Cochrane Library

Cochrane Database of Systematic Reviews

Antibiotics versus placebo for acute bacterial conjunctivitis (Review)

Chen YY, Liu ASH, Nurmatov U, van Schayck OCP, Kuo IC

Chen Y-Y, Liu A-HS, Nurmatov U, van Schayck OCP, Kuo IC.
Antibiotics versus placebo for acute bacterial conjunctivitis.
Cochrane Database of Systematic Reviews 2023, Issue 3. Art. No.: CD001211.
DOI: 10.1002/14651858.CD001211.pub4.

www.cochranelibrary.com

TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 7
OBJECTIVES 7
METHODS 7
RESULTS 10
Figure 1. 11
Figure 2. 14
Figure 3. 15
Figure 4. 17
Figure 5. 18
Figure 6. 19
Figure 7. 20
DISCUSSION 21
AUTHORS' CONCLUSIONS 23
ACKNOWLEDGEMENTS 23
REFERENCES 24
CHARACTERISTICS OF STUDIES 29
RISK OF BIAS 68
DATA AND ANALYSES 73
Analysis 1.1. Comparison 1: Antibiotics vs placebo, Outcome 1: Clinical cure at end of therapy - ITT population 76
Analysis 1.2. Comparison 1: Antibiotics vs placebo, Outcome 2: Clinical cure at end of therapy - mITT population 77
Analysis 1.3. Comparison 1: Antibiotics vs placebo, Outcome 3: Clinical cure at test of cure - mITT population 78
Analysis 1.4. Comparison 1: Antibiotics vs placebo, Outcome 4: Clinical cure at end of therapy - ITT population, by treatment duration 79
Analysis 1.5. Comparison 1: Antibiotics vs placebo, Outcome 5: Clinical cure at end of therapy - mITT population, by treatment duration 80
Analysis 1.6. Comparison 1: Antibiotics vs placebo, Outcome 6: Microbiological efficacy at end of therapy - ITT population 81
Analysis 1.7. Comparison 1: Antibiotics vs placebo, Outcome 7: Microbiological efficacy at end of therapy - mITT population 81
Analysis 1.8. Comparison 1: Antibiotics vs placebo, Outcome 8: Microbiological efficacy at test of cure - mITT population 82
Analysis 1.9. Comparison 1: Antibiotics vs placebo, Outcome 9: Treatment incompletion 83
Analysis 1.10. Comparison 1: Antibiotics vs placebo, Outcome 10: Persistent clinical infection 84
Analysis 1.11. Comparison 1: Antibiotics vs placebo, Outcome 11: Persistent clinical infection - by definition 86
Analysis 1.12. Comparison 1: Antibiotics vs placebo, Outcome 12: Persistent clinical infection - by time point 88
Analysis 1.13. Comparison 1: Antibiotics vs placebo, Outcome 13: Treatment-related ocular adverse events - risk ratio 89
Analysis 1.14. Comparison 1: Antibiotics vs placebo, Outcome 14: Treatment-related ocular adverse events - rate ratio 90
Analysis 1.15. Comparison 1: Antibiotics vs placebo, Outcome 15: Treatment-related ocular adverse events - rate difference per 1000 person-days 91
Analysis 1.16. Comparison 1: Antibiotics vs placebo, Outcome 16: Non-ocular adverse events 92
Analysis 2.1. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 1: Clinical cure at end of therapy - mITT population, excluding trials of high risk bias 94
Analysis 2.2. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 2: Microbiological efficacy at end of therapy - mITT population, excluding age < 1 month or no reporting of age limit 95
Analysis 2.3. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 3: Clinical cure at test of cure - mITT population, excluding Karpecki 2009 96
Analysis 2.4. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 4: Microbiological efficacy at test of cure - mITT population, excluding Karpecki 2009 97
Analysis 2.5. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 5: Persistent clinical infection, excluding Karpecki 2009 98
Analysis 2.6. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 6: Treatment-related ocular adverse events - rate ratio, excluding Karpecki 2009 99

Analysis 2.7. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 7: Treatment-related ocular adverse events - risk ratio, excluding Comstock 2012 100
Analysis 2.8. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 8: Treatment-related ocular adverse events - rate difference per 1000 person-days, excluding Comstock 2012 101
APPENDICES 101
WHAT'S NEW 103
HISTORY 103
CONTRIBUTIONS OF AUTHORS 104
DECLARATIONS OF INTEREST 104
SOURCES OF SUPPORT 104
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 104
INDEX TERMS 105

[Intervention Review]

Antibiotics versus placebo for acute bacterial conjunctivitis

Yu-Yen Chen[1,2,3,4,5], Alison Su-Hsun Liu[6,7], Ulugbek Nurmatov[8], Onno CP van Schayck[9], Irene C Kuo[2]

[1]Department of Ophthalmology, Taichung Veterans General Hospital, Taichung, Taiwan. [2]Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [3]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan. [4]School of Medicine, Chung Shan Medical University, Taichung, Taiwan. [5]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan. [6]Department of Ophthalmology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA. [7]Department of Epidemiology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA. [8]Division of Population Medicine, School of Medicine, the National Centre for Population Health and Wellbeing Research, Cardiff University, Cardiff, UK. [9]Department of Family Medicine, Maastricht University (CAPHRI), Maastricht, Netherlands

Contact: Irene C Kuo, ickuo@jhmi.edu.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2023.

Citation: Chen Y-Y, Liu A-HS, Nurmatov U, van Schayck OCP, Kuo IC. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2023, Issue 3. Art. No.: CD001211. DOI: 10.1002/14651858.CD001211.pub4.

ABSTRACT

Background

Acute bacterial conjunctivitis is an infection of the conjunctiva and is one of the most common ocular disorders in primary care. Antibiotics are generally prescribed on the basis that they may speed recovery, reduce persistence, and prevent keratitis. However, many cases of acute bacterial conjunctivitis are self-limited, resolving without antibiotic therapy. This Cochrane Review was first published in *The Cochrane Library* in 1999, then updated in 2006, 2012, and 2022.

Objectives

To assess the benefits and side effects of antibiotic therapy in the management of acute bacterial conjunctivitis.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2022, Issue 5), MEDLINE (January 1950 to May 2022), Embase (January 1980 to May 2022), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases in May 2022.

Selection criteria

We included randomized controlled trials (RCTs) in which any form of antibiotic treatment, with or without steroid, had been compared with placebo/vehicle in the management of acute bacterial conjunctivitis. This included topical and systemic antibiotic treatments.

Data collection and analysis

Two authors independently reviewed the titles and abstracts of identified studies. We assessed the full text of all potentially relevant studies and determined the included RCTs, which were further assessed for risk of bias using Cochrane methodology. We performed data extraction in a standardized manner and conducted random-effects meta-analyses using RevMan Web.

Main results

We included 21 eligible RCTs, 10 of which were newly identified in this update. A total of 8805 participants were randomized. All treatments were topical in the form of drops or ointment. The trials were heterogeneous in terms of their eligibility criteria, the nature of the intervention (antibiotic drug class, which included fluoroquinolones [FQs] and non-FQs; dosage frequency; duration of treatment), the outcomes assessed and the time points of assessment. We judged one trial to be of high risk of bias, four as low risk of bias, and the others as raising some concerns.

Based on intention-to-treat (ITT) population, antibiotics likely improved clinical cure (resolution of clinical symptoms or signs) by 26% (RR 1.26, 95% CI 1.09 to 1.46; 5 trials, 1474 participants; moderate certainty) as compared with placebo. Subgroup analysis showed no differences by antibiotic class (P = 0.67) or treatment duration (P = 0.60). In the placebo group, 55.5% (408/735) of participants had spontaneous clinical resolution by days 4 to 9 versus 68.2% (504/739) of participants treated with an antibiotic. Based on modified ITT population, in which participants were analyzed after randomization on the basis of positive microbiological culture, antibiotics likely increased microbiological cure (RR 1.53, 95% CI 1.34 to 1.74; 10 trials, 2827 participants) compared with placebo at the end of therapy; there were no subgroup differences by drug class (P = 0.60). No study evaluated the cost-effectiveness of antibiotic treatment. Patients receiving antibiotics had a lower risk of treatment incompletion than those in the placebo group (RR 0.64, 95% CI 0.52 to 0.78; 13 trials, 5573 participants; moderate certainty) and were 27% less likely to have persistent clinical infection (RR 0.73, 95% CI 0.65 to 0.81; 19 trials, 5280 participants; moderate certainty).

There was no evidence of serious systemic side effects reported in either the antibiotic or placebo group (very low certainty). When compared with placebo, FQs (RR 0.70, 95% CI 0.54 to 0.90) but not non-FQs (RR 4.05, 95% CI 1.36 to 12.00) may result in fewer participants with ocular side effects. However, the estimated effects were of very low certainty.

Authors' conclusions

The findings of this update suggest that the use of topical antibiotics is associated with a modestly improved chance of resolution in comparison to the use of placebo. Since no evidence of serious side effects was reported, use of antibiotics may therefore be considered to achieve better clinical and microbiologic efficacy than placebo. Increasing the proportion of participants with clinical cure or increasing the speed of recovery or both are important for individual return to work or school, allowing people to regain quality of life. Future studies may examine antiseptic treatments with topical antibiotics for reasons of cost and growing antibiotic resistance.

PLAIN LANGUAGE SUMMARY

What are the benefits and harms of antibiotics for acute bacterial conjunctivitis?

Key messages

Topical antibiotics may improve signs and symptoms as well as bacterial clearance in participants with acute bacterial conjunctivitis. However, some antibiotics can cause unwanted effects on the eyes or eyelids; no evidence suggests that antibiotics cause unwanted effects in other parts of the body.

What is acute bacterial conjunctivitis?

Acute bacterial conjunctivitis is a condition in which the thin layer over the white areas and the inside lining of the eyelids of one or both eyes becomes red and inflamed from a bacterial infection. Acute bacterial conjunctivitis is usually contagious and hence children and working adults are advised to avoid going to school or work when affected. Fortunately, it resolves spontaneously in most cases.

How is acute bacterial conjunctivitis treated?

People with acute bacterial conjunctivitis are often given treatment at the site of the infection, usually as antibiotic eye drops or ointment, to speed recovery. However, the benefits of antibiotics have been questioned when considering they can cause irritation or allergic reaction in and around the eyes or surrounding skin.

What did we want to find out?

We examined whether antibiotics alone or in combination with steroid, can improve signs and symptoms of conjunctivitis or help clear the associated bacteria. We also evaluated whether antibiotics would result in undesirable effects on the eyes.

What did we do?

We performed a systematic review by searching for studies that compared antibiotics in eyedrop, ointment, or tablet form with inactive controls. We summarized these study findings and reported the results together with our level of confidence in them based on how studies were conducted.

What did we find?

We found that antibiotics likely increase clinical cure and microbiological cure after a course of treatment in comparison with placebo. Antibiotic use also is associated with fewer participants stopping their treatment earlier than they are supposed to. However, for some individuals, non-fluroquinolone but not fluoroquinolone antibiotics, may result in more unwanted effects on the eyes or eyelids than placebo though we were very uncertain about the relevant evidence. There was no evidence that antibiotics were associated with systemic side effects such as headache or altered sense of smell.

What are the limitations of the evidence?

The current update focused on adults and children aged one month or older. Therefore, the evidence does not pertain to antibiotic treatment for neonatal conjunctivitis in neonates younger than one month old. We did not find studies that compared effects of the same antibiotics used in short versus long duration. Therefore, the current review was unable to suggest for or against the prescription duration for acute bacterial conjunctivitis.

How up-to-date is this evidence?

The evidence is up-to-date as of April 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Antibiotics versus placebo

Antibiotics versus placebo for acute bacterial conjunctivitis

Patient or population: Participants with acute bacterial conjunctivitis

Setting: General practitioners' clinics, eye clinics, or medical centers

Intervention: Antibiotics alone (macrolide, fluoroquinolone, fusidic acid, chloramphenicol), or combined with another antibacteriostatic agent (bacitracin) or steroid (loteprednol etabonate)

Comparison: Placebo or vehicle

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Assumed risk Placebo/vehicle	Corresponding risk Antibiotics				
Clinical efficacy (RR > 1 is favored)	**ITT population, end of therapy (day 4 to 9)**				⊕⊕⊕# **Moderate**[1]	
	56 per 100 persons	71 (61 to 82) per 100 persons	RR 1.26 (1.09 to 1.46)	1474 (5 RCTs)		
	mITT population, end of therapy (day 4 to 9)					
	48 per 100 persons	60 (56 to 66) per 100 persons	RR 1.26 (1.17 to 1.37)	3121 (11 RCTs)		
	mITT population, test of cure, FQ (day 6 to 10)					
	54 per 100 persons	78 (65 to 92) per 100 persons	RR 1.44 (1.21 to 1.71)	284 (3 RCTs)		**Non-FQ(day 6 or 7)**: Combined RR was 1.14 (95% CI 0.94 to 1.39; 515 participants, 2 RCTs)
Microbiological efficacy (RR > 1 favored)	**ITT population, end of therapy (day 8 to 10)**				⊕⊕⊕# **Moderate**[1]	
	31 per 100 persons	79 (46 to 100) per 100 persons	RR 2.54	66		

			(1.48 to 4.37)	(1 RCT)		
	mITT population, end of therapy (day 3 to 9)					
	56 per 100 persons	86 (75 to 97) per 100 persons	RR 1.53 (1.34 to 1.74)	2827 (10 RCTs)		
	mITT population, test of cure (day 6 to 12)					
	58 per 100 persons	80 (74 to 87) per 100 persons	RR 1.38 (1.27 to 1.50)	2295 (12 RCTs)		
Treatment incompletion (RR < 1 favored)	10 per 100 persons	6 (5 to 8) per 100 persons	RR 0.64 (0.52 to 0.78)	5573 (13 RCTs)	⊕⊕⊕# **Moderate**[1]	
Persistent clinical infection after one course of treatment (RR < 1 favored)	43 per 100 persons	31 (28 to 35) per 100 persons	RR 0.73 (0.65 to 0.81)	5280 (19 RCTs)	⊕⊕⊕# **Moderate**[1]	
Cost-effectiveness of treatment	None of the trials measured this outcome					
Treatment-associated ocular complications (RR < 1 or RD ≤ 0 favored)	**Risk for one or more treatment-associated incident ocular AE**				⊕### **Very low**[1,2]	
	FQ					
	7 per 100 persons	5 (4 to 6) per 100 persons	RR 0.70 (0.54 to 0.90)	3455 (4 RCTs)		
	Non-FQ					
	10 per 1000 persons	41 (14 to 120) per 1000 persons	RR 4.05 (1.36 to 12.00)	556 (3 RCTs)		
	Rate for any treatment-associated incident ocular AE					

	18 per 1000 person-days	19 (14 to 26) per 1000 person-days	RR 1.06 (0.79 to 1.44)	23627 person-days (9 RCTs)		
	17 per 1000 person-days	18 (16 to 21) per 1000 person-days	RD 1.41 (-0.93 to 3.75) per 1000 person-days	25027 person-days (11 RCTs)		
Treatment-associated systemic complications (RR < 1 favored)	**Headache**				⊕### **Very low**[1,2]	
	30 per 1000 persons	34 (21 to 54) per 1000 persons	RR 1.12 (0.69 to 1.81)	1910 (4 RCTs)		
	Dysgeusia					
	2 (0.08 to 50) per 1000 persons	3 per 1000 persons	RR 1.49 (0.06 to 36.31)	514 (1 RCT)		

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and the associated 95% CI).

AE, adverse effect; **CI**, confidence interval; **FQ**, fluoroquinolone; **No.**, number; **Non-FQ**, non-fluoroquinolone; **ITT**, intention to treat; **mITT**, modified intention to treat; **RCT**, randomized controlled trial; **RD**, rate difference; **RR**, risk ratio or rate 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 for risk of bias (-1)
[2] Downgraded for extreme imprecision (-2)

BACKGROUND

Acute conjunctivitis, characterized by red eyes, discharge, and discomfort, has been estimated to account for 3% of patients seen in general medical practice (Hovding 1991; Hovding 2008). Being one of the most common eye disorders, conjunctivitis may be caused by allergy or infection (bacteria, virus, fungus). Approximately 78% of acute infectious conjunctivitis in children are cases of bacterial conjunctivitis. Even in adults, half of cases of acute infectious conjunctivitis are bacterial in etiology.

The common pathogens of bacterial conjunctivitis include *Haemophilus influenzae (most common in pediatric populations)*, *Streptococcus pneumoniae, Moraxella catarrhalis,* or *Staphylococcus aureus,* depending on age group and chronicity. Acute bacterial conjunctivitis is regarded as self-limiting. However, antibiotics are generally considered desirable on the grounds that they seem to speed recovery, reduce relapse, and may prevent important sight-threatening complications such as orbital cellulitis, keratitis, and panophthalmitis.

As bacterial and viral conjunctivitis may be difficult to differentiate on clinical grounds, and eye swabs are not considered practical (because of delay and cost), many doctors will treat all presumed cases of infective conjunctivitis with a broad-spectrum antibiotic.

Topical antibiotic treatments are most commonly used; some of these also contain topical steroid. Systemic antibiotic therapy has been advocated by some in order to prevent the development of 'conjunctivitis-otitis syndrome' (i.e. conjunctivitis followed by acute otitis media)(Wald 1997).

One survey found that 95% of general practitioners in the UK prescribe antibiotics for conjunctivitis despite more than half believing that the cause was viral (Everitt 2002). Pressure from patients to return to work or school may drive some of the antibiotic prescriptions (Rose 2006). The widespread use of broad-spectrum antibiotics can lead to antibiotic resistance (D'Oria 2023; Peng 2018). A topical antibiotic that is effective and may pose lower risk of resistance is chloramphenicol, but it is rarely prescribed in the United States because of the risk of fatal bone marrow aplasia. However, the risks of bone marrow aplasia may have been over-stated (Lancaster 1998; Walker 1998). Therefore, chloramphenicol eye drops have been reclassified to be available over the counter in the United Kingdom since 2005.

The management of common infections encountered in primary care has undergone a radical transformation over the past 25 years. Previously antibiotics were standard of care for infections such as sinusitis, otitis media and sore throat (pharyngitis/tonsillitis). Randomized controlled trials and systematic reviews have since cast doubt on the effectiveness and cost-effectiveness of antibiotic therapy for these conditions, especially as many of these conditions resolve on their own (Jefferis 2011); also antibiotic therapy carries the risk of drug sensitivity or allergy and increases the risk of antibiotic resistance (Ahovuo-Saloranta 2008; Ahovuo-Saloranta 2014; Del Mar 2004; Falagas 2008; Glasziou 2004; Rosenfeld 2007). Even an earlier systematic review found that 65% of patients with conjunctivitis had resolution of the condition without antibiotic treatment within two to five days of symptom onset (Rose 2007).

Given these developments (CDC 2019; CDC 2021a; CDC 2021b), it is timely to assess whether antibiotic therapy confers significant benefit in the treatment of acute bacterial conjunctivitis. This review reports an updated assessment of the question, incorporating data on newer available treatments (McLean 2010), and in so doing updates previous versions of this review (Hurwitz 2005; Sheikh 2012).

Description of the condition

It is estimated that 2% to 5% of all general practice consultations are eye-related (Dart 1986; McCormick 1995; McDonnell 1988). Data from Norway suggest that acute infectious conjunctivitis is suspected in approximately 3% of patients seen in general medical practice, with this diagnosis being correct in two-thirds of patients (Hovding 1991; Hovding 2008). Acute infectious conjunctivitis is therefore one of the most frequently encountered ocular disorders in primary care. Such infection is usually viral or bacterial in etiology. Infection of the conjunctiva produces a number of local symptoms including red eyes, discharge, and discomfort. Conjunctivitis can be an indication for absence from work or school. Treatment that cures conjunctivitis as assessed by clinical exam or by microbiological testing or both will have an impact on the number of such absences.

Description of the intervention

Acute bacterial conjunctivitis is self-limiting. However, antibiotics are considered in some situations. As bacterial and viral conjunctivitis may be difficult to distinguish on clinical grounds, and microbiological evaluation is not considered practical because of accessibility, delay in diagnosis, and cost, many doctors will treat presumed cases of infectious conjunctivitis with a broad-spectrum topical antibiotic, either in eye drops or ointment.

How the intervention might work

Antibiotics may hasten recovery, decrease chances of relapse, and prevent extension of infection, causing complications that could lead to vision loss.

Why it is important to do this review

This review assesses whether antibiotic therapy confers significant benefit in the treatment of acute bacterial conjunctivitis and updates previous versions of this review (Hurwitz 2005; Sheikh 2012).

OBJECTIVES

To assess effectiveness and safety of antibiotic therapy (topical or systemic) for acute bacterial conjunctivitis based on evidence from randomized, placebo-controlled trials.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized, placebo-controlled trials.

Types of participants

Participants were people with acute bacterial conjunctivitis, aged one month or older. The diagnosis of bacterial conjunctivitis may have been on clinical or microbiological grounds. 'Acute' was defined as symptoms of less than four weeks duration. However, we did include one trial that enrolled infants younger than one month old (Leibowitz 1991), which only reported on microbiological but not clinical efficacy (see Differences between protocol and review). We performed a post hoc sensitivity analysis on one of the critical outcomes to assess the impact of including this trial (see Sensitivity analysis).

Types of interventions

We included studies in which any form of antibiotic treatment was compared with placebo (or vehicle) in the management of acute bacterial conjunctivitis; this included topical, systemic, and combination treatments with steroid.

Types of outcome measures

We considered the following outcome measures.

Primary outcomes

Critical outcomes

1. Clinical efficacy (or clinical cure), as measured by proportion of participants (or eyes) with clinical recovery based on resolution of signs or symptoms of acute conjunctivitis as defined by the primary study after one course of treatment;
2. Microbiological efficacy (or microbiological cure), as quantified by proportion of participants (or eyes) with microbiological clearance as defined by the primary study after one course of treatment.

Secondary outcomes

Important outcomes

1. Treatment incompletion, as quantified by proportion of participant dropouts, withdrawals, or loss to follow-up before the end of the treatment period, but not because of missing culture data at follow-up visits;
2. Persistent clinical infection, as assessed by proportion of participants (or eyes) with persistent clinical signs of conjunctivitis, such as injection or discharge depending on which led to a higher proportion of clinical persistency, after one course of antibiotic therapy;
3. Cost-effectiveness of treatment, as quantified by previously-published measures, such as the ratio of the incremental costs and the incremental clinical benefits in dollars per quality-adjusted life-year (Hlatky 2006), or other economic evaluation outcomes (Ballouz 2019);
4. Adverse outcome: treatment-associated ocular complications, as quantified by the proportion of participants experiencing any of the following ocular complications: allergic, sensitivity, or toxic reaction, the latter two of which might be indicated by follicular conjunctival reaction; ocular pain; discomfort; or swelling of the eyelids;
5. Adverse outcome: treatment-associated systemic complications, as measured by the proportion of participants experiencing any of the following systemic complications: sensitivity to systemic antibiotics (gastrointestinal and other), allergic or anaphylactic reaction, or bacterial overgrowth from long-term antibiotic use.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (accessed 11 May 2022), MEDLINE (January 1950 to May 2022), Embase (January 1980 to May 2022), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 11 May 2022.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), Embase (Appendix 3), OpenGrey (Appendix 4), *m*RCT (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources

We searched the reference lists of identified trial reports to find additional trials. We also contacted the corresponding and the first author of a previously identified meta-analysis (Kodjikian 2010) to request clarifications of reported results from the three trials deemed eligible for the current update (C-01-66). In addition, we searched relevant regulatory documents online for the three clinical trials (C-00-02; C-00-55; C-01-66) using the Google search engine.

Data collection and analysis

Selection of studies

The information specialist performed the update searches, the results of which were imported into Covidence. After removing duplicates, two review authors worked independently in pairs to screen titles and abstracts against the eligibility criteria and then categorized each record as 'relevant (yes)', 'maybe relevant (maybe)', or 'not relevant (no)'. For records categorized as 'relevant' or 'maybe relevant', two review authors independently evaluated the eligibility of each full-text report against 'Criteria for considering studies for this review' to determine its inclusion or exclusion. We documented reasons for exclusion for studies at the full-text screening stage in the 'Characteristics of excluded studies' table. We labeled studies as 'awaiting classification' when they met the eligibility criteria, documented completion of study, but did not have publicly available study results. We resolved any discrepancies by discussion within the author team.

Data extraction and management

Two review authors independently extracted data using a template form in Covidence developed by the Cochrane Eyes and Vision US Project. Review authors discussed discrepancies before exporting the consensus data extracted to RevMan Web for subsequent data analysis. To be consistent with information abstracted from previously-included studies, we extracted the following information: publication year, contact information about the

corresponding author, source of funding, and authors' financial disclosures; study design elements (randomization, masking); characteristics of study participants; intervention medications (dosage, duration); study outcomes (domain, measurement, metrics); study visits; and follow-up duration.

We contacted study investigators or publication authors to request clarification or additional data whenever necessary. If we did not receive a response within two weeks of time, we proceeded with the information available to us. When outcome data were only presented in figures, two review authors extracted numerical data using image-digitalization tools as recommended in Chapter 5 of the Handbook (Li 2022).

Assessment of risk of bias in included studies

We applied Cochrane's RoB 2 tool for risk assessment (Higgins 2022). Two review authors independently assessed the risk of bias for one of the critical outcomes, 'clinical effectiveness'. Disagreements were resolved by discussion within the author team.

We assessed the five domains:

1. Bias arising from the randomization process
2. Bias introduced by deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in outcome measurement
5. Bias in selective reporting of outcome data

For each eligible study, we judged each domain as either low risk of bias, some concerns, or high risk of bias after answering the signaling questions. At the study level, we provided an overall assessment on the risk of bias as:

1. 'Low' if all domains were judged to be at low risk of bias;
2. 'Some concerns' if one or more domains were judged to have some concerns, and none were at high risk;
3. 'High' if one or more domains were considered as at high risk, or if multiple domains were judged to have some concerns (Higgins 2022).

Measures of treatment effect

For continuous outcomes (visual acuity and quality of life scores), we calculated mean differences (MD) with 95% confidence intervals (CI). For dichotomous outcomes, we estimated risk ratios (RR) with 95% CIs for proportions of participants with clinical or microbiological treatment success or proportions of participants with prespecified adverse events. For trials that reported numbers of ocular adverse events by event type, such as allergic conjunctivitis, lid swelling, or eye pain, we calculated cumulative incidence ratios and cumulative incidence differences as well as the associated 95% CIs to approximate RR and risk difference (RD) during the treatment period for selected ocular adverse events that were judged to be treatment-associated in accordance with Chapter 6 of the Handbook (Li 2022). We decided to use treatment duration, rather than the overall trial period, for calculating the associated person-time at risk for treatment-related ocular adverse events.

Unit of analysis issues

Acute bacterial conjunctivitis is usually a bilateral condition; all outcomes were assessed at the patient level.

Dealing with missing data

Depending on how the authors approached missing data, we extracted data from the trials as reported. We did not impute missing data.

Assessment of heterogeneity

We assessed the included trials for both clinical and methodological diversity by examining characteristics of the trial design, eligibility of trial participants, intervention and comparator differences, and outcome definitions. We evaluated the amount of statistical heterogeneity using the I^2 statistic and considered the following thresholds when interpreting I^2 values (Deeks 2022):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We assessed selective outcome reporting by comparing the outcomes specified in the study protocol that was published on trial registry sites or the methods section of the study report with the data that were reported in the study results, as guided by relevant signaling questions in the RoB2 tool (Higgins 2022).

Data synthesis

According to the guidelines provided in Chapter 9 (McKenzie 2022a) and Chapter 10 (Deeks 2022) of *Cochrane Handbook for Systematic Reviews of Interventions,* we performed meta-analyses of outcomes on an intention-to-treat basis using random-effects modelling when we had two or more studies contributing data to the same outcome. If the direction of treatment effects was inconsistent across studies or subgroups, or we assessed that there was considerable clinical or statistical heterogeneity, we did not combine study results in pooled analysis. Instead, we provided a structured qualitative summary of the study results as recommended by Chapter 12 (McKenzie 2022b) of the Handbook.

Subgroup analysis and investigation of heterogeneity

The original review protocol or review did not specify subgroup analysis (Sheikh 2000; Sheikh 2006), except in Sheikh 2012 where the authors proposed a subgroup analysis by antibiotic class to explore potential sources of heterogeneity in future updates given sufficient numbers of trials included (> 10 trials). In the current update, we performed subgroup analysis by antibiotic class on the critical outcome of 'clinical efficacy' and 'microbiological efficacy'. We also performed post hoc subgroup analysis by treatment duration (see Differences between protocol and review).

Sensitivity analysis

No prior sensitivity analysis was planned. We performed post hoc sensitivity analysis on 'clinical efficacy' by excluding trials that were assessed to be at high risk of bias. We also performed sensitivity

analysis on 'microbiological efficacy' that excluded trials enrolling infants younger than one-month-old or trials that did not report the minimum age of participants. None of the trials that reported 'clinical efficacy' involved participants younger than one-month-old.

Summary of findings and assessment of the certainty of the evidence

We provided a Summary of findings table, which includes the assumed risk and corresponding risk for the following outcomes based on the risk across control groups in the included studies:

- Clinical efficacy, as measured by proportion of participants (or eyes) with clinical recovery at the end of the treatment period;
- Microbiological efficacy, as quantified by proportion of participants (or eyes) with microbiological clearance at the end of the treatment period;
- Treatment adherence, as measured by proportion of dropouts or withdrawals before the end of the treatment period;
- Proportion of participants (or eyes) with persistent infection after one week of antibiotic therapy;
- Cost-effectiveness of treatment;
- Proportion of participants experiencing any ocular complications;
- Proportion of participants experiencing any systemic complications.

We graded the overall quality of the evidence for each outcome using the GRADE classification (Schünemann 2022a). We assessed the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' according to (1) high risk of bias; (2) indirectness of evidence; (3) unexplained heterogeneity or inconsistency of results; (4) imprecision; (5) high probability of publication bias as described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022a). We also adopted the recent guidance on rating imprecision when assessing contextualized certainty of evidence (Schünemann 2022b).

RESULTS

Description of studies

Results of the search

The review protocol was published in 1998, the citation of which was replaced by the subsequent review published in 1999, whose citation was further replaced by the first update (Sheikh 2000).

In the initial electronic searches, authors screened 155 records and identified three eligible trials (Gigliotti 1984; Leibowitz 1991; Miller 1992). Although two interim updated searches in 2002 and 2007 did not identify additional eligible studies, updated searches in December 2006 (Sheikh 2006) and July 2012 (Sheikh 2012) separately identified two (Rietveld 2005; Rose 2005) and six (Abelson 2008; Gross 2003; Karpecki 2009; Silverstein 2011; Tauber 2011; Tepedino 2009) new trials.

For the current update, our searches in May 2022 yielded 524 records, with one additional report (Hwang 2003) identified manually in the reference list of an excluded report (Bremond-Gignac 2014). We identified three additional RCTs (C-00-02; C-00-55; C-01-66) from a published meta-analysis (Kodjikian 2010) along with their associated regulatory documents (NDA-21-598; RMS Public Assessment Report).

Overall, we screened 528 titles and abstracts, excluded 512 records, and reviewed 12 full-text publications. This effort yielded seven new trials (C-00-02; C-00-55; C-01-66; Comstock 2012; Hwang 2003; Malhotra 2013; Yang 2013) after excluding four studies (Belfort 2012; Bremond-Gignac 2014; Bremond-Gignac 2015; Zhang 2019) for various reasons. We updated Silverstein 2011 (interim report) with its full publication (DeLeon 2012).

In addition, three trials that were previously labeled as 'await classification' were included because a full-text publication now was available (Malhotra 2013) or trial results now were published online (NCT01175590; NCT00509873; NCT00518089). In particular, authors of Heller 2014 reported secondary analysis of data from two RCTs, but only one of them was a placebo-controlled trial (NCT00509873). In total, we included 21 trials in the current update, listed two as awaiting classification, and did not identify any ongoing study (Figure 1).

Figure 1. PRISMA flow diagram

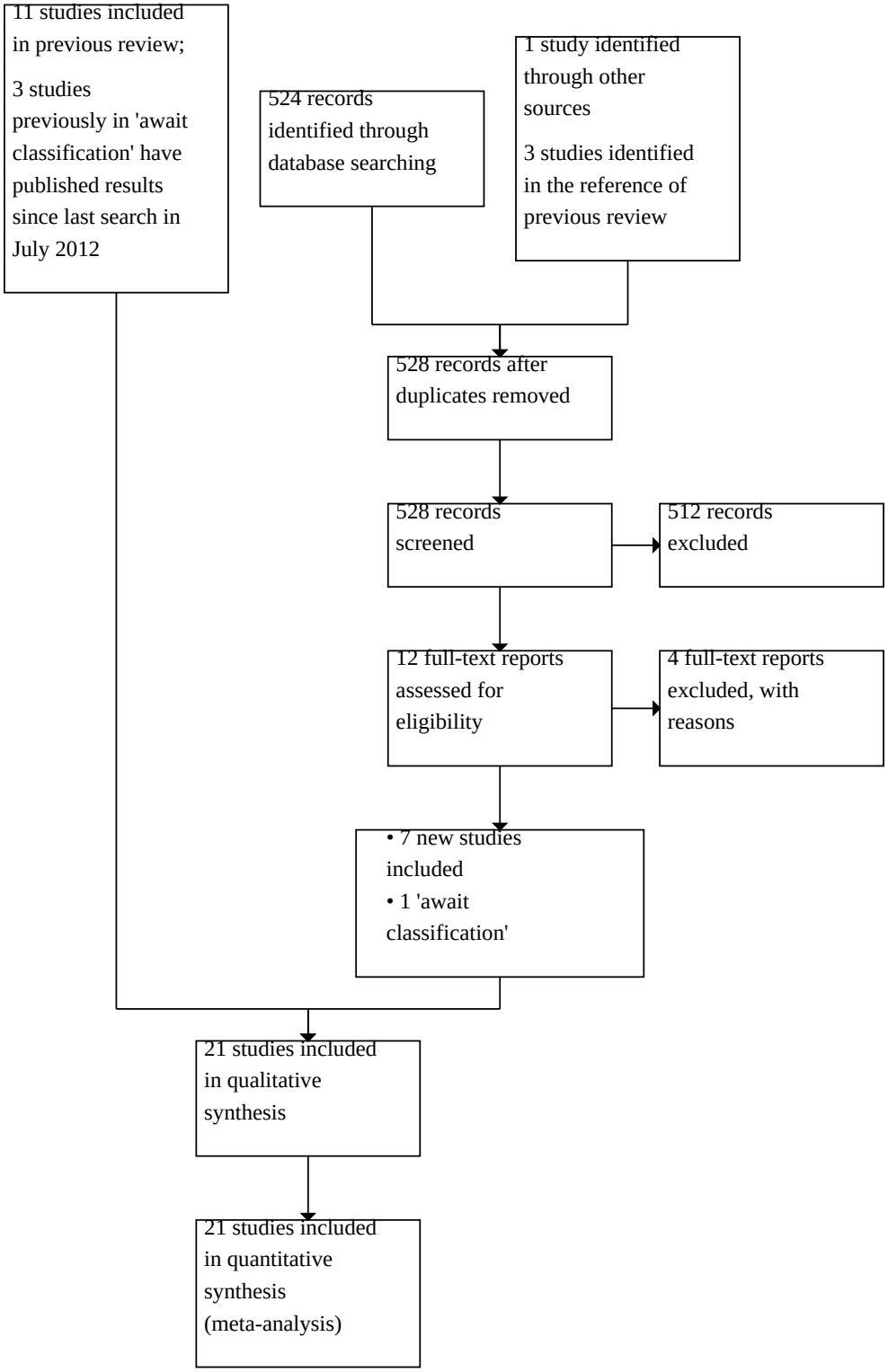


Figure 1. (Continued)

Studies 'await classification' or 'ongoing'

A conference abstract (Ofloxacin 1990) that was categorized as 'await classification' in the 2000 update (Sheikh 2000) was no longer retrievable despite the librarians' efforts. In the current update, we added one new trial registry record to the 'await classification' category because of lack of published trial results (NCT02432807).

