Overview of Reviews

The Cochrane Library and trachoma: an overview of reviews

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Abstract

Background: Trachoma is the leading infectious cause of blindness worldwide. Active trachoma is caused by the bacterium *Chlamydia trachomatis*. Recurrent infection over many years may lead to scarring of the conjunctiva, entropion, trachomatous trichiasis and corneal opacity.

Objective: To summarize Cochrane reviews that assess the effect of SAFE strategy (surgery, antibiotics, face washing and environmental change) for trachoma in developing countries.

Methods: The *Cochrane Database of Systematic Reviews* was searched for any intervention to prevent or treat trachoma. Data was extracted in duplicate and analyzed.

Main Results: There were four systematic reviews addressing trachoma, all of which met the inclusion criteria. There was some evidence that the prevalence of active trachoma was reduced by the use of antibiotics. At three months, six of nine trials found a significant reduction in relative risk of active trachoma in the intervention groups. At 12 months, only three of six studies found a significant reduction. Oral azithromycin performed better than topical tetracycline at clearing infection at three months, but not at resolving clinical signs. There is evidence that face washing in combination with topical tetracycline antibiotics can reduce the prevalence of severe trachoma compared to face washing alone. Insecticide spray as a fly control measure significantly reduced trachoma and health education may be effective in reducing active trachoma.

Full thickness incision of the tarsal plate was found to be the most successful type of surgery for trichiasis. Tarsal rotation surgery was also found to be more effective than non-surgical techniques for minor trichiasis. This surgery was equally effective when performed by appropriate trained ophthalmic nurses and ophthalmologists and also when conducted in a health centre or village setting.

Authors' Conclusions: There are no clinical trials of the full SAFE strategy for trachoma control on blindness prevention, or on reducing active trachoma, or ocular *Chlamydia trachomatis* infection. However, there is some evidence that separately supports each of the components of SAFE: surgery, antibiotics, facial cleanliness, and environmental improvements. Programmatically, continued delivery of the full SAFE strategy is warranted and can be expected to have a positive impact on the control of blinding trachoma.

Editors' note: *Overviews of reviews, compiling evidence from multiple Cochrane reviews into one accessible and usable document, are a regular feature of this journal. Our aim for each overview is to focus on the treatment question, 'which treatment should I use for this condition?' It is our hope that the overview of reviews will serve as a 'friendly front end' to* The Cochrane Library, *allowing the reader a quick overview (and an exhaustive list) of Cochrane reviews relevant to the clinical decision at hand.*

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Background

Description of the condition

Trachoma is the leading infectious cause of blindness worldwide. Recurrent infection by the bacterium *Chlamydia trachomatis* produces a chronic keratoconjunctivitis (inflammation affecting both the conjunctiva and cornea) referred to as Active Trachoma. The infection is spread from person to person by fingers and clothes used to wipe away eye discharge. It is also transmitted through fly-eye contact (1). The repeated cycle of infection and inflammation causes the inner surface of the upper eyelid to scar. Progressive scarring results in distortion and shortening of the inside of the eyelid. As the lid margin turns inward (entropion) it causes the eyelashes to also turn inwards and touch the surface of the eye, a condition known as trachomatous trichiasis. This condition can damage the cornea by direct trauma and secondary bacterial infection unless corrected surgically, by rotating the lid margin and lashes away from the eye. Without surgical correction, blinding corneal opacification can develop (2). Although trachoma is easily controlled, blindness from trachoma is essentially irreversible.

The World Health Organization (WHO) lists the national trachoma prevalence estimates for 52 endemic countries (http://globalatlas.who.int/globalatlas): approximately 460 million people are at risk for blinding trachoma; 63 million have active trachoma; and 9.5 million have unoperated trichiasis. It has also been estimated that trachoma is responsible for 3.6% of global blindness (approximately 1.3 million people) making it the world's leading cause of preventable blindness (3).

Description of the interventions

WHO has adopted an integrated control strategy to prevent blindness from trachoma and to control trachoma transmission. The strategy has the name 'SAFE' and consists of: Surgery to correct trachomatous trichiasis; Antibiotics to treat active infections and reduce the community reservoir of infection; and Facial cleanliness and Environmental change to suppress transmission by modifying factors that favour it (4,5).

How the interventions might work

Surgery is usually the first component of the SAFE strategy to be implemented, as it can stop corneal damage from progressing, and hence prevent blindness in those at immediate risk, before irreversible corneal opacification has occurred (6). Epilation (plucking the eyelashes) and eyelid taping (forcing eyelashes back to the correct position and holding them with sticking plaster) can be used in lieu of surgery, although the long-term efficacy of these interventions in preventing blindness is not certain. The most common surgical procedures are bilamellar tarsal rotation (full thickness incision through the eyelid), posterior lamellar tarsal rotation (incision only through the scarred tarsal plate and conjunctiva) and tarsal advance and rotation (incision in the tarsal plate and rotation of the terminal portion, in which the upper part of the tarsus is separated from the anterior lamellar and advanced) (6). All of the surgical procedures reverse the in-turned lashes characteristic of trachomatous trichiasis so that they are returned to their original, outward-pointing position.

For treatment with antibiotics, the WHO currently recommends either: (a) 1% tetracycline eye ointment twice a day for six weeks applied topically on the inner surface of the lower eyelid, or (b) a single oral dose of azithromycin (1000 mg for an adult and 20 mg/kg for children) (7). Antibiotics effectively treat current infections and are used for both individual treatment and in mass drug administration (without individual diagnoses) in hyperendemic communities to reduce the community reservoir of ocular *Chlamydia trachomatis*. Mass drug administration is recommended in a community where the prevalence of the characteristic signs of follicular trachoma (Grade TF in the Simplified WHO Grading System, (8)) exceeds 10% in children aged 1–9 years (7).

Washing the face removes potentially infectious ocular and nasal discharge from those with current infections who are shedding *Chlamydia trachomatis*, preventing contamination of fomites and reducing hand-eye transmission. Washing away the bacteria may also play a role in reducing self-reinfection. Children with clean faces have also been observed to have a reduced frequency of fly-eye contact with the trachoma vector, *Musca sorbens* (9). This is important in the reduction of both acquisition and transmission of infection as flies that contact the eyes of children who are shedding *Chlamydia trachomatis* can carry the bacteria to the eyes of those who are not infected. The increase of clean faces is where the F and E of the SAFE strategy come together. Facial cleanliness is implemented as hygiene promotion in its broader sense including personal grooming, use of soap, not sharing towels, and frequent washing of clothes and bed sheets, and this is facilitated and enhanced by the provision of water and sanitation – which are the primary Environmental changes that form the E component of SAFE.

Other environmental interventions that aim to control eye-seeking flies and address other trachoma risk factors include: water provision; reducing environmental contamination with human faeces; promotion of latrine use; moving animals away from domestic residences; village cleaning with the promotion of refuse dumps; and fly control with insecticides (2,10,11,12).

Some studies looked at infection with *C. trachomatis* in addition to active trachoma as an outcome. The relationship between infection (as compared to clinical signs) and trichiasis and blindness is yet to be

established, but it is likely that the control of infection in addition to reduction in clinical signs will be of long-term benefit.

Why it is important that we do this review

The brunt of the burden of blinding trachoma is borne by the most impoverished populations in the world, populations whose poverty comes hand-in-hand with the unhygienic overcrowded living conditions and poor access to water and sanitation, which are associated with trachoma. The economic impact of the disability caused by trichiasis and blindness on those who are already poor contributes to keeping them in the cycle of poverty. Trachoma has disappeared from Europe, North America and individual countries without specific or large-scale control programs. It has also been demonstrated that it is possible to control trachoma using the SAFE strategy in even the most disadvantaged parts of the world such as Southern Sudan (13). The global elimination of blinding trachoma should be possible, and it is necessary to investigate the efficacy of the interventions that aim to do so.

Objectives

To summarize Cochrane reviews related to the WHO's SAFE Strategy, evaluating the effectiveness of interventions to control active trachoma and to surgically correct established trachomatous trichiasis.

Methods

Search Strategy

The *Cochrane Database of Systematic Reviews* was searched for all systematic reviews examining any intervention for the treatment of trachoma. The term 'trachoma' was entered and restricted to record title, abstract or keyword. Four reviews were found, one of which was being updated, and all of which were included in this overview of reviews.

