penicillin	24, 36, 42, and 54 months

Table 8. Studies reporting antibiotic resistance: characteristics (*Continued*)

	southern Ethiopia)							TMP-SMX	

AZ: azithromycin
MDA: mass drug administration
TMP-SMX: trimethoprim-sulfamethoxazole
*All the studies were cluster-randomised trials, and AZ was delivered to the whole community (mass drug administration).

Table 9. Antibiotic resistance to *Streptococcus pneumoniae*

Study*	Follow-up**	Intervention***			Comparator			Risk ratio	95% confidence intervals
		Number of communities	n/N	%	Number of communities	n/N	%		
AZITHROMYCIN									
PRET The Gambia	1 month before 3rd annual round of MDA	2	0/415	0	6	-	-	-	-
PRET The Gambia--	1 month after 3rd annual round of MDA	2	5/417	1.2	6	-	-	-	-
PRET The Gambia	6 months after 3rd annual round of MDA (intervention group) 30 months after 1 annual round of MDA (comparator group)	2	3/343	0.9	6	1/400	0.3	3.5	0.4 to 33.5
PRET The Gambia (as a per-	1 month before 3rd an-	2	-	-	-	-	-	-	-

Table 9. Antibiotic resistance to *Streptococcus pneumoniae* (*Continued*)

centage pneumococcal isolates)¶	nual round of MDA								
PRET The Gambia (as a percentage pneumococcal isolates)¶	1 month after 3rd annual round of MDA	2	-	-	-	-	-	-	-
PRET The Gambia (as a percentage pneumococcal isolates)¶	6 months after 3rd annual round of MDA (intervention group) 30 months after 1 annual round of MDA (comparator group)	2	-	-	-	-	-	-	-
TANA	Baseline	11	-	-	-	-	-	-	-
TANA	12 months	12	56/119	46.9	12	11/120	9.2	5.1	2.8 to 9.3
TANA (as a percentage pneumococcal isolates)¶	Baseline	11	5/76	6.3	-	-	-	-	-
TANA (as a percentage pneumococcal isolates)¶	12 months	12	58/93	62.3	12	11/98	11.6	5.6	3.1 to 9.9
TEF	24 months	8	34/120	28.2	8	1/120	0.9	34.0	4.7 to 244
TEF	36 months	8	92/120	76.8	8	0/119	0	183.4	11.5 to 2922
TEF	42 months	8	37/120	30.6	8	-	-	-	-

Table 9. Antibiotic resistance to *Streptococcus pneumoniae* (*Continued*)

TEF	54 months	8	25/120	20.8	8	-	-	-	-
CLINDAMYCIN									
TANA	Baseline	11	2/110	1.5	-	-	-	-	-
TANA	12 months	12	16/119	13.3	12	4/120	3.3	4	1.4 to 11.7
TANA (as a percentage pneumococcal isolates)¶	Baseline	11	1/76	1.5	-	-	-	-	-
TANA (as a percentage pneumococcal isolates)¶	12 months	12	14/83	16.9	12	4/98	3.9	4.1	1.4 to 12.1
PENICILLIN									
TANA	Baseline	11	0/110	0	-	-	-	-	-
TANA	12 months	12	0/119	0	12	1/120	0.8	0.34	0.01 to 8.2
TANA (as a percentage pneumococcal isolates)¶	Baseline	11	0/76	0	-	-	-	-	-
TANA (as a percentage pneumococcal isolates)¶	12 months	12	0/83	0	12	1/98	1.0	0.39	0.02 to 9.52
TEF	24 months	8	1/120	0.9	8	0/120	0	3.0	0.12 to 72.9
TEF	36 months	8	0/120	0	8	0/119	0	-	-
TEF	42 months	8	0/120	0	8	-	-	-	-
TEF	54 months	8	0/120	0	8	-	-	-	-
TETRACYCLINE									
TANA	Baseline	11	11/110	10.0	-	-	-	-	-

Table 9. Antibiotic resistance to *Streptococcus pneumoniae* (*Continued*)