Included studies

We updated design features and study-level information about population, intervention medications, and outcome specification as well as sources of research funding for each included trial in the 'Characteristics of included studies' table.

Types of studies

All 21 included trials were placebo-controlled, parallel-group, two-arm RCTs, except for one (Comstock 2012), in which the treatment effects of tobramycin 0.3%, loteprednol etabonate (LE), and the combination (tobramycin 0.3% + LE) were compared with those of vehicle. We extracted only relevant data from the tobramycin group, the combination therapy group, and the vehicle group.

Nineteen trials were conducted in the following countries: China (Yang 2013), United Kingdom (Rose 2005), the Netherlands (Rietveld 2005), and U.S.A. (C-00-02; C-00-55; C-01-66; Comstock 2012; DeLeon 2012; Gigliotti 1984; Hwang 2003; Karpecki 2009; Leibowitz 1991; Malhotra 2013; Miller 1992; NCT00509873; NCT01740388; Tauber 2011; Tepedino 2009). Authors of Gross 2003 did not specify where this multicenter trial was conducted but it was likely in the U.S.A. as suggested by the Acknowledgement section of the publication. Two trials were conducted in multiple study sites in two or more countries (Abelson 2008; NCT00518089). Fifteen trials recruited participants from two or more clinical sites (71%), whereas the other six did not provide such information (C-00-02; C-01-66; DeLeon 2012; Leibowitz 1991; Miller 1992; NCT01740388).

More than two-thirds of the trials were funded by pharmaceutical companies; Leibowitz 1991 also reported funding from non-profit organizations. Two trials were supported by an academic institution or government agency (Rietveld 2005; Rose 2005). Authors of four trials did not disclose funding information (Gigliotti 1984; Gross 2003; Miller 1992; Yang 2013).

Types of participants

In total, the included trials randomized 8805 eligible participants, with a median number of 326 participants (IQR: 180 to 544) per trial. Randomization was performed at the person level in all trials, mostly, if not totally, based on clinical diagnosis of acute bacterial conjunctivitis. If both eyes were treated, they received the same treatment (medication or placebo).

Two-thirds of the included trials enrolled participants aged one year or older, covering a wide age range (1 to 97 years). Two trials recruited only adults aged ≥ 18 years old (Miller 1992; Rietveld 2005), with an average age of 38 and 31, respectively. Five trials included study participants between one month (or 30 days) and one year of age (C-00-55; C-01-66; Gigliotti 1984; Rose 2005; Tauber 2011). Amongst these trials, Gigliotti 1984 and Rose 2005 exclusively enrolled pediatric participants, whose age ranged from one month to 18 years and from 1.4 to 4.9 years, respectively. Participants of one trial (Comstock 2012) were pediatric, with an age range between 0 and six years; the mean age was 2.8 years (SD 1.95). Amongst 17 trials that reported composition of study population by gender, a female preponderance was noted [median proportion of 58% (IQR 56% to 59%)]. White or Caucasian was the predominant race/ethnicity in 11 trials that provided this information (median 74.6%, IQR 67.8% to 79.7%).

Types of interventions

All interventions were topical drops or ointment. Fifteen of the 21 trials (71%) examined treatment efficacy of fluoroquinolone drops, including besifloxacin 0.6% (DeLeon 2012; Karpecki 2009; Malhotra 2013; NCT01740388; Tepedino 2009), ciprofloxacin 0.3% (Leibowitz 1991), gatifloxacin 0.5% (NCT00509873; NCT00518089), levofloxacin 0.5% (Hwang 2003), moxifloxacin 0.5% (C-00-02; C-00-55; C-01-66; Gross 2003; Tauber 2011), and norfloxacin 0.3% (Miller 1992). Although C-00-02 was a four-arm, dose-ranging trial, we combined and analyzed data of the two intervention groups versus the two placebo groups as reported by the investigators.

Two trials tested azithromycin 1%, a macrolide, against placebo (Abelson 2008; Yang 2013). Comstock 2012 was the only three-arm trial, examining efficacy of aminoglycoside tobramycin 0.3% and the combination therapy of tobramycin and LE against placebo. The authors did not report on clinical or microbiological efficacy but only adverse events after treatment. Three trials evaluated treatment effects of other antibiotic classes, such as polymyxin plus 1% bacitracin (Gigliotti 1984), fusidic acid (Rietveld 2005), or chloramphenicol 0.3% (Rose 2005). Polymyxin plus bacitracin (Gigliotti 1984) and fusidic acid (Rietveld 2005) were the only ophthalmic ointments (ung); all others were ophthalmic solutions.

Treatment schedules varied across trials. Dosing frequency ranged from twice per day to every two hours while awake and up to eight times per day. Participants in eight trials (38%) began with a loading dose schedule for the first one to two days, followed by a tapering schedule in the subsequent one to six days (Abelson 2008; Hwang 2003; Leibowitz 1991; Miller 1992; NCT00509873; NCT00518089; Rose 2005; Yang 2013). Participants in the other 13 trials followed a fixed dosing schedule throughout the treatment duration. Treatment duration was variable, with an average of five days (IQR 3 to 7). The only exception was Rose 2005, in which participants were instructed to continue the medication 'until 48 h after the infection had resolved'.

Types of outcomes

Critical outcomes

Clinical efficacy

Eighteen trials (86%) defined this outcome as the resolution of at least two of the following three signs: bulbar conjunctival injection (hyperemia), palpebral conjunctival injection, and discharge (exudate). These trials included Tauber 2011, in which the investigators reported only microbiological cure in the full-text publication but included both microbiological cure and clinical cure data on clinicaltrials.gov. The other three trials provided only microbiological evaluation results (Leibowitz 1991), safety outcomes (Comstock 2012), or patient dropouts (C-01-66).

In a meta-analysis report (Kodjikian 2010), authors described the conduct of three clinical trials and reported proportions of participants with 'clinical cure', 'persistent infection', and 'dropout rates' (C-00-02; C-00-55; C-01-66). However, the authors did not clearly describe how they obtained or estimated these trial results. In particular, numeric data for clinical cure, results of clinical cure, and results of persistent infection were inconsistent for C-01-66, which was thus excluded from the meta-analysis in this update. For the other two trials (C-00-02; C-00-55), we cross-checked and collected data reported for clinical cure and microbiological cure in a publicly available regulatory document (NDA-21-598).

Twelve of the 21 trials (57%) estimated the clinical efficacy only from a modified intention-to-treat (mITT) population, defined by the trial investigators as a subset of randomized participants whose baseline culture results confirmed bacterial conjunctivitis. The only exceptions were Gigliotti 1984, Miller 1992, and Yang 2013, in all of which investigators reported this outcome based on the intention-to-treat (ITT) population, i.e. the numbers of participants randomized. Another three trials provided outcome data based on both the ITT and mITT population (C-00-02; C-00-55; Rose 2005).

Despite different treatment durations, 12 of the 21 trials (57%) assessed 'clinical cure' at the study visit following the completion of antibiotic therapy, and labeled that time point as the '**end-of-therapy**' visit. Eight of these 12 trials also reported clinical efficacy at a second time point, the '**test-of-cure**' visit, which was two to four days after the 'end-of-therapy' visit. In NCT00509873 and NCT00518089, participants returned to this 'test-of-cure' visit at variable times after the end of therapy. Gigliotti 1984 was the only trial that reported clinical resolution when participants were still under treatment.

Microbiological efficacy

Nearly all (90%) trials reported this outcome, except for two (C-01-66; Comstock 2012). Eleven trials assessed this outcome at the 'end of therapy' visit (11/19 = 58%), four of which also reported this outcome at the 'test-of-cure' visit (DeLeon 2012; Malhotra 2013; NCT01740388; Tepedino 2009). In all, 12 trials reported this outcome at the 'test-of-cure' visit with variable durations since the completion of the antibiotic treatment.

Investigators of one trial (Gigliotti 1984) estimated microbiological efficacy based on the ITT population alone; 18 other trials used the mITT population. Specifically, authors in Rose 2005 considered only 'pathogenic bacteria', including *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, as relevant to the trial, such that 250 out of 261 participants were considered eligible for evaluation of microbiological cure or improvement after treatment.

Important outcomes

Treatment incompletion

No trial employed specific techniques or mechanisms to monitor participants' adherence to the prescribed therapy. Therefore, we estimated treatment non-adherence from the reported rates of incompletion or dropout by the end of the trial. Twelve (57%) trials reported data of this outcome for each comparison group, whereas authors of one trial reported no dropouts (Yang 2013).

Persistent clinical infection

One trial defined and reported 'treatment failure' as one of the study outcomes (Gross 2003); the authors defined it as "no clinically significant response or worsening of signs or symptoms of conjunctivitis" observed at the 'test-of-cure' visit.

Six other trials (29%) monitored and reported proportions of participants whose bulbar injection or conjunctival discharge remained unresolved at either the 'test-of-cure' visit or the 'end-of-therapy' visit. For each of these trials, we chose the highest proportions as reported by the primary study. Five reported the persistence of bulbar hyperemia (DeLeon 2012; Hwang 2003; Karpecki 2009; Malhotra 2013; Tepedino 2009); one reported unspecified 'ocular signs' (NCT00509873).

We derived estimates for reported clinical cure data for another 12 trials (57%) at the corresponding 'end-of-therapy' visit or the 'test-of-cure' visit.

Cost-effectiveness of treatment

No included trials measured or reported this outcome.

Adverse outcome

Treatment-associated ocular complications

The majority of trials documented and reported ocular AEs (N = 16, 76%), some as specific complaints (eye pain, allergic reactions, discomfort). Eye pain, discomfort, irritation, or burning were amongst the most frequently reported ocular AEs (57%), followed by local allergic reactions (24%), which might include pruritis, erythema, or swelling of eyelids.

Seven trials reported this outcome in a quantitative manner in terms of proportion of participants (Comstock 2012; Miller 1992; Rietveld 2005; Rose 2005; Tauber 2011) or proportion of eyes (DeLeon 2012; Tepedino 2009) suffering from one or more ocular AEs that were judged to be treatment-associated.

For trials that did not provide subject-level proportions data (N = 14), we estimated event rates and reported both absolute rate differences and rate ratios when comparing AEs of antibiotics with those of placebo (see Differences between protocol and review).

Treatment-associated systemic complications

Nine trials (43%) reported numeric results of specific systemic AEs, such as heart failure, anxiety, and depression. Some of these non-ocular complications were considered as 'not treatment-related' (C-00-02; C-00-55; Comstock 2012; Karpecki 2009; NCT00509873; NCT00518089) while others as 'probably'

treatment-related (Malhotra 2013) or unclear (Karpecki 2009; Tepedino 2009). No trial reported incidents of sensitivity seen with systemic antibiotics (e.g. gastrointestinal symptoms), allergic or anaphylactic reaction such as Stevens Johnson Syndrome, or other complications associated with systemic antibiotic use.

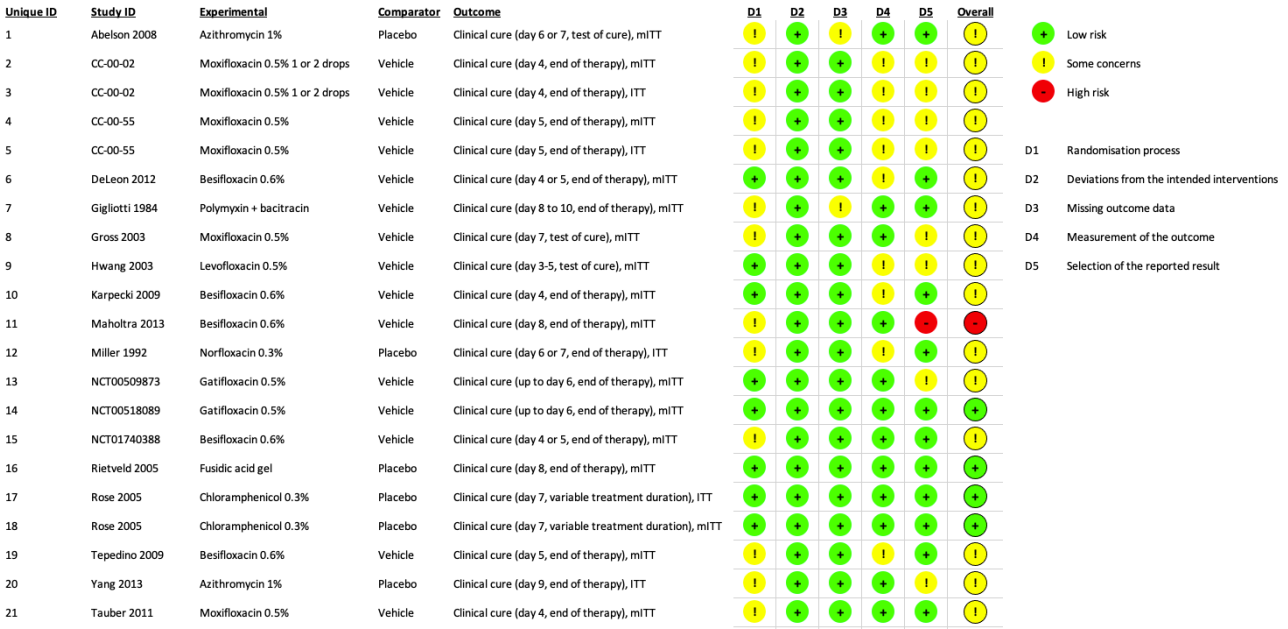
Excluded studies

In this update, we excluded four studies because none of them compared intervention treatment with a placebo group (Characteristics of excluded studies). In total, 12 of the 14 excluded studies were ineligible because of use of active-treatment in the comparator group (86%) whereas Leibowitz 1976 was a single-masked RCT and Mitsui 1986 was a review article.

Risk of bias in included studies

We assessed 18 of the 21 included trials that reported 'clinical efficacy' for risk of bias using the Cochrane RoB 2 tool, leading to 21 trial results reported based on the ITT or mITT population being assessed. For three trials that reported 'clinical efficacy' results for both ITT and mITT populations (C-00-02; C-00-55; Rose 2005), we assessed risk of bias for these reported results separately though the assessment results were the same in a given trial. Overall, four (19%) of the 21 trial results assessed were judged to possess low overall risk of bias (NCT00518089; Rietveld 2005; Rose 2005), one had high overall risk of bias (5%)(Malhotra 2013), and the remaining 16 (76%) trials raised some concerns for risk of bias (Figure 2). Detailed risk of bias assessment data with consensus responses to each signaling question of the domains are available upon reasonable request.

Figure 2. Risk of bias results across five domains of individual trials that reported on clinical cure. Abbreviations: mITT, modofied intention-to-treat population; ITT, intention-to-treat population.



Unique ID	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
1	Abelson 2008	Azithromycin 1%	Placebo	Clinical cure (day 6 or 7, test of cure), mITT	!	+	!	+	+	!
2	CC-00-02	Moxifloxacin 0.5% 1 or 2 drops	Vehicle	Clinical cure (day 4, end of therapy), mITT	!	+	+	!	!	!
3	CC-00-02	Moxifloxacin 0.5% 1 or 2 drops	Vehicle	Clinical cure (day 4, end of therapy), ITT	!	+	+	!	!	!
4	CC-00-55	Moxifloxacin 0.5%	Vehicle	Clinical cure (day 5, end of therapy), mITT	!	+	+	!	!	!
5	CC-00-55	Moxifloxacin 0.5%	Vehicle	Clinical cure (day 5, end of therapy), ITT	!	+	+	!	!	!
6	DeLeon 2012	Besifloxacin 0.6%	Vehicle	Clinical cure (day 4 or 5, end of therapy), mITT	+	+	+	!	+	!
7	Gigliotti 1984	Polymyxin + bacitracin	Vehicle	Clinical cure (day 8 to 10, end of therapy), mITT	!	+	!	+	+	!
8	Gross 2003	Moxifloxacin 0.5%	Vehicle	Clinical cure (day 7, test of cure), mITT	!	+	+	+	!	!
9	Hwang 2003	Levofloxacin 0.5%	Vehicle	Clinical cure (day 3-5, test of cure), mITT	+	+	+	!	!	!
10	Karpecki 2009	Besifloxacin 0.6%	Vehicle	Clinical cure (day 4, end of therapy), mITT	+	+	+	!	+	!
11	Maholtra 2013	Besifloxacin 0.6%	Vehicle	Clinical cure (day 8, end of therapy), mITT	!	+	+	+	-	-
12	Miller 1992	Norfloxacin 0.3%	Placebo	Clinical cure (day 6 or 7, end of therapy), ITT	!	+	+	!	+	!
13	NCT00509873	Gatifloxacin 0.5%	Vehicle	Clinical cure (up to day 6, end of therapy), mITT	+	+	+	+	!	!
14	NCT00518089	Gatifloxacin 0.5%	Vehicle	Clinical cure (up to day 6, end of therapy), mITT	+	+	+	+	+	+
15	NCT01740388	Besifloxacin 0.6%	Vehicle	Clinical cure (day 4 or 5, end of therapy), mITT	!	+	+	+	+	!
16	Rietveld 2005	Fusidic acid gel	Placebo	Clinical cure (day 8, end of therapy), mITT	+	+	+	+	+	+
17	Rose 2005	Chloramphenicol 0.3%	Placebo	Clinical cure (day 7, variable treatment duration), ITT	+	+	+	+	+	+
18	Rose 2005	Chloramphenicol 0.3%	Placebo	Clinical cure (day 7, variable treatment duration), mITT	+	+	+	+	+	+
19	Tepedino 2009	Besifloxacin 0.6%	Vehicle	Clinical cure (day 5, end of therapy), mITT	!	+	+	!	+	!
20	Yang 2013	Azithromycin 1%	Placebo	Clinical cure (day 9, end of therapy), ITT	!	+	+	+	!	!
21	Tauber 2011	Moxifloxacin 0.5%	Vehicle	Clinical cure (day 4, end of therapy), mITT	!	+	+	+	+	!

Bias arising from the randomization process

Seven trials (NCT00509873, NCT00518089, DeLeon 2012, Hwang 2003, Karpecki 2009, Rietveld 2005, Rose 2005) provided sufficient information for eight outcome results of the randomization process, the concealment of allocation, and comparable baseline characteristics of participants between the comparison groups, and thus were judged to have low risk of bias (38%). The remaining 14 trials provided insufficient information to provide a judgment on allocation concealment and were judged as raising some concerns.

Bias from deviations from the intended intervention

Because we decided the aim was assessing 'the effect of assignment to the intervention' (the 'intention-to-treat' effect), all trials were judged to be at low risk of bias regardless of the reported masking status of the participants or the trial site personnel.

Bias from missing outcome data

Sixteen trials reporting 18 outcome results were judged to have low risk of bias (86%). Two trials (Abelson 2008; Gigliotti 1984) were judged to possess some risk of bias in this domain because of evidence suggesting participants in the comparison groups were differentially excluded from the analysis (Abelson 2008) or because of lack of information regarding how participants were excluded from the comparison groups (Gigliotti 1984).

Bias in measurement of the outcome

Seven trials reporting nine outcome results (C-00-55; C-00-02; DeLeon 2012; Hwang 2003; Karpecki 2009; Miller 1992; Tepedino 2009) were deemed to have some risk of bias (43%) because it was unclear whether clinicians were masked to the intervention the participants received. Particularly, in two trials (Hwang 2003; Karpecki 2009), some concerns existed that because of lack of masking, investigator knowledge of the intervention the

participants received may have influenced their assessment of the outcome. The 12 other trial results were judged to have low risk of bias in this domain (57%).

Bias in selection of the reported result

Twelve of the 21 trial results (57%) were judged to have low risk of bias in this domain. We judged four trial results (Gross 2003; Hwang 2003; NCT00509873; Yang 2013) to have some risk because either the trialists had reported outcome data at time points other than those they specified for the primary efficacy outcome or they did not specify time points for primary data collection and reporting. The trial result reported by Malhotra 2013 was deemed to possess high risk of bias because the authors planned and analyzed the data for clinical efficacy as shown in clinicaltrials.gov but did not present them in the full-text publication.

Effects of interventions

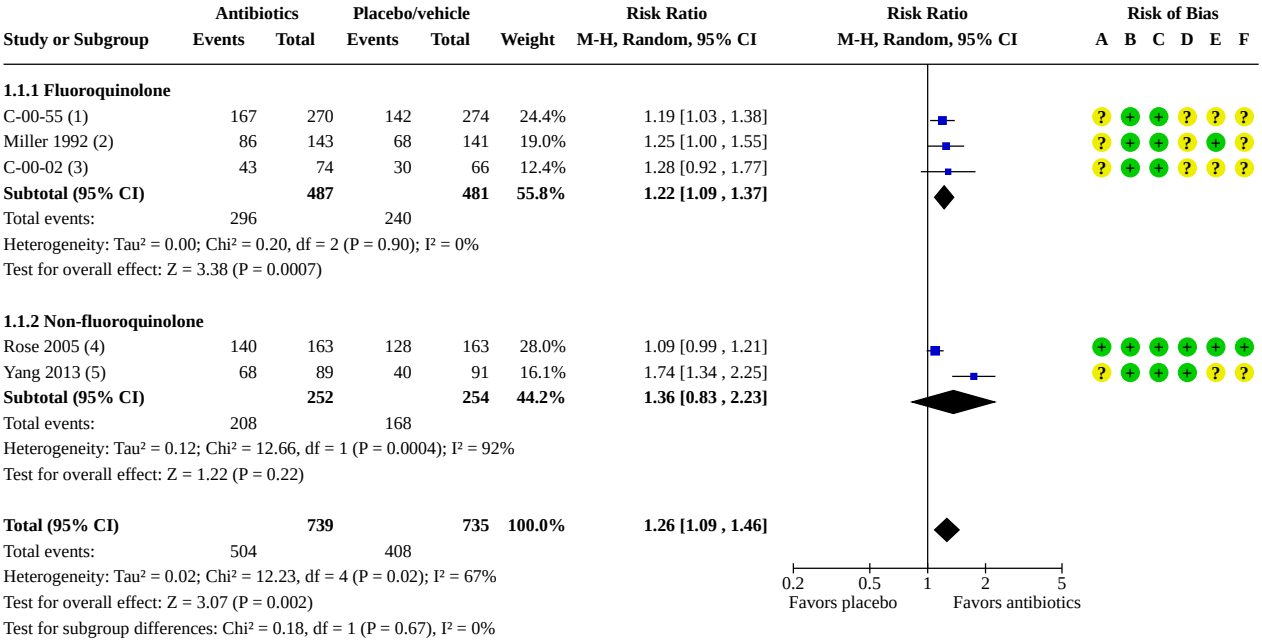
See: **Summary of findings 1** Antibiotics versus placebo

Critical outcomes

Clinical efficacy

Five trials reported clinical efficacy outcomes at the end-of-therapy visit based on the ITT population (C-00-55; Miller 1992; C-00-02; Rose 2005; Yang 2013), resulting in a combined RR of 1.26 (95% CI 1.09 to 1.46; P = 0.02, I^2 = 67%; 5 trials, 1474 participants; Analysis 1.1) comparing antibiotics with placebo. Results of subgroup analysis by antibiotic class (fluoroquinolone [FQ] versus non-fluoroquinolone [on-FQ]) showed that, in contrast to FQ (RR 1.22, 95% CI 1.09 to 1.37; n = 968), non-FQ may have little to no effects on clinical cure at the end of a treatment course (RR 1.36, 95% CI 0.83 to 2.23; P = 0.22, I^2 = 92%; 2 trials, 506 participants; Figure 3). Despite the different results of subgroup analysis, there was no evidence of subgroup differences (P = 0.67).

Figure 3.



Footnotes

(1) Day 5, moxifloxacin 0.5%, end-of-therapy visit, mixed pediatric and participants (including children < 1 years)
(2) Dat 7 or 8, norfloxacin 0.3%, end-of-therapy visit
(3) Day 4, moxifloxacin 0.5%, end-of-therapy visit
(4) Day 7, chloramphenicol 0.3% with variable treatment duration, end-of-study visit, only pediatric participants (including children < 1 years)
(5) Day 8 or 9, azithromycin 1%, end-of-therapy visit

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Most of the included trials (N = 11) reported clinical cure at the end-of-therapy visit based on the mITT population. When compared to placebo, non-FQs probably provide little to no treatment benefits (RR 1.16, 95% CI 0.95 to 1.41; P = 0.15, I^2 = 23%; 2 trials, 229 participants; Analysis 1.2). Because there was no evidence of subgroup differences by antibiotic class (P = 0.34), we pooled the

two subgroups and obtained a combined RR of 1.26 (95%CI 1.17 to 1.41; P < 0.00001, I^2 = 27%; 11 trials, 3121 participants), suggesting that topical antibiotics may increase participants' likelihood of clinical cure by 26% at the end of a given treatment course.

Using data from a mITT population, five trials reported clinical efficacy at the test-of-cure visit (Abelson 2008; Gross 2003; Hwang 2003; Karpecki 2009; Rose 2005). Results of subgroup analysis by antibiotic class showed consistent treatment effects of FQ (RR 1.44, 95% CI 1.21 to 1.71; I^2 = 0%; 3 trials, 284 participants; Analysis 1.3) but not of non-FQ antibiotics (RR 1.14, 95% CI 0.94 to 1.39; I^2 = 64%; 2 trials, 515 participants). We chose not to combine the two subgroups due to evidence of subgroup differences (P = 0.08).

Results of post hoc subgroup analysis at the end-of-therapy visit by duration of treatment course were comparable between short and long treatment courses for trials that reported ITT results (Analysis 1.4). In contrast, amongst trials that reported mITT results, treatment effects were slightly attenuated in trials of longer treatment duration compared with those of treatment courses shorter than 5 days (P = 0.06 for subgroup differences)(Analysis 1.5).

Per-protocol, we performed sensitivity analysis by excluding trials that were judged to possess high risk of bias. Only one trial reporting clinical cure based on the mITT population was deemed to have high risk of bias (Analysis 1.2). The combined results were similar (RR 1.29, 95% CI 1.21 to 1.38; I^2 = 0%; 10 trials, 2832 participants; Analysis 2.1) after excluding the high-risk trial, suggesting that antibiotics (both FQ and non-FQ) are associated with a 29% increased chance of clinical cure compared with placebo.

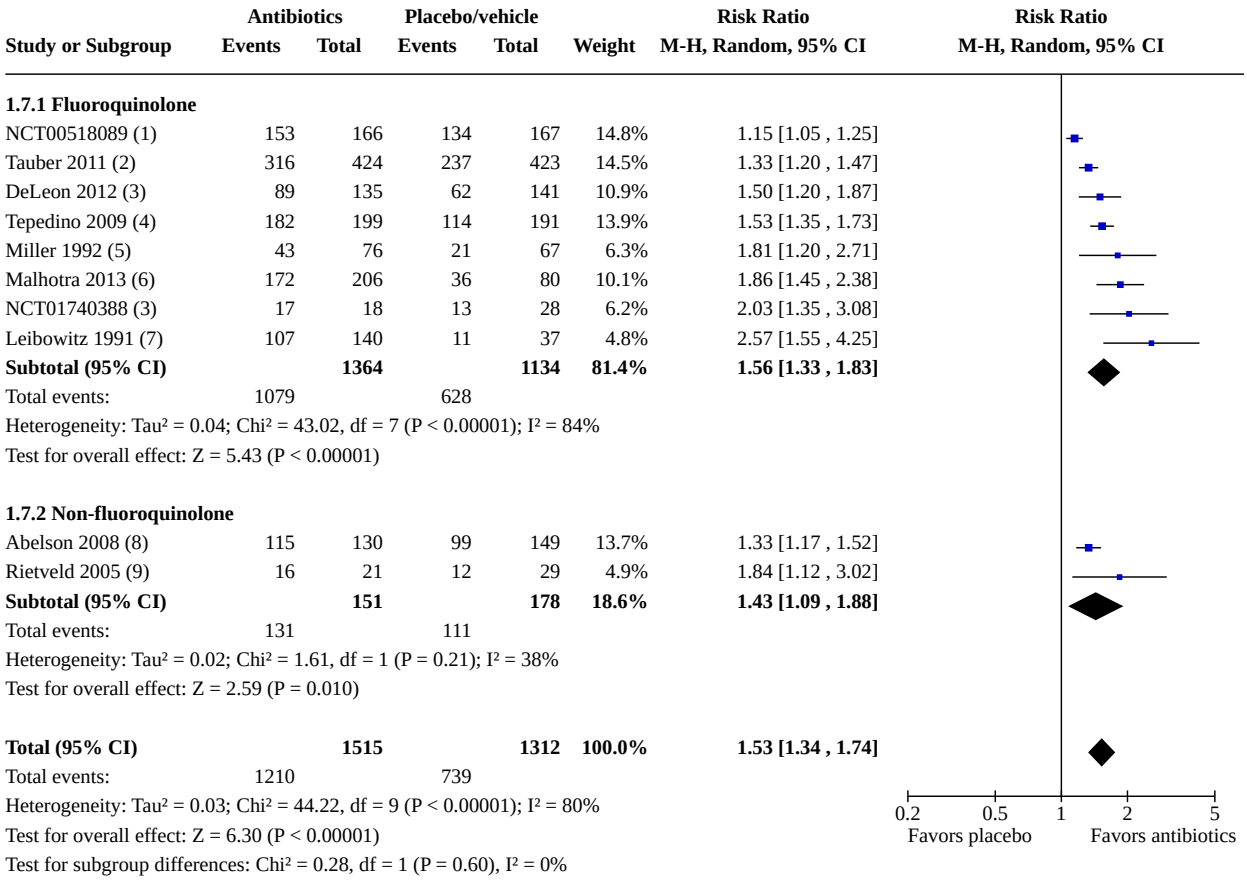
Overall, antibiotic therapy likely results in clinical cure after a treatment course of varying duration, either at the end-of-therapy or the test-of-cure visit. We rated the certainty of evidence for this outcome as moderate after downgrading it for risk of bias (-1).

Microbiological efficacy

Only one trial (Gigliotti 1984) assessed and reported microbiological cure rate at the end-of-therapy visit based on the ITT analysis. Topical antibiotics increased participants' likelihood of microbiological cure when compared with placebo at the end of therapy (RR 2.54, 95% CI 1.48 to 4.37; 1 trial, 66 participants; Analysis 1.6).

Another 10 trials (Abelson 2008; DeLeon 2012; Leibowitz 1991; Malhotra 2013; Miller 1992; NCT00518089; NCT01740388; Rietveld 2005; Tauber 2011; Tepedino 2009) reported microbiological efficacy outcomes at the end-of-therapy visit based on the mITT population. The combined estimate of RR was 1.53 (95% CI 1.34 to 1.74; I^2 = 80%; 10 trials, 2827 participants; Figure 4), an increase in microbiological cure by topical antibiotics by 53%. There was no evidence of subgroup differences by antibiotic class (P = 0.60).

Figure 4.



Footnotes

(1) Up to day 6, gatifloxacin 0.5%, end-of-therapy visit
(2) Day 4, moxifloxacin 0.5%, end-of-therapy visit, mixed pediatric and adult participants (including children < 1 years)
(3) Day 4 or 5, besifloxacin 0.6%, end-of-therapy visit
(4) Day 5, besifloxacin 0.6%, end-of-therapy visit
(5) Day 7 or 8, norfloxacin 0.3%, end-of-therapy visit
(6) Day 8 or 9, besifloxacin 0.6%, end-of-therapy visit
(7) Day 3, ciprofloxacin 0.3%, end-of-therapy visit
(8) Day 6 or 7, azithromycin 1%, end-of-therapy visit
(9) Day 8, fusidic acid gel, end-of-therapy visit

Using data from the mITT population, another 12 trials assessed and reported microbiological efficacy at the test-of-cure visit. The combined RR was comparable to that obtained at the end-of-therapy visit (RR = 1.38, 95% CI 1.27 to 1.50; I^2 = 48%; 12 trials, 2295 participants; Analysis 1.8); there was no evidence of subgroup differences by drug class (P = 0.40).

In the planned sensitivity analysis to exclude one trial that had enrolled infants younger than one month old (Leibowitz 1991), the resulting combined RR was similar (RR 1.48, 95% CI 1.30 to 1.67; I^2 = 78%; 9 trials, 2650 participants; Analysis 2.2).

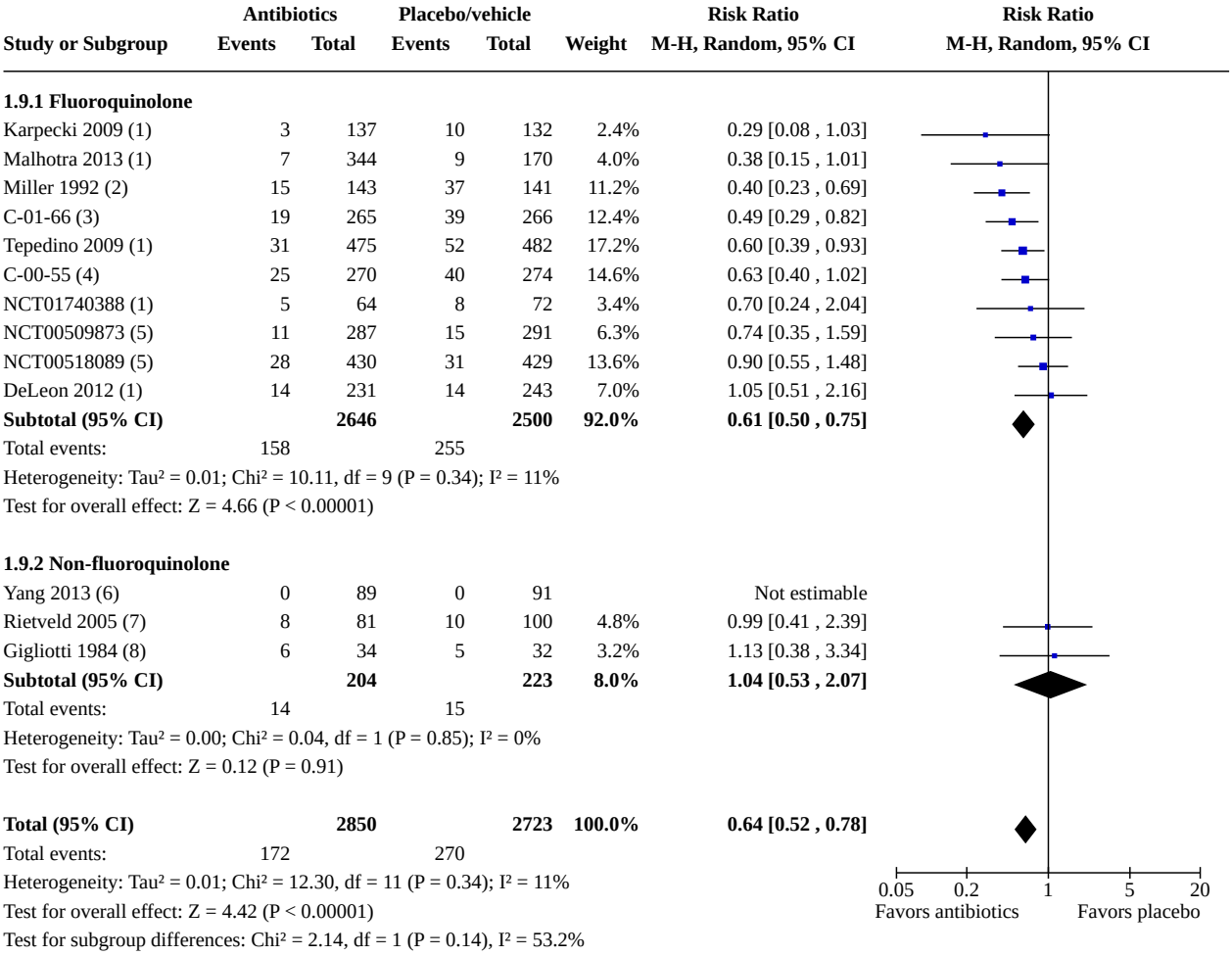
Overall evidence suggested that topical antibiotics may improve microbiological cure after one treatment course for acute bacterial conjunctivitis. The certainty of evidence was judged as moderate after we downgraded it for risk of bias (-1).