Selection of reviews

Each of the reviews retrieved assessed one of the four components of the WHO's SAFE strategy to prevent trachoma; surgery, antibiotics, facial cleanliness and environmental changes (2,6,12,14). The characteristics of the reviews can be found in Table I. All included randomized trials. While the focus of some of these reviews was active trachoma and infection in children, adults were included in this analysis since most interventions to control trachoma are aimed at the community and all the surgery trials were conducted in adults. Subjects in the trials of surgery and trichiasis recurrence were graded as having major (more than five lashes touching the eye) or minor trichiasis (one

to five lashes touching the eye), or as having defective lid closure.

Data extraction and management

Two authors, Elizabeth Sumamo (primary) and Krystal Harvey, were responsible for the extraction of outcome data from the four reviews. Tables were created to capture the statistical measures of interest; relative risk (RR), risk difference (RD) and control group risk. Three community level trials adjusted for clustering within their published statistics; however the RR and RD presented in this review was calculated at the individual level without adjusting for clustering in the included tables (1,15,16). Any difficulties encountered during data extraction were discussed between both authors and all statistical issues were resolved with the assistance of a biostatistician.

Assessment of quality of evidence

All reviews stated that the quality was assessed according to the methods set out in Section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* using the Cochrane Eyes and Vision Group Review Development Guidelines.

Data synthesis

The data were extracted from the four systematic reviews and displayed in Tables II, III, IV and V. One review had an analysis portion from which RR, RD and control group risk could be directly taken (2). In the other three reviews, not all the statistical numbers were expressed in this way. In one study, only odds ratios (OR) were reported and there was insufficient information available to calculate RR, RD and control group risk (17). Besides this one instance, uniform reporting across all of the reviews was possible.

Involvement of authors

The team of authors for this overview of reviews included Elizabeth Sumamo and Krystal Harvey who extracted the data and participated in writing. Matthew Burton and Paul Emerson reviewed the data, edited the document and were the main authors for all sections.

Results

Four systematic reviews of 27 studies that examined interventions for trachoma control were found within the *Cochrane Database of Systematic Reviews*. Four additional recent studies were included due to their high relevance and because they will be included in future updates of included systematic reviews (16,18,19,20). The details of the individual studies are found in Tables II, III, IV and V. The interventions to control active disease included topical and

Table I. Characteristics of included reviews

Title	Authors	Date last updated	Population	Intervention	Comparisons	Outcomes
Antibiotics for trachoma (2)	Mabey D Fraser-Hurt N Powell C	Feb 2005	Adults and children	• Topical and oral antibiotics at any dose or frequency • Topical administration of antibiotics at any dose or frequency	• Placebo or no treatment • Oral administration of any antibiotic and any dose or frequency	Primary - Active trachoma Secondary - Positive test for *Chlamydia trachomatis* infection - Adverse side effects
Face washing promotion for preventing active trachoma (14)	Ejere H Alhassan MB Rabiu M	Mar 2004	1–14 years	• Face washing promotion • Face washing promotion and mass antibiotic treatment	• No intervention • Mass antibiotic treatment alone	Primary - Active trachoma Secondary - Participants with unclean faces - Severe trachoma
Environmental sanitary interventions for preventing active trachoma (12)	Rabiu M Alhassan M Ejere H	Feb 2005	Adults and children	• Fly control • Water provision • Health education	• No intervention	Primary - Active trachoma Secondary - Fly density - Latrine utilization - Water utilization - Adverse effects

| Interventions for trachoma trichiasis (6) | Yorston D Mabey D Hatt S Burton M | Mar 2006 | Adults | • Bilamellar tarsal rotation

• Bilamellar tarsal rotation
• Tarsal advance and rotation
• Eversion splinting
• Tarsal advance
• Tarsal grooving
• Electrolysis, cryotherapy or bilamellar tarsal rotation
• Bilamellar tarsal rotation
• Tarsal advance and rotation

• Epilation (manual removal of eyelashes
• Posterior lamellar tarsal rotation, tetracycline and azithromycin
• Providing surgery in participants' own village
• Surgery by non-ophthalmologist integrated eye care workers | • Posterior lamellar tarsal rotation
• No control group, participants randomized to one of three operations

• No control group, participants randomized to one of five operations
• Tarsal advance and rotation
• Tarsal advance with buccal mucosal membrane graft
• Double-sided sticking plaster
• Posterior lamellar tarsal rotation and tetracycline
• Providing surgery in nearest health centre
• Surgery by ophthalmologists | Primary
- Recurrence of trichiasis

Secondary
- Visual acuity
- Acceptance of treatment |

Table II. Active Trachoma (TF or TI)

Author/year	Intervention and comparison	No. subjects	Control group risk [baseline risk]	Risk difference (95% CI)	Relative risk (95% CI)	Comments
Antibiotics studies						
Oral antibiotics versus control group						
Darougar 1980b (25)	Treatment: oral doxycycline, one dose per month for 12 months Comparison: vitamin pills 1 dose per month for 12 months	3 mo. 91 12 mo. 91	72.3% 70.2%	0.00 (−0.18, 0.19) −0.16 (−0.35, 0.04)	1.01 (0.78, 1.29) 0.78 (0.56, 1.08)	Household treatment
Dawson 1969i (26)	Treatment: oral trisulfapyrimidines 3 daily during 3 consecutive weeks Comparison: lactose-placebo 3 daily for 3 consecutive weeks	12 mo. 36	83.3%	−0.50 (−0.78, −0.22)	0.40 (0.20, 0.79)	Only active trachoma cases treated
Dawson 1969ii (26)	Treatment: oral trisulfapyrimidines 3 daily during 3 consecutive weeks Comparison: lactose-placebo 3 daily for 3 consecutive weeks	3 mo. 29	7.1%	0.00 (−0.19, 0.18)	0.93 (0.06, 13.54)	Only active trachoma cases treated
Foster 1966 (42)	Treatment: oral sulphamethoxypyridazine once daily for 5 consecutive days every week for 3 weeks Comparison: no treatment	3 mo. 219 12 mo. 219	82.2% 63.6%	−0.05 (−0.16, 0.05) 0.08 (−0.04, 0.20)	0.93 (0.82, 1.07) 1.12 (0.93, 1.35)	Only active trachoma cases treated
Hoshiwara 1973 (27)	Treatment: oral doxycycline once daily for 5 consecutive days every week up to 28 doses in 40 days Comparison: placebo once daily for 5 consecutive days every week up to 28 doses in 40 days	3 mo. 103	81.5%	−0.24 (−0.42, −0.07)	0.70 (0.53, 0.92)	Only active trachoma cases treated
Shukla 1966 (43)	Treatment 1: topical sulphafurazole + sulphadimethoxine twice daily for 5 consecutive days every month for 5 months/bi-weekly for 5 months Treatment 2: sulphadimethoxine biweekly or weekly dose for 5 months Comparison: no treatment	3 mo. 125 12 mo. 125	85.7% 83.3%	−0.22 (−0.37, −0.07) −0.40 (−0.55, −0.24)	0.74 (0.61, 0.91) 0.52 (0.39, 0.69)	Only active trachoma cases treated. Treatments were pooled and compared with control Only active trachoma cases treated. Treatments were pooled and compared with control