TANA	12 months	12	34/119	28.4	12	21/120	17.5	1.6	1.01 to 2.6
TANA (as a percentage pneumococcal isolates)¶	Baseline	11	12/76	15.2	-	-	-	-	-
TANA (as a percentage pneumococcal isolates)¶	12 months	12	29/83	35.5	12	21/98	21.5	1.6	1.01 to 2.6
TEF	24 months	8	44/120	36.5	8	23/120	18.9	1.9	1.2 to 3.0
TEF	36 months	8	82/120	68.7	8	19/119	15.7	4.3	2.8 to 6.6
TEF	42 months	8	69/120	57.2	8	-	-	-	-
TEF	54 months	8	46/120	38.7	8	-	-	-	-
TRIMETHOPRIM-SULFAMETHOXAZOLE									
TEF	24 months	8	0/120	0	8	3/120	2.7	0.14	0.01 to 2.7
TEF	36 months	8	9/120	7.9	8	8/119	6.7	1.1	0.5 to 2.8
TEF	42 months	8	11/120	8.8	8	-	-	-	-
TEF	54 months	8	8/120	6.8	8	-	-	-	-

n/N: number of isolates with resistance/total number of isolates
AZ: azithromycin
MDA: mass drug administration
*Studies were all cluster-randomised controlled trials. PRET The Gambia compared AZ once a year for 3 years with AZ once a year for 1 year; TANA compared AZ every 3 months for 12 months with no AZ; TEF compared AZ twice a year for 3 years with no AZ.
**Follow-up is months after baseline (i.e. first MDA) unless otherwise indicated.
***TANA and TEF reported average percentages across communities, and these are the percentages reported in this table. We estimated n/N using these percentages and additional information in the text of the paper. Figures for n/N were used to calculate the risk ratio and 95% confidence interval in RevMan 5. There may be minor discrepancies due to rounding between the raw numbers, percentages and risk ratios. The 95% confidence intervals for the risk ratio are are not adjusted for the cluster design.
¶ Denominator is isolates with pneumococcal carriage only.

Table 10. Antibiotic resistance to *Staphylococcus aureus*

Study*	Follow-up**	Intervention			Comparator			Risk ratio	95% confidence interval***
		Number of communities	n/N	%	Number of communities	n/N	%		
AZITHROMYCIN									
PRET The Gambia	1 month before 3rd annual round of MDA	2	37/414	8.9	6	-	-	-	-
PRET The Gambia	1 month after annual round of MDA	2	142/417	34.1	6	-	-	-	-
PRET The Gambia	6 months after 3rd annual round of MDA (intervention group) 30 months after 1 annual round of MDA (comparator group)	2	25/343	7.3	6	6/375	1.6	4.6	1.9 to 11.0
PRET The Gambia **(as a percentage of isolates)¶**	1 month before 3rd annual round of MDA	2	37/102	36.3	6	-	-	-	-
PRET The Gambia **(as a percentage of isolates)¶**	1 month after 3rd annual round of MDA	2	142/161	88.2	6	-	-	-	-
PRET The Gambia	6 months af-	2	25/30	83.3	6	6/25	24.0	3.5	1.7 to 7.1

Table 10. Antibiotic resistance to *Staphylococcus aureus* (*Continued*)

(as a percentage of isolates)¶	ter 3rd annual round of MDA (intervention group) 30 months after 1 annual round of MDA (comparator group)								
CLINDAMYCIN									
PRET The Gambia	1 month before 3rd annual round of MDA	2	24/414	5.8	6	-	-	-	-
PRET The Gambia	1 month after 3rd annual round of MDA	2	128/417	30.7	6	-	-	-	-
PRET The Gambia	6 months after 3rd annual round of MDA (intervention group) 30 months after 1 annual round of MDA (comparator group)	2	20/343	5.8	6	3/375	0.8	7.3	2.2 to 24.3
PRET The Gambia **(as a percentage of isolates)¶**	1 month before 3rd annual round of MDA	2	24/102	23.5	6	-	-	-	-

Table 10. Antibiotic resistance to *Staphylococcus aureus* (*Continued*)

PRET The Gambia **(as a percentage of isolates)¶**	1 month after annual round of MDA	2	128/161	79.5	6	-	-	-	-
PRET The Gambia **(as a percentage of isolates)¶**	6 months after 3rd annual round of MDA (intervention group) 30 months after 1 annual round of MDA (comparator group)	2	20/30	66.7	6	3/25	12.0	5.6	1.9 to 16.5

n/N: number of isolates with resistance/total number of isolates
AZ: azithromycin
MDA: mass drug administration
*Studies were all cluster-randomised controlled trials. PRET The Gambia compared AZ once a year for three years with AZ once a year for one year.
**Follow-up is months after baseline (i.e. first mass drug administration) unless otherwise indicated.
***The 95% confidence intervals for the risk ratio are are not adjusted for the cluster design.
¶ Denominator is isolates with *S.aureus* carriage only.