Important outcomes

Treatment incompletion

Thirteen trials (C-00-55; C-01-66; DeLeon 2012; Gigliotti 1984; Karpecki 2009; Kodjikian 2010; Kodjikian 2010; Malhotra 2013; Miller 1992; NCT00509873; NCT00518089; NCT01740388; Rietveld 2005; Tepedino 2009; Yang 2013) reported treatment incompletion rate. The combined RR was 0.64 (95% CI 0.52 to 0.78; I^2 = 11%; 14 trials, 5573 participants; Analysis 1.9), suggesting that antibiotic use may decrease treatment incompletion for patients with acute bacterial conjunctivitis when compared with placebo; there was no evidence of substantial subgroup differences (P = 0.14; Figure 5). We deemed the evidence for this outcome as of moderate certainty after downgrading it due to risk of bias (-1).

Figure 5.



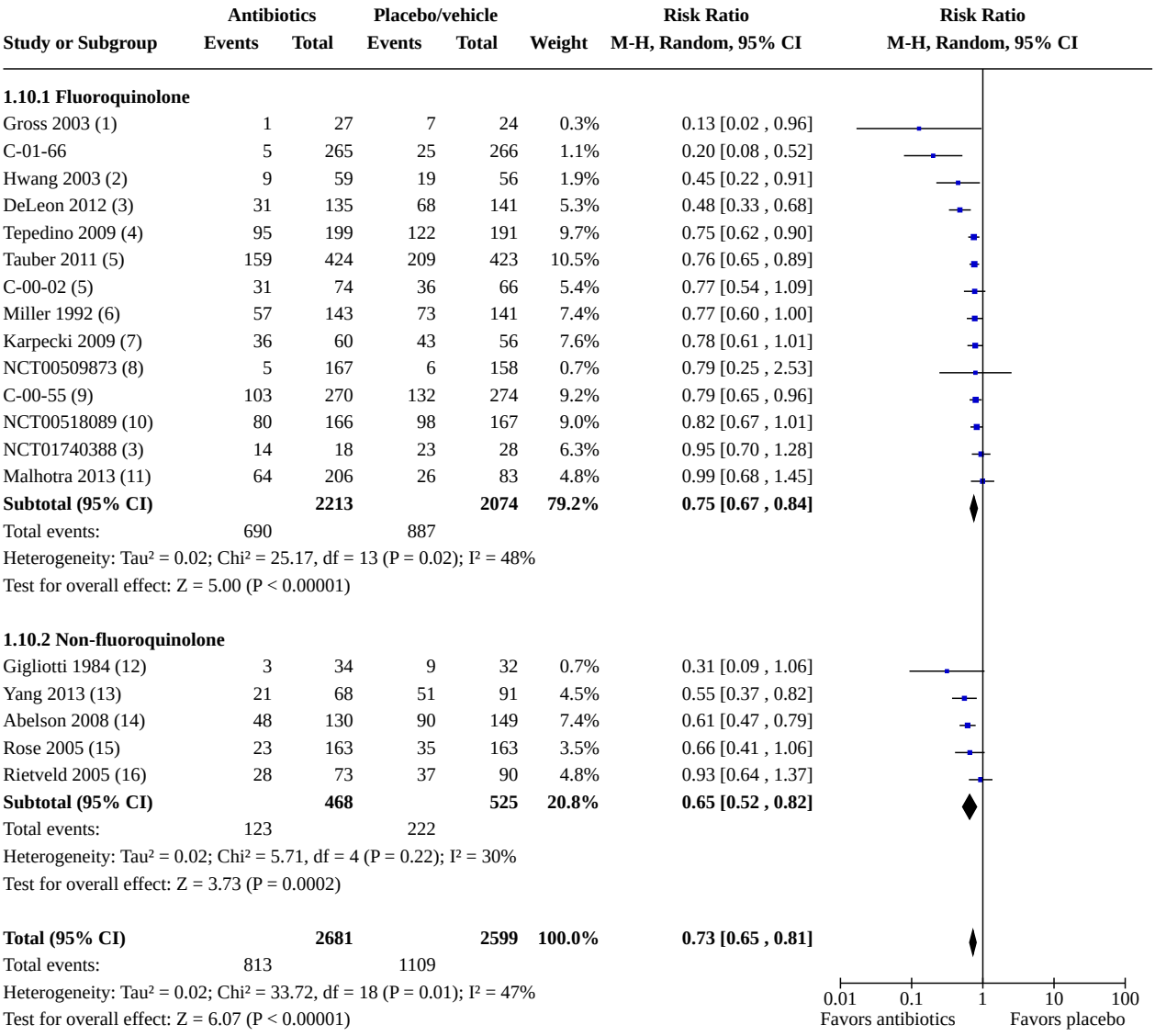
Footnotes

(1) Besifloxacin 0.6%
(2) Norfloxacin 0.3%
(3) Moxifloxacin 0.5%, data source: Kodijigan 2010
(4) Moxifloxacin 0.5%
(5) Gatifloxacin 0.5%
(6) Azithromycin 1%
(7) Fusidic acid gel
(8) Polymyxin + bacitracin

Persistent clinical infection

All included trials reported persistent clinical infection, resulting in a combined RR of 0.73 (95% CI 0.65 to 0.81; I^2 = 47%; 19 trials, 5280 participants; Figure 6) without evidence of subgroup differences (P = 0.29; Analysis 1.10).

Figure 6.



Footnotes

(1) Day 7, moxifloxacin 0.5%, test-of-cure visit
(2) Day 6 to 10, levofloxacin 0.5%, test-of-cure visit
(3) Day 4 or 5, besifloxacin 0.6%, end-of-therapy visit
(4) Day 5, besifloxacin 0.6%, end-of-therapy visit
(5) Day 4, moxifloxacin 0.5%, end-of-therapy visit
(6) Day 7 or 8, Norfloxacin 0.3%, end-of-therapy visit
(7) Day 4, besifloxacin 0.6%, end-of-therapy visit
(8) Day 6, gatifloxacin 0.5%, test-of-cure visit
(9) Day 5, moxifloxacin 0.5%, end-of-therapy visit
(10) Day 6, gatifloxacin 0.5%, end-of-therapy visit
(11) Day 8, besifloxacin 0.6%, end-of-therapy visit
(12) Day 8 to 10, polymyxin + bacitracin, end-of-therapy visit
(13) Day 8 or 9, azithromycin 1%, end-of-therapy visit
(14) Day 6 or 7, azithromycin 1%, test-of-cure visit
(15) Day 7, chloramphenicol 0.3%, end-of-study visit

Figure 6. (Continued)

(14) Day 6 or 7, azithromycin 1%, test-of-cure visit
(15) Day 7, chloramphenicol 0.3%, end-of-study visit
(16) Day 8, fusidic acid gel, end-of-therapy visit

Subgroup analysis by operational definition for determining 'persistence' did not reveal evidence of between-group differences (P = 0.56; Analysis 1.11). In contrast, subgroup analysis by time point of this outcome suggested considerable heterogeneity (P = 0.02; Analysis 1.12) between data reported at the end-of-therapy visit (RR 0.77, 95% CI 0.69 to 0.85; 12 trials, 4025 participants) and those at the test-of-cure visit (RR 0.59, 95% CI 0.49 to 0.71; 6 trials, 1255 participants). However, estimates of both subgroups were consistent and comparable.

Overall, topical antibiotics may decrease the risk of persistent clinical infection compared with placebo, with the certainty of evidence rated as moderate after we downgraded it for risk of bias (-1).

Cost-effectiveness of treatment

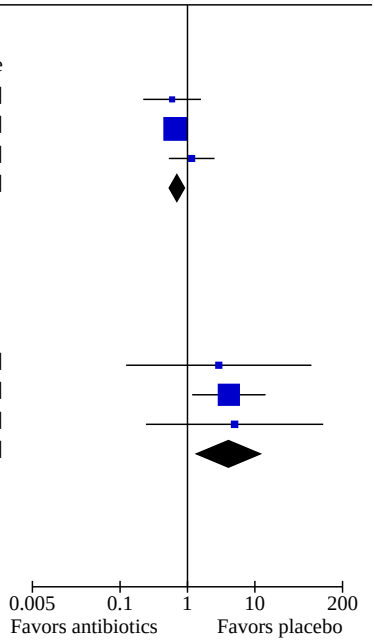
No included trials measured or reported this outcome.

Treatment-associated ocular complications

Seven trials reported treatment-related ocular adverse events (Comstock 2012; DeLeon 2012; Miller 1992; Rietveld 2005; Rose 2005; Tauber 2011; Tepedino 2009). Authors of Comstock 2012 reported only one ocular adverse event (eye pain) in one of the three arms (the combined tobramycin + LE group) but no other treatment-emergent events in the tobramycin or vehicle group. In contrast to a decreased risk of ocular complications associated with FQs (RR 0.70, 95% CI 0.54 to 0.90; P = 0.39, I^2 = 0%; 4 trials, 3455 participants; Figure 7) compared with placebo, non-FQs were associated with an increased risk of ocular side effects (RR 4.05, 95% CI 1.36 to 12.0; I^2 = 0%; 3 trials, 556 participants; Figure 7). Because of evidence of significant subgroup differences (P = 0.002), the two drug class subgroups were not combined (Analysis 1.13).

Figure 7.

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Fluoroquinolone						
Tauber 2011 (1)	0	593	0	586		Not estimable
Miller 1992 (2)	6	143	10	141	7.0%	0.59 [0.22 , 1.58]
Tepedino 2009 (3)	68	741	106	760	81.9%	0.66 [0.49 , 0.88]
DeLeon 2012 (4)	12	228	12	263	11.1%	1.15 [0.53 , 2.52]
Subtotal (95% CI)		**1705**		**1750**	**100.0%**	**0.70 [0.54 , 0.90]**
Total events:	86		128			
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
1.13.2 Non-fluoroquinolone						
Comstock 2012 (5)	1	34	0	33	11.8%	2.91 [0.12 , 69.08]
Rietveld 2005 (6)	10	73	3	90	75.3%	4.11 [1.17 , 14.38]
Rose 2005	2	163	0	163	12.9%	5.00 [0.24 , 103.35]
Subtotal (95% CI)		**270**		**286**	**100.0%**	**4.05 [1.36 , 12.00]**
Total events:	13		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Footnotes

(1) Moxifloxacin 0.5%, reporting threshold 5%
(2) Norfloxacin 0.3%
(3) Besifloxacin 0.6%, unit of analysis was eye, reporting threshold 0.5%
(4) Besifloxacin 0.6%, reporting threshold 0.5%
(5) Loteprednol etabonate + tobramycin ophthalmic suspension; the tobramycin alone group (n = 34) had no ocular adverse events
(6) Fusidic acid gel

We included nine trials that had reported item-wise treatment-related ocular adverse events in estimating incidence rate ratios (Abelson 2008; C-00-55; DeLeon 2012; Hwang 2003; Karpecki 2009; Malhotra 2013; NCT00518089; NCT01740388; Tepedino 2009). The combined rate ratio was 1.06 (95% CI 0.79 to 1.44; I^2 = 44%; 23,627 person-days; Analysis 1.14) with no evidence of subgroup differences (P = 0.14).

Additionally, we included 11 trials in estimating incidence rate differences (Abelson 2008; C-00-55; Comstock 2012; DeLeon 2012; Gigliotti 1984; Hwang 2003; Karpecki 2009; Malhotra 2013; NCT00518089; NCT01740388; Tepedino 2009). Although non-FQs may slightly increase the rate of ocular complications as compared to placebo by 2.45 events per 1000 person-days (95% CI 0.15 to 4.74; P = 0.90, I^2 = 0%; 3 trials, 4815 person-days; Analysis 1.15), there was no evidence of subgroup differences (P = 0.36; Analysis 1.15). The combined rate difference comparing antibiotics with placebo was 1.41 per 1000 person-days (95% CI -0.93 to 3.75; P = 0.24, I^2 = 25%; 11 trials, 25,027 person-days).

In post hoc sensitivity analysis, we further excluded Comstock 2012 that compared the combination therapy of tobramycin and steroid with vehicle and found no changes to the subgroup (Analysis 2.7) or overall (Analysis 2.8) results.

In brief, we concluded that non-FQ antibiotics, but not FQs, are likely to increase treatment-associated ocular complications. However, the certainty of evidence is very low because of risks of bias (-1) and extreme imprecision (-2).

Treatment-associated systemic complications

In Karpecki 2009 and Tepedino 2009, the investigators observed that headache was the most common non-ocular AE reported by both treatment groups. As in two other trials (C-00-02; C-00-55), headache occurred nearly evenly between the treatment groups. Overall, the combined RR was 1.12 (95% CI 0.69 to 1.81; 1910 participants), suggesting FQ eye drops may have few effects on participants' risk for headache (Analysis 1.16).

As the only non-ocular AE that is 'probably' treatment-related, dysgeusia was reported by one participant in the besifloxacin group (344 participants) in Malhotra 2013; none in the vehicle group complained about altered taste (170 participants). The single-study estimate was 1.49 (95% CI 0.06 to 36.31), indicating lack of evidence of an association (Analysis 1.16).

Overall, we found no evidence that antibiotics increase participants' risk of systemic complications. Nevertheless, we deemed the certainty of evidence on treatment-associated systemic complications as very low after downgrading it for extreme imprecision (-2) and risk of bias in selective reporting (-1).

DISCUSSION

[left for empty]

Summary of main results

In this review, we reported data from 21 double-masked, randomized, placebo-controlled trials that compared topical antibiotics with placebo in the treatment of acute bacterial conjunctivitis. The evidence is of moderate certainty that compared with placebo, antibiotics likely improved clinical cure at the end of therapy, increased treatment completion rates, and reduced persistent clinical infection after one course of treatment. The evidence also is of moderate certainty that compared with placebo, antibiotic use was associated with more participants with microbiological cure and resulted in better treatment adherence, perhaps because of the increased clinical efficacy of antibiotic compared with placebo. Overall, topical antibiotics may decrease the risk of persistent clinical infection by about 25%. The largest advantage conferred by antibiotics compared with placebo was in microbiological cure, where the proportion of cure was about 50% higher in the antibiotic group than the placebo group at the end-of-therapy time point. No study evaluated or reported the cost-effectiveness of antibiotic treatment in comparison with placebo. Because a participant can experience more than one adverse event per trial period, the incidence risk ratio was estimated, and the estimate was consistent with no difference between antibiotics and placebo in ocular complications. Compared with placebo, FQs may not increase participants' risk for treatment-associated eye discomfort, hypersensitivity, or other adverse events. This finding was not established for non-FQs. The certainty of evidence of ocular adverse effects or of frequently reported systemic complications such as headache or dysgeusia was very low.

Overall completeness and applicability of evidence

Population representativeness and diagnosis of acute bacterial conjunctivitis

We planned to include patients with acute bacterial conjunctivitis aged one month or older in the protocol (Sheikh 2000). However, the previous reviews (Sheikh 2006; Sheikh 2012) and the current review included one trial that enrolled infants younger than one month old (Leibowitz 1991). Our sensitivity analysis showed that the effect of antibiotics on clinical cure was not altered. The findings of the current review may be more applicable to acute bacterial conjunctivitis in the older pediatric and adult population than to neonatal bacterial conjunctivitis, which is usually caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae* contracted in the birth canal. Moreover, whereas the most common cause of acute bacterial conjunctivitis in the non-neonatal, pediatric population is *Haemophilus influenzae*, the most common etiology in adults is *Staphylococcus aureus* (Mahvan 2014).

It is noteworthy that, of participants in the placebo group, 55.5% (408/735) had spontaneous clinical resolution by days 4 to 9 vs. 68.2% (504/739) of participants treated with an antibiotic. This finding is consistent with clinical observations. In addition, this finding may argue against reflexive requirements of many school districts that children with conjunctivitis be prescribed an antibiotic before returning to school (Lee 2022). This finding was established amongst trials that reported mITT results, in which various classes of antibiotics for up to five days was clinically and microbiologically effective. Future trials examining the same antibiotics for different durations of therapy would help confirm or refute whether shorter treatment (up to 5 days) has different effects than longer treatment.

The diagnosis of bacterial conjunctivitis included in the primary studies of the current update was mostly, if not totally, based

on clinical grounds. 'Acute' was defined as symptoms of less than four weeks' duration as has been widely accepted clinically. However, the exact timing of disease onset was often poorly defined or not defined. Therefore, it was highly likely that after enrolling eligible participants in a trial, the disease might resolve spontaneously (without any antibiotic treatment) in less than four weeks. Of course, self-resolution would not be expected in cases of hyperacute conjunctivitis (usually caused by *Neisseria gonorrhoeae* or *Neisseria meningitides)* that can cause corneal ulceration, corneal opacification, corneal perforation, and panophthalmitis.

Because most cases of acute conjunctivitis present to primary or urgent care (i.e. non-ophthalmologists) and because many cases resolve without treatment, microbiological work-up (conjunctival swabs for culture) is rarely done in the clinical setting. Therefore, most studies enrolled and randomized clinically diagnosed cases of acute bacterial conjunctivitis. To recruit and enroll microbiologically confirmed cases of acute bacterial conjunctivitis would be difficult. Hence, most studies included in this review analyzed a mITT population - participants who were clinically diagnosed and randomized, then included in the analysis only when baseline culture results confirmed bacterial conjunctivitis.

Types of pharmacologic interventions

A variety of topical antibiotics were tested in the included trials. We further classified these antibiotics into FQ and non-FQ classes. FQs possess bactericidal effects by inhibiting the activity of bacterial DNA gyrase and/or topoisomerase, both of which are essential for bacterial DNA replication. In particular, newer FQs including besifloxacin target both enzymes, which may allow treatment duration to be shorter than older FQs targeting one enzyme or the other. The evidence suggested that FQs were effective in increasing clinical and microbiological cure compared with placebo. In contrast, non-FQs increased only the microbiological, not the clinical, efficacy of cure. In particular, results of subgroup analysis showed that a shorter treatment with FQ might be associated with a larger treatment effect than did a longer treatment with various non-FQ medications, some of which are bacteriostatic. However, because of the different drug classes of the non-FQs and different lengths of treatment, the evidence identified in the current update does not support any conclusions about head-to-head comparisons between FQ and non-FQ, as have been done in trials of non-ophthalmic preparations (Huang 2018; Ramos 2019). Further trials will be needed to compare classes of ophthalmic antibiotics. The World Health Organization has launched the AWaRe tool to classify antibiotics (a total of 258 in 2021) into three groups – access, watch and reserve – to curb antimicrobial resistance (WHO AWaRe 2021). Further studies will also compare the efficacy and safety for the antibiotics classified by the AWaRe tool. It is possible that future reviews will compare antiseptic treatment (for example, povidone iodine, against which there is little to no known resistance and which is low cost) with topical antibiotics.

Outcome measurement and report

The outcomes measured and reported in our review are comprehensive, including clinical efficacy, microbiological efficacy, adherence, persistent clinical infection, and treatment-associated adverse events (both ocular and non-ocular). Unfortunately, not all trials recorded (or reported) outcomes at the same treatment time points. Therefore, we chose to compare and report comparisons of the outcomes either at 'end-of-therapy' visit or 'test-of -cure' visit or both, depending on available data. Of note, treatment effects of two different antibiotics reported at the 'end-of-therapy' visit could have varied treatment durations. For example, clinical cure at the 'end-of-therapy' visit was assessed at day four after a 3-day course with mofloxacin 0.5% in C-00-02 but at day eight or nine after a 7-day course with azithromycin 1% in Yang 2013.

Findings of this update may be limited in providing evidence on comparative efficacy for short (3 to 5 days) versus long (≥ 7 days) courses of antibiotic therapy as the treatment duration varied by the specific antibiotics used. Only trials of a different duration of treatment with the same antibiotic would help answer the question of comparative efficacy.

Certainty of the evidence

Potential risk of bias amongst studies downgraded the certainty of the body of evidence to moderate for most outcomes. Although we did not include safety outcomes for risk of bias assessment using the RoB 2 tool, we judged that ocular and especially non-ocular adverse events were likely under-reported, resulting in further downgrading due to imprecision.

Quality of the evidence

[left for empty]

Potential biases in the review process

Throughout the review process, we applied standard Cochrane methods by conducting comprehensive searches in multiple databases; defining review eligibility criteria and outcomes, including evaluation time points, *a priori*; critical appraisal and data extraction by independent review authors; and transparent data analysis and consensus interpretation of analysis results. We also contacted study authors to request additional information about trial design (Kodjikian 2010) or the full-text article in the original publication language (Yang 2013). Therefore, the review process should have minimum bias.

Agreements and disagreements with other studies or reviews

The previous version of the review concluded that, compared with placebo, antibiotics are associated with modest improvements in clinical and bacterial remission rate (Sheikh 2012). Compared with the previous review in 2012, the current update included ten more studies and found similar conclusions about the treatment effects of antibiotics on clinical and microbiological cure.

A non-Cochrane systematic review published in 2014 included five trials that examined besifloxacin ophthalmic suspension 0.6% against placebo (4 trials, DeLeon 2012; Karpecki 2009; Silverstein 2011; Tepedino 2009) or moxifloxacin 0.5% (one trial, McDonald 2009) with a fixed treatment duration of five days (Mahvan 2014). The authors concluded that, when compared with placebo, besifloxacin improved clinical and microbiological efficacy at the end-of-the therapy visit (3 trials) or at the test-of-cure visit (1 trial, Karpecki 2009). However, as detailed in the Results section (see Results of the search), trial results of Silverstein 2011 and DeLeon 2012 should not be interpreted separately

because the former was an interim report of the latter. Notably, the authors warned against the interpretation of results in Karpecki 2009 when comparing antibiotics to a non-active control because the vehicle (benzalkonium chloride 0.01%) used in the trial as placebo preservative was later found to provide synergistic effects when combined with FQ (Hesje 2009). We therefore performed post hoc sensitivity analysis to exclude Karpecki 2009 from relevant analyses (Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6) but did not find our conclusions altered.

A more recently published non-Cochrane meta-analysis by Wang and colleagues further investigated the treatment efficacy of besifloxacin against other treatments (2 trials) or placebo (4 trials, Wang 2019). The authors included DeLeon 2012; Karpecki 2009; Malhotra 2013; and Tepedino 2009 as we did, but reported additional data of clinical and microbiological eradication rates by selected Gram-positive strains, Gram-negative strains, overall and by individual bacterial species (Wang 2019). In addition to reporting higher clinical and microbiological efficacy of besifloxacin compared with placebo, the authors noted that the combined estimated number of AEs was higher in the placebo group than that in the besifloxacin group. However, they did not clearly define AEs (ocular or non-ocular, by person or by incident) a priori.

Both of the two non-Cochrane reviews (Mahvan 2014; Wang 2019) additionally compared the treatment effects between besifloxacin and other antibiotics, which was beyond the scope of the current update and might be subject to evidence synthesis using network meta-analysis.

AUTHORS' CONCLUSIONS

Implications for practice

Acute bacterial conjunctivitis remains almost entirely a clinical diagnosis with few physicians performing microbiological evaluation at the outset of symptoms or after test-of-cure or end-of-therapy with antibiotics of various drug classes. Cultures, however, are needed in neonates with presumed bacterial conjunctivitis and in older patients with recurrent, severe, and chronic purulent conjunctivitis or in drug resistance.

Although it can be a self-limited disease, evidence from this updated review was of moderate certainty to support the use of antibiotics over placebo in clinical resolution and microbiological cure. The evidence is less certain about treatment-induced ocular adverse effects. Although non-FQs offer clinical efficacy as do FQs, very low level-certainty evidence suggests non-FQs increase risks of ocular adverse effects when compared with placebo in contrast with FQs, which may decrease the risk of such effects. Since no serious complications were reported in the antibiotics arm, antibiotic therapy is a reasonable treatment which offers benefits in improving symptoms/signs and bacterial cure.

Implications for research

Further research is required to assess the clinical and microbiological efficacy amongst different antibiotics or bacterial species. The answer to this question could be determined in head-to-head trials especially as there was a suggestion from the current review that non-FQs were not as efficacious in clinical or microbiological cure as were FQs though the evidence was of very low certainty: trials were of different duration, antibiotic classes, and dosing frequency. Future research would be bolstered by attainment of consensus on time points at which efficacy outcomes are assessed and recorded, whether at end-of-therapy or at a later point as in some trials in this review.

Patient-important outcomes, such as cost-effectiveness measures, would be important to examine. Costs could be divided into direct and indirect costs that are incurred (or saved). Direct costs would include the cost of a doctor's visit to obtain a diagnosis and prescription for antibiotic and the cost of the antibiotic. Indirect costs would include time off from work or school. For children, the costs would include time off for parents or guardians to accompany them to doctors' visits and to care for them at home if they are not allowed at school.

Another outcome important to patients is shorter duration of treatment, which may be associated with adherence to therapy and lower cost. For this outcome, trials with a different duration of an antibiotic vs. placebo could be performed. Additionally, reviews of trials of antiseptic agents versus topical antibiotics should be performed for reasons of lower cost of antiseptic agents like povidone iodine and concerns of growing antibiotic resistance.

ACKNOWLEDGEMENTS

Acknowledgements from the authors

We would like to acknowledge the contributions of Aziz Sheikh (Uversity of Edinburgh), Brian Hurwitz (King's College London), James Cave (The Downland Practice, Newbury), and Susannah McLean (University of Edinburgh) on the previous versions of the review.

Editorial and peer-reviewer contributions

CEV@US supported the authors in the development of this update. The following people conducted the editorial process for this update:

- Sign-off Editors (final editorial decision): Dr. Tianjing Li (University of Colorado Anschutz Medical Campus), Dr. Gianni Virgilli (Queen's University Belfast)
- Managing Editor and Assistant Managing Editors (selected peer reviewers, collated peer-reviewer comments): Anupa Shah (Queen's University Belfast); Louis Leslie (University of Colorado Anschutz Medical Campus), Genie Han (Johns Hopkins University)
- Methodologist (provided methodological and editorial guidance to authors, edited the article): Valerie Tsz Wing Yim (University of Colorado Anschutz Medical Campus)
- Information Specialist: Iris Gordon (CEV)
- Copy Editor: Anne Lethaby (Cochrane Central Editorial Service)
- Peer reviewers: Dr. Darren Ting (University of Nottingham) and an anonymous reviewer

REFERENCES

References to studies included in this review

Abelson 2008 *{published data only}*

* Abelson MB, Heller W, Shapiro AM, Si E, Hsu P, Bowman LM. Clinical cure of bacterial conjunctivitis with azithromycin 1%: vehicle-controlled, double-masked clinical trial. *American Journal of Ophthalmology* 2008;**145**:959-65.

NCT00105534. Evaluation of clinical and microbial efficacy and safety of Azasite compared to vehicle for bacterial conjunctivitis (C-01-401-003). clinicaltrials.gov/ct2/show/NCT00105534 (first received 16 Mar 2005).

C-00-02 *{published data only}*

* Center for Drug Evaluation and Research. Medical Officer's Review of NDA - Application Number 21-598. www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-598_Vigamox_medr.PDF (accessed 23 May 2022).

Kodjikian L, Lafuma A, Khoshnood B, Laurendeau C, Berdeaux G. [Efficacy of moxifloxacin in treating bacterial conjunctivitis: a meta-analysis]. *Journal of French Ophthalmology* 2010;**33**(4):227-33.

C-00-55 *{published data only}*

Alcon Pharma GmbH. Moxifloxacin Alcon Eye drops, solution - DE/H/1588/001/DC. regroup-production.s3.amazonaws.com/documents/ReviewReference/496258225/RMS-h102202.pdf (accessed 01 June 2022).

* Center for Drug Evaluation and Research. Medical Officer's Review of NDA - Application Number 21-598. www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-598_Vigamox_medr.PDF (accessed 23 May 2022).

Kodjikian L, Lafuma A, Khoshnood B, Laurendeau C, Berdeaux G. [Efficacy of moxifloxacin in treating bacterial conjunctivitis: a meta-analysis]. *Journal of French Ophthalmology* 2010;**33**(4):227-33.

C-01-66 *{published data only}*

Kodjikian L, Lafuma A, Khoshnood B, Laurendeau C, Berdeaux G. [Efficacy of moxifloxacin in treating bacterial conjunctivitis: a meta-analysis]. *Journal of French Ophthalmology* 2010;**33**(4):227-33.

Comstock 2012 *{published data only}*

Comstock Tl, Paterno MR, Bateman KM, Decory HH, Gearinger M. Safety and tolerability of loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension in pediatric subjects. *Paediatric Drugs* 2012;**14**(2):119-30.

DeLeon 2012 *{published data only}*

* DeLeon J, Silverstein BE, Allaire C, Gearinger LS, Bateman KM, Morris TW, Comstock TL. Besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days in the treatment of bacterial conjunctivitis in adults and children. *Clinical Drug Investigation* 2012;**32**(5):303-17.

Haas W, Gearinger LS, Hesje CJ, Sanfilippo CM, Morris TW. Microbiological etiology and susceptibility of bacterial conjunctivitis isolates from clinical trials with ophthalmic, twice-daily besifloxacin. *Advances in Therapy* 2012;**29**(5):442-55.

NCT00972777. Efficacy of besifloxacin ophthalmic suspension in the treatment of bacterial conjunctivitis. www.clinicaltrials.gov/ct2/show/NCT00972777 (first received 9 September 2009).

Silverstein BE, Allaire C, Bateman KM, Gearinger LS, Morris TW, Comstock TL. Efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days in the treatment of bacterial conjunctivitis: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study in adults and children. *Clinical Therapeutics* 2011;**33**(1):13-26.

Gigliotti 1984 *{published data only}*

Gigliotti F, Hendley JO, Morgan J, Michaels R, Dickens M, Lohr J. Efficacy of topical antibiotic therapy in acute conjunctivitis in children. *Journal of Pediatrics* 1984;**104**:623-6.

Gross 2003 *{published data only}*

Gross RD, Lichtenstein SJ, Schlech BA, Gower LA, Potts SL. Early clinical and microbiological responses in the treatment of bacterial conjunctivitis with moxifloxacin ophthalmic solution 0.5% (Vigamox TM) using b.i.d dosing. *Today's Therapeutic Trends* 2003;**21**(2):227-37.

Hwang 2003 *{published data only}*

Hwang DG, Schanzlin DJ, Rotberg MH, Foulks G, Raizman MB. A phase III, placebo controlled clinical trial of 0.5% levofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis. *British Journal of Ophthalmology* 2003;**87**(8):1004-9.

Karpecki 2009 *{published data only}*

* Karpecki P, DePaolis M, Hunter JA, White EM, Rigel L, Brunner LS, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: a multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. *Clinical Therapeutics* 2009;**31**(3):514-26.

NCT00622908. Clinical and microbial efficacy of ISV403 in bacterial conjunctivitis. clinicaltrials.gov/ct2/show/NCT00622908 (first received 25 February 2008).

Leibowitz 1991 *{published data only}*

Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. *American Journal of Ophthalmology* 1991;**112**:29S-33S.

Malhotra 2013 *{published data only}*

* Malhotra R, Ackerman S, Gearinger LS, Morris TW, Allaire C. The safety of besifloxacin ophthalmic suspension 0.6 % used three times daily for 7 days in the treatment of bacterial conjunctivitis. *Drugs Research & Development* 2013;**13**(4):243-52.

NCT01175590. Safety of Besivance™ (Besifloxacin ophthalmic suspension) 0.6% compared to vehicle. clinicaltrials.gov/ct2/show/NCT01175590 (first received 5 August 2010).

Miller 1992 *{published data only}*

Miller IM, Wittreich J, Vogel R, Cook TJ. The safety and efficacy of topical norfloxacin compared with placebo in the treatment of acute, bacterial conjunctivitis. *European Journal of Ophthalmology* 1992;**2**:58-66.

NCT00509873 *{published data only}*

Heller W, Cruz M, Bhagat Yr, De Leon Jm, Felix C, Villanueva L, et al. Gatifloxacin 0.5% administered twice daily for the treatment of acute bacterial conjunctivitis in patients one year of age or older. *Journal of Ocular Pharmacology and Therapeutics* 2014;**30**(10):815-22.

* NCT00509873. A study of the safety and efficacy of gatifloxacin in patients with bacterial conjunctivitis. clinicaltrials.gov/ct2/show/NCT00509873 (first received 1 August 2007).

NCT00518089 *{published data only}*

Heller W, Cruz M, Bhagat Yr, De Leon Jm, Felix C, Villanueva L, et al. Gatifloxacin 0.5% administered twice daily for the treatment of acute bacterial conjunctivitis in patients one year of age or older. *Journal of Ocular Pharmacology and Therapeutics* 2014;**30**(10):815-22.

* NCT00518089. A study of the safety and efficacy of gatifloxacin in patients with bacterial conjunctivitis. clinicaltrials.gov/ct2/show/NCT00518089 (first received 20 August 2007).

NCT01740388 *{published data only}*

NCT01740388. Clinical and microbial efficacy of besifloxacin ophthalmic suspension, 0.6% in the treatment of bacterial conjunctivitis. clinicaltrials.gov/ct2/show/NCT01740388 (first received 4 December 2012).

Rietveld 2005 *{published data only}*

* Rietveld RP, Ter Riet G, Bindels PJ, Bink D, Sloos JH, Van Weert HC. The treatment of acute infectious conjunctivitis with fusidic acid: a randomised controlled trial. *British Journal of General Practice* 2005;**55**:924-30.