Topical antibiotic versus control group

Study	Treatment/Comparison	Follow-up, N	%	RD (95% CI)	RR (95% CI)	Notes
Attiah 1973 (44)	Treatment 1: topical tetracycline derivative once every school day for 11 weeks. Treatment 2: topical terramycin once every school day for 11 weeks. Comparison: no treatment	3 mo. 228	76.3%	−0.21 (−0.33, −0.09)	0.72 (0.60, 0.88)	Only active trachoma cases treated
Darougar	Treatment: topical oxytetracycline twice daily for 7 consecutive days every month for 12 months. Comparison: vitamin pills 1 dose per month for 12 months	3 mo. 85	72.3%	0.04 (−0.15, 0.23)	1.05 (0.82, 1.35)	Household treatment
		12 mo. 85	70.2%	−0.20 (−0.41, 0.00)	0.71 (0.49, 1.03)	
Foster 1966 (42)	Treatment: topical tetracycline 3 times daily on 5 consecutive days every week for 6 weeks. Comparison: no treatment	3 mo. 213	82.2%	−0.08 (−0.19, −0.03)	0.91 (0.79, 1.04)	Only active trachoma cases treated
		12 mo. 213	63.6%	−0.02 (−0.15, 0.11)	0.96 (0.78, 1.19)	
Peach 1986 (22)	Treatment: topical oily tetracycline daily for 5 days once a month for 3 months. Comparison: no treatment	3 mo. 641	78.1%	−0.09 (−0.15, −0.02)	0.89 (0.81, 0.98)	Community-wide treatment
Shukla 1966 (43)	Treatment 1: topical sulphafurazole + oral sulphadimethoxine twice daily for 5 consecutive days every month for 5 months/bi-weekly for 5 months. Treatment 2: topical sulphafurazole twice daily for 5 consecutive days every month for 5 months. Comparison: no treatment	3 mo. 104	85.7%	−0.39 (−0.55, −0.23)	0.55 (0.41, 0.73)	Treatments were pooled and compared with control
		12 mo. 104	83.3%	−0.27 (−0.44, −0.10)	0.68 (0.52, 0.88)	
Woolridge 1967 (45)	Treatment: topical tetracycline twice daily for 6 consecutive days per week for 6 weeks. Comparison: no treatment	3 mo. 322	85.8%	−0.17 (−0.26, −0.08)	0.80 (0.71, 0.90)	Only active trachoma cases treated
		12 mo. 322	83.3%	−0.10 (−0.19, −0.01)	0.89 (0.79, 0.99)	

Oral vs topical antibiotic

Study	Treatment/Comparison	Follow-up, N	%	RD (95% CI)	RR (95% CI)	Notes
Bowman 2000 (24)	Treatment: oral azithromycin (single dose, 20 mg/kg). Comparison: unsupervised 6 week course of topical tetracycline twice daily	10 wk. 291	53.2%	−0.17 (−0.28, −0.06)	0.65 (0.48, 0.86)	Only active trachoma cases treated. RR and RD are based on per protocol analysis; those that missed follow up are not included
		6 mo. 295	27.0%	−0.15 (−0.24, −0.06)	0.46 (0.28, 0.76)	

(continued overleaf)

Table II. (*Continued*)

Author/year	Intervention and comparison	No. subjects	Control group risk [baseline risk]	Risk difference (95% CI)	Relative risk (95% CI)	Comments
Darougar 1980b (25)	Treatment: oral doxycycline one dose per month for 12 months. Comparison: topical oxytetracycline twice daily for 7 consecutive days every month for 12 months	3 mo. 82 12 mo. 82	76.3% 50.0%	−0.04 (−0.22, 0.15) 0.05 (−0.17, 0.26)	0.95 (0.75, 1.23) 1.09 (0.72, 1.66)	Household treatment
Dawson 1997 (28)	Treatment 1: oral azithromycin (1 dose of 20 mg/kg) Treatment 2: oral azithromycin (1 dose/week for 3 weeks) Treatment 3: oral azithromycin 1 dose every 4 weeks for 6 doses) Comparison: topical oxytet/polymyxin + oral placebo once daily for 5 consecutive days every 28 days for 6 times	2 mo. 160 1 yr. 159	66.7% 57.1%	1 Dose 0.05 (−0.15, 0.25) 3 Doses −0.09 (−0.30, 0.12) 6 Doses −0.03 (−0.23, 0.18) Pooled treatment arm −0.02 (−0.19, 0.14) 1 Dose −0.08 (−0.30, 0.13) 3 Doses −0.14 (−0.35, 0.08) 6 Doses 0.04 (−0.17, 0.26) Pooled treatment arm −0.06 (−0.23, 0.12)	1 Dose 1.08 (0.81, 1.44) 3 Doses 0.86 (0.61, 1.21) 6 Doses 0.96 (0.70, 1.32) Pooled treatment arm 0.97 (0.75, 1.24) 1 Dose 0.85 (0.56, 1.29) 3 Doses 0.76 (0.49, 1.19) 6 Doses 1.08 (0.75, 1.54) Pooled treatment arm 0.90 (0.65, 1.23)	Only active trachoma cases treated
Foster 1966 (42)	Treatment 1: oral sulphamethoxypyridazine once daily for 5 consecutive days every week for 3 weeks Treatment 2: topical tetracycline 3 times daily on 5 consecutive days every week for 6 weeks Comparison: no treatment	3 mo. 218 12 mo. 218	74.5% 61.3%	0.02 (−0.09, 0.14) 0.10 (−0.02, 0.23)	1.03 (0.89, 1.20) 1.16 (0.96, 1.41)	Only active trachoma cases treated
Schachter 1999i (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1g, children 20 mg/kg) Comparison: oxytetracycline once daily for 6 weeks	3 mo. 1825 12 mo. 1941	25.7% 19.6%	−0.12 (−0.16, −0.09) −0.05 (−0.08, −0.02)	0.52 (0.43, 0.64) 0.74 (0.61, 0.90)	Community-wide treatment. Country: Egypt

Study	Treatment/Comparison	Duration, N	%	RD (95% CI)	RR/OR (95% CI)	Notes
Schachter 1999ii (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1 g, children 20 mg/kg) Comparison: oxytetracycline once daily for 6 weeks	3 mo. 1600; 12 mo. 1197	6.1%; 15.7%	−0.01 (−0.04, 0.01); −0.07 (−0.11, −0.03)	0.76 (0.50, 1.15); 0.55 (0.40, 0.75)	Community-wide treatment. Country: The Gambia
Schachter 1999iii (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1 g, children 20 mg/kg) Comparison: oxytetracycline once daily for 6 weeks	3 mo. 2577; 12 mo. 2276	19.2%; 20.6%	0.03 (0.00, 0.06); 0.04 (0.01, 0.07)	1.16 (1.00, 1.36); 1.19 (1.02, 1.40)	Community-wide treatment. Country: Tanzania
Shukla 1966 (43)	Treatment: oral sulphadimethoxine biweekly or weekly dose for 5 months Comparison: sulphafurazole twice daily for 5 consecutive days every month for 5 months	3 mo. 125; 12 mo. 145	85.7%; 56.5%	−0.22 (−0.37, −0.07); −0.13 (−0.29, 0.03)	0.74 (0.61, 0.91); 0.77 (0.55, 1.07)	Treatments were pooled and compared with control
Tabbara 1996 (46)	Treatment: oral azithromycin (20 mg/kg) Comparison: topical tetracycline twice daily for 5 consecutive days per week over 6 weeks	3 mo. 64; 6 mo. 56	37.5%; 34.6%	0.09 (−0.15, 0.33); 0.02 (−0.23, 0.27)	1.25 (0.70, 2.23); 1.06 (0.52, 2.15)	Only active trachoma cases treated

Face washing and health education
Face washing studies

Study	Treatment/Comparison	Duration, N	%	RD (95% CI)	RR/OR (95% CI)	Notes
Peach 1987 (22)	Treatment 1: Tetracycline eye drops daily for one week every month for 3 months Treatment 2: Eye washing daily for 3 months Treatment 3: Tetracycline eye drops plus eye washing Comparison: No treatment	3 mo. 1143	75.8%	Eye drops −0.09 (−0.16, −0.01); Eye washing 0.02 (−0.06, 0.10); Eye drops + eye washing −0.07 (−0.15, 0.01)	Eye drops 0.88 (0.79, 0.98); Eye washing 1.02 (0.93, 1.13); Eye drops + eye washing 0.91 (0.82, 1.01)	No meta-analysis conducted as trials differed in several respects. All participants lost to follow up assumed to have follicles at the end of the study and intention to treat principle was applied in the analysis of results.
West 1995 (17)	Treatment: Face washing promotion combined with mass tetracycline ointment Comparison: Mass tetracycline ointment only.	12 mo. 1417	Pair 1 60% Pair 2 50% Pair 3 65%		OR: 0.81 (0.42, 1.59)	Tetracycline ointment was administered topically once daily for 30 days. Relative risk and risk differences approximated from percentages. Differences are not statistically significant. However, authors do not report the RR and RD values.