Table 11. Antibiotic resistance to *Escherichia coli*

Study*	Follow-up**	Intervention			Comparator			Risk ratio	95% confidence intervals***
		Number of communities	n/N	%	Number of communities	n/N	%		
AZITHROMYCIN									
PRET Tanzania	Baseline	4	20/163	16.3	4	20/96	20.8	0.6	0.3 to 1.04
PRET Tanzania	1 month	4	79/129	61.2	4	25/134	18.7	3.3	2.3 to 4.8

Table 11. Antibiotic resistance to *Escherichia coli* *(Continued)*

PRET Tanzania	3 months	4	56/133	42.1	4	20/126	15.9	2.7	1.7 to 4.2
PRET Tanzania	6 months	4	26/83	31.3	4	10/50	20.0	1.6	0.8 to 3.0
PRET Tanzania (as a percentage of isolates)¶	Baseline	4	30/300	10.0	4	39/205	19.0	0.5	0.3 to 0.8
PRET Tanzania (as a percentage of isolates)¶	1 month	4	153/347	44.1	4	46/325	14.2	3.1	2.3 to 4.2
PRET Tanzania (as a percentage of isolates)¶	3 months	4	104/347	30.0	4	32/324	9.9	3.0	2.1 to 4.4
PRET Tanzania (as a percentage of isolates)¶	6 months	4	44/191	23.0	4	14/118	11.9	1.9	1.1 to 3.4
ERYTHROMYCIN									
PRET Tanzania	Baseline	4	32/123	26.0	4	22/96	22.9	1.2	0.6 to 2.2
PRET Tanzania	1 month	4	98/129	76.0	4	38/134	28.4	8.0	4.6 to 13.9
PRET Tanzania	3 months	4	73/133	54.9	4	30/126	23.8	3.9	2.3 to 6.6
PRET Tanzania	6 months	4	32/83	38.6	4	13/50	26.0	1.8	0.8 to 3.9
PRET Tanzania (as a percentage of isolates)¶	Baseline	4	51/300	17.0	4	35/205	17.1	1.0	0.6 to 1.6

Table 11. Antibiotic resistance to *Escherichia coli* (*Continued*)

PRET Tanzania (as a percentage of isolates)¶	1 month	4	219/347	63.1	4	65/325	20.0	6.8	4.8 to 9.7
PRET Tanzania (as a percentage of isolates)¶	3 months	4	149/347	42.9	4	52/324	16.0	3.9	2.7 to 5.7
PRET Tanzania (as a percentage of isolates)¶	6 months	4	61/191	31.9	4	20/118	16.9	2.3	1.3 to 4.1

n/N: number of isolates with resistance/total number of isolates
AZ: azithromycin
*Studies were all cluster-randomised controlled trials. PRET Tanzania compared AZ once a year for three years with no AZ.
**Follow-up is months after baseline (i.e. first mass drug administration) unless otherwise indicated.
***The 95% confidence intervals for the risk ratio are not adjusted for the cluster design.
¶ Denominator is isolates with *E.coli* carriage only.

Table 12. Adverse effects: cluster-randomised studies

	Study	Antibiotic (number of communities and people treated)	Report
1, 2 & 3	ACT 1999 Egypt; ACT 1999 Tanzania; ACT 1999 The Gambia	Azithromycin (6 communities, approximately 3800) Tetracycline (6 communities, approximately 2400)	No comment on adverse effects in report
4	Atik 2006	A total of 4 communities included in the study. Azithromycin (214) Tetracycline (161)	No comment on adverse effects in report
5	NCT00618449	Azithromycin (1139)	Reported no adverse events on clinical trials register (clinicaltrials.gov/ct2/show/results/NCT00618449)
6	PRET Niger	Azithromycin (48 communities, approximately 6000)	No comment on adverse effects in report, but "a data and safety monitoring committee met annually to review re-