Rose 2005 *{published data only}*

* Rose PW, Harnden A, Brueggemann AB, Perera R, Sheikh A, Crook D, et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomised double-blind placebo-controlled trial. *Lancet* 2005;**366**:37-43.

Tauber 2011 *{published data only}*

NCT00759148. Moxifloxacin AF ophthalmic solution for treatment of bacterial conjunctivitis. clinicaltrials.gov/ct2/show/NCT00759148 (first received 25 September 2008).

* Tauber S, Cupp G, Garber R, Bartell J, Vohra F, Stroman D. Microbiological efficacy of a new ophthalmic formulation of moxifloxacin dosed twice-daily for bacterial conjunctivitis. *Advances in Therapy* 2011;**28**(7):566-74.

Tepedino 2009 *{published data only}*

NCT00347932. A study to determine if 0.6% ISV-403 is safe and effective in the treatment of bacterial conjunctivitis. clinicaltrials.gov/ct2/show/NCT00347932 (first received 4 July 2006).

* Tepedino ME, Heller WH, Usher DW, Brunner LS, Morris TW, Haas W, et al. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. *Current Medical Research and Opinion* 2009;**25**(5):1159-69.

Yang 2013 *{published data only}*

* Yang SS, Pan XJ, Wang HG, Zhao GQ. A randomized, double-blind and placebo-controlled clinical trail of topical administration of 1% azithromycin eye drops for acute bacterial conjunctivitis. *Zhonghua Shiyan Yanke Zazhi [Chinese Journal of Experimental Ophthalmology]* 2013;**31**(2):182-5.

References to studies excluded from this review

Belfort 2012 *{published data only}*

Belfort R Jr, Gabriel L, Martins Bispo PJ, Muccioli C, Zacharias Serapicos PC, Clark L, et al. Safety and efficacy of moxifloxacin-dexamethasone eyedrops as treatment for bacterial ocular infection associated with bacterial blepharitis. *Advances in Therapy* 2012;**29**(5):416-26.

Bremond-Gignac 2010 *{published data only}*

Bremond-Gignac D, Mariani-Kurkdjian P, Beresniak A, El Fekih L, Bhagat Y, Pouliquen P, et al. Efficacy and safety of azithromycin 1.5% eye drops for purulent bacterial conjunctivitis in pediatric patients. *Pediatric Infectious Disease Journal* 2010;**29**(3):222-6.

Bremond-Gignac 2014 *{published data only}*

Bremond-Gignac D, Nezzar H, Bianchi PE, Messaoud R, Lazreg S, Voinea L, et al. Efficacy and safety of azithromycin 1.5% eye drops in paediatric population with purulent bacterial conjunctivitis. *British Journal of Ophthalmology* 2014;**98**(6):739-45.

Bremond-Gignac 2015 *{published data only}*

Bremond-Gignac D, Messaoud R, Lazreg S, Speeg-Schatz C, Renault D, Chiambaretta F, et al. A 3-day regimen with azithromycin 1.5% eyedrops for the treatment of purulent bacterial conjunctivitis in children: efficacy on clinical signs and impact on the burden of illness. *Clinical Ophthalmology* 2015;**9**:725-32.

Denis 2008 *{published data only}*

Denis F, Chaumeil C, Goldschmidt P, Delval L, Pouliquen P, Cochereau I, et al. Microbiological efficacy of 3-day treatment with azithromycin 1.5% eye-drops for purulent bacterial conjunctivitis. *European Journal of Ophthalmology* 2008;**18**(6):858-68.

Everitt 2006 *{published data only}*

Everitt HA, Little PS, Smith PW. A randomised controlled trial of management strategies for acute infective conjunctivitis in general practice. *BMJ* 2006;**333**(7563):321.

Granet 2008 *{published data only}*

Granet DB, Dorfman M, Stroman D, Cockrum P. A multicenter comparison of polymyxin B sulfate/trimethoprim ophthalmic solution and moxifloxacin in the speed of clinical efficacy for the treatment of bacterial conjunctivitis. *Journal of Pediatric Ophthalmology and Strabismus* 2008;**45**(6):340-9.

Leibowitz 1976 *{published data only}*

Leibowitz HM, Pratt MV, Flagstad IJ, Berrospi AR, Kundsin R. Human conjunctivitis. II. Treatment. *Archives of Ophthalmology* 1976;**94**:1752-6.

McDonald 2009 *{published data only}*

McDonald MB, Protzko EE, Brunner LS, Morris TW, Haas W, Paterno MR, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. *Ophthalmology* 2009;**116**(9):1615-23.

Mitsui 1986 *{published data only}*

Mitsui Y, Matsuda H, Miyajima T, Tazawa, Kumagai S. Therapeutic effects of ofloxacin eye drops (DE-055) on external infection of the eye: multicentral double blind test. *Japanese Review of Clinical Ophthalmology* 1986;**80**:1813-28.

Robert 2010 *{published data only}*

Robert PY, Bourcier T, Meddeb-Ouertani A, Khairallah M, Zaghloul K, Amraoui A, et al. Efficacy assessment of azithromycin 1.5% eye drops versus tobramycin 0.3% on clinical signs of purulent bacterial conjunctivitis [Evaluation de l'efficacité d'un collyre azithromycine 1,5% versus tobramycine 0,3% sur les signes cliniques de la conjonctivite bactérienne purulente]. *Journal Français D'Ophtalmologie* 2010;**33**(4):241-8.

Szaflik 2009 *{published data only}*

Szaflik J, Szaflik JP, Kaminska A, Levofloxacin Bacterial Conjunctivitis Dosage Study Group. Clinical and microbiological efficacy of levofloxacin administered three times a day for the treatment of bacterial conjunctivitis. *European Journal of Ophthalmology* 2009;**19**(1):1-9.

Ta 2007 *{published data only}*

Ta CN, Sinnar S, He L, Myung D, Mino De Kaspar H. Prospective randomized comparison of 1-day versus 3-day application of topical levofloxacin in eliminating conjunctival flora. *European Journal of Ophthalmology* 2007;**17**(5):689-95.

Zhang 2019 *{published data only}*

Zhang Y, He X, Yin Z, Wang L, Li L, Zhang H, et al. Efficacy and safety of pazufloxacin mesylate eye drops for bacterial conjunctivitis: a multicenter randomized, double-masked, parallel controlled clinical trial. *Zhonghua Shiyan Yanke Zazhi [Chinese Journal of Experimental Ophthalmology]* 2019;**37**(7):546-52.

References to studies awaiting assessment

NCT02432807 *{published data only}*

NCT02432807. Safety and efficacy of vancomycin ophthalmic ointment in patients with moderate to severe bacterial conjunctivitis. clinicaltrials.gov/ct2/show/NCT02432807 (first received 4 May 2015).

Ofloxacin 1990 *{published data only}*

Oxfloxacin Study Group III. A placebo-controlled clinical study of the fluoroquinolone ofloxacin in patients with external ocular infection. *Investigative Ophthalmology & Visual Science* 1990;**31**:Abstract number 2803.

Additional references

Ahovuo-Saloranta 2008

Ahovuo-Saloranta A, Borisenko OV, Kovanen N, Varonen H, Rautakorpi UM, Williams JW Jr, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No: CD000243. [DOI: 10.1002/14651858.CD000243.pub2]

Ahovuo-Saloranta 2014

Ahovuo-Saloranta A, Rautakorpi UM, Borisenko OV, Liira H, Williams JW Jr, Mäkelä M. Antibiotics for acute maxillary sinusitis in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No: CD000243. [DOI: 10.1002/14651858.CD000243.pub3]

Ballouz 2019

Ballouz D, Maganti N, Tuohy M, Errickson J, Woodward MA. Medication burden for patients with bacterial keratitis. *Cornea* 2019;**38**(8):933-7.

CDC 2019

Centers for Disease Control and Prevention. Sinus infection (sinusitis). www.cdc.gov/antibiotic-use/sinus-infection.html (accessed 30 August 2022).

CDC 2021a

Centers for Disease Control and Prevention. Ear infection. www.cdc.gov/antibiotic-use/ear-infection.html (accessed 30 August 2022).

CDC 2021b

Centers for Disease Control and Prevention. Sore throat. www.cdc.gov/antibiotic-use/sore-throat.html (accessed 30 August 2022).

Covidence [Computer program]

Covidence. Melbourne, Australia: Veritas Health Innovation, Accessed 27 April 2022. Available at covidence.org.

D'Oria 2023

D'Oria F, Buonamassa R, Rizzo T, Boscia F, Alessio G, Guerriero S. Bacterial isolates and antimicrobial susceptibility pattern of ocular infection at a tertiary referral hospital in the South of Italy. *European Journal of Ophthalmology* 2023;**33**(1):370-6.

Dart 1986

Dart JK. Eye disease at a community health centre. *BMJ* 1986;**293**(6560):1477-80.

Deeks 2022

Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Del Mar 2004

Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No: CD000023. [DOI: 10.1002/14651858.CD000023.pub3]

Everitt 2002

Everitt H, Little P. How do GPs diagnose and manage acute infective conjunctivitis? A GP survey. *Family Practice* 2002;**19**(6):658-60.

Falagas 2008

Falagas ME, Giannopoulou KP, Vardakas KZ, Dimopoulos G, Karageorgopoulos DE. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. *Lancet Infectious Diseases* 2008;**8**(9):543-52.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;**94**(2):130-6.

Glasziou 2004

Glasziou PP, Del Mar CB, Sanders SL, Hayem M. Antibiotics versus placebo for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No: CD000219. [DOI: 10.1002/14651858.CD000219.pub2]

Heller 2014

Heller W, Cruz M, Bhagat YR, De Leon JM, Felix C, Villanueva L, et al. Gatifloxacin 0.5% administered twice daily for the treatment of acute bacterial conjunctivitis in patients one year of age or older. *Journal of Ocular Pharmacology and Therapeutics* 2014;**30**(10):815-22.

Hesje 2009

Hesje CK, Borsos SD, Blondeau JM. Benzalkonium chloride enhances anti-bacterial activity of gatifloxacin and reduces its propensity to select for fluoroquinolone-resistant strains. *Journal of Ocular Pharmacology and Therapeutics* 2009;**25**(4):329-34.

Higgins 2022

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Hlatky 2006

Hlatky MA, Owens DK, Sanders GD. Cost-effectiveness as an outcome in randomized clinical trials. *Clinical Trials* 2006;**3**(6):543-51.

Hovding 1991

Hovding G, Bratland SZ, Digranes A. Rodt Oye - Praktisk Veiledning i Allmenn Praksis. Oslo: Lovens Kemiske Fabrik, 1991.

Hovding 2008

Hovding G. Acute bacterial conjunctivitis. *Acta Ophtalmologica* 2008;**86**(1):5-17.

Huang 2018

Huang YC, Lin YT, Wang FD. Comparison of the therapeutic efficacy of fluoroquinolone and non-fluoroquinolone treatment in patients with Elizabethkingia meningoseptica bacteraemia. *International Journal of Antimicrobial Agents* 2018;**51**(1):47-51.

Hurwitz 2005

Hurwitz B, Sheikh A. Topical antibiotics for acute bacterial conjunctivitis: Cochrane systematic review and meta-analysis update. *British Journal of General Practice* 2005;**55**(521):962-4.

Jefferis 2011

Jefferis J, Perera R, Everit H, Van Weert H, Rietveld R, Glasziou P, et al. Acute infective conjunctivitis in primary care: who needs antibiotics? An individual patient data-analysis. *British Journal of General Practice* 2011;**61**(690):e542-8.

Kodjikian 2010

Kodjikian L, Lafuma A, Khoshnood B, Laurendeau C, Berdeaux G. Efficacy of moxifloxacin in treating bacterial conjunctivitis: a meta-analysis [Efficacité de la moxifloxacine dans le traitement de la conjonctivite bactérienne aiguë: une méta-analyse]. *Journal Francais D'Ophtalmologie* 2010;**33**(4):227-33.

Lancaster 1998

Lancaster T, Swart AM, Jick H. Risk of serious haematological toxicity with use of chloramphenicol eye drops in a British general practice database. *BMJ* 1998;**316**(7132):667.

Lee 2022

Lee T, Kuo IC. Survey of state conjunctivitis policies for school-aged students. *Journal of American Association for Pediatric Ophthalmology and Strabismus* 2022;**26**(3):115.e1-115.e5.

Li 2022

Li T, Higgins JPT, Deeks JJ. Chapter 5: Collecting data. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Mahvan 2014

Mahvan TD, Hornecker JR, Buckley WA, Clark S. The role of besifloxacin in the treatment of bacterial conjunctivitis. *Annals of Pharmacotherapy* 2014;**48**(5):616-25.

McCormick 1995

McCormick A, Fleming D, Charlton J. Morbidity Statistics from General Practice. Fourth National Study 1991-2. London: HMSO, 1995.

McDonnell 1988

McDonnell PJ. How do general practitioners manage eye disease in the community? *British Journal of Ophthalmology* 1988;**72**(10):733-6.

McKenzie 2022a

McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV. Chapter 9: Summarizing study characteristics and preparing for synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

McKenzie 2022b

McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

McLean 2010

McLean S, Sheikh A. Effectiveness, tolerability and safety of azithromycin 1% in DuraSite for acute bacterial conjunctivitis. *Patient Preference and Adherence* 2010;**4**:69-76.

MECIR Standards 2022

Higgins JPT, Lasserson T, Chandler J, Tovey D, Thomas J, Flemyng E, et al. Methodological Expectations of Cochrane Intervention Reviews (Cochrane: London, Version February 2022). community.cochrane.org/mecir-manual/key-points-and-introduction/how-cite-mecir-standards accessed prior to 5 March 2023.

NCT01175590

NCT01175590. Safety of Besivance™ (Besifloxacin ophthalmic suspension) 0.6% compared to vehicle. clinicaltrials.gov/ct2/show/NCT01175590 (first received 5 August 2010).

NDA-21-598

Center for Drug Evaluation and Research. Medical Officer's Review of NDA - Application Number 21-598. www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-598_Vigamox_medr.PDF (accessed 23 May 2022).

Peng 2018

Peng MY, Cevallos V, McLeod SD, Lietman TM, Rose-Nussbaumer J. Bacterial keratitis: isolated organisms and antibiotic resistance patterns in San Francisco. *Cornea* 2018;**37**(1):84-7.

Ramos 2019

Ramos K, Allen B, Cannon C, Cunningham K, Tucker C. Comparison of fluoroquinolone versus non-fluoroquinolone therapy for inpatient treatment of chronic obstructive pulmonary disease exacerbations. *Journal of Pharmacy Technology* 2019;**35**(6):251-7.

RevMan Web [Computer program]

Review Manager Web (RevMan Web). Version 4.2.1. The Cochrane Collaboration, 2022. Available at revman.cochrane.org.

RMS Public Assessment Report

Alcon Pharma GmbH. Moxifloxacin Alcon Eye drops, solution - DE/H/1588/001/DC.. regroup-production.s3.amazonaws.com/documents/ReviewReference/496258225/RMS-h102202.pdf (accessed 01 June 2022).

Rose 2006

Rose PW, Ziebland S, Harnden A, Mayon-White R, Mant D, Oxford Childhood Infection Study group (OXCIS). Why do general practitioners prescribe antibiotics for acute infective conjunctivitis in children? Qualitative interviews with GPs and a questionnaire survey of parents and teachers. *Family Practice* 2006;**23**(2):226-32.

Rose 2007

Rose P. Management strategies for acute infective conjunctivitis in primary care: a systematic review. *Expert Opinion in Pharmacotherapy* 2007;**8**(12):1903-21.

Rosenfeld 2007

Rosenfeld RM, Singer M, Jones S. Systematic review of antimicrobial therapy in patients with acute rhinosinusitis. *Otolaryngology - Head and Neck Surgery* 2007;**137**(3 Suppl):S32-S45.

Schünemann 2022a

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Schünemann 2022b

Schünemann HJ, Neumann I, Hultcrantz M, Brignardello-Petersen R, Zeng L, Murad MH, et al, for the GRADE Working Group. GRADE Guidance article 35: Update on rating imprecision for assessing contextualized certainty of evidence and making decisions. Journal of Clinical Epidemiology 2022 (Epub online). [DOI: doi.org/10.1016/j.jclinepi.2022.07.015]

Silverstein 2011

Silverstein BE, Allaire C, Bateman KM, Gearinger LS, Morris TW, Comstock TL. Efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days in the treatment of bacterial conjunctivitis: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study in adults and children. *Clinical Therapeutics* 2011;**33**(1):13-26.

Wald 1997

Wald ER. Conjunctivitis in infants and children. *Pediatric Infectious Diseases Journal* 1997;**16**:S17-20.

Walker 1998

Walker S, Diaper CJ, Bowman R, Sweeney G, Seal DV, Kirkness CM. Lack of evidence for systemic toxicity following topical chloramphenicol use. *Eye (London)* 1998;**12** (Pt 5):875-9.

Wang 2019

Wang JJ, Gao XY, Li HZ, Du SS. Treating with besifloxacin for acute bacterial conjunctivitis: a meta-analysis. *International Journal of Ophthalmology* 2019;**12**(12):1898-907.

WHO AWaRe 2021

WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, 2021 (Geneva: World Health Organization; 2021 (WHO/MHP/HPS/EML/2021.04)). Available at www.who.int/publications/i/item/2021-aware-classification (accessed prior to 5 March 2023).

References to other published versions of this review

Sheikh 2000

Sheikh A, Hurwitz B, Cave J. Antibiotics for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2000, Issue 2. Art. No: CD001211. [DOI: 10.1002/14651858.CD001211]

Sheikh 2006

Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No: CD001211. [DOI: 10.1002/14651858.CD001211.pub2]

Sheikh 2012

Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No: CD001211. [DOI: 10.1002/14651858.CD001211.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abelson 2008

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (block randomization) **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" **Study visits and time points:** visit 1 (day 1, study entry), visit 2 (day 3 or 4), and visit 3 (day 6 or 7) **Treatment duration:** 5 days **How missing data was handled:** "If data were missing for visit 3 (last efficacy visit), a last observation carried forward method was used." **Power and sample size calculation:** "The planned target enrollment was set at 560 participants (to enroll at least 224 participants with bacterially confirmed conjunctivitis, with 112 per treatment group) calculated based on a power of 0.90 and 0.05." **Reporting threshold for ocular adverse events:** 1%
Participants	**Countries:** U.S.A., Mexico, Guatemala, and the Dominican Republic **Setting:** 58 clinical centers **Inclusion criteria:** 1. Male or female 2. Age one year or older 3. Had a positive clinical diagnosis of acute bacterial conjunctivitis with signs and symptoms present for fewer than 3 days. A minimum score of 1 (on a scale from 0 (absent/normal) to 3 (severe)) for ocular discharge and either bulbar or palpebral conjunctival injection in the same eye 4. A best–corrected visual acuity (BCVA) score of 20/100 or better in each eye was also required. **Exclusion criteria:** Any uncontrolled, systemic, debilitating disease

Abelson 2008 *(Continued)*

1. Use of topical ophthalmic solutions including tear substitutes within 2 hours before and during the study.
2. Use of any topical ophthalmic anti-inflammatory agents within 48 hours before and during the study.
3. Any active upper respiratory tract infection.
4. Pregnant or nursing females.
5. Use of any antibiotic (topical or systemic) within 72 hours of enrollment

Interventions

- **Intervention group:** azithromycin 1%

Age, mean ± SD (range): 31.0 ± 23.2 (1 to 84)
Female, n (%): NR
Predominant race/ethnicity, n (%): NR
Participants (eyes) randomized: 335
Participants (eyes) analyzed for efficacy outcome(s): 130
Participants (eyes) analyzed for safety outcome(s): 333

- **Comparison group:** vehicle

Age, mean ± SD (range): 31.0 ± 23.9 (1 to 96)
Female, n (%): NR
Predominant race/ethnicity, n (%): NR
Participants (eyes) randomized: 350
Participants (eyes) analyzed for efficacy outcome(s): 149
Participants (eyes) analyzed for safety outcome(s): 350

- **Overall**

Age, mean ± SD (range): 31.0 ± 23.5 (1 to 96)
Female, n (%): NR
Predominant race/ethicity, n (%): NR
Participants (eyes) randomized: 685
Participants (eyes) analyzed for efficacy outcome(s): 279
Participants (eyes) analyzed for safety outcome(s): 683

Baseline comparison: "There were no significant differences between the treatment groups in age, gender, race, or eye color."

Interventions	• Azithromycin 1% in DuraSite • Vehicle A single (topical) drop twice daily on days 1 and 2 and once daily on days 3 through 5
Outcomes	**Primary study outcome** 1. Clinical resolution, was evaluated at the test-of-cure visit (visit 3 on day 6 or 7) in the per-protocol population, defined as all randomized subjects who received at least one drop of the study medication and who had baseline culture results indicating pathogenic bacteria levels. Clinical resolution was defined as the absence of the three clinical signs (ocular discharge, bulbar conjunctival injection, and palpebral conjunctival injection). **Secondary study outcome** 1. Bacterial eradication at visit 3 (on day 6 or 7), as indicated by the absence of bacterial growth. Bacterial outcome was scored categorically from 0 (eradicated) to 3 (worsening) compared with baseline. 2. Safety was assessed by the incidence of adverse events (AEs) and changes in BCVA, biomicroscopy, and ophthalmoscopy. All AEs and ocular AEs occurring in more than 5% in either treatment group were summarized. Ocular AEs were classified as ocular burning or stinging or for-

Abelson 2008 *(Continued)*

	eign body sensation on instillation, other subject-reported ocular changes, clinically significant worsening of BCVA, and treatment-emergent changes observed with biomicroscopy and ophthalmoscopy.
Notes	**Funding source:** Insite Vision, Alameda CA **Declaration of interest:** The authors indicate no financial conflict of interest. Yet, "Drs Abelson and Shapiro are employees of Ophthalmic Research Associates (ORA). Drs Si, Hsu, and Bowman are employees of InSite Vision. Drs Bowman and Si have patents related to this article." **Trial registry:** NCT00105534 (clinicaltrials.gov) **Publication language:** English

C-00-02

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, four-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-blinded" **Study visits and time points:** Day 1 (screening), Day 2, Day 3, Day 4 (end of therapy), Day 7 (test of cure) **Treatment duration:** 3 days **How missing data was handled:** "a recurrence event was imputed if, for a previously nonrecurrent study eye, the study eye was treated with a prohibited local or systemic medication, or the participant had a missing ophthalmic assessment at the 6- or 12-month visit". **Power and sample size calculation:** NR, except that "targeted enrollment was 35 patients per arm" **Reporting threshold for ocular adverse events:** 1%
Participants	**Countries:** USA **Setting:** NR **Interventions** • **Intervention group:** moxifloxacin 0.5% Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 39 (one drop) + 35 (two drops) Participants (eyes) analyzed for efficacy outcome(s): 53 Participants (eyes) analyzed for safety outcome(s): 39 (one drop) + 35 (two drops) • **Comparison group:** vehicle Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 34 (one drop) + 32 (two drops) Participants (eyes) analyzed for efficacy outcome(s): 50 Participants (eyes) analyzed for safety outcome(s): 34 (one drop) + 32 (two drops) • **Overall**

C-00-02 *(Continued)*

	Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 140 Participants (eyes) analyzed for efficacy outcome(s): 103 Participants (eyes) analyzed for safety outcome(s): 140 **Inclusion criteria:** Patients at least one year of age with suspected bacterial conjunctivitis **Exclusion criteria:** NR **Baseline comparison:** NR
Interventions	• Moxifloxacin 0.5% group, including one drop (N = 39) and two drops (N = 35) arms • Vehicle group, including one drop (N = 34) and two drops (N = 32) arms One or two drops two times a day for 3 days
Outcomes	1. The eradication rate of the ocular pathogens at the 'test of cure' visit (Day 7) 2. Clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection (the sum of bulbar conjunctival injection and conjunctival discharge/exudate scores equals zero) at the test of cure visit (Day 7)
Notes	**Funding source:** Alcon Research **Declaration of interest:** Not reported **Trial registry:** None **Publication language:** English **Comments:** Trial information and results from NDA-21-598

C-00-55

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (both eyes treated) **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" **Study visits and time points:** Day 1 (screening), Day 3 ± 1 (Visit 2), Day 5 ± 1 (Visit 3), Day 9 ± 1 (Visit 4) **Treatment duration:** 4 days **How missing data was handled:** NR **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** 1%
Participants	**County:** USA **Setting:** Multicenter

C-00-55 *(Continued)*

Inclusion criteria:
1. Patients greater one (1) month of age, any race and either sex
2. Have a diagnosis of bacterial conjunctivitis based on clinical observation. All patients must have a ratings ≥ 1 for bulbar conjunctival injection and a rating ≥ 1 for conjunctival discharge/exudate at the Day 1 visit.
3. Must be able to understand and sign an informed consent form that has been approved by an institutional Review Board/Independent Ethics Committee. If the patient is under 18 years of age, the informed consent should be obtained from patients over 6 and under 18 years of age.
4. Must agree to comply with the visit schedule and other requirements of the study. The parent or guardian must agree to ensure compliance of patients less than 18 years of age.
5. Males or females who are not pregnant and are not lactating. All females of childbearing potential (those who are not premenstrual, not postmenopausal or surgically sterile) may participate only if they have a negative urine pregnancy test prior to randomization, and if they agree to use adequate birth control methods to prevent pregnancy throughout the study. Adequate birth control methods include hormonal - oral, implantable or injectable contraceptives; mechanical spermicide in conjunction with a barrier such condom or diaphragm; intrauterine device; or surgical sterilization of partner.

Exclusion criteria:
(Up to 17 items listed in the FDA regulatory document)

Interventions

- **Intervention group:** moxifloxacin 0.5%

Age, mean ± SD (range): 18.9 ± 18.7 (0 to 89)
Female, n (%): 162 (60.0%)
Predominant race/ethnicity, n (%): Caucasian 168 (62.2%)
Participants (eyes) randomized: 270
Participants (eyes) analyzed for efficacy outcome(s): 143
Participants (eyes) analyzed for safety outcome(s): 270

- **Comparison group:** vehicle

Age, mean ± SD (range): 19.0 ± 19.0 (0 to 85)
Female, n (%): 151 (55.1%)
Predominant race/ethnicity, n (%): Caucasian 171 (62.4%)
Participants (eyes) randomized: 274
Participants (eyes) analyzed for efficacy outcome(s): 144
Participants (eyes) analyzed for safety outcome(s): 274

- **Overall**

Age, mean ± SD (range): 19. ± 18.8 (0 to 89)
Female, n (%): 313 (57.5%)
Predominant race/ethnicity, n (%): Caucasian 339 (62.3%)
Participants (eyes) randomized: 544
Participants (eyes) analyzed for efficacy outcome(s): 287
Participants (eyes) analyzed for safety outcome(s): 544

Baseline comparison: Baseline characteristics of the ITT and mITT population appeared comparable as reported in NDA-21-598

Interventions	• Moxifloxacin 0.5% • Vehicle One drops three times a day for 4 days
Outcomes	**Primary study outcome** 1. The assessment of clinical cure rate (the sum of the ratings for bulbar conjunctival injection and conjunctival discharge/exudate is zero) at Day 5 (end of therapy).

C-00-55 *(Continued)*

	Secondary study outcomes 1. Visual acuity, biomicroscopy (cornea and iris/anterior chamber), fundus exam, and adverse events (ocular: discomfort and pain events) were assessed but not reported in the meta-analysis (Kodjikian 2010). 2. Ocular bacteriological cultures and fundus exams were performed at Visit 1 and at the time a patient exited from the study (Exit Visit).
Notes	**Funding source:** Alcon Research **Declaration of interest:** Not reported **Trial registry:** None **Publication language:** English **Comments:** Trial information and results from NDA-21-598

C-01-66

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" **Study visits and time points:** NR **Treatment duration:** 4 days **How missing data was handled:** NR **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** NR
Participants	**Countries:** USA **Setting:** NR **Inclusion criteria:** Patients in these studies were adults and infants over 1 month of age, of any ethnicity and of both sexes, with bacterial conjunctivitis diagnosed by clinical observation and associated with severity scores greater than or equal to 1 on the two scales described. Diagnosis of bacterial conjunctivitis was based on clinical observations with values greater than or equal to 1, for bulbar conjunctival injection and conjunctival discharge/exudate, on severity rating scales ranging from 0 ''absence'' to 3 ''severe''. Clinical remission was defined by a score of 0 on both scales (Kodjikian 2010). **Exclusion criteria:** NR **Interventions** • **Intervention group:** moxifloxacin 0.5% Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 265 Participants (eyes) analyzed for efficacy outcome(s): NR Participants (eyes) analyzed for safety outcome(s): NR • **Comparison group:** vehicle

C-01-66 *(Continued)*

	Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 266 Participants (eyes) analyzed for efficacy outcome(s): NR Participants (eyes) analyzed for safety outcome(s): NR • **Overall** Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 531 Participants (eyes) analyzed for efficacy outcome(s): NR Participants (eyes) analyzed for safety outcome(s): NR **Baseline comparison:** NR
Interventions	• Moxifloxacin 0.5% • Vehicle One or two drops three times a day for 4 days
Outcomes	Source: Kodjikian 2010 1. Clinical remission rate 2. Treatment failure (persistence of clinical signs) 3. Dropout rates
Notes	**Funding source:** Alcon Research **Declaration of interest:** NR **Trial registry:** NR **Publication language:** French **Comments:** Trial information and results from Kodjikian 2010

Comstock 2012

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" (participants and investigators) **Study visits and time points:** 4 visits: day 1 (visit 1), 3 (±1 day), 7 (±1 day), and 15 (±1 day) **Treatment duration:** 14 days **How missing data was handled:** NR **Power and sample size calculation:** "Approximately 145 subjects were planned to be enrolled in the blepharoconjunctivitis study to yield at least 30 evaluable subjects in each treatment group. In this study, 30 subjects within a treatment group were calculated to yield at least 90% probability of observing a specific AE, when that AE occurs at a rate of 7.2% or higher, or 95% probability of observing a specific AE, when that AE occurs at a rate of 9.5% or higher." **Reporting threshold for ocular adverse events:** NR

Comstock 2012 *(Continued)*

*Results of two trials were reported in the report: one compared loteprednol etabonate (LE) + tobramycin vs vehicle for lid inflammation; the other one compared LE + tobramycin, LE, tobramycin, vehicle for blepharoconjunctivitis. Only relevant results of the second trial (LE + tobramycin vs vehicle, tobramycin vs vehicle) were extracted and included in the review.

Participants	**Countries:** USA **Setting:** 18 clinical sites **Inclusion criteria:** 1. Age 0-6 years 2. Clinical diagnosis of blepharoconjunctivitis in at least one eye 3. In good health with no current or past relevant medical history as judged by the investigator 4. Subject's parent/guardian willing and able to comply with all treatment and follow-up procedures 5. Subject's parent/guardian willing to provide informed consent **Exclusion criteria:** Any uncontrolled, systemic, debilitating disease 1. Known hypersensitivity to corticosteroids, aminoglycosides, or any component of the study medication 2. Use of concurrent ocular therapy with nonsteroidal anti-inflammatory agent, mast cell stabilizer, antihistamine, or decongestant within 48 hours before and during the study 3. Use of oral/topical ophthalmic corticosteroids or systemic/topical ophthalmic antibiotics (other than study medication) during the study or within 2 or 3 days, respectively, prior to the study 4. A history of ocular surgery, including laser procedures, within the past 6 months 5. Suspected vernal conjunctivitis, glaucoma of any kind, viral conjunctivitis, preseptal cellulitis that required systemic antibiotics, dacryocystitis, uveitis, or any other disease conditions that could interfere with the safety and efficacy evaluations of the study medication 6. A history of any severe/serious ocular pathology or medical condition that could result in the subject's inability to complete the study 7. Participation in an ophthalmic drug or device research study within 30 days prior to entry in the study **Interventions** • **Intervention group:** LE + tobramycin Age, mean ± SD (range): 3.2 ± 2.0 Female, n (%): 10 (29%) Major race/ethnicity, n (%): White, 29 (85%) Participants (eyes) randomized: 34 Participants (eyes) analyzed for efficacy outcome(s): NR Participants (eyes) analyzed for safety outcome(s): 34 • **Intervention group:** tobramycin Age, mean ± SD (range): 2.9 ± 2.0 Female, n (%): 15 (44%) Major race/ethnicity, n (%): White, 21 (62%) Participants (eyes) randomized: 34 Participants (eyes) analyzed for efficacy outcome(s): NR Participants (eyes) analyzed for safety outcome(s): 34 • **Comparison group:** vehicle Age, mean ± SD (range): 2.3 ± 1.8 Female, n (%): 13 (39%) Major race/ethnicity, n (%): White, 24 (73%)

Comstock 2012 *(Continued)*

	Participants (eyes) randomized: 34 Participants (eyes) analyzed for efficacy outcome(s): NR Participants (eyes) analyzed for safety outcome(s): 33 • **Overall** Age, mean ± SD (range): 2.8 ± 1.95 Female, n (%): 74/102 (72.5%) Major race/ethnicity, n (%): White, 74/102 (72.5%) Participants (eyes) randomized: 102 Participants (eyes) analyzed for efficacy outcome(s): NR Participants (eyes) analyzed for safety outcome(s): 101 **Baseline comparison:** "Demographics were similar between treatment groups."
Interventions	• LE + tobramycin 0.3% • Tobramycin 0.3% • Vehicle One or two drops four times per day at 4-hour intervals for 14 days
Outcomes	**Primary study outcome** 1. The incidence of AEs as to severity (mild, moderate, or severe) and causal relationship to study medication (unrelated, unlikely, possibly, probably, definitely, or not assessable/unclassified) **Secondary study outcome** 1. Bilateral vision assessment (Snellen distance VA in both eyes) and 2. Bilateral IOP
Notes	**Funding source:** "The study was sponsored, designed, and conducted by Bausch & Lomb Global Clinical Programs, Rochester NY, USA." **Declaration of interest:** Drs. Comstock, Paterno, Bateman, and DeCory are employees of Bausch & Lomb. Dr. Gearinger is a consultant to Bausch & Lomb and developed the protocols and acted as medical monitor. **Trial registry:** NR **Publication language:** English

DeLeon 2012

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (one eye per person)* **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" (participants and investigators) **Study visits and time points:** Day 1 (the baseline visit), Day 4/5 (visit 2), and Day 7 ± 1 (visit 3) **Treatment duration:** 3 days **How missing data was handled:** Missing data were imputed using the LOCF method **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** 0.5%

DeLeon 2012 *(Continued)*

*"for each randomized patient, a single eye was represented in the analysis of efficacy endpoints not specific to microbial species"; "if both eyes had at least one bacterial species at or above threshold, the study eye was the one with the highest combined severity of conjunctival discharge and bulbar conjunctival injection at baseline; if severity was the same in each eye, the right eye was considered the study eye".