(continued overleaf)

Table II. (*Continued*)

Author/year	Intervention and comparison	No. subjects	Control group risk [baseline risk]	Risk difference (95% CI)	Relative risk (95% CI)	Comments
Health Education						
Resnikoff 1995 (23)	Treatment: Health education one week per month for 6 months. Comparison: No health education	6 mo. 1810	7.1%	−0.03 (−0.06, 0.00)	0.59 (0.34, 1.04)	Comparisons were only done between one village and the control village.
Edwards 2006 (18)	Treatment: Communities targeted by NGOs and SAFE strategy (surgery, antibiotics, face washing, and environmental improvements) which received radio broadcasts and may have received video screenings. Comparison: Communities received radio broadcasts only	12 mo. 1842	66.7%	−0.04 (−0.09, 0.01)	0.94 (0.87, 1.01)	
Environmental studies						
Fly control interventions						
Emerson 1999 (15)	Treatment: spray with 0.175% volume to volume deltamethrin up to 20 m outside each village. Twice weekly in the wet season and once weekly in the dry season for 3 months. Comparison- No insecticide spray.	3 mo. 1134	15.7%	−0.10 (−0.10, −0.09)*	0.39 (0.27, 0.56)*	Both Emerson 1999 and Emerson 2004 assess insecticide spray but no meta-analysis conducted because of significant clinical heterogeneity.
Emerson 2004 (1)	Treatment: Spray with water soluble permethrin for 6 months. Comparison: No intervention	6 mo. 4850	6.2%	−0.04 (−0.04, −0.03)*	0.44 (0.33, 0.59)*	
West 2006 (16)	Intervention: All members of intervention balozi were given a single dose of azithromycin and then households and surrounding areas were sprayed with insecticide (10% permethrin in water) throughout the year. Comparison: All members of control balozi were given a single dose of azithromycin.	6 mo. 229	33%	−0.13 (−0.25, −0.02)*	0.60 (0.37, 0.96)*	Observations were on children aged <8 years.
		12 mo. 206	44%	−0.01 (−0.15, 0.13)*	0.97 (0.70, 1.34)*	Observations were on children aged <8 years.
Latrine provision						
Emerson 2004 (1)	Treatment: Latrine provision Comparison: No intervention	6 mo. 2836	6.2%	−1.21 (1.22, −1.20)*	0.72 (0.53, 0.96)*	Analysis was by cluster, and not individual n = 7 in each group.

* The RR and RD is calculated in this review at the individual level without adjusting for clustering.

Table III. Severe trachoma

Author/ year	Intervention and comparison	No. subjects	Control group risk	Risk difference	Relative risk (95% CI)	Comments
Bowman 2000 (24)	Treatment: oral azithromycin (single dose 20 mg/kg) Comparison: Unsupervised 6 week course of tetracycline twice daily	6 mo. 23	75%	−0.55 (−0.91, −0.19)	0.27 (0.09, 0.79)	Only those with severe trachoma at baseline were included
West 1995 (17)	Treatment: Face washing promotion combined with mass tetracycline ointment Comparison: Mass tetracycline ointment only. Tetracycline ointment was administered topically once daily for 30 days.	12 mo. 1417 (total number of participants in trial)	Information not available			This paper only presents odds ratios for the intervention villages. Severe trachoma: 0.62 (0.40, 0.97). Any trachoma: 0.81 (0.42, 1.59)
Schachter 1999i (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1 g, children 20 mg/kg) Comparison: oxytetracycline once daily for 6 weeks	12 mo. 1938	4.6%	0.01 (0.00, 0.03)	1.37 (0.91, 2.07)	Community-wide treatment. Country: Egypt
Schachter 1999ii (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1 g, children 20 mg/kg) Comparison: oxytetracycline once daily for 6 weeks	12 mo. 1197	7.1%	0.00 (−0.02, 0.01)	0.83 (0.40, 1.70)	Community-wide treatment. Country: The Gambia
Schachter 1999iii (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1 g, children 20 mg/kg) Comparison: oxytetracycline once daily for 6 weeks	12 mo. 2213	8.4%	0.03 (0.01, 0.04)	1.74 (1.17, 2.58)	Community-wide treatment. Country: Tanzania

oral antibiotics at any dose or frequency, face washing promotion with or without antibiotic treatment, fly control, and health education. Interventions for trichiasis included bilamellar tarsal rotation, tarsal advance and rotation, eversion splinting, tarsal advance, tarsal grooving, electrolysis, cryotherapy, epilation, posterior lamellar tarsal rotation, tetracycline and azithromycin at surgery, providing surgery in participants' own village, and surgery by non-ophthalmologist integrated eye care workers.

Table IV. Chlamydia trachomatis infection

Author/ year	Intervention and comparison	No. subjects	Control group risk	Risk difference	Relative risk (95% CI)	Comments
Antibiotic versus control						
Darougar 1980b (25)	Treatment 1: topical oxytetracycline twice daily for 7 consecutive days every month for 12 months	3 mo. 129	14.9%	−0.05 (−0.17, 0.07)	0.66 (0.25, 1.69)	Intervention arms are pooled
	Treatment 2: oral doxycycline one dose per month for 12 months Comparison: vitamin pills 1 dose per month for 12 months	12 mo. 129	19.1%	−0.14 (−0.26, −0.02)	0.25 (0.08, 0.78)	
Dawson 1969i (26)	Treatment: oral trisulfapyrimidines 3 daily during 3 consecutive weeks Comparison: lactose-placebo 3 daily for 3 consecutive weeks	3 mo. 36	77.8%	−0.17 (−0.46, 0.13)	0.79 (0.50, 1.22)	

Table IV. (*Continued*)

Author/ year	Intervention and comparison	No. subjects	Control group risk	Risk difference	Relative risk (95% CI)	Comments
Dawson 1969ii (26)	Treatment: oral trisulfapyrimidines 3 daily during 3 consecutive weeks Comparison: lactose-placebo 3 daily for 3 consecutive weeks	3 mo. 29	71.4%	−0.25 (−0.59, 0.10)	0.65 (0.35, 1.23)	
Hoshiwara 1973 (27)	Treatment: oral doxycycline once daily for 5 consecutive days every week up to 28 doses in 40 days Comparison: placebo once daily for 5 consecutive days every week up to 28 doses in 40 days	3 mo. 103	53.7%	−0.05 (−0.24, 0.15)	0.81 (0.63, 1.04)	
Oral versus topical antibiotic						
Dawson 1997 (28)	Treatment 1: oral azithromycin (1 dose of 20 mg/kg)	3 mo. 160	7.3%	−0.03 (−0.12, 0.06)	0.57 (0.14, 2.30)	
	Treatment 2: oral azithromycin (1 dose/week for 3 weeks)	12 mo. 138	15.2%	−0.08 (−0.22, 0.05)	0.44 (0.15, 1.29)	
	Treatment 3: oral azithromycin 1 dose every 4 weeks for 6 doses) Comparison: topical oxytet/polymyxin + oral placebo once daily for 5 consecutive days every 28 days for 6 times					
Schachter 1999i (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1g, children 20 mg/kg)	3 mo. 1782	4.5%	−0.04 (−0.05, −0.02)	0.22 (0.11, 0.44)	Community-wide treatment
	Comparison: oxytetracycline once daily for 6 weeks	12 mo. 1914	6.2%	−0.03 (−0.05, −0.01)	0.48 (0.31, 0.74)	
Schachter 1999ii (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1 g, children 20 mg/kg)	3 mo. 1453	13.6%	−0.07 (−0.10, −0.04)	0.51 (0.37, 0.70)	Community-wide treatment
	Comparison: oxytetracycline once daily for 6 weeks	12 mo. 1126	13.5%	−0.05 (−0.09, −0.01)	0.62 (0.44, 0.87)	
Schachter 1999iii (21)	Treatment: oral azithromycin once a week for 3 weeks (adults 1 g, children 20 mg/kg)	3 mo. 2538	6.2%	−0.02 (−0.04, 0.00)	0.68 (0.49, 0.95)	Community-wide treatment
	Comparison: oxytetracycline once daily for 6 weeks	12 mo. 2236	8.0%	0.00 (−0.02, 0.02)	1.01 (0.76, 1.35)	
Darougar 1980b (25)	Treatment 1: topical oxytetracycline twice daily for 7 consecutive days every month for 12 months	3 mo. 82	2.6%	0.13 (0.01, 0.25)	6.05 (0.78, 46.95)	
	Treatment 2: doxycycline one dose per month for 12 months Comparison: vitamin pills 1 dose per month for 12 months	12 mo. 82	2.6%	−0.03 (−0.05, 0.00)	2.59 (0.28, 23.88)	

Active Trachoma

Antibiotics and active trachoma

One review examined the antibiotic arm of the SAFE strategy by measuring the effects of antibiotic treatment on both active trachoma and *Chlamydia trachomatis* infection of the conjunctiva (defined as a positive nucleic acid amplification test result from an ocular swab) (2). There were 15 included trials that randomized 8,678 participants and looked for the presence of active trachoma at either three or 12 months after starting treatment. The review divided the analysis of studies into those who received any antibiotics (topical or oral) versus placebo/no

treatment and those who received oral versus topical antibiotics. Trial participants were usually resident in areas where trachoma is endemic, but were from a number of different countries and resided in various locations, including villages and boarding schools. One set of studies randomized entire communities rather than individuals to the intervention (21). The WHO currently recommends either topical tetracycline or oral azithromycin for individual and mass treatment of trachoma, although the studies have used various antibiotic treatment regimens.