Table 12. Adverse effects: cluster-randomised studies (*Continued*)

			sults and serious adverse events"
7	PRET Tanzania	Azithromycin (32 communities, approximately 12,000)	"There were no serious adverse events reported in either arm."
8	PRET The Gambia	Azithromycin (48 communities, 29,091)	No comment on adverse effects in report
9	Resnikoff 1995	Oxytetracycline (346)	No comment on adverse effects in report
10	TANA	Azithromycin (over 16,000)	"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. Four (0.6%) patients reported haemorrhoid or other as side effects" (House and colleagues, page 1115). "In a trachoma-endemic area, mass distribution of oral azithromycin was associated with reduced mortality in children" (Porco and colleagues, conclusion of abstract)
11	TEF	Azithromycin (16 communities, 4790)	"There were no serious adverse events due to the study medicine reported"
12	Wilson 2018	Azithromycin (48 communities, unclear how many people)	"No serious adverse events were associated with MDA."

MDA: mass drug administration

Table 13. Azithromycin (single-dose) every 3 months for 12 months: mean community prevalence of infection with *C trachomatis* at 12 months

	Intervention: children aged 1 to 10 years offered single-dose oral azithromycin every 3 months (n = 12 communities)		Comparator: everyone aged 1 year and older offered single-dose oral azithromycin at first visit (baseline) (n = 12 communities)	
	Prevalence %	**95% confidence interval**	**Prevalence %**	**95% confidence interval**
Children aged 1 to 10 years	3.6	0.8 to 6.4	14.6	7.2 to 22.1
Children and adults aged 11 years and older	8.2	5.1 to 11.4	6.2	2.9 to 9.4

Table 14. Azithromycin (single-dose) every 6 months compared with annual treatment: mean community prevalence of infection with *C trachomatis*

	Intervention: everyone aged 1 year and older offered single-dose oral azithromycin every 6 months		Comparator: everyone aged 1 year and older offered single-dose oral azithromycin annually	
	Prevalence %	**95% confidence interval**	**Prevalence %**	**95% confidence interval**
PRET Niger Children aged 0 to 5 years Follow-up: 36 months	3.8	2.2 to 6.0	5.8	3.2 to 9.0
PRET Niger Adults aged 15 years or older Follow-up: 36 months	0.0	0 to 7	0.3	0 to 7
TANA Children aged 0 to 9 years Follow-up: 12 months	1.7	0.7 to 2.6	6.2	2.9 to 9.4
TANA Children aged 0 to 9 years Follow-up: 24 months	1.5	0.2 to 2.8	2.3	0.8 to 3.8
TANA Children aged 0 to 9 years Follow-up: 36 months	0.2	0.0 to 0.6	1.5	0.1 to 3.0

Table 14. Azithromycin (single-dose) every 6 months compared with annual treatment: mean community prevalence of infection with *C trachomatis* (*Continued*)

TANA Children and adults aged 10 years and older Follow-up: 12 months	1.7	0.7 to 2.6	6.2	2.9 to 9.4
TANA Children and adults aged 10 years and older Follow-up: 24 months	1.5	0.2 to 2.8	2.3	0.8 to 3.8
TANA Children and adults aged 10 years and older Follow-up: 36 months	0.2	0.0 to 0.6	1.5	0.1 to 3.0
TEF Children aged 1 to 5 years Follow-up: 12 months	1.3	0.3 to 2.6	10.9	0.1 to 21.8
TEF Children aged 1 to 5 years Follow-up: 24 months	0.9	0.0 to 2.1	6.8	1.2 to 12.4

PRET Niger: 24 communities in each group; only children aged 0 to 12 years treated in intervention group.
TANA: 12 communities in each group.
TEF: 8 communities in each group.

Table 15. Antimicrobial resistance in non-randomised studies

Citation and location	Study design	Age group	Antibiotic	Follow-up	Comment
C trachomatis					
Solomon 2005 Rombo district, Tanzania	Antimicrobial resistance assessed before and after azithromycin treatment in people with *C trachomatis* infection.	Not reported	Azithromycin Tetracycline	2 months	956/978 residents examined at baseline; 56 with eye infection; 43 isolates from these people at baseline "We conclude that no clinically or programmatically sig-