Participants	**Countries:** USA **Setting:** 32 centers or study sites **Inclusion criteria:** 1. aged ≥ 1 year 2. clinical diagnosis of acute bacterial conjunctivitis at least one eye based on the presence of grade 1 or greater purulent conjunctival discharge and bulbar conjunctival injection (on a 0-3 scale) 3. had a pinhole VA of at least 20/200 in both eyes in age-appropriate individuals 4. willing to discontinue use of contact lenses for the duration of the study 5. female patients of childbearing age were required to be using a reliable method of contraception and have a negative urine pregnancy test at screening. **Exclusion criteria:** Any uncontrolled, systemic, debilitating disease 1. had a known hypersensitivity or contraindication to besifloxacin, other fluoroquinolones, or any of the ingredients in the study medication 2. if expected to require any other concurrent ocular therapy, including tear substitutes, in either eye or systemic antibacterials, antihistamines, corticosteroids or NSAIDs (except aspirin) during the duration of the study 3. had used an ocular immunosuppressant in either eye within 30 days of the start of the study; systemic or ocular (either eye) antibacterial agents within 3 days; systemic or ocular (either eye) corticosteroids or antihistamine within 2 days; ocular (either eye) mast cell stabilizers, decongestants, or NSAIDs within 2 days; or any other opthalmic medications, including tear substitutes, within 2 hours 4. had undergone ocular surgery in either eye within 6 weeks before the study 5. had suspected viral or allergic conjunctivitis, iritis, active ulcerative keratitis or a history of recurrent corneal erosion syndrome 6. were immunocompromised - had any disease that the investigator believed could affect the results of the study **Interventions** • **Intervention group:** besifloxacin 0.6% Age, mean ± SD (range): 29.4 ± 25.2 Female, n (%): 142 (61.5%) Major race/ethnicity, n (%): White, 167 (72.3%) Participants (eyes) randomized: 231 Participants (eyes) analyzed for efficacy outcome(s): 135 Participants (eyes) analyzed for safety outcome(s): 228 • **Comparison group:** vehicle Age, mean ± SD (range): 26.4 ± 23.5 Female, n (%): 133 (54.7%) Major race/ethnicity, n (%): White, 166 (68.3%) Participants (eyes) randomized: 243 Participants (eyes) analyzed for efficacy outcome(s): 141 Participants (eyes) analyzed for safety outcome(s): 236 • **Overall**

DeLeon 2012 *(Continued)*

	Age, mean ± SD (range): 27.9 ± 24.3 Female, n (%): 275 (58.0%) Major race/ethnicity, n (%): White, 333 (70.3%) Participants (eyes) randomized: 474 Participants (eyes) analyzed for efficacy outcome(s): 276 Participants (eyes) analyzed for safety outcome(s): 464 **Baseline comparison:** "There were no significant differences in demographic characteristics between treatment groups (table II)".
Interventions	• Besifloxacin ophthalmic suspension 0.6% • Vehicle One drop in the affected eye(s) twice per day at 8-hour intervals during waking hours for 3 days
Outcomes	**Primary study outcome** 1. Clinical Resolution [time frame: Visit 2] a. The absence of bothconjunctival discharge and bulbar conjunctival injection. 2. Microbial Eradication [time frame: Visit 2] a. The absence of ocular bacteria that were present at or above pathogenic threshold levels at baseline. In publication, the authors reported the study outcomes as: 1. Eradication of the baseline bacterial infection and 2. Clinical resolution of the signs of conjunctivitis at day 4/5 in patients with culture-confirmed bacterial conjunctivitis a. The absence of bothconjunctival discharge and bulbar conjunctival injection. 3. Bacterial eradication was defined as the absence of all ocular bacterial species that were present at or above the Cagle threshold at baseline or Visit 1. **Secondary study outcome** 1. Clinical Resolution [time frame: Visit 3] a. The absence of both conjunctival discharge and bulbar conjunctival injection. 2. Microbial Eradication [time frame: Visit 3] a. The absence of ocular bacteria that were present at or above pathogenic threshold levels at baseline. In publication, the authors reported the secondary study outcomes as: 1. Bacterial eradication and clinical resolution at Day 7 ± 1 2. Individual clinical outcomes (ocular conjunctival discharge and bulbar conjunctival injection) at each follow-up visit 3. Microbial and clinical outcomes for overall bacterial species, overall Gram-positive species, overall Gram-negative species at each follow-up visit (grading scales shown in Table 1)
Notes	**Funding source:** "The study was sponsored by Bausch & Lomb, Inc., who designed and managed the study." **Declaration of interest:** NR **Trial registry:** NCT00972777(clinicaltrials.gov) **Publication language:** English **Comments:** "Results of an interim study analysis were reported elsewhere (Silverstein et al. Clin Ther 2011;33(1)"13-26)"

Gigliotti 1984

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" **Study visits and time points:** Initial visit, follow-up visit (days 3 to 5), and after completion of therapy (days 8 to 10) **Treatment duration:** 7 days **How missing data was handled:** NR **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** 1%
Participants	**Country:** USA **Setting:** a private pediatric clinic, pediatric clinic of a university, and Children's Hospital of Pittsburgh **Inclusion criteria:** 1. Age 1 month to 18 years 2. Clinical diagnosis of acute conjunctivitis, which was based on the presence of conjunctival inflammation or exudate 3. The requirement of conjunctival cultures being positive for either H. influenzae or S. pneumoniae was only true for participants recruited from the pediatric clinic at University of Virgina **Exclusion criteria:** 1. Patients who had a history suggesting allergy, the presence of a foreign body, or trauma to the eye 2. Patients who had received systemic or topical antibiotics during the previous week **Interventions** • **Intervention group:** polymyxin 10,000 U/gm and bacitracin 500 U/gm 1% Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 34 Participants (eyes) analyzed for efficacy outcome(s): 34 Participants (eyes) analyzed for safety outcome(s): 34 • **Comparison group:** vehicle Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 32 Participants (eyes) analyzed for efficacy outcome(s): 32 Participants (eyes) analyzed for safety outcome(s): 32 • **Overall** Age, mean ± SD (range): (1 mo to 18 years) Female, n (%): NR Predominant race/ethnicity, n (%): NR

Gigliotti 1984 *(Continued)*

	Participants (eyes) randomized: 66 Participants (eyes) analyzed for efficacy outcome(s): 66 Participants (eyes) analyzed for safety outcome(s): 66 **Baseline comparison:** "The frequency of physical findings at the time of diagnosis in the 84 patients with bacterial conjunctivitis was not statistically different among the three treatment groups except for conjunctival erythema (Table I)." *Note: Participants in the "systemic antibiotic" arm (8 received topical intervention and 10 topical placebo) were "given appropriate systemic antibiotics" because of another infectious process (usually otitis media). Data of these 18 participants were not included in the current review.
Interventions	• Topical ointment containing 10,000 U/gm polymyxin and 500 U/gm bacitracin • Ointment vehicle without antibiotic Four times daily for 7 days
Outcomes	1. Clinical cure at the 3 to 5-day visit: if the eye was normal by physical exam and remained normal when re-examined at day 8 to 10. 2. Clinical cure at day 8 to 10: patients with a normal findings only at the final visit 3. Microbiologic cure by day 3 to 5: if the culture was negative for H. influenzae and S. pneumoniae at the 3 to 5-day visit and remained negative at the final visit 4. Microbiologic cure at day 8 to 10: patients with a negative culture at the final visit only
Notes	**Funding source:** NR **Declaration of interest:** NR **Trial registry:** NR **Publication language:** English

Gross 2003

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" (investigators and their staff were masked as to treatment group assignment) **Study visits and time points:** Initial visit (day 1), follow-up visits (day 2, 3, and 4) and 'test-of-cure' visit (day 7) **Treatment duration:** 3 days **How missing data was handled:** NR **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** NR
Participants	**Country:** USA **Setting:** multicenter **Inclusion criteria:** 1. One year of age 2. Either sex and any race

Gross 2003 *(Continued)*

3. With a presumptive diagnosis of bacterial conjunctivitis based on clinical observation
4. All patients had to have a rating of 1 (mild) or greater on a scale of 0 to 3 (absent to severe) for conjunctival discharge/exudates;
   a. patients ≤ 5 years of age a rating of at least 1 (mild) on a scale of 0 to 3 (normal to severe) for bulbar conjunctival injection, and
   b. patients > 5 years of age a rating of at least 2 for bulbar conjunctival injection.

Exclusion criteria: NR

Interventions

- **Intervention group:** moxifloxacin 0.5%

Age, mean ± SD (range): 30 (1 to 89)
Female, n (%): 24 (62%)
Predominant race/ethnicity, n (%): Caucasian, 35 (90%)
Participants (eyes) randomized: 39
Participants (eyes) analyzed for efficacy outcome(s): 27
Participants (eyes) analyzed for safety outcome(s): NR

- **Comparison group:** vehicle

Age, mean ± SD (range): 21 (1 to 70)
Female, n (%): 22 (65%)
Predominant race/ethnicity, n (%): Caucasian, 28 (82%)
Participants (eyes) randomized: 34
Participants (eyes) analyzed for efficacy outcome(s): 24
Participants (eyes) analyzed for safety outcome(s): NR

- **Overall**

Age, mean ± SD (range): 26 (1 to 89 years)
Female, n (%): 46 (63%)
Predominant race/ethnicity, n (%): Caucasian, 63 (86%)
Participants (eyes) randomized: 73
Participants (eyes) analyzed for efficacy outcome(s): 51
Participants (eyes) analyzed for safety outcome(s): NR

Baseline comparison: NR

Interventions	• Moxifloxacin ophthalmic solution 0.5% • Vehicle Twice per day for 3 days
Outcomes	1. Treatment efficacy a. Clinical success: clinical cure or the disappearance of signs and symptoms of the disease during the course of the treatment. b. Microbiological success: the eradication of the original pathogen at the Day 7 test-of-cure visit, which occurred 3-4 days after the last treatment with antibiotics. c. Therapeutic improvement: combines **clinical success** with **microbiological success** to obtain an overall study success outcome at Day 7 test-of-cure visit. d. Clinical utility: the clinical utility scale ranked the patients based on the day they were considered cured as well as their microbiological outcome (Table 1). e. Treatment failure: If the patient did not respond adequately to the assigned study therapy and needed treatment different from the assigned study regimen, the patient was classified as a "Treatment Failure" and immediately discontinued from the study. 2. Safety a. An evaluation of safety was conducted on all patients who were randomized into the study and received at least one dose of the study drug.

Gross 2003 *(Continued)*

	In this study, clinical cure occurred when the rating of each of the two cardinal ocular signs (bulbar conjunctival injection and conjunctival discharge/exudate) was 0 (normal or absent) at the Day 7 test-of-cure visit. Clinical success included both patients whose scores went to 0 for the two cardinal signs and those patients whose scores improved. "All patients who received drug, had at least one on-therapy visit, met inclusion criteria and were culture-positive for bacteria on Day 1 were included in the analyses reported herein."
Notes	**Funding source:** NR **Declaration of interest:** NR **Trial registry:** NR **Publication language:** English

Hwang 2003

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" **Study visits and time points:** Study medication was dispensed on day 1, and patients returned to the study site for interim (days 3–5) and final (days 6–10) visits **Treatment duration:** 5 days **How missing data was handled:** NR **Power and sample size calculation:** "Based on the results from previous studies of 0.5% levofloxacin and placebo, this study had an estimated power of at least 90% to detect differences in response rates at the significance level of α = 0.05." **Reporting threshold for ocular adverse events:** 2% (in either treatment group)
Participants	**Countries:** USA **Setting:** 14 sites **Inclusion criteria:** Male and female subjects who were at least 2 years of age and had a clinical diagnosis of bacterial conjunctivitis, characterized by purulent ocular discharge and redness in at least one eye (minimum scores of 1 for conjunctival discharge and conjunctival and/or palpebral injection as described in Table 1) **Exclusion criteria:** Preverbal children who could not communicate their symptoms were excluded from this analysis **Interventions** • **Intervention group:** levofloxacin 0.5% Age, mean ± SD (range): 34.5 ± 20.2 (2 to 91) Female, n (%): 78/124 (62.9%) Major race/ethnicity, n (%): White, 94/124 (75.8%) Participants (eyes) randomized: 126 Participants (eyes) analyzed for efficacy outcome(s): 60

Hwang 2003 *(Continued)*

	Participants (eyes) analyzed for safety outcome(s): 124 • **Comparison group:** vehicle Age, mean ± SD (range): 33.8 ± 21.6 (2 to 86) Female, n (%): 61/120 (50.8%) Major race/ethnicity, n (%): White, 94/120 (78.3%) Participants (eyes) randomized: 123 Participants (eyes) analyzed for efficacy outcome(s): 57 Participants (eyes) analyzed for safety outcome(s): 120 • **Overall** Age, mean ± SD (range): 34.16 ± 20.86 (2 to 91) Female, n (%): 139/244 (57.0%) Major race/ethnicity, n (%): White, 188/244 (77.0%) Participants (eyes) randomized: 249 Participants (eyes) analyzed for efficacy outcome(s): 117 Participants (eyes) analyzed for safety outcome(s): 244 **Baseline comparison:** "In both populations, there were no significant differences between treatment groups for age or race," except that female were slightly more in the intervention than the placebo group of the per-protocol population (63% vs 44%, P value 0.036).
Interventions	• Levofloxacin ophthalmic solution 0.5% • Vehicle One to two drops of study medication into the affected eye(s) every 2 hours (up to eight times per day) while awake on days 1 and 2, then every 4 hours (up to four times per day) while awake on days 3–5
Outcomes	1. Microbial eradication (change from baseline in CFUs of causative pathogens); 2. The physician's clinical impression of change from baseline in cardinal signs (conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection); and 3. Change from baseline in ocular signs (erythema/swelling, corneal epithelial disease, corneal stromal disease, and uveitis) and symptoms (burning/stinging, itching, tearing, foreign body sensation, photophobia, and discomfort). Preverbal children who could not communicate their symptoms were excluded from this analysis. "End point" was defined as the last observation made, which may or may not have corresponded to the final planned study visit, depending on whether or not the subject completed all planned follow-up visits.
Notes	**Funding source:** Santen Inc, Napa, CA **Declaration of interest:** NR **Trial registry:** NR **Publication language:** English

Karpecki 2009

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (block randomization) **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked"

Karpecki 2009 *(Continued)*

Study visits and time points: visit 1 (day 1), visit 2 (day 4 ± 1), and visit 3 (day 8 or 9)

Treatment duration: 5 days

How missing data was handled: "Missing data and discontinued patients were imputed as failures in both analyses."

Power and sample size calculation: "A minimum sample size of 98 patients with culture-confirmed acute bacterial conjunctivitis (49 in each treatment group) was needed for a power of 0.80 at an ex of 0.05 (2-sided X^2 test, active treatment vs vehicle) to detect a difference in microbial eradication rates, based on estimates of 89% and 64% in the active-treatment and vehicle groups, respectively, derived from studies of other ophthalmic fluoroquinolones."

Reporting threshold for ocular adverse events: 5%

Participants

Country: USA

Setting: 35 centers

Inclusion criteria:
At least 1 year of age and in good health; had a clinical diagnosis of acute bacterial conjunctivitis, as evidenced by a minimum of grade 1 for purulent conjunctival discharge (crusty or sticky eyelids) and a minimum of grade 1 for either bulbar or palpebral conjunctival injection in at least 1 eye on ocular examination; and had pinhole visual acuity in each eye. Females of childbearing potential had to be using a reliable method of contraception and have a negative result on pregnancy testing at the baseline visit.

Exclusion criteria:
Patients were excluded if they had a known hypersensitivity to fluoroquinolones, besifloxacin ophthalmic suspension, or any of the ingredients in the study medications; had used topical ophthalmic anti-inflammatory agents within 48 hours before or during the study or other topical ophthalmic solutions (including artificial tears) within 2 hours before or during the study; had used antibacterial medications within 72 hours of study entry; or had suspected viral or allergic conjunctivitis, suspected iritis, a history of recurrent corneal erosion syndrome, or any active ulcerative keratitis.

Interventions

- **Intervention group:** besifloxacin 0.6%

Age, mean ± SD (range): 33.3 ± 22.3 (1 to 92)
Female, n (%): 86 (62.8%)
Predominant race/ethnicity, n (%): white, 116 (84.7%)
Participants (eyes) randomized: 137
Participants (eyes) analyzed for efficacy outcome(s): 60
Participants (eyes) analyzed for safety outcome(s): 137

- **Comparison group:** vehicle

Age, mean ± SD (range): 35.1 ± 22.4 (1 to 81)
Female, n (%): 76 (57.6%)
Predominant race/ethnicity, n (%): white, 106 (80.3%)
Participants (eyes) randomized: 132
Participants (eyes) analyzed for efficacy outcome(s): 58
Participants (eyes) analyzed for safety outcome(s): 132

- **Overall**

Age, mean ± SD (range): 31.0 ± 23.5 (1 to 92)
Female, n (%): 162 (60.2%)
Predominant race/ethnicity, n (%): white, 222 (82.5%)
Participants (eyes) randomized: 269
Participants (eyes) analyzed for efficacy outcome(s): 118

Karpecki 2009 *(Continued)*

	Participants (eyes) analyzed for safety outcome(s): 269 **Baseline comparison:** "The 2 treatment groups were comparable with respect to demographic characteristics (Table I)."
Interventions	• Besifloxacin ophthalmic suspension 0.6% • Vehicle Three times daily for 5 days
Outcomes	**Primary efficacy end points** 1. Clinical resolution, defined as the absence of conjunctival discharge and bulbar conjunctival injection at visit 3 (day 8 or 9); 2. Eradication of the baseline bacterial infection, defined as the absence at visit 3 of bacterial species that were present at or above the threshold on day 1. **Secondary efficacy variables** 1. Clinical resolution of baseline conjunctivitis at visit 2; 2. Eradication of the baseline bacterial infection at visit 2; and 3. Improvements in investigators' ratings of individual signs and symptoms, 4. Global change in clinical signs and symptoms, microbiologic outcomes, and clinical outcomes. Safety measurements included adverse events; changes in visual acuity, as determined by age-appropriate visual acuity testing; and changes in ocular health (changes in severity of abnormalities of the lids, limbus, conjunctiva, cornea, anterior chamber, lens, vitreous, and fundus).
Notes	**Funding source:** "The study was sponsored by Bausch & Lomb Global Clinical Programs, Rochester, New York, which also designed and conducted the study. Publication was sponsored by Bausch & Lomb." **Declaration of interest:** "Dr. Karpecki is a consultant for Bausch & Lomb and has received consulting fees/payment for advisory board participation from Bausch & Lomb Advanced Medical Optics, Inc.; OCuSOFT, Inc.; Inspire Pharmaceuticals Inc.; OcuSense, Inc.; Odyssey Medical, Inc.; Rapid Pathogen Screening Inc.; and Allergan, Inc. Dr. DePaolis has received consulting fees/payment for advisory board participation and lecture fees from Bausch & Lomb; Advanced Medical Optics; and Alcon Laboratories, Inc.; he has also received lecture fees from CooperVision, Inc. Dr. White has received consulting fees/payment for advisory board participation from Primary Eyecare Network; Vistakon Pharmaceuticals, LLC; Alcon; and CooperVision; he has also received lecture fees from Alcon, Optos Eye Care, and Ciba Vision. Ms. Brunner and Drs. Usner, Paterno, and Comstock are employees of Bausch & Lomb." **Trial registry:** NCT00622908 (clinicaltrials.gov) **Publication language:** English

Leibowitz 1991

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" **Study visits and time points:** visit 1 (day 0, study entry), visit 2 (day 1), and visit 3 (day 3)

Leibowitz 1991 *(Continued)*

	Treatment duration: 3 days **How missing data was handled:** NR **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** NR
Participants	**Country:** USA **Setting:** NR **Inclusion criteria:** swab-proven conjunctivitis **Exclusion criteria:** antibiotics or anti-inflammatory medication during the preceding 48 hours **Interventions** • **Intervention group:** ciprofloxacin 0.3% Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 390 Participants (eyes) analyzed for efficacy outcome(s): 140 Participants (eyes) analyzed for safety outcome(s): NR • **Comparison group:** placebo Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 88 Participants (eyes) analyzed for efficacy outcome(s): 37 Participants (eyes) analyzed for safety outcome(s): NR • **Overall** Age, mean ± SD (range): NR Female, n (%): NR Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 478 Participants (eyes) analyzed for efficacy outcome(s): 177 Participants (eyes) analyzed for safety outcome(s): NR **Baseline comparison:** NR
Interventions	• Ciprofloxacin 0.3% • Placebo One to two drops into affected eye every 2 hours while awake on days 0 and 1, and every 4 hours while awake on day 2 (3 days in total)
Outcomes	1. Microbiologic outcomes on day 3: pathogen eradication; pathogen reduction; pathogen persistence; pathogen proliferation
Notes	**Funding source:** "This study was supported in part by a grant from Alcon Laboratories, Inc., Fort Worth, TX; by an unrestricted departmental grant from Research To Prevent Blindness, Inc., New York, NY; and by a grant from the Massachusetts Lion Eye Research Fund, Inc., Boston, MA." **Declaration of interest:** NR **Trial registry:** NR **Publication language:** English

Leibowitz 1991 *(Continued)*

	Comments: two multicenter, prospective, double-masked, randomized clinical studies were reported in the same publication, with one comparing ciprofloxacin 0.3% with placebo and the other with tobramycin 0.3%. Only data of the placebo-controlled study were extracted in the review.

Malhotra 2013

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (only one eye from each subject was designated as the study eye) **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked." "The investigators, subjects, and all other study personnel involved in the monitoring or conduct of the study were masked to the treatment received." **Study visits and time points:** Beginning at the first visit (Visit 1, Day 1), subjects instilled one drop of study treatment, outcome was assessed on day 8 (or +1 day, visit 2); day 11 (± 1 day, visit 3) **Treatment duration:** 7 days **How missing data was handled:** "missing or discontinued subjects were not imputed". **Power and sample size calculation:** "Sample size calculations determined that at least 324 subjects were needed in the besifloxacin group to provide a 95% probability of detecting TEAEs that occur at a rate of 1%, and 162 subjects were needed in the vehicle group to provide an 80% probability of detecting TEAEs that occur at a rate of 1%. Assuming a 10% dropout rate, it was planned to enroll 540 subjects to yield the minimum required total of 486 patients." **Reporting threshold for ocular adverse events:** NR
Participants	**Countries:** USA **Setting:** 24 sites **Inclusion criteria:** 1. Age 1 year or greater; 2. Clinical diagnosis of bacterial conjunctivitis as evidenced by a minimum grade of 1 for both purulent conjunctival discharge (scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe) and bulbar conjunctival injection (Scale: 0 = normal; 1 = mild; 2 = moderate; 3 = severe) in at least one eye; and 3. Pin-hole visual acuity (VA) equal to or better than 20/200 in both eyes (using age- appropriate VA testing). All subjects using contact lenses were instructed to discontinue contact lens wear for the entire study. **Exclusion criteria:** 1. Uncontrolled systemic and/or debilitating disease; 2. Known hypersensitivity to besifloxacin, fluoroquinolones, or any component of the study medication; 3. Current or expected treatment with systemic NSAIDs (exception: B81 mg/day of acetylsalicylic acid), systemic corticosteroids, systemic antihistamines, systemic antibacterial agents; 4. Current or anticipated ocular therapy (either eye) with any ophthalmic solutions (tear substitutes, corticosteroids, NSAIDs, mast cell stabilizers, antihistamines, decongestants, antibacterial agents, immunosuppressant agents); 5. Ocular surgery (including laser surgery), either eye, within 6 weeks prior to study entry; 6. Suspected viral or allergic conjunctivitis; suspected iritis;

Malhotra 2013 *(Continued)*

	7. History of recurrent corneal erosion syndrome; active ulcerative keratitis; and compromised immunity. **Interventions** • **Intervention group:** besifloxacin 0.6% Age, mean ± SD (range): 29.6 ± 25.1 (1 to 97) Female, n (%): 204/344 (59.3%) Major race/ethnicity, n (%): White, 210/344 (61.0%) Participants (eyes) randomized: 347 Participants (eyes) analyzed for efficacy outcome(s): 212 Participants (eyes) analyzed for safety outcome(s): 344 • **Comparison group:** vehicle Age, mean ± SD (range): 30.5 ± 22.5 (1 to 92) Female, n (%): 95/170 (55.9%) Major race/ethnicity, n (%): White, 102/170 (60.0%) Participants (eyes) randomized: 170 Participants (eyes) analyzed for efficacy outcome(s): 87 Participants (eyes) analyzed for safety outcome(s): 170 • **Overall** Age, mean ± SD (range): 29.9 ± 24.25 (1 to 97) Female, n (%): 299/514 (58.2%) Major race/ethnicity, n (%): White, 312/514 (60.7%) Participants (eyes) randomized: 514 Participants (eyes) analyzed for efficacy outcome(s): 299 Participants (eyes) analyzed for safety outcome(s): 514 **Baseline comparison:** "In both populations (ITT and mITT), baseline demographics were similar between treatment groups (Table 1), as was ocular medical history."
Interventions	• Besifloxacin ophthalmic suspension 0.6 % • Vehicle One drop in the infected eye(s) three times daily at approximately 6-h intervals, continuing through Day 7.
Outcomes	**Primary study outcome** 1. The primary safety variable was the incidence of ocular and non-ocular treatment-emergent adverse events (TEAEs). For each TEAE, the investigator assessed the severity and causality with respect to treatment. Ocular TEAEs observed in baseline-designated study eyes were of primary interest and are reported here. **Secondary study outcome** 1. Bacterial eradication assessed at Visits 2 and 3, which was defined as the absence of all ocular bacterial species present at or above threshold at baseline.
Notes	**Funding source:** This study was sponsored by Bausch & Lomb Incorporated (Rochester, NY, USA). Clinical monitoring and clinical trial supplies were provided by Bausch & Lomb. **Declaration of interest:** NR **Trial registry:** NCT01175590 (clinicaltrials.gov) **Publication language:** English

Miller 1992

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" (details not reported) **Study visits and time points:** visit 1 (day 1), visit 2 (day 3 or 4), and visit 3 (day 6 or 7) **Treatment duration:** 7 days **How missing data was handled:** NR **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** NR *Patients who did not improve clinically after three days treatment were to be withdrawn from the study.
Participants	**Country:** USA **Setting:** NR **Inclusion criteria:** 1. Age 18 years old or older 2. A clinical diagnosis of acute bacterial conjunctivitis or blepharoconjunctivitis 3. The presence of conjunctival hyperemia **Exclusion criteria:** 1. Conjunctivitis due to *Neiserria gonorrhoeae*, 2. A history of sensitivity to quinolones or benzalkonium chloride, or 3. Those who had received topical antibacterial agents in the preceding 48 hours. **Interventions** • **Intervention group:** norfloxacin 0.3% Age, mean ± SD (range): 38 Female, n (%): 73 (51.0%) Predominant race/ethnicity, n (%): Caucasian, 107 (74.8%) Participants (eyes) randomized: 143 Participants (eyes) analyzed for efficacy outcome(s): 143 Participants (eyes) analyzed for safety outcome(s): NR • **Comparison group:** placebo Age, mean ± SD (range): 38 Female, n (%): 86 (61.0%) Predominant race/ethnicity, n (%): Caucasian, 105 (74.5%) Participants (eyes) randomized: 141 Participants (eyes) analyzed for efficacy outcome(s): 141 Participants (eyes) analyzed for safety outcome(s): NR • **Overall** Age, mean ± SD (range): 38 Female, n (%): 159 (56.0%) Predominant race/ethnicity, n (%): Caucasian, 212 (74.6%) Participants (eyes) randomized: 284 Participants (eyes) analyzed for efficacy outcome(s): 284 Participants (eyes) analyzed for safety outcome(s): NR

Miller 1992 *(Continued)*

	Baseline comparison: "None of the differences between treatment groups was statistically significant".
Interventions	• Norfloxacin 0.3% + 0.0025% benzalkonium chloride preservative • Placebo containing 0.01% benzalkonium chloride One drop into each affected eye every 2 hours of the waking day for the first day, and then 4 times a day for a maximum of 7 days
Outcomes	• Clinical outcome after the test drug was discontinued: cured (signs and symptoms of infection clear), improved (signs and/or symptoms still present but of less severity), no change or worsened • Microbiological outcome, based on cultures taken during and or within 24 hours after treatment was discontinued, was categorized as: pathogen eradication, pathogen suppression or pathogen persistence All symptoms and signs were recorded, specifically including: symptoms of blurred vision, eye burning, foreign body sensation, photophobia, tearing and itching of eye; signs of conjunctival hyperemia, discharge, edema and follicles, active infiltrates and corneal staining with fluorescein, lid edema and exudates "Patients returned for their second visit after day three or four and at the end of therapy (at day six or seven) and the ocular examination was repeated at each visit."
Notes	**Funding source:** NR **Declaration of interest:** NR **Trial registry:** NR **Publication language:** English

NCT00509873

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "quadruple-masked" (participant, care provider, investigator, outcomes assessor) **Study visits and time points:** Visits were scheduled on day 1 (baseline), day 4, and day 6; the day 6 visit must have occurred between 12 h (minimum) and 48h (maximum) after the last dose of study medication. **Treatment duration:** 5 days **How missing data was handled:** "The last observation carried forward method was used to impute missing values for efficacy analyses of the mITT and ITT populations." **Power and sample size calculation:** "Power calculations for each of the individual studies in this pooled analysis were based on a 2-sided Pearson chi-square test for the primary efficacy measure using the mITT population." "Assuming clinical success in 57% of patients in the vehicle group and a type-I error rate of 0.05, a sample size of 140 patients per treatment group in the mITT population was estimated to achieve 80% power to detect a difference of 16 percentage points in clinical success, between gatifloxacin 0.5% and vehicle." "With an expected 60% culture-positive rate, 467 patients were projected to be randomized in each study to attain 280 patients (140 per treatment group assuming an equal distribution of positive cultures in each treatment group) for the mITT population." **Reporting threshold for ocular adverse events:** 3%

NCT00509873 *(Continued)*

Participants	**Countries:** USA **Setting:** 51 sites **Inclusion criteria:** Patients at least 1 year of age were eligible for participation if they were clinically diagnosed in one or both eyes with acute bacterial conjunctivitis (or blepharoconjunctivitis). Eligible patients must have had a best-corrected visual acuity equivalent to Snellen acuity of 20/80 or better. For children younger than 3 years old, visual acuity measurement was at the discretion of the investigator. **Exclusion criteria:** Patients were excluded if they had used antibiotics or corticosteroids for treatment of other infections during the past 1 or 2 weeks, respectively, before study enrollment; had signs and/or symptoms of conjunctivitis for more than 96 h or suggestive of fungal, viral, chlamydial, or allergic etiology; or were positive for adenovirus antigen using the RPS Adeno Detector™ at baseline. Patients also were excluded from the trials if they had a clinical diagnosis of orbital cellulitis, preseptal cellulitis or ulcerative keratitis, infectious blepharitis as the primary cause of ocular hyperemia and discharge in the opinion of the investigator, uncontrolled systemic disease, serious systemic infection, immunosuppression, or known contraindications to any study medication component. **Interventions** • **Intervention group:** gatifloxacin 0.5% Age, mean ± SD (range): 123/287 in age 1 to 18 years; 126/287 in aged 19 to 65 years; 38/287 in age 65 or older Female, n (%): 161/287 (56.1%) Major race/ethnicity, n (%): NR Participants (eyes) randomized: 287 Participants (eyes) analyzed for efficacy outcome(s): 167 Participants (eyes) analyzed for safety outcome(s): 288 • **Comparison group:** vehicle Age, mean ± SD (range): 123/291 in age 1 to 18 years; 141/291 in aged 19 to 65 years; 27/291 in age 65 or older Female, n (%): 172/291 (58.8%) Major race/ethnicity, n (%): NR Participants (eyes) randomized: 291 Participants (eyes) analyzed for efficacy outcome(s): 158 Participants (eyes) analyzed for safety outcome(s): 289 • **Overall** Age, mean ± SD (range): 246/578 in age 1 to 18 years; 267/578 in aged 19 to 65 years; 65/578 in age 65 or older Female, n (%): 333/578 (57.6%) Major race/ethnicity, n (%): NR Participants (eyes) randomized: 578 Participants (eyes) analyzed for efficacy outcome(s): 325 Participants (eyes) analyzed for safety outcome(s): 577 **Baseline comparison:** "Baseline characteristics of the mITT population (those whose baseline culture was positive) appeared comparable in Table 1 (Heller 2014)".
Interventions	• Gatifloxacin ophthalmic solution 0.5% • Vehicle One drop of study medication every 2 hrs up to 8 times total for day 1; one drop twice daily for day 2 to 5
Outcomes	**Primary study outcome**

NCT00509873 *(Continued)*

1. Percentage of patients with clearing (clinical success) of conjunctival hyperemia and conjunctival discharge at day 6 [time frame: day 6]
   a. Conjunctival hyperemia and conjunctival discharge were each assessed on a 4-point severity grade scale (0 = none, +1 = mild, +2 = moderate, +3 = severe).

Secondary study outcome

1. Percentage of patients with microbiological cure at day 6 [time frame: day 6]
   a. percentage of patients with microbiological cure, defined such that all bacteria present in the study eye at day 1 (baseline) are eradicated (or absent) at day 6 based on a classification of microbial response. (eradication = pathogen is absent in follow-up culture; reduction = pathogen is reduced from baseline below threshold count in follow-up culture; persistence = pathogen reduced from baseline but is above or equal to threshold count in follow-up culture; and proliferation = pathogen has increased in count from baseline in follow-up culture)
2. Percentage of patients with clinical improvement of ocular signs at day 6 [time frame: day 6]
   a. percentage of patients with clinical improvement of ocular signs at day 6 based on a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe), defined as a decrease (improvement) from day 1 (baseline) in the total score of conjunctival hyperemia and mucopurulent discharge (pus), with no increase (worsening) from day 1 (baseline) in either individual variable in the study eye
3. Percentage of patients with clinical improvement of ocular symptoms at day 6 [time frame: day 6]
   a. percentage of patients with clinical improvement of ocular symptoms at day 6, defined as a decrease (improvement) from day 1 (baseline) in the total score of itching and tearing (each on 4-point scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe), with no increase (worsening) from day 1 (baseline) in any individual score in the study eye diagnosed with bacterial conjunctivitis

Notes

Funding source: This study was sponsored by Allergan, Inc.
Declaration of interest: W.H., M.C., Y.R.B., and J.M.D. have no competing conflicts of interest; C.F., L.V., D.A.H., and H.J. are employees of Allergan, Inc. Writing and editorial assistance were provided to the authors by Kakuri Omari, PhD, and Gayle Scott, PharmD, of Evidence Scientific Solutions (Philadelphia, PA), and funded by Allergan, Inc. (Irvine, CA).
Trial registry: NCT00509873 (clinicaltrials.gov)
Publication language: English
Comments: One of the two trials reported in Heller 2014; the other was NCT00518089

NCT00518089

Study characteristics

Methods

Study design: parallel-group, randomized controlled trial, two-arm

Unit of randomization: Person (one eye per person)

Masking of participants, treatment allocator, outcome assessor, or data analyzer: "quadruple-masked" (participant, care provider, investigator, outcomes assessor)

Study visits and time points: visits were scheduled on day 1 (baseline), day 4, and day 6; the day 6 visit must have occurred between 12 h (minimum) and 48 h (maximum) after the last dose of study medication.

Treatment duration: 5 days

How missing data was handled: "The last observation carried forward method was used to impute missing values for efficacy analyses of the mITT and ITT populations."