(A) Antibiotics versus placebo/no treatment Summary statistics could not be performed in studies where oral and topical antibiotics were compared with placebo or with no treatment due to the degree of heterogeneity.

(I) Active trachoma at three months

When measuring the effect of treatment with antibiotics on active trachoma at three months, the point estimates were consistent with the antibiotics having an effect with a risk reduction. The results were as follows:

(a) any antibiotic
  (i) RR < 1 in six trials (P < 0.05)
  (ii) RR < 1 in two trials (non significant (n.s.))
  (iii) RR > 1 in one trial (n.s.)
(b) oral antibiotics
  (i) RR < 1 in three trials (P < 0.05)
  (ii) RR < 1 in two trials (n.s.)
  (iii) RR > 1 in one trial (n.s.)
(c) topical antibiotics
  (i) RR < 1 in four trials (P < 0.05)
  (ii) RR < 1 in one trial (n.s.)
  (iii) RR > 1 in one trial (n.s.)

(II) Active trachoma at 12 months

The relative risks of study participants exhibiting active trachoma at 12 months after treatment with antibiotic were consistent with there being no effect of antibiotics at 12 months. The results are as follows:

(a) any antibiotic
  (i) RR < 1 in three trials (P < 0.05)
  (ii) RR > 1 in three trials (n.s.)
(b) oral antibiotics
  (iii) RR < 1 in one trial (P < 0.05)
  (iv) RR < 1 in one trial (n.s.)
  (v) RR > 1 in one trial (n.s.)
(c) topical antibiotics
  (vi) RR < 1 in two trials (P < 0.05)
  (vii) RR < 1 in two trials (n.s.)

(B) Oral antibiotics versus topical antibiotics When azithromycin or other oral antibiotics were compared with topical tetracycline or other topical antibiotics, the data suggest that oral antibiotics are neither more nor less effective than topical antibiotic treatment in reducing the prevalence of active trachoma after three or 12 months.

When oral azithromycin versus topical tetracycline were compared, the point estimates of relative risk of active trachoma at three months were as follows:

(i) RR < 1 in two trials (P < 0.05)
(ii) RR < 1 in two trials (n.s.)
(iii) RR > 1 in two trials (n.s.)

When other oral and topical antibiotics were compared, the relative risks of active trachoma at three months were as follows:

(i) RR < 1 in one trial (P < 0.05)
(ii) RR < 1 in one trial (n.s.)
(iii) RR > 1 in one trial (n.s.)

When oral azithromycin versus topical tetracycline were compared, the point estimates of relative risk of active trachoma at 12 months were as follows:

(i) RR < 1 in two trials (P < 0.05)
(ii) RR < 1 in one trial (n.s.)
(iii) RR > 1 in one trial (n.s.)

When other oral and topical antibiotics were compared, the relative risks of active trachoma at 12 months were as follows:

(i) RR < 1 in one trial (n.s.)
(ii) RR > 1 in two trials (n.s.)

All of the trials were of poor to moderate quality and intention to treat analysis was not performed in most of them.

Face washing and active trachoma

There were only two trials included in the face washing review. They employed different interventions and measured different outcome measures and therefore, meta-analysis was deemed inappropriate.

Face washing promotion combined with mass tetracycline ointment versus mass tetracycline ointment only In the one study that included this comparison, three pairs of villages were recruited and one of each pair randomly assigned to tetracycline eye ointment only, with the other assigned to combined intervention of tetracycline eye ointment plus a community-based behaviour change program to promote face washing (17). All pre-school children in all villages were screened for clinical signs of trachoma at baseline and after 12 months. In one pair of villages at 12 months, the prevalence of active trachoma (WHO grade TF) was lower in the village that received the combination of face washing and antibiotics (55%) than the village that received antibiotics alone (60%). In a second pair, the same trend occurred and lower levels of active trachoma were found in the combination village (40%) than the antibiotic alone village (50%). In the third village, in which there had been poor uptake of the behaviour change program, statistically similar levels of active trachoma were seen in the combination village (70%)

Table V. Recurrence of trachoma trichiasis

Author/year	Intervention and comparison	No. subjects	Control group risk [trichiasis at follow-up]	Risk difference	Relative risk (95% CI)	Comments
Surgery technique Adamu 2002 (29)	1) Bilamellar Tarsal Rotation (BTR) 2) Tarsotomy (Transverse Tarsotomy and lid margin Rotation = TTR)	3 mo. 153 patients (256 eyes)	Minor trichiasis 4.9% Major trichiasis 16.0%	Minor trichiasis (TTR as control) 0.06 (−0.07, 0.18) Major trichiasis (TTR as control) −0.06 (−0.16, 0.05)	Minor trichiasis (TTR as control) 2.12 (0.38, 11.9) Major trichiasis (TTR as control) 0.65 (0.29, 1.44)	
Reacher 1990 (30)	Intervention: Bilamellar tarsal rotation (BTR) Controls: 1) Tarsal grooving (TG) 2) Tarsal advance and rotation (TAR) 3) Eversion splinting (ES) 4) Tarsal advance (TA)	Mean follow up per group 7.4 to 8.8 mo. 1) 76 eyes 2) 65 eyes 3) 65 eyes 4) 82 eyes	1) 88.6% 2) 54.2% 3) 70.8% 4) 73.2%	1) −0.31 (−0.52, −0.11) 2) −0.21 (−0.45, 0.02) 3) −0.37 (−0.60, −0.14) 4) −0.37 (−0.56, −0.17)	1) 0.35 (0.17, 0.75) 2) 0.53 (0.27, 1.06) 3) 0.32 (0.15, 0.68) 4) 0.32 (0.15, 0.66)	
Reacher 1992 (31)	Minor Trichiasis Trial 1) Bilamellar tarsal rotation 2) Electrolysis 3) Cryotherapy Major Trichiasis Trial 1) Bilamellar tarsal rotation 2) Tarsal advance and rotation	9 mo. follow-up 166 eyes 9 or 21 mo. after follow-up 199 eyes	62.3% 45.5%	−0.51 (−0.63, −0.38) −0.27 (−0.40, −0.15)	0.19 (0.09, 0.40) 0.40 (0.25, 0.64)	Minor Trichiasis Major Trichiasis
Non-operative treatment Graz 1999 (32)	1) Sticking plaster 12 weeks 2) Sticking plaster 8 weeks and epilation 4 weeks 3) Epilation only	12 weeks 39	100%	12 weeks plaster vs. Epilation −0.71 (−0.92, −0.51)	12 weeks plaster vs. Epilation 0.29 (0.15, 0.56)	100% Coverage
Antibiotic treatment Burton 2005 (33)	1) Unilamellar surgery accompanied by unsupervised tetracycline eye ointment twice a day for 2 weeks as well as single dose azithromycin to the patient at surgery and six months. Family members were also treated with azithromycin at both occasions.	6 mo. 410 12 mo. 426	26.1% 41.4%	0.11 (0.02, 0.20) 0.00 (−0.10, 0.09)	1.43 (1.07, 1.91) 0.99 (0.79, 1.25)	Median ages of the groups are 57.3 and 57.2