Table 15. Antimicrobial resistance in non-randomised studies (*Continued*)

					nificant changes in C. trachomatis azithromycin or tetracycline susceptibilities were induced"
Hong 2009 Gurage zone, Ethiopia	Samples taken before and after treatment.	1 to 5 years	Azithromycin Doxycycline	18 months after 4 bi-annual mass treatment (2 years)	Found no significant differences in susceptibilities to azithromycin and doxycycline in 6 post-treatment and 4 pre-treatment samples
West 2014 Kongwa district, Tanzania	Isolates obtained before and after mass drug administration.	0 to 9 years	Azithromycin Doxycycline	12 months after 3 years of mass treatment	Compared resistance to *C trachomatis* in children with/without continuing infection and found similar levels of resistance
S pneumoniae					
Leach 1997 Northern territory (Aboriginal community), Australia	Antimicrobial resistance assessed before and after azithromycin treatment in children with trachoma	5 to 14 years	Azithromycin Erythromycin (results not reported)	2 to 3 weeks, 2 months, and 6 months following azithromycin treatment	79 children with trachoma: • 1/79 resistant before treatment; • 6/38 at 2 to 3 weeks; • 10/37 at 6 months.
Fry 2002 Western Nepal	Antimicrobial resistance assessed before and after azithromycin treatment in children	1 to 10 years	Azithromycin Penicillin Chloramphenicol Sulfamethoxazole	10 days and 6 months	At 180 days, 5% of 104 children with 2 previous treatments carriage of azithromycin-resistant *S pneumoniae* compared with 0% of children with 1 (150 children) or 0 (149 children) previous treatments
Batt 2003 Rombe district, northern Tanzania	Antimicrobial resistance assessed before and after azithro-	0 to 7 years	Azithromycin Penicillin	2 months and 6 months	"At the 2-month and 6-month

Table 15. Antimicrobial resistance in non-randomised studies (*Continued*)

	mycin treatment in children		Erythromycin Cotrimoxazole		points, macrolide-re-sistant isolates were 0% and 1%, respectively"
Gaynor 2003 Western Nepal	Cross-sectional survey 1 year after mass distribution of azithromycin	1 to 10 years	Azithromycin Trimethoprim/ sulfamethoxazole	1 year	No macrolide resistance observed in 50 nasopharyngeal samples positive for *S pneumoniae*.
Gaynor 2005 Kailali district, western Nepal	Cross-sectional survey 6 months after the 3rd annual treatment with azithromycin or tetracycline or no treatment	1 to 10 years	Azithromycin Trimethoprim/ sulfamethoxazole	12 months	5/163 (3%) isolates were resistant to azithromycin in the azithromycin-treated communities compared with 0 in 126 children in tetracycline-treated communities and 91 in untreated. Tetracycline resistance was higher in tetracycline-treated communi-ties (39/126, 31%) compared with 17% and 16% in azithromycin-treated and untreated communities, respectively
Bloch 2017 KIlosa district, Tanzania	Cross-sectional survey 4 years after mass distribution of azithromycin	1 month to 59 months	Azithromycin	4 years	Re-sistance to azithromycin was observed in 14.3%, 29.0%, and 16.6% of the *S pneumoniae*, *S aureus*, and *E coli* isolates, respectively.

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 Ovid 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 2006.

Appendix 3. Embase Ovid 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. ISRCTN search strategy

(trachoma OR tracoma) AND antibiotics

Appendix 5. ClinicalTrials.gov search strategy

(trachoma OR tracoma) AND Antibiotics

Appendix 6. WHO ICTRP search strategy

Condition = trachoma OR tracoma AND Interventions = antibiotics

Appendix 7. Changes made to data in the 2011 update of the review

		Current review				Original review				Comments
		Treatment		Control		Treatment		Control		
	Study	n	N	n	N	n	N	n	N	
Active trachoma at 3 months	Peach 1986	216	340	138	189	284	408	182	233	Missing data counted twice in original review.
Active trachoma at 12 months	Woolridge 1967	121	202	95	120	149	202	100	120	Error in data extraction in original review
Active trachoma at 3 months	Peach 1986	216	340	138	189	284	408	182	233	Missing data counted twice in original review.
Active trachoma at 12 months	Woolridge 1967	121	202	95	120	149	202	100	120	Error in data extraction in original review
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
Active trachoma at 3 months	Shukla 1966	53	83	29	62	53	83	34	42	Error in data extraction in original review

(*Continued*)