Power and sample size calculation: "Power calculations for each of the individual studies in this pooled analysis were based on a 2-sided Pearson chi-square test for the primary efficacy measure

NCT00518089 *(Continued)*

using the mITT population. Assuming clinical success in 57% of patients in the vehicle group and a type-I error rate of 0.05, a sample size of 140 patients per treatment group in the mITT population was estimated to achieve 80% power to detect a difference of 16 percentage points in clinical success, between gatifloxacin 0.5% and vehicle. With an expected 60% culture-positive rate, 467 patients were projected to be randomized in each study to attain 280 patients (140 per treatment group assuming an equal distribution of positive cultures in each treatment group) for the mITT population."

Reporting threshold for ocular adverse events: 3%

Participants	**Countries:** USA and India **Setting:** 10 sites in USA and 29 sites in India **Inclusion criteria:** according to Heller 2014, patients at least 1 year of age were eligible for participation if they were clinically diagnosed in one or both eyes with acute bacterial conjunctivitis (or blepharoconjunctivitis). Eligible patients must have had a best-corrected visual acuity equivalent to Snellen acuity of 20/80 or better. For children younger than 3 years old, visual acuity measurement was at the discretion of the investigator. **Exclusion criteria:** according to Heller 2014, patients were excluded if they had used antibiotics or corticosteroids for treatment of other infections during the past 1 or 2 weeks, respectively, before study enrollment; had signs and/or symptoms of conjunctivitis for more than 96 h or suggestive of fungal, viral, chlamydial, or allergic etiology; or were positive for adenovirus antigen using the RPS Adeno Detector™ at baseline. Patients also were excluded from the trials if they had a clinical diagnosis of orbital cellulitis, preseptal cellulitis or ulcerative keratitis, infectious blepharitis as the primary cause of ocular hyperemia and discharge in the opinion of the investigator, uncontrolled systemic disease, serious systemic infection, immunosuppression, or known contraindications to any study medication component. **Interventions** • **Intervention group:** gatifloxacin 0.5% Age, mean ± SD (range): age 1-18 years: 66/430 (15.3%); 19-65 years: 316/430 (73.5%); 65 years or older: 48/430 (11.2%) Female, n (%): 183/430 (42.6%) Major race/ethnicity, n (%): NR Participants (eyes) randomized: 430 Participants (eyes) analyzed for efficacy outcome(s): 166 Participants (eyes) analyzed for safety outcome(s): 429 • **Comparison group:** vehicle Age, mean ± SD (range): age 1-18 years: 74/429 (17.2%); 19-65 years: 313/429 (73.0%); 65 years or older: 42/429 (9.8%) Female, n (%): 156/429 (36.4%) Major race/ethnicity, n (%): NR Participants (eyes) randomized: 429 Participants (eyes) analyzed for efficacy outcome(s): 167 Participants (eyes) analyzed for safety outcome(s): 427 • **Overall** Age, mean ± SD (range): age 1-18 years: 140/859 (16.3%); 19-65 years: 629/859 (73.2%); 65 years or older: 90/859 (10.5%) Female, n (%): 339/859 (39.5%) Major race/ethnicity, n (%): NR Participants (eyes) randomized: 859 Participants (eyes) analyzed for efficacy outcome(s): 333 Participants (eyes) analyzed for safety outcome(s): 856

NCT00518089 *(Continued)*

	Baseline comparison: "Baseline characteristics of the mITT population appeared comparable in the pooled analysis (Heller 2014) but the intervention group appeared to have more female participants (42.6% vs. 36.4%) in the ITT population."
Interventions	• Gatifloxacin 0.5% ophthalmic solution • Vehicle On day 1, patients instilled 1 drop of study medication every 2 h for up to 8 doses. On days 2 to 5, patients instilled 1 drop of study medication twice a day in the qualified eye(s).
Outcomes	**Primary study outcome** 1. Percentage of patients with clearing (clinical success) of conjunctival hyperemia and conjunctival discharge up to day 6 [time frame: 6 days] **Secondary study outcome** 1. Percentage of patients with clearing (clinical success) of conjunctival hyperemia and conjunctival discharge at day 6 [time frame: day 6] percentage of patients that achieved clinical success, defined as achievement of a score of zero for both conjunctival hyperemia and conjunctival discharge in the study eye at day 6. Conjunctival hyperemia and conjunctival discharge were each assessed on a 4-point severity grade scale (0 = none, +1 = mild, +2 = moderate, +3 = severe). 2. Percentage of patients with microbiological cure up to day 6 [time frame: 6 days] percentage of patients with microbiological cure, defined such that all bacteria present in the study eye at day 1 (baseline) are eradicated up to day 6 based on a classification of microbial response. (eradication = pathogen is absent in follow-up culture; reduction = pathogen is reduced from baseline below threshold count in follow-up culture; persistence = pathogen reduced from baseline but is above or equal to threshold count in follow-up culture; and proliferation = pathogen has increased in count from baseline in follow-up culture). 3. Percentage of patients with clinical improvement of ocular signs up to day 6 [time frame: 6 days] percentage of patients with clinical improvement of ocular signs up to day 6 based on a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe), defined as a decrease (improvement) from day 1 (baseline) in the total score of conjunctival hyperemia and mucopurulent discharge (pus), with no increase (worsening) from day 1 (baseline) in either individual variable in the study eye. 4. Percentage of patients with clinical improvement of ocular symptoms up to day 6 [time frame: 6 days] percentage of patients with clinical improvement of ocular symptoms, defined as a decrease (improvement) up to day 6 from day 1 (baseline) in the total score of itching and tearing (each on 4-point scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe), with no increase (worsening) from day 1 (baseline) in any individual score in the study eye diagnosed with bacterial conjunctivitis.
Notes	**Funding source:** Allergan, Inc. **Declaration of interest:** W.H., M.C., Y.R.B., and J.M.D. have no competing conflicts of interest; C.F., L.V., D.A.H., and H.J. are employees of Allergan, Inc. Writing and editorial assistance were provided to the authors by Kakuri Omari, PhD, and Gayle Scott, PharmD, of Evidence Scientific Solutions (Philadelphia, PA), and funded by Allergan, Inc. (Irvine, CA). **Trial registry:** NCT00518089 (clinicaltrials.gov) **Publication language:** English **Comments:** one of the two trials reported in Heller 2014; the other was NCT00509873.

NCT01740388

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person

NCT01740388 *(Continued)*

Masking of participants, treatment allocator, outcome assessor, or data analyzer: "double-masked" (participants, investigators)

Study visits and time points: baseline (visit 1), Day 4 or 5 (visit 2), Day 6, 7, or 8 (visit 3)

Treatment duration: 3 days

How missing data was handled: LOCF

Power and sample size calculation: Not reported but reported an estimated enrollment number of 476

Reporting threshold for ocular adverse events: 2%

Participants

Countries: USA

Setting: NR

Inclusion criteria:

1. One year and older
2. All sexes
3. Have a clinical diagnosis of acute bacterial conjunctivitis and exhibit mucopurulent/purulent conjunctival discharge (crusty or sticky eyelids) and redness in at least 1 eye. A minimum score of 1 should be present for both discharge and for bulbar conjunctival injection.
4. Have monocular pin-holed Snellen visual acuity (VA) equal to or better than 20/200 in both eyes. Age-appropriate VA testing will be performed. Every effort should be made to obtain a VA measurement in children. If VA is unobtainable in children, it is at the Investigator's discretion to include the subject in the study. Be willing to discontinue contact lens wear for the duration of the study.

Exclusion criteria:

1. Have a severe/serious ocular condition or history/presence of chronic generalized systemic disease that the Investigator feels might increase the risk to the subject or confound the result(s) of the study.
2. Have a known hypersensitivity or contraindications to besifloxacin, fluoroquinolones, or any of the ingredients in the study drugs.
3. Be expected to require treatment with systemic or ocular (either eye) nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, or corticosteroids during the study or have used any of these medications within 2 days prior to study start.
4. Be expected to require concurrent ocular therapy in either eye with any ophthalmic solutions (unless specified below), including tear substitutes, during the study or have used any ophthalmic solutions within 2 hours prior to study start. Be expected to require concurrent ocular therapy (either eye) with mast cell stabilizers or decongestants during the study or have used any of the above within 2 days prior to study start.
5. Be expected to require concurrent systemic or ocular therapy with immunosuppressants (e.g. Restasis) during the study or have used systemic or ocular immunosuppressants within 30 days prior to study start.
6. Be expected to require treatment with systemic or ocular (either eye) antibacterials (other than study drug) during the study or have used any systemic or ocular antibacterial within 3 days prior to study start.
7. Be likely to require antimicrobial therapy for conditions such as respiratory tract infection, urinary tract infection, skin/soft tissue infection, or otitis media during the study.
8. Have had ocular surgery (including laser surgery) in either eye within 6 weeks prior to entry into this study.
9. Have suspected viral or allergic conjunctivitis or any other disease conditions that could interfere with the efficacy and safety evaluations of the study medication.
10. Have suspected iritis.

NCT01740388 *(Continued)*

11. Have a history of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome.
12. Have any active ulcerative keratitis, specifically any epithelial loss greater than punctate keratitis. Be immune-compromised.

Interventions

- **Intervention group:** besifloxacin 0.6%

Age, mean ± SD (range): 44.6 ± 22.5
Female, n (%): 44/64 (69%)
Major race/ethnicity, n (%): White, 51/64 (80%)
Participants (eyes) randomized: 64
Participants (eyes) analyzed for efficacy outcome(s): 18
Participants (eyes) analyzed for safety outcome(s): 64

- **Comparison group:** vehicle

Age, mean ± SD (range): 50.6 ± 21.4
Female, n (%): 44/72 (61%)
Major race/ethnicity, n (%): White, 56/72 (78%)
Participants (eyes) randomized: 72
Participants (eyes) analyzed for efficacy outcome(s): 28
Participants (eyes) analyzed for safety outcome(s): 72

- **Overall**

Age, mean ± SD (range): 47.8 ± 22.0
Female, n (%): 88/136 (64.7%)
Major race/ethnicity, n (%): White, 107/136 (78.7%)
Participants (eyes) randomized: 136
Participants (eyes) analyzed for efficacy outcome(s): 46
Participants (eyes) analyzed for safety outcome(s): 136

Baseline comparison: Baseline characteristics of those randomized appeared comparable (clinicaltrials.gov)

Interventions	• Besifloxacin ophthalmic suspension 0.6% • Vehicle One drop administered 2 times daily for 3 days
Outcomes	**Primary study outcome** 1. Clinical resolution [time frame: Visit 2 (Day 4 or 5)] absence of both conjunctival discharge and bulbar conjunctival injection, after 3 days of treatment with besifloxacin ophthalmic suspension 0.6% 2. Microbial eradication [time frame: Visit 2 (Day 4 or 5)] absence of all accepted ocular bacterial species that were present at or above threshold at baseline, after 3 days of treatment with besifloxacin ophthalmic suspension 0.6% **Secondary study outcome** 1. Clinical resolution [time frame: Visit 3 (Day 6, 7, or 8)] absence of both conjunctival discharge and bulbar conjunctival injection, after 3 days of treatment with besifloxacin ophthalmic suspension 0.6% 2. Microbial eradication [time frame: Visit 3 (Day 6, 7, or 8)] absence of all accepted ocular bacterial species that were present at or above threshold at baseline, after 3 days of treatment with besifloxacin ophthalmic suspension 0.6% 3. Other Outcome Measures:

NCT01740388 *(Continued)*

a. Ocular conjunctival discharge [time frame: At each follow-up visit (Visit 1, Visit 2 and Visit 3)] ocular conjunctival discharge measures on a scale of 0-3 where 0 = Absent, 1 = Mild, 2 = Moderate and 3 = Severe
b. Bulbar conjunctival injection [time frame: At each follow-up visit (Visit 1, Visit 2 and Visit 3)] bulbar conjunctival injection measured on a scale of 0-3 where 0 = Normal, 1 = Mild, 2 = Moderate and 3 = Severe

Notes	**Funding source:** Bausch & Lomb, Inc. **Declaration of interest:** NR **Trial registry:** NCT1740388 (clinicaltrials.gov) **Publication language:** English **Comments:** "Terminated (Strategic business decision)" in November 2013

Rietveld 2005

Study characteristics

Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" (participants and GPs) **Study visits and time points:** visit 1 (day 1, study entry), visit 2 (day 8) **Treatment duration:** variable ("The patients were advised to use the study medication until 1 day after the signs and symptoms were recovered.") **How missing data was handled:** excluded from the analysis **Power and sample size calculation:** "With a postulated recovery rate after 7 days of 95% in the intervention group and 80% in the placebo group, a difference in recovery of 15% was considered clinically relevant. With the type I and type II error rates at 0.05, and 0.20, respectively, the required sample size was 88 patients per group." **Reporting threshold for ocular adverse events:** NR
Participants	**Country:** the Netherlands **Setting:** 41 GPs working in 25 care centers in the Amsterdam and Almaar region; all eligible patients were referred for inclusion to nine designated 'study' GPs who worked in nine of the 25 centers. **Inclusion criteria:** Patients with a red eye and either (muco)purulent discharge or sticking of the eyelids **Exclusion criteria:** "The exclusion criteria were age younger than 18 years, pre-existing symptoms longer than 7 days, acute loss of vision, wearing of contact lenses, systemic or local antibiotic use within the previous 2 weeks, ciliary redness, eye trauma, and a history of eye operation." **Interventions** • **Intervention group:** fusidic acid gel Age, mean ± SD (range): 45.8 ± 14.7 Female, n (%): 42 (52%) Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 81

Rietveld 2005 *(Continued)*

	Participants (eyes) analyzed for efficacy outcome(s): 73 Participants (eyes) analyzed for safety outcome(s): 73 • **Comparison group:** placebo Age, mean ± SD (range): 41 ± 14.6 Female, n (%): 64 (645) Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 100 Participants (eyes) analyzed for efficacy outcome(s): 90 Participants (eyes) analyzed for safety outcome(s): 90 • **Overall** Age, mean ± SD (range): 31.0 ± 23.5 (1 to 96) Female, n (%): 106 (59%) Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 181 Participants (eyes) analyzed for efficacy outcome(s): 163 Participants (eyes) analyzed for safety outcome(s): 163 **Baseline comparison:** "With regard to baseline characteristics, the groups appeared comparable with possible exception of age, sex, history of infectious conjunctivitis, a foreign body sensation in the eye, and bilateral involvement (Table 1)."
Interventions	• Fusidic acid gel 10 mg/g (Fucithalmic®) • Placebo gel (Vidisic® 2 mg/g) One drop 4 times daily for 7 days; "the patients were advised to use the study medication until 1 day after the signs and symptoms were recovered."
Outcomes	**Primary outcome measure** 1. Difference in the proportions of patients recovered after 7 days of treatment. Recovery was defined as absence of any signs and symptoms, objectified by the GP, indicating conjunctivitis. **Secondary outcome measures** 1. Difference in bacterial eradication rates after 7 days, 2. Adverse effects, and 3. A survival time analysis of the duration of symptoms 4. Differences in the 7-day recovery rates between culture-positive and culture-negative patients.
Notes	**Funding source:** Dutch College of General Practitioners (ZonMw) **Declaration of interest:** None declared **Trial registry:** NR **Publication language:** English

Rose 2005

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (block randomization) **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked"

Rose 2005 *(Continued)*

	Study visits and time points: visit 1 (day 1, study entry), visit 2 (day 7); a telephone follow-up at 6 weeks **Treatment duration:** variable ("until 48 h after the infection had resolved") **How missing data was handled:** One patient had missing diary for self-reported resolution of symptoms; nurse's record was used instead; when mother's social class information was missing, mother's partner's information was used. **Power and sample size calculation:** "The initial planned sample size (n = 500) cited in the original protocol was sufficient to detect this difference with a power of 80%, α = 0·05 using a two-tailed test based on a placebo cure rate of 72%, and a prevalence of bacterial events of 60% (with the assumption that viral events would be unaffected by the antibiotic)." "However, the sample size was recalculated (without breaking the randomization code) when these later assumptions clearly did not hold..." **Reporting threshold for ocular adverse events:** NR
Participants	**Country:** UK **Setting:** 12 practices in Oxfordshire, UK **Inclusion criteria:** 1. Age 6 months to 12 years old 2. Children who presented during office hours with a working diagnosis of acute infective conjunctivitis **Exclusion criteria:** Children were excluded if they were known to be allergic to chloramphenicol, were taking any antibiotic currently or within the previous 48 h, were immunocompromised, or had evidence of severe infection (e.g. periorbital cellulitis). **Interventions** • **Intervention group:** chloramphenicol 0.5% Age, mean ± SD (IQR): 3.3 ± 2.8 (1.2 to 4.3) Female, n (%): 80 (49.1%) Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 163 Participants (eyes) analyzed for efficacy outcome(s): 163 Participants (eyes) analyzed for safety outcome(s): 163 • **Comparison group:** placebo Age, mean ± SD (IQR): 3.3 ± 2.6 (1.3 to 4.3) Female, n (%): 76 (46.7%) Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 163 Participants (eyes) analyzed for efficacy outcome(s): 163 Participants (eyes) analyzed for safety outcome(s): 163 • **Overall** Age, mean ± SD (IQR): 3.7 ± 2.9 (1.4 to 4.9) Female, n (%): 156 (47.9%) Predominant race/ethnicity, n (%): NR Participants (eyes) randomized: 326 Participants (eyes) analyzed for efficacy outcome(s): 326 Participants (eyes) analyzed for safety outcome(s): 326 **Baseline comparison:** "No clinical differences were seen between the baseline characteristics of the children in both the chloramphenicol and placebo groups (table 1)."
Interventions	• Chloramphenicol 0.5% (preservative-free eye drops)

Rose 2005 *(Continued)*

	• Placebo (distilled water with the excipients boric acid 1.5% and borax 0.3%) One drop in each of the affected eye every 2 h for the first 24 h when their child was awake and then four times daily until 48 h after the infection had resolved
Outcomes	1. Clinical cure rate at 7 days, as stated by parents. The length of time from recruitment to cure was determined from the diary; the time of cure was the first recorded time in the diary after which none of three symptoms (pain, redness, or discharge) was recorded. Any discrepancy between the recorded time of cure and the continuous entries in the diary was resolved by discussion amongst the researchers. 2. Microbiological outcome measures by comparing the number of colony-forming units at recruitment and at day 7 for these three organisms (*H influenzae*, *S pneumoniae*, and *M catarrhalis* identified) in every case at day 7
Notes	**Funding source:** Medical Research Council as part of a programme grant in childhood infection in primary care (G0000340) **Declaration of interest:** The authors indicate no financial conflict of interest. **Trial registry:** NR **Publication language:** English

Tauber 2011

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (block randomization) **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" **Study visits and time points:** visit 1 (day 1, screening/baseline), visit 2 (day 3), and visit 3 (day 4, end of therapy), which took place 12-48 hours after administration of the last dose **Treatment duration:** 3 days **How missing data was handled:** NR **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** 5% (clinicaltrials.gov)
Participants	**Country:** USA **Setting:** 82 sites and 27 states across the U.S. **Inclusion criteria:** 1. Age > 28 days old 2. Had a clinical diagnosis of bacterial conjunctivitis in one or both eyes based on bulbar conjunctival injection and discharge (minimum score of 1 on a 4-point scale for each sign) and matting 3. Patient eligibility was independent of a positive bacterial culture at day 1. **Exclusion criteria:** patients were excluded from the study if signs and symptoms of bacterial conjunctivitis had begun longer than 4 days prior to the first visit. **Interventions** • **Intervention group:** moxifloxacin 0.5% Age, mean ± SD (range): 26.8 (calculated)

Tauber 2011 *(Continued)*

Female, n (%): 353 (59.5%)
Predominant race/ethnicity, n (%): White, 463 (78.1%)
Participants (eyes) randomized: 593
Participants (eyes) analyzed for efficacy outcome(s): 424
Participants (eyes) analyzed for safety outcome(s): NR

- **Comparison group:** vehicle

Age, mean ± SD (range): 26.8 (calculated)
Female, n (%): 338 (57.7%)
Predominant race/ethnicity, n (%): White, 488 (83.3%)
Participants (eyes) randomized: 586
Participants (eyes) analyzed for efficacy outcome(s): 423
Participants (eyes) analyzed for safety outcome(s): NR

- **Overall**

Age, mean ± SD (range): 26.8 (30 days to 92 years)
Female, n (%): 691 (58.6%)
Predominant race/ethnicity, n (%): White, 951 (80.7%)
Participants (eyes) randomized: 1179
Participants (eyes) analyzed for efficacy outcome(s): 847
Participants (eyes) analyzed for safety outcome(s): NR

Baseline comparison: "For all demographic categories, the distribution of patients in the two treatment arms was comparable."

Interventions	• Moxifloxacin ophthalmic solution 0.5% • Vehicle One drop in the conjunctival sac of both eyes twice per day (morning and evening) for 3 days
Outcomes	**Study outcomes** 1. Microbiological efficacy outcome, based on the response of one eye, the “worst eye” or “study eye” on day 1. In the case that both eyes were affected and the clinical signs and symptoms were the same, the right eye was chosen as the “study eye” for analysis. 2. The bacterial species eradication rate, calculated by dividing the number of eradicated isolates of a particular species by the total number of isolates of that species (eradicated plus persisting isolates), multiplied by 100. "For purposes of this calculation, eradicated isolates in the “study eye” of a patient declared as a microbiological failure were not counted because of the clinical failure." The intent-to-treat (ITT) dataset included all randomized patients who received treatment. Only those ITT patients from whose affected eye(s) bacteria were recovered on day 1 were included in the microbiological intention-to-treat (MBITT) dataset. The modified per protocol (MPP) dataset included only those MBITT patients who finished the study; that is, completed an exit visit and complied with all conditions of the study protocol.
Notes	**Funding source:** Alcon Research, Ltd. Financial support for this publication was provided by Alcon Research, Ltd. (Fort Worth, TX, USA). Writing and editorial assistance was provided by Heather A. Edens, PhD, H EDENS, LLC, Marietta, GA, USA. **Declaration of interest:** "Shachar Tauber is a consultant for Allergan, Inc., Ista Pharmaceuticals, and Inspire Pharmaceuticals, and a founder and owner of Ocugenics which has received funding from the U.S. Department of Defense. Shachar Tauber’s wife is an employee of Alcon Laboratories, Inc. Gale Cupp, Richard Garber, Firoz Vohra, John Bartell and David Stroman are employees of Alcon Research, Ltd. Alcon Research, Ltd. designed the study and performed the data analysis." **Trial registry:** NCT00759148 (clinicaltrials.gov) **Publication language:** English

Tepedino 2009

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (block size of four) **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" **Study visits and time points:** visit 1 (day 1), visit 2 (day 5 ± 1), and visit 3 (day 8 or 9) **Treatment duration:** 5 days **How missing data was handled:** "Pearson chi-squared test with missing data and discontinued patients imputed as failures" **Power and sample size calculation:** "A sample size of 170 patients with culture-confirmed acute bacterial conjunctivitis per treatment group, assuming a dropout rate of 10%, was determined to have 90% power to detect a difference in the microbial eradication and clinical resolution rates between besifloxacin ophthalmic suspension and vehicle (using a two-sided, alpha = 0.05, chi-squared test) based on assumptions of a microbial eradication rate of 90% in the besifloxacin ophthalmic suspension group and 55% in the vehicle group and a clinical resolution rate of 33% in the besifloxacin ophthalmic suspension group and 18% in the vehicle group." **Reporting threshold for ocular adverse events:** 0.5%
Participants	**Country:** USA **Setting:** 58 sites in the US **Inclusion criteria:** 1. Age at least 1 year of age 2. Had clinical manifestations of acute bacterial conjunctivitis (i.e. purulent conjunctival discharge [crusty or sticky eyelids] and bulbar conjunctival redness) in at least one eye 3. Pin-holed visual acuity (VA) equal to or better than 20/200 in both eyes for verbal patients *Female patients of childbearing potential were required to use a reliable contraceptive method and have a negative pregnancy test prior to enrollment. Patients wearing contact lenses were instructed to discontinue use for the duration of the study. **Exclusion criteria:** 1. Patients receiving any systemic or topical antimicrobial medication within 72 hours of enrollment, topical ophthalmic solutions (including tear substitutes) within 2 hours before or during the study, or any ophthalmic topical anti-inflammatory agent within 48 hours before and during the study 2. Patients who had participated in an ophthalmic drug or device research study within the prior 30 days 3. Pregnant or nursing females and patients with suspected viral or allergic conjunctivitis or iritis, a history of recurrent corneal erosion syndrome, any active ulcerative keratitis, uncontrolled systemic disease or debilitating disease, or those who were immune-compromised or likely to require antimicrobial therapy for a systemic infection 4. Additional exclusion criteria included known hypersensitivity to besifloxacin, fluoroquinolones, or any of the ingredients in the study medication, and ocular surgery in either eye within the previous 6 weeks. **Interventions** • **Intervention group:** besifloxacin 0.6%

Tepedino 2009 *(Continued)*

Age, mean ± SD (range): 27.3 ± 21.8 (1 to 98)
Female, n (%): 302 (63.6%)
Predominant race/ethnicity, n (%): White, 312 (65.7%)
Participants (eyes) randomized: 475
Participants (eyes) analyzed for efficacy outcome(s): 199
Participants (eyes) analyzed for safety outcome(s): 473*

- **Comparison group:** vehicle

Age, mean ± SD (range): 27.3 ± 21.7 (10 mo to 97)
Female, n (%): 300 (62.2%)
Predominant race/ethnicity, n (%): White, 312 (64.7%)
Participants (eyes) randomized: 482
Participants (eyes) analyzed for efficacy outcome(s): 191
Participants (eyes) analyzed for safety outcome(s): 484*

- **Overall**

Age, mean ± SD (range): 31.0 ± 23.5 (1 to 96)
Female, n (%): 602 (62.9%)
Predominant race/ethnicity, n (%): White, 624, (65.2%)
Participants (eyes) randomized: 957
Participants (eyes) analyzed for efficacy outcome(s): 390
Participants (eyes) analyzed for safety outcome(s): 957

Baseline comparison: "Demographic characteristics were similar between treatment groups for both the ITT (Table 1) and mITT populations."

*Fourteen patients randomized to besifloxacin received vehicle and 12 patients randomized to vehicle received besifloxacin.

Interventions	• Besifloxacin ophthalmic suspension 0.6% • Vehicle One drop of study drug into the affected eye three times per day at approximately 6-hour intervals for 5 days
Outcomes	**Primary efficacy end points** 1. The primary efficacy end points were clinical resolution of the baseline conjunctivitis and eradication of the baseline bacterial infection at Visit 2 recorded as a binary response. 2. Microbial eradication was defined as the absence (grade 0 on the ordinal scale) of all bacterial species that were present at or above threshold at baseline. Primary efficacy end points were evaluated in all patients randomized to treatment who had culture-confirmed bacterial conjunctivitis (modified intention-to-treat [mITT] population). **Secondary efficacy end points** 1. Clinical resolution at Visit 3, 2. Eradication of baseline bacterial infection at Visit 3, 3. Individual clinical outcomes (i.e. ocular discharge and bulbar conjunctival injection), and 4. IGA at each follow-up visit, and 5. Microbial outcome by each baseline organism and by baseline gram-positive and gram-negative organisms.
Notes	**Funding source:** Bausch & Lomb, Rochester, NY **Declaration of interest:** "M.E.T. has been a principal investigator for Alcon, Allergan, Aventis, Bausch & Lomb, Chakshu, Insite, Incyte, Otsuka, Pfizer, QLT, Santen, and Sirion. W.H.H. has no financial or other affiliations to disclose. D.W.U., T.W.M., W.H., M.R.P., T.L.C., and L.S.B. are employees of Bausch & Lomb." **Trial registry:** NCT00347932 (clinicaltrials.gov)

Tepedino 2009 *(Continued)*

	Publication language: English

Yang 2013

Study characteristics	
Methods	**Study design:** parallel-group, randomized controlled trial, two-arm **Unit of randomization:** Person (one eye per person) **Masking of participants, treatment allocator, outcome assessor, or data analyzer:** "double-masked" (participants, investigators) **Study visits and time points:** Visit 1 (study entry, treatment initiated), visit 2 (day 4 or 5), visit 3 (day 8 or 9) **Treatment duration:** 7 days **How missing data was handled:** NA **Power and sample size calculation:** NR **Reporting threshold for ocular adverse events:** NR
Participants	**Countries:** China **Setting:** 2 study sites **Inclusion criteria:** 1. All patients have different degrees of redness, yellow secretions, hyperemia, foreign body sensation, photophobia, lacrimation, bulbar conjunctival hyperemia, edema, etc. 2. The onset was less than 72h. 3. Without any treatment before enrollment 4. Blood routine, urine routine, liver function, renal function and electrocardiogram were normal. 5. Subjects have good compliance and can be followed up on time and guaranteed not to wear contact lenses during the trial. 6. Not participating in clinical trials of other drugs within 1 month. Before treatment and at the end point of treatment, bacterial culture of conjunctival sac secretion was performed. All participating trial patients read and sign the Informed consent approved by the ethics committee of the Beijing Tongren Hospital before entering the trial cohort. **Exclusion criteria:** 1. Antibiotics or steroid eye drops have been used within 2 weeks before the start of the trial. 2. Symptoms and signs of conjunctivitis presented for more than 72 hours 3. Pregnant and lactating women 4. Those who are allergic to any component of the eye drops in this study 5. Serious digestive, lung, liver, kidney dysfunction 6. There are some diseases that cannot be cured at the same time, such as diseases of eyelid, lacrimal apparatus, conjunctiva, glaucoma, uveitis and limbal stem cell abnormalities (lagophthalmos, dry eye, entropion, trichiasis, severe corneal and conjunctival chemical burns, etc.). 7. Uncontrollable chronic eye diseases or other systemic diseases. The investigators think that it will not be possible to evaluate the efficacy or to complete the expected course of treatment and follow-up. 8. With infections of other sites requiring additional antibiotic therapy, or at risk of serious drug interactions due to multiple drugs 9. Those who have a history of intraocular surgery or laser surgery within 6 months

Yang 2013 *(Continued)*

10.Patients in clinical trials of other drugs or previously enrolled in this trial
11.Not suitable to participate in this research due to other reasons

Interventions

- **Intervention group:** azithromycin 1%

Age, mean ± SD (range): 45
Female, n (%): 48/89 (54%)
Major race/ethnicity, n (%): NR
Participants (eyes) randomized: 89
Participants (eyes) analyzed for efficacy outcome(s): 89
Participants (eyes) analyzed for safety outcome(s): 89

- **Comparison group:** vehicle

Age, mean ± SD (range): 36
Female, n (%): 56/91 (62%)
Major race/ethnicity, n (%): NR
Participants (eyes) randomized: 91
Participants (eyes) analyzed for efficacy outcome(s): 91
Participants (eyes) analyzed for safety outcome(s): 91

- **Overall**

Age, mean ± SD (range): 41 (9 to 87)
Female, n (%): 104/180 (58%)
Major race/ethnicity, n (%): NR
Participants (eyes) randomized: 180
Participants (eyes) analyzed for efficacy outcome(s): 180
Participants (eyes) analyzed for safety outcome(s): 180

Baseline comparison: "no statistically significant differences in age or gender composition"

Interventions	• 1% azithromycin • Vehicle One drop twice per day initially for 2 days and once per day later for 3rd to 7th days
Outcomes	**Primary study outcome** 1. Clinical cure rate as defined by resolution of conjunctival discharge, palpebral conjunctival hyperemia, and bulbar conjunctival hyperemia **Secondary study outcome** 1. Bacterial outcomes, such as (1) clearance as confirmed by culture; (2) presumptive clearance in patients whose signs of infections had disappeared to allow for sample collection; (3) persistence as confirmed by positive culture results; (4) presumptive failure because of clinical inefficacy; (5) partial clearance with culture-confirmed reduction but not clearance of previously identified bacterial species 2. Safety of drug, including signs of ocular irritation, lens transparency and IOP
Notes	**Funding source:** NR **Declaration of interest:** NR **Trial registry:** NR **Publication language:** abstract in English, full text in Simplified Chinese as courtesy of the Journal Editor

AE: adverse events; BCVA: best–corrected visual acuity; FDA: U.S. Food Drug and Administration; IOP: intraocular pressure; ITT: intention-to-treat; IQR: interquartile range; LE: loteprednol etabonate; mITT: modified intention-to-treat; mo: month; n: number; NA: not applicable; NR: not reported; NSAID: nonsteroidal anti-inflammatory drug; SD: standard deviation; VA: visual acuity.