Study	Interventions	Timing	N	Recurrence %	Mean difference (95% CI)	Effect measure (95% CI)	Notes
West 2006 (19)	1) Trichiasis surgery followed by 1g of oral azithromycin (20 mg/kg up to 1g) for the patient or single-dose azithromycin for the patient and all household members 2) Trichiasis surgery followed by twice per day topical tetracycline for six weeks 2) Unilamellar surgery and unsupervised tetracycline eye ointment twice a day for 2 weeks	When recurrence was detected or at 12 mo.	1406	6.8%	−0.03 (−0.06, −0.01)	0.53 (0.33, 0.85)	Mean ages were 50 (household azithromycin), 48.5 (patient only azithromycin), and 48 (tetracycline)
Zhang 2006 (20)	1) Bilamellar tarsal rotation surgery and a single dose of azithromycin immediately after surgery 2) Bilamellar tarsal rotation surgery and placebo administered after surgery * All patients with active trachoma or inflammatory trachoma received tetracycline ointment at baseline and follow up.	6 mo. 12 mo.	111 114	27.6% 28.1%	−0.01 (−0.18, 0.15) 0.02 (−0.15, 0.18)	0.96 (0.52, 1.77) 1.06 (0.60, 1.89)	81.7% of population was aged >40 years.
Surgery setting Bowman 2000 (34)	1) Surgery in village 2) Surgery in health centre	3 mo.	89	6.3%	0.03 (−0.09, 0.14)	1.40 (0.29, 6.83)	Median age was 53 and 56 years. Coverage was 66% in the village and 44% in the health care centres.
Personnel performing surgery Alemayehu 2004 (35)	1) Bilamellar tarsal rotation carried out by integrated eye worker 2) Bilamellar tarsal rotation carried out by ophthalmologist (control)	3 mo. 6 mo.	731	12.1% At six months, authors did not report specific recurrence rates. Authors reported no statistical difference in recurrence between the 2 types of surgeons.	−0.03 (−0.07, 0.02)	0.78 (0.51, 1.18)	3.2% of the population were children younger than 15 years.

and in the antibiotics alone village (65%). There was an overall reduction in the odds of trachoma (WHO grade TF) in the combined combination villages than in the antibiotics alone villages, but this effect was not statistically significant: OR: 0.81 (0.42, 1.59).

Tetracycline eye drops plus eye washing, eye drops alone, eye washing alone versus no treatment   Another study assessed the efficacy of tetracycline drops alone, eye washing alone as well as their use in combination in reducing trachoma infection (22). The relative risks of follicles being seen at three months for each intervention compared to controls were as follows:

(a) Eye drops + eye washing: RR = 0.91 (0.82, 1.01)
(b) Eye washing alone: RR = 1.02 (0.93, 1.13)
(c) Eye drops alone: 0.88 (0.79, 0.98)

The results suggested no statistically significant benefit from tetracycline eye drops and eye washing, or eye washing alone compared to no intervention. A modest benefit from eye drops alone compared to no intervention was reported.

Health education and active trachoma

Two studies measured active trachoma after a health education intervention was delivered. One study found a significant decrease in relative risk associated with health education when compared to no education (23). The intervention included weekly information regarding personal and family hygiene and household sanitation. Another study compared the rate of active trachoma in communities targeted by non-governmental organizations (NGOs) and the SAFE strategy that received radio broadcasts and video screenings against communities who were not targeted by NGOs and who only received radio broadcasts (18). No significant differences in the rate of active trachoma at one year were observed between communities targeted by the SAFE strategy and those who were not, but a small significant reduction was observed at the one year follow up compared to the baseline survey (18).

Environmental factors

Three trials assessed the environmental arm of the SAFE Strategy (1,15,16). Emerson *et al.* 2004 looked at the effect of insecticide spray and latrine provision whilst Emerson *et al.* 1999 and West *et al.* assessed insecticide spray only. Meta-analysis was inappropriate due to significant heterogeneity between trials.

Insecticide spray versus no intervention on active trachoma
At three months one study, in which two pairs of villages were recruited and one of each pair randomly assigned to insecticide spray whilst the other was a control, found there to be a prevalence of 6.2% in the intervention villages compared to 15.7% in the control villages (15). The relative risk of active trachoma at

three months was 0.39 (0.27, 0.56) suggesting that insecticide spray significantly reduced the magnitude of active trachoma. In a second study, in which there were seven pairs of insecticide spray and control villages, clinical signs of active trachoma (WHO grade TF) were 55.8% lower in the intervention clusters compared to the control (1). The relative risk was 0.44 (0.33, 0.59) at six months, indicating that community-wide insecticide spray also significantly reduced the magnitude of active trachoma in this study. A third study found a significant reduction (RR: 0.60 (0.37, 0.96)) in active trachoma in children at six months when insecticide spray was used on control neighbourhoods rather than villages (16). When this difference was analysed by neighbourhood, however, a non-significant reduction was observed. There were no significant differences in active trachoma between intervention and control groups at one year in this study.

Latrine provision versus no intervention on active trachoma   The one study that looked at latrine provision found a 29.5% reduction of active trachoma at six months (WHO grades TF and TI combined) in the clusters that received latrines compared to the controls (1). The relative risk was 0.72 (0.53, 0.96) when analysed at the individual level, although the confidence interval included 1.0 when analysed at the community level.

Severe trachoma (WHO grade TI)

Five trials captured data on the prevalence of severe trachoma (WHO grade TI). Detailed statistics from these studies are found in Table III. One trial used a face washing intervention while the others used antibiotics (17,21,24). In the face washing trial the overall prevalence of severe trachoma was lower in children from the village from each of the three pairs that had received a combination of face washing and antibiotics (8%) than the villages that had received antibiotic alone (14%) at 12 months. This difference was found to be statistically significant: OR: 0.62 (0.40, 0.97). In the other studies the efficacy of oral azithromycin was compared to that of tetracycline in three different countries, Egypt, The Gambia and Tanzania (21,24). One study found a significant effect of azithromycin over tetracycline at six months, whilst another study found no difference between azithromycin and tetracycline at 12 months (21,24).

Ocular infection with *Chlamydia trachomatis*

Antibiotics versus placebo or no treatment

When looking at *C. trachomatis* infection at three months, the point estimates in all four trials suggested a reduced risk in the antibiotic group (2,25,26,27). However, none found a significant difference between the pooled antibiotic and control groups (2). Only one trial reported outcomes at 12 months and found a significantly reduced risk in the antibiotic group (25).

Oral antibiotics versus topical antibiotics

There were five trials assessing oral versus topical antibiotics on *C. trachomatis* infection. At three months, a significant reduction in relative risk was found in three of the four trials that compared azithromycin to a topical antibiotic whilst the fourth showed a non-significant reduction (21,28). At 12 months, there was a significant reduction in two trials, Dawson *et al*. found some reduction and Schachter *et al*. showed some increase (21,28). The fifth trial compared oral doxycycline with topical oxytetracycline and found a non-significant increase at both three and 12 months (25).

Process indicators

Active and severe trachoma and evidence of infection with *Chlamydia trachomatis* are the endpoints of most trials and have been discussed above. However, the reviews also assessed process indicators (clean faces and fly-eye contact) that are not in the tables and are reported in the narrative below.

Clean faces

In the only face-washing study that addressed this outcome, the percentage of children with clean faces increased in both the combination face washing plus antibiotic villages and the antibiotic alone villages, in comparison to the controls (17). The effect was greater in the face washing plus antibiotic combination villages compared to the antibiotic alone villages: face washing and antibiotic combination; 18% at baseline; to 33% at six months; and 35% at 12 months, compared to the antibiotic alone group: 19% at baseline; 30% at six months; and 26% at 12 months. The difference between the groups was statistically significant (P < 0.05).

Fly-eye contact

Two studies measured frequencies of fly-eye contact as a process indicator (1,15). The first study reported that fly-eye contact by the trachoma vector, *Musca sorbens*, was decreased by 96% with the community-wide spraying of deltamethrin in comparison to controls. The second study reported a reduction in fly-eye contact by *Musca sorbens* of 88% with community-wide insecticide spraying with permethrin, and a 30% reduction in villages that had received latrine provision compared to controls. All three reductions were statistically significant (P < 0.05).