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
Chlamydia trachomatis infection at 3 months	Tabbara 1996	6	30	4	26	-	-	-	-	Not included in previous review
Active trachoma at 12 months	Bowman 2000	32	149	45	139	-	-	-	-	Not included in previous review
Chlamydia trachomatis infection at 12 months	Dawson 1997	8	105	5	33	7	105	5	33	Error in data extraction in original review
Active trachoma at 12 months	Atik 2006	21	523	35	994	-	-	-		Not included in previous review
Chlamydia trachomatis infection at 12 months	Atik 2006	23	659	68	1192	-	-	-		Not included in previous review
Chlamydia trachomatis infection at 12 months	Lee 2007, now included under TEF	2	170	56	185	-	-	-		Not included in previous review
	ACT 1999 Egypt; ACT	Data for the ACT trial in the original review were not exactly the same as the published data and included unpublished outcomes. The original review authors had access to individual patient data that were not available to the current authors. In the absence of access to the original data, we felt it was unwise to make								

(*Continued*)

	1999 Tanzania; ACT 1999 The Gambia	any changes to the data included in the review.

WHAT'S NEW

Date	Event	Description
4 January 2019	New citation required and conclusions have changed	Issue 9, 2019: Review substantively updated. New authorship.
4 January 2019	New search has been performed	Issue 9, 2019: Electronic searches updated and 4 new trials included. New outcome on antimicrobial resistance added

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 the writing of the review. Christine 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 the search results; assessed risk of bias of all included studies; extracted data from newly included trials; and substantially rewrote the text of the review.

Major update of review and change of authors 2019: JE and EHE screened the search results; assessed risk of bias of all included studies; extracted data from newly included trials; and substantially rewrote the text of the review. Other authors reviewed and contributed to the manuscript and collected data on non-randomised studies for the Discussion.

DECLARATIONS OF INTEREST

Previous versions of this review

The Edna McConnell Clark Foundation supported Denise Mabey and Nicole Fraser-Hurt for one half-day a week over a 10-month period to undertake the original review. SightSavers International in part funded JE's salary to update the review in 2011.

Current 2019 version of this review

JE: None known.
AWS: None known.
RK: None known.
AP: None known.
BPS: None known.
RMS: None known.
EHE: The International Trachoma Initiative (ITI) pays for EHE's salary. ITI is a program of The Task Force for Global Health, and receives funding from Pfizer Inc. Neither ITI nor Pfizer Inc. had any role in the review's research questions and design; in the collection, analysis and interpretation of data; in the writing of the review; or in the decision to submit for publication.
Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision (CEV) signed off the review for publication. Peter Tugwell, Senior Editor and Nuala Livingstone, Associate Editor for the Cochane Musculoskeletal, Oral, Skin and Sensory (MOSS) Network reviewed a draft prior to publication. This was to avoid a potential conflict of interest as one of the authors (JE) is the joint Co-ordinating Editor for CEV.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The Edna McConnell Clark Foundation, USA.
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- Sightsavers International, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Objectives

When this review was first published in 2002 (Mabey 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 2011 (Evans 2011). It was decided to consider individually randomised and cluster-randomised trials separately, as the new author team felt that they were addressing different questions and were likely to be measuring different effects. The individually randomised studies address the question: what is the effect of antibiotic treatment on individuals? The cluster-randomised trials address the question: what is the effect of antibiotic treatment on communities? The effect of treatment in individuals in treated communities may be different because as well as the individual-level effect, there may be an additional impact via reduction in transmission. The following two objectives were identified.
1. What is the effect of antibiotic treatment of 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?

We further expanded the objectives for the current update, including the effect of different treatment frequencies and adding antimicrobial resistance as an outcome.

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

- What is the effect of antibiotic treatment versus no treatment?
- What is the effect of oral versus topical antibiotic?
- What is the effect of oral azithromycin compared to topical tetracycline?

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

- What is the effect of mass administration of antibiotic compared to no treatment?
- What is the effect of mass administration of oral azithromycin versus topical tetracycline?
- What is the effect of annual versus different treatment frequencies?

(3) What are the adverse effects of antibiotic treatment?

- What are the adverse effects at the individual level?
- What is the effect of mass administration of oral azithromycin or topical tetracycline on resistance in (i) *C trachomatis* and (ii) other bacteria?

Other changes

In the 2011 update (Evans 2011), we implemented Cochrane's tool for assessing risk of bias and updated some aspects of the methods - such as assessment of heterogeneity - that 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 and current updated versions of the review were 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