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

Study	Reason for exclusion
Belfort 2012	Not a placebo-controlled trial
Bremond-Gignac 2010	Not a placebo-controlled trial
Bremond-Gignac 2014	Not a placebo-controlled trial
Bremond-Gignac 2015	Not a placebo-controlled trial
Denis 2008	Not a placebo-controlled trial
Everitt 2006	Not a placebo-controlled trial
Granet 2008	Not a placebo-controlled trial
Leibowitz 1976	Single-masked
McDonald 2009	Not a placebo-controlled trial
Mitsui 1986	Review article
Robert 2010	Not a placebo-controlled trial
Szaflik 2009	Not a placebo-controlled trial
Ta 2007	Not a placebo-controlled trial
Zhang 2019	Not a placebo-controlled trial

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

NCT02432807

Methods	**Trial type:** parallel-group **Masking:** quadruple-masked **Study period:** May 2015 to May 2018
Participants	**Country:** USA **Number recruited:** 303 participants
Interventions	• Vancomycin hydrochloride ophthalmic ointment 1.1% • Placebo ointment dosed approximately 1 cm of ointment four times daily for 7 days
Outcomes	Primary outcome measure:

NCT02432807 *(Continued)*

	• Clinical resolution [time frame: 8 days]: Between-group difference in clinical resolution of bacterial conjunctivitis (defined as absence of conjunctival discharge, bulbar conjunctival injection and palpebral conjunctival injection) at Day 8 Secondary outcome measures: • Microbial eradication [time frame: 8 days]: Between-group difference in microbial eradication (absence of all Gram-positive bacterial species present at or above the pathological threshold at baseline) at Day 8 • Safety as measured by an evaluation of the incidence of adverse events [time frame: 8 days]: Evaluation of the incidence of adverse events
Notes	**Source of sponsorship:** Kurobe LLC

Ofloxacin 1990

Methods	**Trial type:** parallel-group **Masking:** double-masked **Study period:** not reported
Participants	**Country:** USA **Number recruited:** 132 patients
Interventions	• Loxacin 0.3% eye drops • Placebo instilled 6 times daily for 2 days
Outcomes	• Efficacy and safety • Microbial reinfection rate
Notes	Conference abstract at ARVO 1990

RISK OF BIAS

Legend: Low risk of bias | High risk of bias | Some concerns

Risk of bias for analysis 1.1 Clinical cure at end of therapy - ITT population

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Fluoroquinolone						
C-00-55	~	✓	✓	~	~	~
C-00-02	~	✓	✓	~	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Miller 1992	~	✓	✓	~	✓	~
Subgroup 1.1.2 Non-fluoroquinolone						
Rose 2005	✓	✓	✓	✓	✓	✓
Yang 2013	~	✓	✓	✓	~	~

Risk of bias for analysis 1.2 Clinical cure at end of therapy - mITT population

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 Fluoroquinolone						
Tauber 2011	~	✓	✓	✓	✓	~
Tepedino 2009	~	✓	✓	~	✓	~
NCT00509873	✓	✓	✓	✓	~	~
NCT00518089	✓	✓	✓	✓	✓	✓
C-00-55	~	✓	✓	~	~	~
C-00-02	~	✓	✓	~	~	~
DeLeon 2012	✓	✓	✓	~	✓	~
Malhotra 2013	~	✓	✓	✓	✗	✗
NCT01740388	~	✓	✓	✓	✓	~
Subgroup 1.2.2 Non-fluoroquinolone						
Rietveld 2005	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gigliotti 1984	~	✓	~	✓	✓	~

Risk of bias for analysis 1.3 Clinical cure at test of cure - mITT population

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.3.1 Fluoroquinolone						
Gross 2003	~	✓	✓	✓	~	~
Karpecki 2009	✓	✓	✓	~	✓	~
Hwang 2003	✓	✓	✓	~	~	~
Subgroup 1.3.2 Non-fluoroquinolone						
Abelson 2008	~	✓	~	✓	✓	~
Rose 2005	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 Clinical cure at end of therapy - ITT population, by treatment duration

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.4.1 Treatment for 3 to 5 days						
C-00-55	~	✓	✓	~	~	~
C-00-02	~	✓	✓	~	~	~
Subgroup 1.4.2 Treatment for > 5 days						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Miller 1992	~	✓	✓	~	✓	~
Yang 2013	~	✓	✓	✓	~	~
Rose 2005	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.5 Clinical cure at end of therapy - mITT population, by treatment duration

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.5.1 Treatment duration for 3 to 5 days						
Tauber 2011	~	✓	✓	✓	✓	~
Tepedino 2009	~	✓	✓	~	✓	~
C-00-55	~	✓	✓	~	~	~
C-00-02	~	✓	✓	~	~	~
DeLeon 2012	✓	✓	✓	~	✓	~
NCT01740388	~	✓	✓	✓	✓	~
Subgroup 1.5.2 Treatment for > 5 days						
NCT00509873	✓	✓	✓	✓	~	~
NCT00518089	✓	✓	✓	✓	✓	✓
Rietveld 2005	✓	✓	✓	✓	✓	✓
Malhotra 2013	~	✓	✓	✓	✗	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gigliotti 1984	~	✓	~	✓	✓	~

Risk of bias for analysis 2.1 Clinical cure at end of therapy - mITT population, excluding trials of high risk bias

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 Low risk of bias						
NCT00518089	✓	✓	✓	✓	✓	✓
Rietveld 2005	✓	✓	✓	✓	✓	✓
Subgroup 2.1.2 Some concerns						
Tepedino 2009	~	✓	✓	~	✓	~
NCT00509873	✓	✓	✓	✓	~	~
DeLeon 2012	✓	✓	✓	~	✓	~
Tauber 2011	~	✓	✓	✓	✓	~
C-00-55	~	✓	✓	~	~	~
C-00-02	~	✓	✓	~	~	~
NCT01740388	~	✓	✓	✓	✓	~
Gigliotti 1984	~	✓	~	✓	✓	~

Risk of bias for analysis 2.3 Clinical cure at test of cure - mITT population, excluding Karpecki 2009

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.3.1 Fluoroquinolone						
Gross 2003	~	✓	✓	✓	~	~
Hwang 2003	✓	✓	✓	~	~	~
Subgroup 2.3.2 Non-fluoroquinolone						
Abelson 2008	~	✓	~	✓	✓	~
Rose 2005	✓	✓	✓	✓	✓	✓

DATA AND ANALYSES

Comparison 1. Antibiotics vs placebo

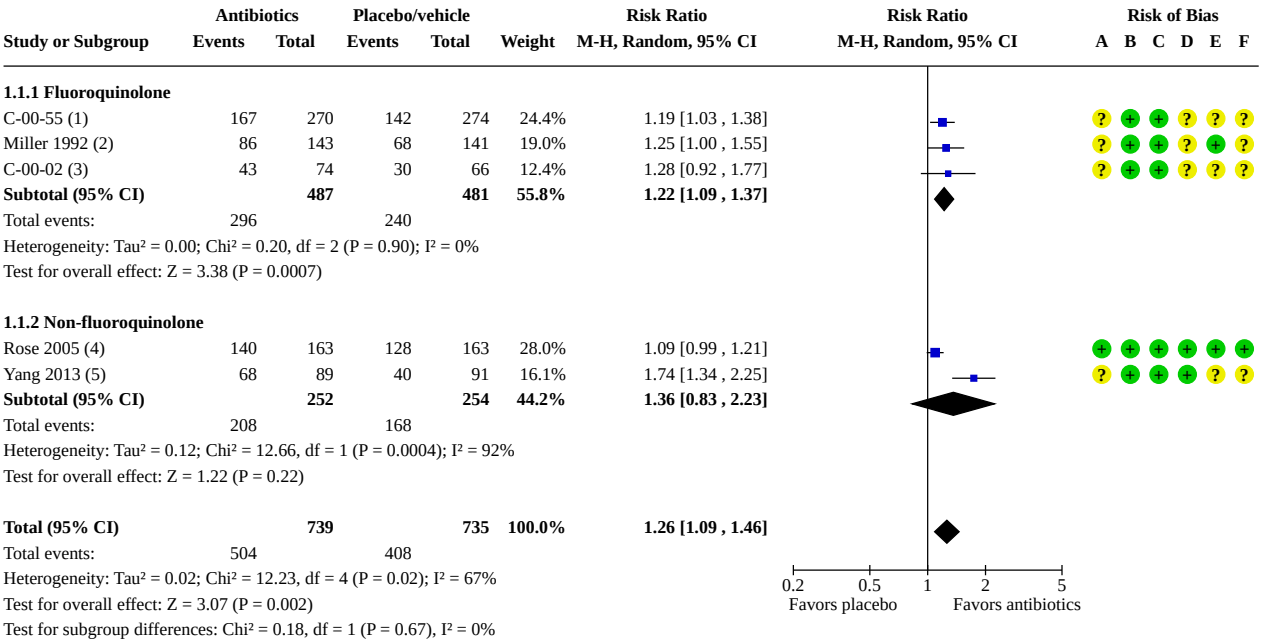
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Clinical cure at end of therapy - ITT population	5	1474	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.09, 1.46]
1.1.1 Fluoroquinolone	3	968	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.09, 1.37]
1.1.2 Non-fluoroquinolone	2	506	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.83, 2.23]
1.2 Clinical cure at end of therapy - mITT population	11	3121	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.17, 1.37]
1.2.1 Fluoroquinolone	9	2892	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.18, 1.40]
1.2.2 Non-fluoroquinolone	2	229	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.95, 1.41]
1.3 Clinical cure at test of cure - mITT population	5	799	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.08, 1.55]
1.3.1 Fluoroquinolone	3	284	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.21, 1.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.2 Non-fluoroquinolone	2	515	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.94, 1.39]
1.4 Clinical cure at end of therapy - ITT population, by treatment duration	5	1474	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.09, 1.46]
1.4.1 Treatment for 3 to 5 days	2	684	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.06, 1.38]
1.4.2 Treatment for > 5 days	3	790	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.00, 1.72]
1.5 Clinical cure at end of therapy - mITT population, by treatment duration	11	3121	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.17, 1.37]
1.5.1 Treatment duration for 3 to 5 days	6	1945	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.23, 1.45]
1.5.2 Treatment for > 5 days	5	1176	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.05, 1.30]
1.6 Microbiological efficacy at end of therapy - ITT population	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7 Microbiological efficacy at end of therapy - mITT population	10	2827	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.34, 1.74]
1.7.1 Fluoroquinolone	8	2498	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.33, 1.83]
1.7.2 Non-fluoroquinolone	2	329	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.09, 1.88]
1.8 Microbiological efficacy at test of cure - mITT population	12	2295	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.27, 1.50]
1.8.1 Fluoroquinolone	10	1979	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.25, 1.50]
1.8.2 Non-fluoroquinolone	2	316	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.20, 1.93]
1.9 Treatment incompletion	13	5573	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.52, 0.78]
1.9.1 Fluoroquinolone	10	5146	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.50, 0.75]
1.9.2 Non-fluoroquinolone	3	427	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.53, 2.07]
1.10 Persistent clinical infection	19	5280	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.65, 0.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.1 Fluoroquinolone	14	4287	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.67, 0.84]
1.10.2 Non-fluoroquinolone	5	993	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.52, 0.82]
1.11 Persistent clinical infection - by definition	19	5280	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.65, 0.81]
1.11.1 Persistence of one or both ocular signs	7	1562	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.54, 0.87]
1.11.2 Derived from "clinical cure"	12	3718	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.66, 0.83]
1.12 Persistent clinical infection - by time point	19	5280	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.65, 0.81]
1.12.1 End-of-therapy visit	13	4025	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.69, 0.85]
1.12.2 Test-of-cure visit	6	1255	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.49, 0.71]
1.13 Treatment-related ocular adverse events - risk ratio	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.13.1 Fluoroquinolone	4	3455	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.54, 0.90]
1.13.2 Non-fluoroquinolone	3	556	Risk Ratio (M-H, Random, 95% CI)	4.05 [1.36, 12.00]
1.14 Treatment-related ocular adverse events - rate ratio	9		Rate Ratio (IV, Random, 95% CI)	1.06 [0.79, 1.44]
1.14.1 Non-fluoroquinolone	1		Rate Ratio (IV, Random, 95% CI)	5.25 [0.61, 44.93]
1.14.2 Fluoroquinolone	8		Rate Ratio (IV, Random, 95% CI)	1.03 [0.77, 1.37]
1.15 Treatment-related ocular adverse events - rate difference per 1000 person-days	11		Rate difference (IV, Random, 95% CI)	1.41 [-0.93, 3.75]
1.15.1 Non-fluoroquinolone	3		Rate difference (IV, Random, 95% CI)	2.45 [0.15, 4.74]
1.15.2 Fluoroquinolone	8		Rate difference (IV, Random, 95% CI)	0.11 [-4.39, 4.60]
1.16 Non-ocular adverse events	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.16.1 Headache	4	1910	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.69, 1.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.2 Dysgeusia	1	514	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.06, 36.31]

Analysis 1.1. Comparison 1: Antibiotics vs placebo, Outcome 1: Clinical cure at end of therapy - ITT population



Footnotes

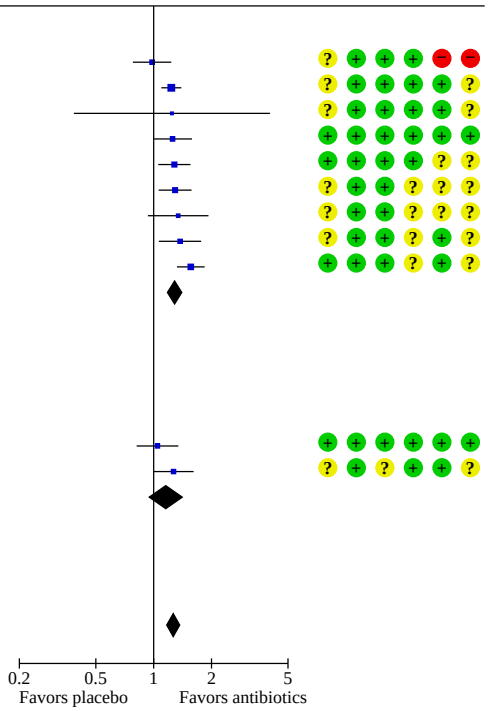
(1) Day 5, moxifloxacin 0.5%, end-of-therapy visit, mixed pediatric and participants (including children < 1 years)
(2) Dat 7 or 8, norfloxacin 0.3%, end-of-therapy visit
(3) Day 4, moxifloxacin 0.5%, end-of-therapy visit
(4) Day 7, chloramphenicol 0.3% with variable treatment duration, end-of-study visit, only pediatric participants (including children < 1 years)
(5) Day 8 or 9, azithromycin 1%, end-of-therapy visit

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Antibiotics vs placebo, Outcome 2: Clinical cure at end of therapy - mITT population

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Fluoroquinolone						
Malhotra 2013 (1)	112	206	46	83	8.7%	0.98 [0.78 , 1.23]
Tauber 2011 (2)	265	424	214	423	19.3%	1.24 [1.10 , 1.39]
NCT01740388 (3)	4	18	5	28	0.4%	1.24 [0.38 , 4.03]
NCT00518089 (4)	86	166	69	167	8.5%	1.25 [0.99 , 1.58]
NCT00509873 (5)	107	167	79	158	11.2%	1.28 [1.06 , 1.55]
C-00-55 (6)	95	143	74	144	10.9%	1.29 [1.06 , 1.57]
C-00-02 (7)	34	53	22	46	4.1%	1.34 [0.93 , 1.93]
Tepedino 2009 (8)	90	199	63	191	7.5%	1.37 [1.06 , 1.77]
DeLeon 2012 (9)	115	135	77	141	13.6%	1.56 [1.32 , 1.84]
Subtotal (95% CI)		**1511**		**1381**	**84.2%**	**1.28 [1.18 , 1.40]**
Total events:	908		649			
Heterogeneity: Tau² = 0.00; Chi² = 11.33, df = 8 (P = 0.18); I² = 29%						
Test for overall effect: Z = 5.71 (P < 0.00001)						
1.2.2 Non-fluoroquinolone						
Rietveld 2005 (10)	45	73	53	90	7.6%	1.05 [0.82 , 1.34]
Gigliotti 1984 (11)	31	34	23	32	8.1%	1.27 [1.00 , 1.61]
Subtotal (95% CI)		**107**		**122**	**15.8%**	**1.16 [0.95 , 1.41]**
Total events:	76		76			
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 1 (P = 0.25); I² = 23%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)		**1618**		**1503**	**100.0%**	**1.26 [1.17 , 1.37]**
Total events:	984		725			
Heterogeneity: Tau² = 0.00; Chi² = 13.73, df = 10 (P = 0.19); I² = 27%						
Test for overall effect: Z = 5.88 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.34), I² = 0%						



Footnotes

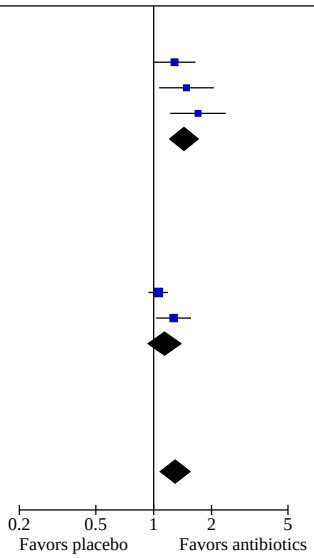
(1) Day 8 or 9, besifloxacin 0.6%
(2) Day 4, moxifloxacin 0.5%, mixed pediatric and adult participants (including children < 1 years)
(3) Day 4 or 5, besifloxacin 0.6%
(4) Up to day 6, gatifloxacin 0.5%
(5) Day 6, gatifloxacin 0.5%
(6) Day 5, moxifloxacin 0.5%, mixed pediatric and adult participants (including children < 1 years)
(7) Day 4, moxifloxacin 0.5%, two intervention groups and two vehicle groups were combined separately
(8) Day 5, besifloxacin 0.6%
(9) Day or 5, besifloxacin 0.6%
(10) Day 8, fusidic acid gel
(11) Day 8 to 10, polymyxin + bacitracin, only pediatric participants (including children < 1 years), end-of-therapy visit

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Antibiotics vs placebo, Outcome 3: Clinical cure at test of cure - mITT population

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.3.1 Fluoroquinolone							
Hwang 2003 (1)	46	59	34	56	19.5%	1.28 [1.00 , 1.65]	+ + + ? ? ?
Gross 2003 (2)	25	27	15	24	15.3%	1.48 [1.07 , 2.06]	? + + + ? ?
Karpecki 2009 (3)	44	60	25	58	15.1%	1.70 [1.22 , 2.37]	+ + + ? + ?
Subtotal (95% CI)		**146**		**138**	**49.9%**	**1.44 [1.21 , 1.71]**	
Total events:	115		74				
Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 2 (P = 0.40); I² = 0%							
Test for overall effect: Z = 4.17 (P < 0.0001)							
1.3.2 Non-fluoroquinolone							
Rose 2005 (4)	101	119	94	117	27.9%	1.06 [0.94 , 1.19]	+ + + + + +
Abelson 2008 (5)	82	130	74	149	22.2%	1.27 [1.03 , 1.56]	? + ? + + ?
Subtotal (95% CI)		**249**		**266**	**50.1%**	**1.14 [0.94 , 1.39]**	
Total events:	183		168				
Heterogeneity: Tau² = 0.01; Chi² = 2.79, df = 1 (P = 0.09); I² = 64%							
Test for overall effect: Z = 1.30 (P = 0.19)							
Total (95% CI)		**395**		**404**	**100.0%**	**1.29 [1.08 , 1.55]**	
Total events:	298		242				
Heterogeneity: Tau² = 0.03; Chi² = 12.18, df = 4 (P = 0.02); I² = 67%							
Test for overall effect: Z = 2.83 (P = 0.005)							
Test for subgroup differences: Chi² = 3.09, df = 1 (P = 0.08), I² = 67.6%							



Footnotes

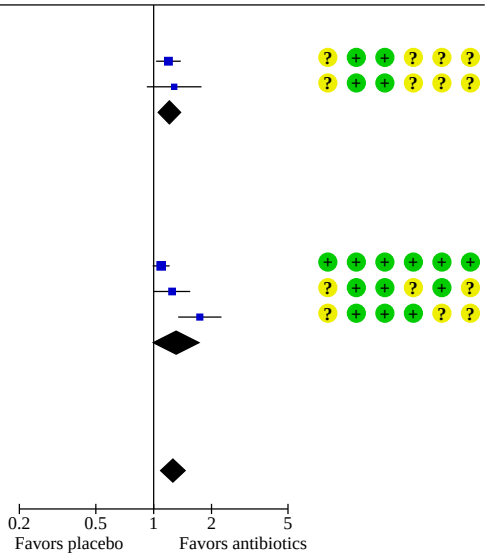
(1) Day 6 to 10, levofloxacin 0.5%
(2) Day 7, moxifloxacin 0.5%
(3) Day 8 to 9, besifloxacin 0.6%
(4) Day 7, chloramphenicol 0.3%, only pediatric participants (including children < 1 years)
(5) Day 6 or 7, azithromycin 1%

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Antibiotics vs placebo, Outcome 4: Clinical cure at end of therapy - ITT population, by treatment duration

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Treatment for 3 to 5 days						
C-00-55 (1)	167	270	142	274	24.4%	1.19 [1.03 , 1.38]
C-00-02 (2)	43	74	30	66	12.4%	1.28 [0.92 , 1.77]
Subtotal (95% CI)		**344**		**340**	**36.8%**	**1.21 [1.06 , 1.38]**
Total events:	210		172			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
1.4.2 Treatment for > 5 days						
Rose 2005 (3)	140	163	128	163	28.0%	1.09 [0.99 , 1.21]
Miller 1992 (4)	86	143	68	141	19.0%	1.25 [1.00 , 1.55]
Yang 2013 (5)	68	89	40	91	16.1%	1.74 [1.34 , 2.25]
Subtotal (95% CI)		**395**		**395**	**63.2%**	**1.31 [1.00 , 1.72]**
Total events:	294		236			
Heterogeneity: Tau² = 0.05; Chi² = 12.68, df = 2 (P = 0.002); I² = 84%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Total (95% CI)		**739**		**735**	**100.0%**	**1.26 [1.09 , 1.46]**
Total events:	504		408			
Heterogeneity: Tau² = 0.02; Chi² = 12.23, df = 4 (P = 0.02); I² = 67%						
Test for overall effect: Z = 3.07 (P = 0.002)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%						



Footnotes

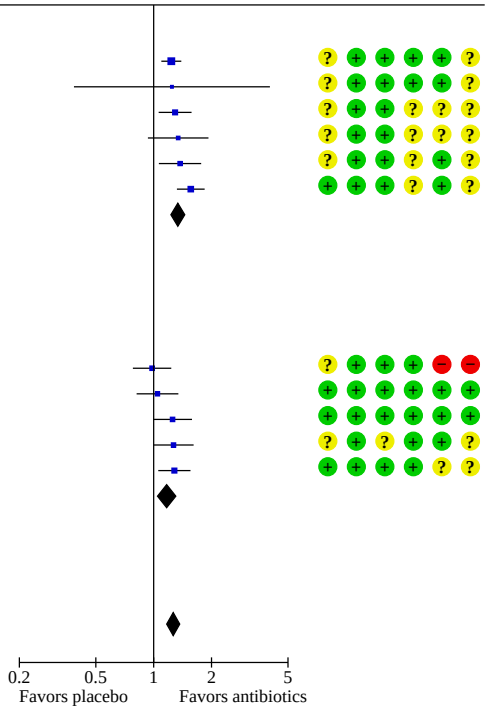
(1) Day 5, moxifloxacin 0.5%, end-of-therapy visit, mixed pediatric and participants (including children < 1 years)
(2) Day 4, moxifloxacin 0.5%, end-of-therapy visit
(3) Day 7, chloramphenicol 0.3% with variable treatment duration, end-of-study visit, only pediatric participants (including children < 1 years)
(4) Dat 7 or 8, norfloxacin 0.3%, end-of-therapy visit
(5) Day 8 or 9, azithromycin 1%, end-of-therapy visit

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Antibiotics vs placebo, Outcome 5: Clinical cure at end of therapy - mITT population, by treatment duration

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Treatment duration for 3 to 5 days						
Tauber 2011 (1)	265	424	214	423	19.3%	1.24 [1.10 , 1.39]
NCT01740388 (2)	4	18	5	28	0.4%	1.24 [0.38 , 4.03]
C-00-55 (3)	95	143	74	144	10.9%	1.29 [1.06 , 1.57]
C-00-02 (4)	34	53	22	46	4.1%	1.34 [0.93 , 1.93]
Tepedino 2009 (5)	90	199	63	191	7.5%	1.37 [1.06 , 1.77]
DeLeon 2012 (2)	115	135	77	141	13.6%	1.56 [1.32 , 1.84]
Subtotal (95% CI)		**972**		**973**	**55.8%**	**1.34 [1.23 , 1.45]**
Total events:	603		455			
Heterogeneity: Tau² = 0.00; Chi² = 5.18, df = 5 (P = 0.39); I² = 4%						
Test for overall effect: Z = 6.83 (P < 0.00001)						
1.5.2 Treatment for > 5 days						
Malhotra 2013 (6)	112	206	46	83	8.7%	0.98 [0.78 , 1.23]
Rietveld 2005 (7)	45	73	53	90	7.6%	1.05 [0.82 , 1.34]
NCT00518089 (8)	86	166	69	167	8.5%	1.25 [0.99 , 1.58]
Gigliotti 1984 (9)	31	34	23	32	8.1%	1.27 [1.00 , 1.61]
NCT00509873 (10)	107	167	79	158	11.2%	1.28 [1.06 , 1.55]
Subtotal (95% CI)		**646**		**530**	**44.2%**	**1.17 [1.05 , 1.30]**
Total events:	381		270			
Heterogeneity: Tau² = 0.00; Chi² = 4.65, df = 4 (P = 0.33); I² = 14%						
Test for overall effect: Z = 2.78 (P = 0.005)						
Total (95% CI)		**1618**		**1503**	**100.0%**	**1.26 [1.17 , 1.37]**
Total events:	984		725			
Heterogeneity: Tau² = 0.00; Chi² = 13.73, df = 10 (P = 0.19); I² = 27%						
Test for overall effect: Z = 5.88 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.64, df = 1 (P = 0.06), I² = 72.5%						



Footnotes

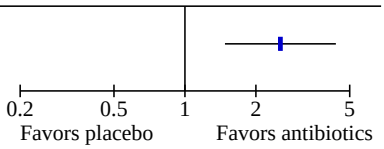
(1) Day 4, moxifloxacin 0.5%, mixed pediatric and adult participants (including children < 1 years)
(2) Day 4 or 5, besifloxacin 0.6%
(3) Day 5, moxifloxacin 0.5%, mixed pediatric and adult participants (including children < 1 years)
(4) Day 4, moxifloxacin 0.5%, two intervention groups and two vehicle groups were combined separately
(5) Day 5, besifloxacin 0.6%
(6) Day 8 or 9, besifloxacin 0.6%
(7) Day 8, fusidic acid gel
(8) Up to day 6, gatifloxacin 0.5%
(9) Day 8 to 10, polymyxin + bacitracin, only pediatric participants (including children < 1 years), end-of-therapy visit
(10) Day 6, gatifloxacin 0.5%

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Antibiotics vs placebo, Outcome 6: Microbiological efficacy at end of therapy - ITT population

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Risk Ratio M-H, Random, 95% CI
Gigliotti 1984 (1)	27	34	10	32	2.54 [1.48 , 4.37]

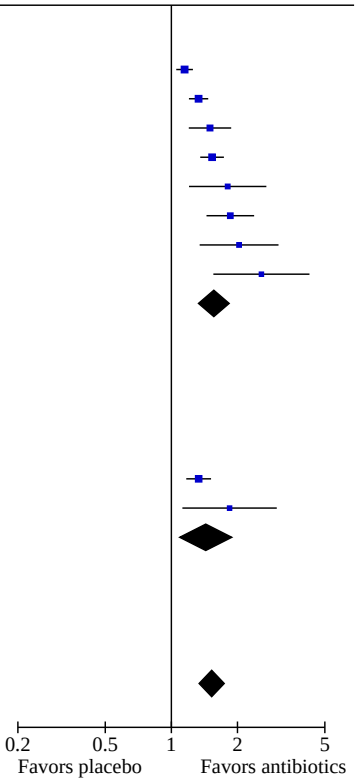


Footnotes

(1) Day 8 to 10, polymyxin + bacitracin, only pediatric participants (including children < 1 years), end-of-therapy visit

Analysis 1.7. Comparison 1: Antibiotics vs placebo, Outcome 7: Microbiological efficacy at end of therapy - mITT population

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Fluoroquinolone						
NCT00518089 (1)	153	166	134	167	14.8%	1.15 [1.05 , 1.25]
Tauber 2011 (2)	316	424	237	423	14.5%	1.33 [1.20 , 1.47]
DeLeon 2012 (3)	89	135	62	141	10.9%	1.50 [1.20 , 1.87]
Tepedino 2009 (4)	182	199	114	191	13.9%	1.53 [1.35 , 1.73]
Miller 1992 (5)	43	76	21	67	6.3%	1.81 [1.20 , 2.71]
Malhotra 2013 (6)	172	206	36	80	10.1%	1.86 [1.45 , 2.38]
NCT01740388 (3)	17	18	13	28	6.2%	2.03 [1.35 , 3.08]
Leibowitz 1991 (7)	107	140	11	37	4.8%	2.57 [1.55 , 4.25]
Subtotal (95% CI)		**1364**		**1134**	**81.4%**	**1.56 [1.33 , 1.83]**
Total events:	1079		628			
Heterogeneity: Tau² = 0.04; Chi² = 43.02, df = 7 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 5.43 (P < 0.00001)						
1.7.2 Non-fluoroquinolone						
Abelson 2008 (8)	115	130	99	149	13.7%	1.33 [1.17 , 1.52]
Rietveld 2005 (9)	16	21	12	29	4.9%	1.84 [1.12 , 3.02]
Subtotal (95% CI)		**151**		**178**	**18.6%**	**1.43 [1.09 , 1.88]**
Total events:	131		111			
Heterogeneity: Tau² = 0.02; Chi² = 1.61, df = 1 (P = 0.21); I² = 38%						
Test for overall effect: Z = 2.59 (P = 0.010)						
Total (95% CI)		**1515**		**1312**	**100.0%**	**1.53 [1.34 , 1.74]**
Total events:	1210		739			
Heterogeneity: Tau² = 0.03; Chi² = 44.22, df = 9 (P < 0.00001); I² = 80%						
Test for overall effect: Z = 6.30 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%						

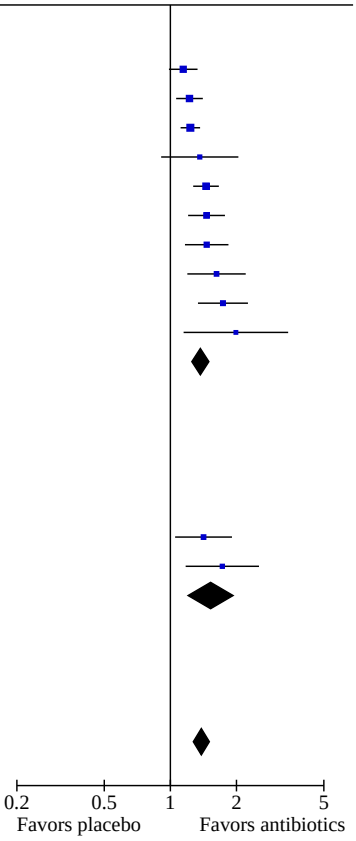


Footnotes

(1) Up to day 6, gatifloxacin 0.5%, end-of-therapy visit
(2) Day 4, moxifloxacin 0.5%, end-of-therapy visit, mixed pediatric and adult participants (including children < 1 years)
(3) Day 4 or 5, besifloxacin 0.6%, end-of-therapy visit
(4) Day 5, besifloxacin 0.6%, end-of-therapy visit
(5) Day 7 or 8, norfloxacin 0.3%, end-of-therapy visit
(6) Day 8 or 9, besifloxacin 0.6%, end-of-therapy visit
(7) Day 3, ciprofloxacin 0.3%, end-of-therapy visit
(8) Day 6 or 7, azithromycin 1%, end-of-therapy visit
(9) Day 8, fusidic acid gel, end-of-therapy visit

Analysis 1.8. Comparison 1: Antibiotics vs placebo, Outcome 8: Microbiological efficacy at test of cure - mITT population

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Fluoroquinolone						
DeLeon 2012 (1)	103	135	94	141	12.4%	1.14 [0.99 , 1.33]
C-00-55 (2)	112	136	93	138	13.0%	1.22 [1.06 , 1.41]
Tepedino 2009 (3)	176	199	137	191	15.7%	1.23 [1.11 , 1.37]
NCT01740388 (1)	14	18	16	28	3.6%	1.36 [0.91 , 2.04]
NCT00509873 (4)	149	167	97	158	13.4%	1.45 [1.27 , 1.66]
Malhotra 2013 (5)	169	200	48	83	9.8%	1.46 [1.20 , 1.77]
Karpecki 2009 (3)	53	60	35	58	8.1%	1.46 [1.17 , 1.84]
C-00-02 (6)	43	53	25	50	5.5%	1.62 [1.19 , 2.20]
Hwang 2003 (7)	54	59	29	55	6.8%	1.74 [1.34 , 2.26]
Gross 2003 (6)	21	27	9	23	2.1%	1.99 [1.15 , 3.44]
Subtotal (95% CI)		**1054**		**925**	**90.4%**	**1.37 [1.25 , 1.50]**
Total events:	894		583			
Heterogeneity: Tau² = 0.01; Chi² = 18.75, df = 9 (P = 0.03); I² = 52%						
Test for overall effect: Z = 6.91 (P < 0.00001)						
1.8.2 Non-fluoroquinolone						
Yang 2013 (8)	24	28	23	38	5.7%	1.42 [1.05 , 1.91]
Rose 2005 (9)	50	125	29	125	3.9%	1.72 [1.17 , 2.53]
Subtotal (95% CI)		**153**		**163**	**9.6%**	**1.52 [1.20 , 1.93]**
Total events:	74		52			
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 3.51 (P = 0.0004)						
Total (95% CI)		**1207**		**1088**	**100.0%**	**1.38 [1.27 , 1.50]**
Total events:	968		635			
Heterogeneity: Tau² = 0.01; Chi² = 21.09, df = 11 (P = 0.03); I² = 48%						
Test for overall effect: Z = 7.58 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%						

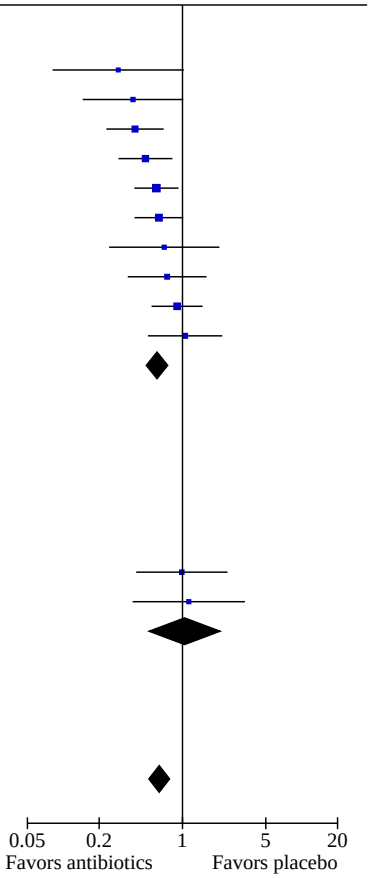


Footnotes

(1) Day 6 to 8, besifloxacin 0.6%
(2) Day 9, moxifloxacin 0.5%, mixed pediatric and adult participants (including children < 1 years)
(3) Day 8 or 9, besifloxacin 0.6%
(4) Day 6 or later, gatifloxacin 0.5%
(5) Day 10 to 12, besifloxacin 0.6%
(6) Day 7, moxifloxacin 0.5%
(7) day 6 to 10, levofloxacin 0.5%
(8) Day 8 or 9, azithromycin 1%, test-of-cure visit
(9) Day 7, chloramphenicol 0.3%, only pediatric participants (including children < 1 years)

Analysis 1.9. Comparison 1: Antibiotics vs placebo, Outcome 9: Treatment incompletion

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Fluoroquinolone						
Karpecki 2009 (1)	3	137	10	132	2.4%	0.29 [0.08 , 1.03]
Malhotra 2013 (1)	7	344	9	170	4.0%	0.38 [0.15 , 1.01]
Miller 1992 (2)	15	143	37	141	11.2%	0.40 [0.23 , 0.69]
C-01-66 (3)	19	265	39	266	12.4%	0.49 [0.29 , 0.82]
Tepedino 2009 (1)	31	475	52	482	17.2%	0.60 [0.39 , 0.93]
C-00-55 (4)	25	270	40	274	14.6%	0.63 [0.40 , 1.02]
NCT01740388 (1)	5	64	8	72	3.4%	0.70 [0.24 , 2.04]
NCT00509873 (5)	11	287	15	291	6.3%	0.74 [0.35 , 1.59]
NCT00518089 (5)	28	430	31	429	13.6%	0.90 [0.55 , 1.48]
DeLeon 2012 (1)	14	231	14	243	7.0%	1.05 [0.51 , 2.16]
Subtotal (95% CI)		**2646**		**2500**	**92.0%**	**0.61 [0.50 , 0.75]**
Total events:	158		255			
Heterogeneity: Tau² = 0.01; Chi² = 10.11, df = 9 (P = 0.34); I² = 11%						
Test for overall effect: Z = 4.66 (P < 0.00001)						
1.9.2 Non-fluoroquinolone						
Yang 2013 (6)	0	89	0	91		Not estimable
Rietveld 2005 (7)	8	81	10	100	4.8%	0.99 [0.41 , 2.39]
Gigliotti 1984 (8)	6	34	5	32	3.2%	1.13 [0.38 , 3.34]
Subtotal (95% CI)		**204**		**223**	**8.0%**	**1.04 [0.53 , 2.07]**
Total events:	14		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Total (95% CI)		**2850**		**2723**	**100.0%**	**0.64 [0.52 , 0.78]**
Total events:	172		270			
Heterogeneity: Tau² = 0.01; Chi² = 12.30, df = 11 (P = 0.34); I² = 11%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.14, df = 1 (P = 0.14), I² = 53.2%						