Trichiasis surgery

The antibiotic, face washing and environmental components of the SAFE strategy are used to control *Chlamydia trachomatis* transmission. The surgery component aims to correct trachomatous trichiasis, which occurs as a result of repeated cycles of infection and resolution of ocular *Chlamydia* infection; is not, in itself, caused by current active trachoma. The primary outcome of surgery trials is usually the rate of recurrence of trichiasis after surgery. See Table V for results from the surgery trials.

Surgery techniques

In one study, there was no significant difference in the recurrence rate at three months between the bilamellar tarsal rotation and transverse tarsotomy and lid margin rotation (similar to Trabut method) (29). In another study, bilamellar tarsal rotation was no more effective than tarsal advance and rotation RR: 0.53 (0.27, 1.06), tarsal grooving RR: 0.35 (0.17, 0.75), eversion splinting RR: 0.32 (0.15, 0.68) or tarsal advance RR: 0.32 (0.15, 0.66) (30). In a third study, however, bilamellar tarsal rotation was more effective in treating those with minor trichiasis (one to five lashes touching the eye) than destroying the lashes by cryotherapy or electrolysis RR: 0.19 (0.09, 0.40) (31). In those with major trichiasis (six or more lashes touching the eye), bilamellar tarsal rotation was more effective than tarsal advance and rotation RR: 0.40 (0.25, 0.64). There was insufficient enrolment to assess these outcomes in those with defective lid-closure.

Non-operative treatment of trichiasis

At three months, one study found that using sticking tape alone was significantly more effective than epilation alone RR: 0.29 (0.15, 0.56) (32). The difference between epilation alone and sticking tape followed by epilation was not statistically significant (P = 0.5). The authors reported good clinical status as: no lashes touching the eyeball, complete lid closure, no conjunctival hyperaemia and no unplanned treatment necessary during follow up.

Post-operative antibiotic treatment

Three trials have examined the effect of post-operative azithromycin on the recurrence of trichiasis (19,20,33). Two of these were published subsequent to the last update of the surgery review (20,19). One trial found no difference in trichiasis recurrence rates between patients who had received post operative azithromycin (41.2%) and those who did not (41.4%) when assessed at 12 months (33). Another trial found no difference in the cumulative incident trichiasis recurrence rates between the azithromycin treated group (29.8%) and the placebo group (28.1%) at 12 months (20). Additional sub-set analysis suggested that there may be some benefit from azithromycin for individuals who had major trichiasis. The third and largest study concluded that a single dose of azithromycin was associated with a 33% reduction in trichiasis recurrence, compared with a 6-week regimen of topical tetracycline (19).

Surgery setting

One study that assessed people with major trichiasis found that there were similar success rates (no recurrence) between patients randomized to village-based surgery (91%) and health centre-based surgery (94%) at three months (34). In another study, the trichiasis recurrence rates among patients who had surgeries conducted by an ophthalmologist was 12.7%, compared to 9.9% among patients operated by an integrated eye care worker at three months (35). The difference was small and did not achieve statistical significance, OR: 1.32 (0.83, 2.11). At six months, the difference between recurrence rates was again not statistically significant.

Visual acuity as a surgical outcome

There were four trials in the surgery review that assessed visual acuity following surgical and non-operative interventions. One trial reported that trichiasis surgery improved vision but the degree of improvement was not quantified; however it was not statistically significant (29). Another study found a statistically significant improvement of about half a line of Snellen Visual Acuity (P < 0.0001) following surgery for major trichiasis, but not those with minor trichiasis (31). A third study reports an overall improvement in visual acuity of 0.14 LogMAR units 12 months after surgery (P < 0.0001), however the data were not reported by randomization groups (33). Follow-up data were not presented in the fourth study (35).

Uptake of surgical intervention

The uptake of intervention was only recorded in three studies. One study reports that 38 participants refused random allocation, with the refusal rate greater in the defective lid closure group (31). Another study did not record attendance for treatment but mentions that there were compliance issues (32). The third study states that surgical uptake was higher for those randomized to village-based surgery (66%) than those who were randomized to the health centre-based surgery (44%) (34).

Quality of life following surgery

Burton *et al.* examined quality of life after surgery, although this was not analyzed by randomization group (33). Among all study participants, 77% reported an improvement in vision and 94% felt more comfort in the operated eye.

Economic evaluation of surgery

Journey time and cost of travel was significantly less for clusters randomized to community-based surgery than for those randomized to health centre-based surgery (34).

Adverse events related to surgery

Four studies reported on adverse events. No details were given but one study stated that lid-notching and pyogenic granuloma were more common in the bilamellar than the posterior lamellar tarsal rotation operations (29). The second study reported one case of over-correction following bilamellar rotation and granulomas in two lids (30). The third study reported two cases of over-correction following bilamellar tarsal rotations but none in the tarsal advance and rotation group (31). The fourth study reported that patients found epilation to be less comfortable than sticking tape (P = 0.002) among those with unilateral trichiasis (32).

Discussion

Trichiasis surgery

The authors of the Cochrane review on interventions for trachomatous trichiasis concluded that the most successful operation type involves full thickness incision of the tarsal plate. Two main procedures are currently in use in most trachoma endemic settings: the bilamellar tarsal rotation and the unilamellar tarsal rotation. No convincing evidence was found that one procedure is better than the other, although the unilamellar technique varied between studies. For minor trichiasis there is evidence that tarsal rotation surgery is more effective than non-surgical techniques including cryotherapy and electrolysis. For mild trichiasis, however, epilation is commonly performed and has never been formally compared to surgery.

The review found good evidence that tarsal rotation surgery can be performed equally well by appropriately trained ophthalmic nurses and ophthalmologists. This is of great programmatic importance as in most trachoma endemic countries the number of ophthalmologists is very limited and the backlog of trichiasis surgery far exceeds what could be delivered by these physicians alone. The review also found evidence that surgery performed at community (village) level had equivalent outcomes to that performed at a health centre. However, the uptake was higher for village-based surgery, which is an important observation as in many endemic regions the uptake of surgery is low.

The three studies investigating whether post-operative azithromycin treatment improves surgical outcome have provided mixed results. Two were published after the last update of the review (19,20). Two studies found no convincing evidence that azithromycin reduces trichiasis recurrence (20,33). The third and largest study did find a significant reduction in trichiasis recurrence with azithromycin (16). This may have been because the study was conducted in a region where *C. trachomatis* infection is hyperendemic. However, no difference in the prevalence of chlamydial infection was demonstrated between the treatment groups, leaving open the question of how

the antibiotic affected the outcome. The additional antibiotic treatment of family members did not confer any extra benefit. Overall, it is difficult to reach any definite conclusions about the effect of azithromycin on trichiasis recurrence, particularly in an operational (rather than research) setting.

Antibiotics

The authors of the review of Antibiotics for Trachoma found only limited evidence that antibiotics reduce the prevalence of active trachoma. There were two main types of study. The first was a very heterogeneous group of trials of antibiotics versus placebo, in which, overall, the results are consistent with a modest beneficial effect on active trachoma at three months but not at one year of follow-up. However, most of these studies targeted treatment to individuals with signs of active disease. Therefore, the full potential of any antibiotic on controlling trachoma has probably never been tested in a placebo-controlled trial, as the impact of treatment in these studies is likely to have been greatly undermined by reinfection from untreated members of the community.

The second group of studies compared oral with topical antibiotics. The authors of the review concluded that there was no evidence of a difference in the results between topical and oral antibiotic treatment. We agree with this conclusion with respect to clinically active disease, but differ in our interpretation with respect to *C. trachomatis* infection. We consider that the evidence supports the view that oral azithromycin is more effective at clearing infection than topical treatment. However, the clinical significance of this finding is currently unclear because in these and other studies the inflammatory disease persists. One possible explanation for this disparity is that the resolution of the clinical signs of active trachoma has been found to lag behind the resolution of infection (36).

Face washing

The authors of the Cochrane review on the promotion of face washing for prevention of active trachoma conclude that from the available data there is some evidence that face washing, when combined with topical tetracycline eye ointment, can be effective in reducing severe trachoma. They additionally conclude that the current evidence does not support a beneficial effect of face washing alone, or in combination with topical tetracycline eye ointment, in reducing the prevalence of active trachoma (14). Since the review was written there have been no additional clinical trials, although clean face, which has a variety of definitions, has been included in many observational studies and cross-sectional surveys since the publication of the original Tanzania 'clean face' study (17). The evidence from these studies has been summarized in a number of traditional reviews (10,11,37). In the absence of a standardized definition of 'clean face' and without an

agreed-upon methodology of when and how it should it measured (the frequency of the components usually used to define a clean face such as food or dust on the face and the presence of ocular and nasal discharge are strongly dependent on the time of day, season and age of the child) it is difficult to interpret the findings of the risk factor studies. The difficulty in interpretation is exacerbated by the fact that two of the components of an unclean face (ocular and nasal discharge) may be a result of active trachoma. All of this notwithstanding, the results of the original trial on severe trachoma, and the observational studies are considered to be sufficient to warrant the continued inclusion of behaviour change communication and promotion of personal grooming to promote clean face as one of the pillars of the SAFE strategy (17).

Environmental change

The authors of the Cochrane review on the E component of SAFE conclude that there is evidence that insecticide spray as a fly control measure reduces trachoma significantly, that latrine provision as a fly control measure has not demonstrated significant trachoma reduction, and that health education may be effective in reducing trachoma. The authors note that there is a dearth of data to determine the effectiveness of all aspects of environmental sanitation in the control of trachoma. Given the shortage of data available in the review (shown again in Table II) and the heterogeneity of study design, a meta-analysis was not conducted. In the absence of any well-conducted intervention trials, there was no reference to the role of water provision in trachoma control in the review, despite access to water being one of the major areas of implementation for control programs.

Since the publication of the Cochrane review, two new studies have been conducted that contribute additional data (16,18). Edwards *et al.* examined the impact of health education through radio broadcasts alone (control), radio plus routine non-governmental organization (NGO) program activities (standard), and radio plus NGO activities plus video (18). There was a small and statistically significant reduction in the prevalence of clinical signs of trachoma in all the communities in the study, but no difference between the three arms. The study lacked a true control arm in which there had been no trachoma intervention, so the observed reduction in prevalence cannot be ascribed with certainty to the health education. West *et al.* examined the effect of insecticide spray for fly control after mass antibiotic treatment in an area of central Tanzania hyperendemic for trachoma (16). The insecticide spray successfully and effectively controlled eye-seeking flies, although there was no statistically significant effect on either clinical signs of trachoma or prevalence of ocular swabs positive for *C. trachomatis* at six or 12 months.

The Cochrane review references a number of traditional reviews of the literature on the F and E

components of SAFE (10,11,38,39). Mabey *et al.* (1992), Mabey *et al.* (2003), and Kuper *et al.* also include useful discussion on the F and E components (37,40,41). These non-systematic reviews focus mainly on the numerous observational studies on trachoma. Although it should be noted that trachoma has disappeared from Europe and North America, and now from parts of the Middle East, as a result of improved living conditions and not as a result of programs based on antibiotic distribution or surgery, the interventions for F and E currently being adopted in endemic areas have not been rigorously tested. Of note, there have been no clinical trials of improving access to water, use of latrines, hygiene promotion, trachoma health education, village cleaning, or moving domestic animals away from living quarters, all of which are currently being used as trachoma control measures in one or more countries.

Conclusions

Implications for practice

The control of blinding trachoma is based on the WHO endorsed integrated SAFE strategy. Whilst it is not possible to state that there are sufficient rigorous clinical trial data to support or refute the use of the SAFE strategy for blindness prevention through trachoma control in its entirety, there is some good evidence for each of the separate components.

There is a reasonably good evidence base to guide practice in the surgical management of trachomatous trichiasis. Surgery should involve a full thickness incision and rotation of the terminal portion of the tarsus. Surgery can be safely and effectively performed by appropriately trained ophthalmic nurses. Results can be equally good for surgery performed at the community level, which can significantly improve uptake of this intervention. Results of the post-operative use of azithromycin are mixed. Given the frequent conjunctival bacterial infection in people with trichiasis, it is appropriate to use some form of post-operative antibiotic.

The evidence for antibiotics in trachoma control is consistent with a modest risk reduction in clinically active trachoma at three months post treatment, but not at twelve months. The data suggest that oral antibiotics have a greater effect on *C. trachomatis* infection than topical treatment at three months and possibly one year. They appear to have an equivalent effect on clinically active trachoma. The impact of mass community–wide treatment may be much greater than treatment targeted at individuals with disease. However, this has not been formally assessed by a randomized placebo-controlled trial. It should be noted that the studies of mass azithromycin treatment used three doses as opposed to the current WHO recommendation of a single annual dose (21). Whether these regimens are equally effective is unknown. In practice, the current recommendation that trachoma be treated with either topical tetracycline or oral azithromycin is unaffected by this review. There are, however, major gaps in the evidence on which to base recommendations for the targeting, frequency and duration of antibiotic treatment.

For the F and E components, there is evidence that face washing in conjunction with antibiotics has an effect on severe trachoma, and that fly control with insecticide spray reduces active trachoma. In terms of process, face washing can increase the prevalence of clean face and latrine promotion can reduce the frequency of fly-eye contact. Operationally, the inclusion of activities that support face washing and fly control are warranted. These include hygiene promotion, water provision, fly spraying, latrine promotion and village cleaning.

Implications for research

Each of the components of the SAFE strategy has been tested in isolation, but the impact of the full strategy on blindness prevention has never been tested. It would now be ethically improper, however, to conduct a longitudinal study of the impact of SAFE in comparison to controls who were screened, but not included in implementation activities. Fortunately, rigorous impact assessments of existing implementation programs, in which there are good quality baseline and follow-up data, coupled with monitoring data giving an insight to the intensity of the interventions delivered, should be adequate. The A, F and E components of the SAFE strategy share a common objective of contributing to a reduction in transmission of the disease. Clinical trials have usually tested just one of these components at a time, yet it could be anticipated that there is a synergistic effect between them. Clinical trials that are designed to test the hypothesis that there is a synergistic effect of these three components of SAFE such that the effect of antibiotic is enhanced by face washing and environmental improvements (and visa versa) should be conducted. For the individual components of SAFE, a number of less complex operational research studies would enhance the delivery of programs.

Trichiasis surgery

The optimal management of minor trichiasis (one to five lashes touching the eye) is uncertain. Currently both early surgery and epilation are practiced. However, it is unknown whether these are equally effective. A randomized controlled trial of these alternatives would be of programmatic value.

Recurrent trichiasis remains a significant problem which limits the effectiveness of surgery in preventing blindness. There is a need to assess simple approaches to improve the long-term outcomes. For example, absorbable sutures may be superior to the currently used silk. The outcome of surgery varies significantly between surgeons. Therefore, realistic strategies to audit results and improve quality are necessary.

The uptake of surgery is often disappointingly low particularly among women who have a disproportionate burden of disease. The barriers to surgery probably vary and need to be assessed in different regions. Strategies designed to overcome these, especially for women in rural areas, need to be tested.

Antibiotics

Mass antibiotic distribution programs are being set up in many trachoma endemic countries. For ethical reasons, it is now unlikely that there will ever be a trial that investigates the effectiveness of mass antibiotic against a placebo as there is a consensus that the current alternatives (oral azithromycin and topical tetracycline) probably have some effect. However, there is a pressing need for evidence to help optimize their use. It remains uncertain who should be given treatment, how often and for how long. Comparative trials of different distribution strategies are needed. Given that the signs of clinically active trachoma can persist long after the infection has been cleared by antibiotics, there is potentially a role for a simple point of care test for the infection to determine whether a community needs an ongoing treatment program.

Facial cleanliness

The combination of available trial and observational data is considered sufficient to warrant the continuation of hygiene promotion and face washing in trachoma control programs. However a repeat of the original face washing trial that included as process indicators azithromycin treatment and face washing, and that had both clinical and microbiological output, would be extremely useful. The current definitions of clean face include ocular and nasal discharge, which are correlated with both the effect of face washing and the absence of disease. This potential impediment to interpretation will have to be addressed in the study design and selected outcome indicators.

Environmental improvements

Whilst there is evidence that insecticide spray for eye-seeking flies reduces active trachoma, other simple and sustainable strategies to control flies have not been tested. There is a need for large randomized controlled trials of the effectiveness of latrines, village cleaning, and moving animals away from domestic residences for trachoma control. The effect of water provision alone, or in combination with other routine trachoma program interventions, on the prevalence of trachoma has not been formally tested.

Declarations of Interest

None.

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