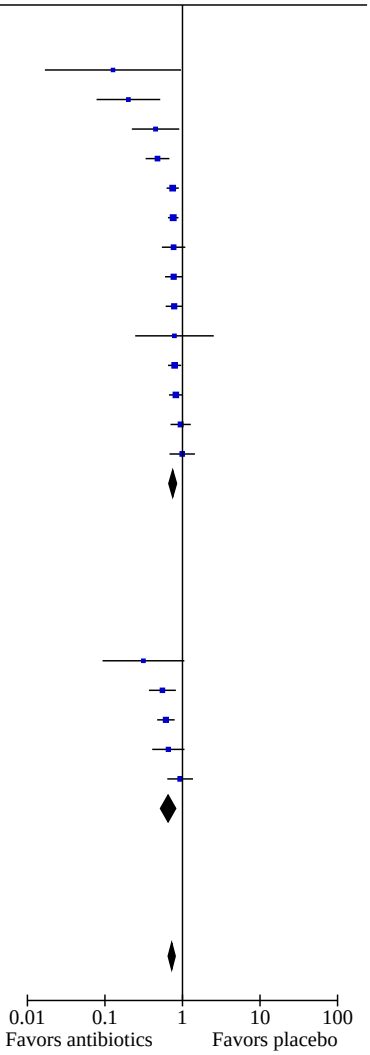


Footnotes

(1) Besifloxacin 0.6%
(2) Norfloxacin 0.3%
(3) Moxifloxacin 0.5%, data source: Kodijigan 2010
(4) Moxifloxacin 0.5%
(5) Gatifloxacin 0.5%
(6) Azithromycin 1%
(7) Fusidic acid gel
(8) Polymyxin + bacitracin

Analysis 1.10. Comparison 1: Antibiotics vs placebo, Outcome 10: Persistent clinical infection

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Fluoroquinolone						
Gross 2003 (1)	1	27	7	24	0.3%	0.13 [0.02 , 0.96]
C-01-66	5	265	25	266	1.1%	0.20 [0.08 , 0.52]
Hwang 2003 (2)	9	59	19	56	1.9%	0.45 [0.22 , 0.91]
DeLeon 2012 (3)	31	135	68	141	5.3%	0.48 [0.33 , 0.68]
Tepedino 2009 (4)	95	199	122	191	9.7%	0.75 [0.62 , 0.90]
Tauber 2011 (5)	159	424	209	423	10.5%	0.76 [0.65 , 0.89]
C-00-02 (5)	31	74	36	66	5.4%	0.77 [0.54 , 1.09]
Miller 1992 (6)	57	143	73	141	7.4%	0.77 [0.60 , 1.00]
Karpecki 2009 (7)	36	60	43	56	7.6%	0.78 [0.61 , 1.01]
NCT00509873 (8)	5	167	6	158	0.7%	0.79 [0.25 , 2.53]
C-00-55 (9)	103	270	132	274	9.2%	0.79 [0.65 , 0.96]
NCT00518089 (10)	80	166	98	167	9.0%	0.82 [0.67 , 1.01]
NCT01740388 (3)	14	18	23	28	6.3%	0.95 [0.70 , 1.28]
Malhotra 2013 (11)	64	206	26	83	4.8%	0.99 [0.68 , 1.45]
Subtotal (95% CI)		**2213**		**2074**	**79.2%**	**0.75 [0.67 , 0.84]**
Total events:	690		887			
Heterogeneity: Tau² = 0.02; Chi² = 25.17, df = 13 (P = 0.02); I² = 48%						
Test for overall effect: Z = 5.00 (P < 0.00001)						
1.10.2 Non-fluoroquinolone						
Gigliotti 1984 (12)	3	34	9	32	0.7%	0.31 [0.09 , 1.06]
Yang 2013 (13)	21	68	51	91	4.5%	0.55 [0.37 , 0.82]
Abelson 2008 (14)	48	130	90	149	7.4%	0.61 [0.47 , 0.79]
Rose 2005 (15)	23	163	35	163	3.5%	0.66 [0.41 , 1.06]
Rietveld 2005 (16)	28	73	37	90	4.8%	0.93 [0.64 , 1.37]
Subtotal (95% CI)		**468**		**525**	**20.8%**	**0.65 [0.52 , 0.82]**
Total events:	123		222			
Heterogeneity: Tau² = 0.02; Chi² = 5.71, df = 4 (P = 0.22); I² = 30%						
Test for overall effect: Z = 3.73 (P = 0.0002)						
Total (95% CI)		**2681**		**2599**	**100.0%**	**0.73 [0.65 , 0.81]**
Total events:	813		1109			
Heterogeneity: Tau² = 0.02; Chi² = 33.72, df = 18 (P = 0.01); I² = 47%						
Test for overall effect: Z = 6.07 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.13, df = 1 (P = 0.29), I² = 11.2%						



Footnotes

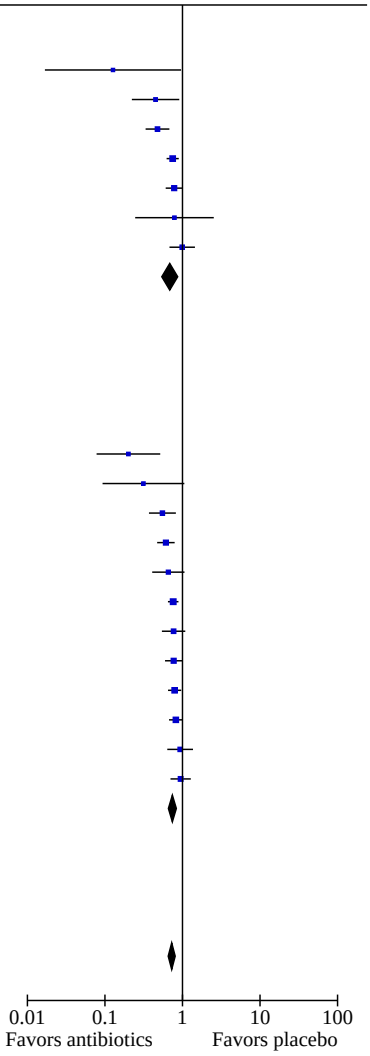
(1) Day 7, moxifloxacin 0.5%, test-of-cure visit
(2) Day 6 to 10, levofloxacin 0.5%, test-of-cure visit
(3) Day 4 or 5, besifloxacin 0.6%, end-of-therapy visit
(4) Day 5, besifloxacin 0.6%, end-of-therapy visit
(5) Day 4, moxifloxacin 0.5%, end-of-therapy visit
(6) Day 7 or 8, Norfloxacin 0.3%, end-of-therapy visit
(7) Day 4, besifloxacin 0.6%, end-of-therapy visit
(8) Day 6, gatifloxacin 0.5%, test-of-cure visit
(9) Day 5, moxifloxacin 0.5%, end-of-therapy visit
(10) Day 6, gatifloxacin 0.5%, end-of-therapy visit
(11) Day 8, besifloxacin 0.6%, end-of-therapy visit
(12) Day 8 to 10, polymyxin + bacitracin, end-of-therapy visit
(13) Day 8 or 9, azithromycin 1%, end-of-therapy visit
(14) Day 6 or 7, azithromycin 1%, test-of-cure visit
(15) Day 7, chloramphenicol 0.3%, end-of-study visit

Analysis 1.10. (Continued)

(14) Day 6 or 7, azithromycin 1%, test-of-cure visit
(15) Day 7, chloramphenicol 0.3%, end-of-study visit
(16) Day 8, fusidic acid gel, end-of-therapy visit

Analysis 1.11. Comparison 1: Antibiotics vs placebo, Outcome 11: Persistent clinical infection - by definition

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Persistence of one or both ocular signs						
Gross 2003 (1)	1	27	7	24	0.3%	0.13 [0.02 , 0.96]
Hwang 2003 (2)	9	59	19	56	1.9%	0.45 [0.22 , 0.91]
DeLeon 2012 (3)	31	135	68	141	5.3%	0.48 [0.33 , 0.68]
Tepedino 2009 (4)	95	199	122	191	9.7%	0.75 [0.62 , 0.90]
Karpecki 2009 (5)	36	60	43	56	7.6%	0.78 [0.61 , 1.01]
NCT00509873 (6)	5	167	6	158	0.7%	0.79 [0.25 , 2.53]
Malhotra 2013 (7)	64	206	26	83	4.8%	0.99 [0.68 , 1.45]
Subtotal (95% CI)		**853**		**709**	**30.2%**	**0.68 [0.54 , 0.87]**
Total events:	241		291			
Heterogeneity: Tau² = 0.05; Chi² = 13.64, df = 6 (P = 0.03); I² = 56%						
Test for overall effect: Z = 3.15 (P = 0.002)						
1.11.2 Derived from "clinical cure"						
C-01-66 (8)	5	265	25	266	1.1%	0.20 [0.08 , 0.52]
Gigliotti 1984 (9)	3	34	9	32	0.7%	0.31 [0.09 , 1.06]
Yang 2013 (10)	21	68	51	91	4.5%	0.55 [0.37 , 0.82]
Abelson 2008 (11)	48	130	90	149	7.4%	0.61 [0.47 , 0.79]
Rose 2005 (12)	23	163	35	163	3.5%	0.66 [0.41 , 1.06]
Tauber 2011 (13)	159	424	209	423	10.5%	0.76 [0.65 , 0.89]
C-00-02 (13)	31	74	36	66	5.4%	0.77 [0.54 , 1.09]
Miller 1992 (14)	57	143	73	141	7.4%	0.77 [0.60 , 1.00]
C-00-55 (15)	103	270	132	274	9.2%	0.79 [0.65 , 0.96]
NCT00518089 (16)	80	166	98	167	9.0%	0.82 [0.67 , 1.01]
Rietveld 2005 (17)	28	73	37	90	4.8%	0.93 [0.64 , 1.37]
NCT01740388 (3)	14	18	23	28	6.3%	0.95 [0.70 , 1.28]
Subtotal (95% CI)		**1828**		**1890**	**69.8%**	**0.74 [0.66 , 0.83]**
Total events:	572		818			
Heterogeneity: Tau² = 0.02; Chi² = 19.76, df = 11 (P = 0.05); I² = 44%						
Test for overall effect: Z = 5.00 (P < 0.00001)						
Total (95% CI)		**2681**		**2599**	**100.0%**	**0.73 [0.65 , 0.81]**
Total events:	813		1109			
Heterogeneity: Tau² = 0.02; Chi² = 33.72, df = 18 (P = 0.01); I² = 47%						
Test for overall effect: Z = 6.07 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%						



Footnotes

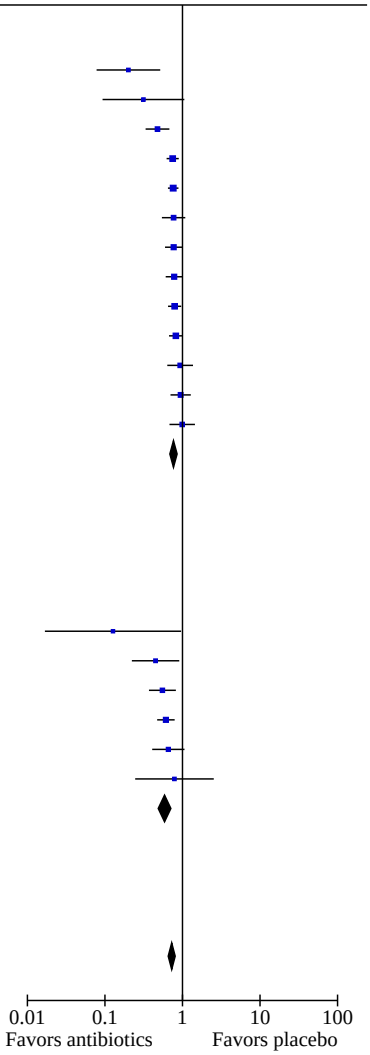
(1) Day 7, moxifloxacin 0.5%, test-of-cure visit
(2) Day 6 to 10, levofloxacin 0.5%, test-of-cure visit
(3) Day 4 or 5, besifloxacin 0.6%, end-of-therapy visit
(4) Day 5, besifloxacin 0.6%, end-of-therapy visit
(5) Day 4, besifloxacin 0.6%, end-of-therapy visit
(6) Day 6, gatifloxacin 0.5%, test-of-cure visit
(7) Day 8, besifloxacin 0.6%, end-of-therapy visit
(8) Unclear, moxifloxacin 0.5%
(9) Day 8 to 10, polymyxin + bacitracin, end-of-therapy visit
(10) Day 8 or 9, azithromycin 1%, end-of-therapy visit
(11) Day 6 or 7, azithromycin 1%, test-of-cure visit
(12) Day 7, chloramphenicol 0.3%, end-of-study visit
(13) Day 4, moxifloxacin 0.5%, end-of-therapy visit
(14) Day 7 or 8, Norfloxacin 0.3%, end-of-therapy visit
(15) Day 5, moxifloxacin 0.5%, end-of-therapy visit

Analysis 1.11. (Continued)

(14) Day 7 or 8, Norfloxacin 0.3%, end-of-therapy visit
(15) Day 5, moxifloxacin 0.5%, end-of-therapy visit
(16) Day 6, gatifloxacin 0.5%, end-of-therapy visit
(17) Day 8, fusidic acid gel, end-of-therapy visit

Analysis 1.12. Comparison 1: Antibiotics vs placebo, Outcome 12: Persistent clinical infection - by time point

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 End-of-therapy visit						
C-01-66	5	265	25	266	1.1%	0.20 [0.08 , 0.52]
Gigliotti 1984 (1)	3	34	9	32	0.7%	0.31 [0.09 , 1.06]
DeLeon 2012 (2)	31	135	68	141	5.3%	0.48 [0.33 , 0.68]
Tepedino 2009 (3)	95	199	122	191	9.7%	0.75 [0.62 , 0.90]
Tauber 2011 (4)	159	424	209	423	10.5%	0.76 [0.65 , 0.89]
C-00-02 (4)	31	74	36	66	5.4%	0.77 [0.54 , 1.09]
Miller 1992 (5)	57	143	73	141	7.4%	0.77 [0.60 , 1.00]
Karpecki 2009 (6)	36	60	43	56	7.6%	0.78 [0.61 , 1.01]
C-00-55 (7)	103	270	132	274	9.2%	0.79 [0.65 , 0.96]
NCT00518089 (8)	80	166	98	167	9.0%	0.82 [0.67 , 1.01]
Rietveld 2005 (9)	28	73	37	90	4.8%	0.93 [0.64 , 1.37]
NCT01740388 (2)	14	18	23	28	6.3%	0.95 [0.70 , 1.28]
Malhotra 2013 (10)	64	206	26	83	4.8%	0.99 [0.68 , 1.45]
Subtotal (95% CI)		**2067**		**1958**	**81.8%**	**0.77 [0.69 , 0.85]**
Total events:	706		901			
Heterogeneity: Tau² = 0.02; Chi² = 22.71, df = 12 (P = 0.03); I² = 47%						
Test for overall effect: Z = 4.87 (P < 0.00001)						
1.12.2 Test-of-cure visit						
Gross 2003 (11)	1	27	7	24	0.3%	0.13 [0.02 , 0.96]
Hwang 2003 (12)	9	59	19	56	1.9%	0.45 [0.22 , 0.91]
Yang 2013 (13)	21	68	51	91	4.5%	0.55 [0.37 , 0.82]
Abelson 2008 (14)	48	130	90	149	7.4%	0.61 [0.47 , 0.79]
Rose 2005 (15)	23	163	35	163	3.5%	0.66 [0.41 , 1.06]
NCT00509873 (16)	5	167	6	158	0.7%	0.79 [0.25 , 2.53]
Subtotal (95% CI)		**614**		**641**	**18.2%**	**0.59 [0.49 , 0.71]**
Total events:	107		208			
Heterogeneity: Tau² = 0.00; Chi² = 3.43, df = 5 (P = 0.63); I² = 0%						
Test for overall effect: Z = 5.57 (P < 0.00001)						
Total (95% CI)		**2681**		**2599**	**100.0%**	**0.73 [0.65 , 0.81]**
Total events:	813		1109			
Heterogeneity: Tau² = 0.02; Chi² = 33.72, df = 18 (P = 0.01); I² = 47%						
Test for overall effect: Z = 6.07 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.78, df = 1 (P = 0.02), I² = 82.7%						



Footnotes

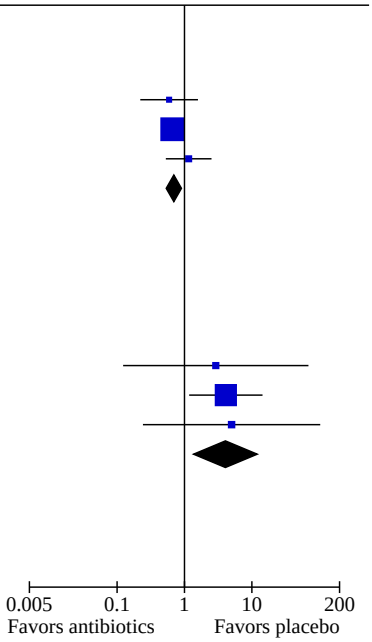
(1) Day 8 to 10, polymyxin + bacitracin, end-of-therapy visit
(2) Day 4 or 5, besifloxacin 0.6%, end-of-therapy visit
(3) Day 5, besifloxacin 0.6%, end-of-therapy visit
(4) Day 4, moxifloxacin 0.5%, end-of-therapy visit
(5) Day 7 or 8, Norfloxacin 0.3%, end-of-therapy visit
(6) Day 4, besifloxacin 0.6%, end-of-therapy visit
(7) Day 5, moxifloxacin 0.5%, end-of-therapy visit
(8) Day 6, gatifloxacin 0.5%, end-of-therapy visit
(9) Day 8, fusidic acid gel, end-of-therapy visit
(10) Day 8, besifloxacin 0.6%, end-of-therapy visit
(11) Day 7, moxifloxacin 0.5%, test-of-cure visit
(12) Day 6 to 10, levofloxacin 0.5%, test-of-cure visit
(13) Day 8 or 9, azithromycin 1%, test-of-cure visit
(14) Day 6 or 7, azithromycin 1%, test-of-cure visit
(15) Day 7, chloramphenicol 0.3%, end-of-study visit

Analysis 1.12. (Continued)

(14) Day 6 or 7, azithromycin 1%, test-of-cure visit
(15) Day 7, chloramphenicol 0.3%, end-of-study visit
(16) Day 6, gatifloxacin 0.5%, test-of-cure visit

Analysis 1.13. Comparison 1: Antibiotics vs placebo, Outcome 13: Treatment-related ocular adverse events - risk ratio

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Fluoroquinolone						
Tauber 2011 (1)	0	593	0	586		Not estimable
Miller 1992 (2)	6	143	10	141	7.0%	0.59 [0.22 , 1.58]
Tepedino 2009 (3)	68	741	106	760	81.9%	0.66 [0.49 , 0.88]
DeLeon 2012 (4)	12	228	12	263	11.1%	1.15 [0.53 , 2.52]
Subtotal (95% CI)		**1705**		**1750**	**100.0%**	**0.70 [0.54 , 0.90]**
Total events:	86		128			
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
1.13.2 Non-fluoroquinolone						
Comstock 2012 (5)	1	34	0	33	11.8%	2.91 [0.12 , 69.08]
Rietveld 2005 (6)	10	73	3	90	75.3%	4.11 [1.17 , 14.38]
Rose 2005	2	163	0	163	12.9%	5.00 [0.24 , 103.35]
Subtotal (95% CI)		**270**		**286**	**100.0%**	**4.05 [1.36 , 12.00]**
Total events:	13		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

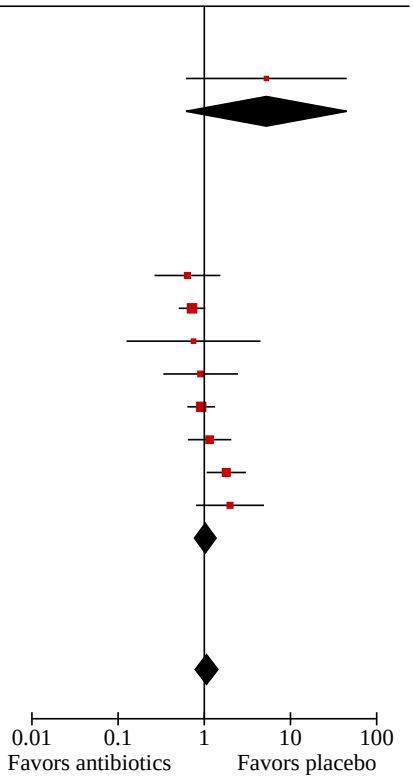


Footnotes

(1) Moxifloxacin 0.5%, reporting threshold 5%
(2) Norfloxacin 0.3%
(3) Besifloxacin 0.6%, unit of analysis was eye, reporting threshold 0.5%
(4) Besifloxacin 0.6%, reporting threshold 0.5%
(5) Loteprednol etabonate + tobramycin ophthalmic suspension; the tobramycin alone group (n = 34) had no ocular adverse events
(6) Fusidic acid gel

Analysis 1.14. Comparison 1: Antibiotics vs placebo, Outcome 14: Treatment-related ocular adverse events - rate ratio

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
1.14.1 Non-fluoroquinolone				
Abelson 2008 (1)	1.659	1.095	1.9%	5.25 [0.61 , 44.93]
Subtotal (95% CI)			**1.9%**	**5.25 [0.61 , 44.93]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.52 (P = 0.13)				
1.14.2 Fluoroquinolone				
DeLeon 2012 (2)	-0.451	0.449	8.5%	0.64 [0.26 , 1.54]
Tepedino 2009 (2)	-0.328	0.181	21.2%	0.72 [0.51 , 1.03]
NCT01740388 (2)	-0.288	0.913	2.6%	0.75 [0.13 , 4.49]
Malhotra 2013 (2)	-0.099	0.508	7.0%	0.91 [0.33 , 2.45]
Karpecki 2009 (2)	-0.082	0.189	20.7%	0.92 [0.64 , 1.33]
Hwang 2003 (3)	0.142	0.296	14.2%	1.15 [0.65 , 2.06]
C-00-55 (4)	0.587	0.267	15.8%	1.80 [1.07 , 3.04]
NCT00518089 (5)	0.688	0.463	8.1%	1.99 [0.80 , 4.93]
Subtotal (95% CI)			**98.1%**	**1.03 [0.77 , 1.37]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 11.84$, df = 7 (P = 0.11); $I^2 = 41\%$				
Test for overall effect: Z = 0.18 (P = 0.86)				
Total (95% CI)			**100.0%**	**1.06 [0.79 , 1.44]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 14.18$, df = 8 (P = 0.08); $I^2 = 44\%$				
Test for overall effect: Z = 0.39 (P = 0.70)				
Test for subgroup differences: $Chi^2 = 2.19$, df = 1 (P = 0.14), $I^2 = 54.2\%$				

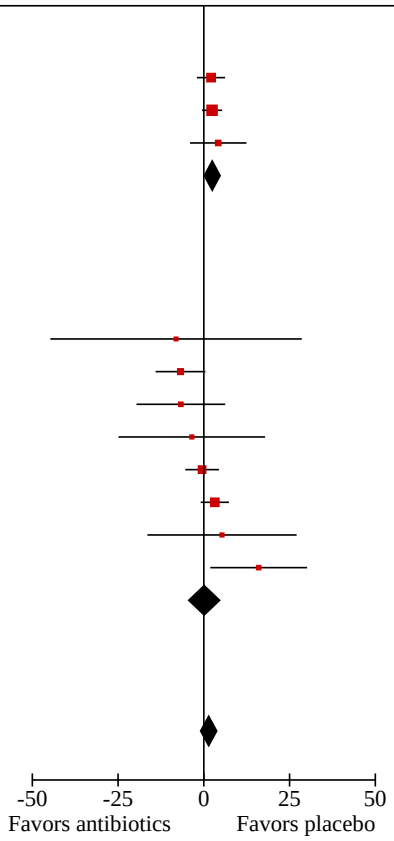


Footnotes

(1) Azithromycin 1%
(2) Besifloxacin 0.6%
(3) Levofloxacin 0.5%
(4) Moxifloxacin 0.5%
(5) Gatifloxacin 0.5%

Analysis 1.15. Comparison 1: Antibiotics vs placebo, Outcome 15: Treatment-related ocular adverse events - rate difference per 1000 person-days

Study or Subgroup	Rate difference	SE	Weight	Rate difference IV, Random, 95% CI
1.15.1 Non-fluoroquinolone				
Comstock 2012 (1)	2.1	2.1	18.3%	2.10 [-2.02 , 6.22]
Abelson 2008 (2)	2.4	1.5	25.2%	2.40 [-0.54 , 5.34]
Gigliotti 1984 (3)	4.2	4.2	6.8%	4.20 [-4.03 , 12.43]
Subtotal (95% CI)			**50.3%**	**2.45 [0.15 , 4.74]**
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.90); I² = 0%				
Test for overall effect: Z = 2.09 (P = 0.04)				
1.15.2 Fluoroquinolone				
Karpecki 2009 (4)	-8.1	18.7	0.4%	-8.10 [-44.75 , 28.55]
Tepedino 2009 (4)	-6.8	3.7	8.3%	-6.80 [-14.05 , 0.45]
DeLeon 2012 (4)	-6.7	6.6	3.0%	-6.70 [-19.64 , 6.24]
NCT01740388 (4)	-3.5	10.9	1.2%	-3.50 [-24.86 , 17.86]
Malhotra 2013 (4)	-0.5	2.5	14.8%	-0.50 [-5.40 , 4.40]
NCT00518089 (5)	3.2	2.1	18.3%	3.20 [-0.92 , 7.32]
Hwang 2003 (6)	5.3	11.1	1.1%	5.30 [-16.46 , 27.06]
C-00-55 (7)	16	7.2	2.6%	16.00 [1.89 , 30.11]
Subtotal (95% CI)			**49.7%**	**0.11 [-4.39 , 4.60]**
Heterogeneity: Tau² = 14.00; Chi² = 12.06, df = 7 (P = 0.10); I² = 42%				
Test for overall effect: Z = 0.05 (P = 0.96)				
Total (95% CI)			**100.0%**	**1.41 [-0.93 , 3.75]**
Heterogeneity: Tau² = 3.41; Chi² = 13.34, df = 10 (P = 0.21); I² = 25%				
Test for overall effect: Z = 1.18 (P = 0.24)				
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%				

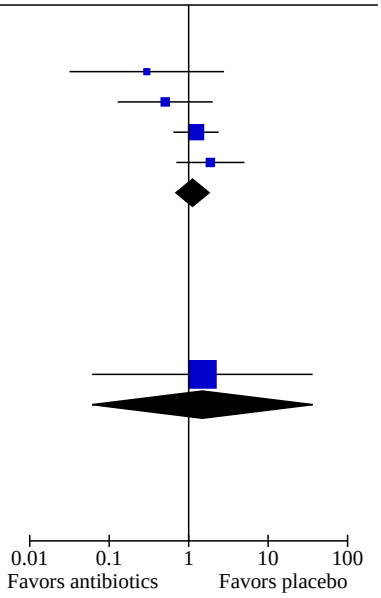


Footnotes

(1) Loteprednol etabonate + tobramycin 0.3%
(2) Azithromycin 1%
(3) Polymyxin + bacitracin
(4) Besifloxacin 0.6%
(5) Gatifloxacin 0.5%
(6) Levofloxacin 0.5%
(7) Moxifloxacin 0.5%

Analysis 1.16. Comparison 1: Antibiotics vs placebo, Outcome 16: Non-ocular adverse events

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Headache						
C-00-02 (1)	1	74	3	66	10.8%	0.30 [0.03 , 2.79]
C-00-55 (2)	3	270	6	274	20.3%	0.51 [0.13 , 2.01]
Karpecki 2009 (3)	18	137	14	132	48.6%	1.24 [0.64 , 2.39]
Tepedino 2009 (4)	11	473	6	484	20.2%	1.88 [0.70 , 5.03]
Subtotal (95% CI)		**954**		**956**	**100.0%**	**1.12 [0.69 , 1.81]**
Total events:	33		29			
Heterogeneity: Chi² = 3.76, df = 3 (P = 0.29); I² = 20%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.16.2 Dysgeusia						
Malhotra 2013 (5)	1	344	0	170	100.0%	1.49 [0.06 , 36.31]
Subtotal (95% CI)		**344**		**170**	**100.0%**	**1.49 [0.06 , 36.31]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						



Footnotes

(1) Headache, moxifloxacin 0.5% for 3 days, association with treatment: unclear
(2) Headache, moxifloxacin 0.5% for 4 days, association with treatment: unclear
(3) Headache, besifloxacin 0.6% for 5 days, association with treatmnet: unclear
(4) Headache, besifloxacin 0.6% for 5 days, association with treatment: unclear
(5) Dysgeusia, besifloxacin 0.6% for 7 days, association with treatmnet: probably

Comparison 2. Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis

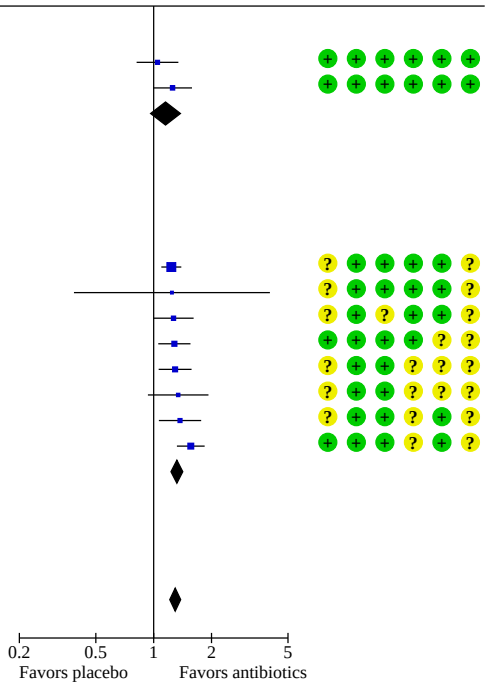
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Clinical cure at end of therapy - mITT population, excluding trials of high risk bias	10	2832	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.21, 1.38]
2.1.1 Low risk of bias	2	496	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.96, 1.38]
2.1.2 Some concerns	8	2336	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.23, 1.42]
2.2 Microbiological efficacy at end of therapy - mITT population, excluding age < 1 month or no reporting of age limit	9	2650	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.30, 1.67]
2.2.1 Minimum age: 18 years	2	193	Risk Ratio (M-H, Random, 95% CI)	1.82 [1.33, 2.49]
2.2.2 Minimum age: one year	6	1610	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.25, 1.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.3 Minimum age: one month	1	847	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.20, 1.47]
2.3 Clinical cure at test of cure - mITT population, excluding Karpecki 2009	4	681	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.04, 1.42]
2.3.1 Fluoroquinolone	2	166	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.11, 1.65]
2.3.2 Non-fluoroquinolone	2	515	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.94, 1.39]
2.4 Microbiological efficacy at test of cure - mITT population, excluding Karpecki 2009	11	2177	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.26, 1.51]
2.4.1 Fluoroquinolone	9	1861	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.24, 1.50]
2.4.2 Non-fluoroquinolone	2	316	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.20, 1.93]
2.5 Persistent clinical infection, excluding Karpecki 2009	18	5164	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.64, 0.80]
2.5.1 Fluoroquinolone	13	4171	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.65, 0.84]
2.5.2 Non-fluoroquinolone	5	993	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.52, 0.82]
2.6 Treatment-related ocular adverse events - rate ratio, excluding Karpecki 2009	8		Rate Ratio (IV, Random, 95% CI)	1.12 [0.76, 1.64]
2.6.1 Non-fluoroquinolone	1		Rate Ratio (IV, Random, 95% CI)	5.25 [0.61, 44.93]
2.6.2 Fluoroquinolone	7		Rate Ratio (IV, Random, 95% CI)	1.07 [0.73, 1.55]
2.7 Treatment-related ocular adverse events - risk ratio, excluding Comstock 2012	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.7.1 Fluoroquinolone	4	3455	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.54, 0.90]
2.7.2 Non-fluoroquinolone	2	489	Risk Ratio (M-H, Random, 95% CI)	4.23 [1.33, 13.46]
2.8 Treatment-related ocular adverse events - rate difference per 1000 person-days, excluding Comstock 2012	10		Rate difference (IV, Random, 95% CI)	1.17 [-1.73, 4.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8.1 Non-fluoroquinolone	2		Rate difference (IV, Random, 95% CI)	2.60 [-0.17, 5.37]
2.8.2 Fluoroquinolone	8		Rate difference (IV, Random, 95% CI)	0.11 [-4.39, 4.60]

Analysis 2.1. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 1: Clinical cure at end of therapy - mITT population, excluding trials of high risk bias

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Low risk of bias						
Rietveld 2005 (1)	45	73	53	90	6.8%	1.05 [0.82 , 1.34]
NCT00518089 (2)	86	166	69	167	7.9%	1.25 [0.99 , 1.58]
Subtotal (95% CI)		**239**		**257**	**14.7%**	**1.15 [0.96 , 1.38]**
Total events:	131		122			
Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 1 (P = 0.29); I² = 9%						
Test for overall effect: Z = 1.56 (P = 0.12)						
2.1.2 Some concerns						
Tauber 2011 (3)	265	424	214	423	29.8%	1.24 [1.10 , 1.39]
NCT01740388 (4)	4	18	5	28	0.3%	1.24 [0.38 , 4.03]
Gigliotti 1984 (5)	31	34	23	32	7.4%	1.27 [1.00 , 1.61]
NCT00509873 (6)	107	167	79	158	11.5%	1.28 [1.06 , 1.55]
C-00-55 (7)	95	143	74	144	11.0%	1.29 [1.06 , 1.57]
C-00-02 (8)	34	53	22	46	3.2%	1.34 [0.93 , 1.93]
Tepedino 2009 (9)	90	199	63	191	6.6%	1.37 [1.06 , 1.77]
DeLeon 2012 (10)	115	135	77	141	15.5%	1.56 [1.32 , 1.84]
Subtotal (95% CI)		**1173**		**1163**	**85.3%**	**1.32 [1.23 , 1.42]**
Total events:	741		557			
Heterogeneity: Tau² = 0.00; Chi² = 5.42, df = 7 (P = 0.61); I² = 0%						
Test for overall effect: Z = 7.70 (P < 0.00001)						
Total (95% CI)		**1412**		**1420**	**100.0%**	**1.29 [1.21 , 1.38]**
Total events:	872		679			
Heterogeneity: Tau² = 0.00; Chi² = 8.56, df = 9 (P = 0.48); I² = 0%						
Test for overall effect: Z = 7.74 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.93, df = 1 (P = 0.16), I² = 48.1%						



Footnotes

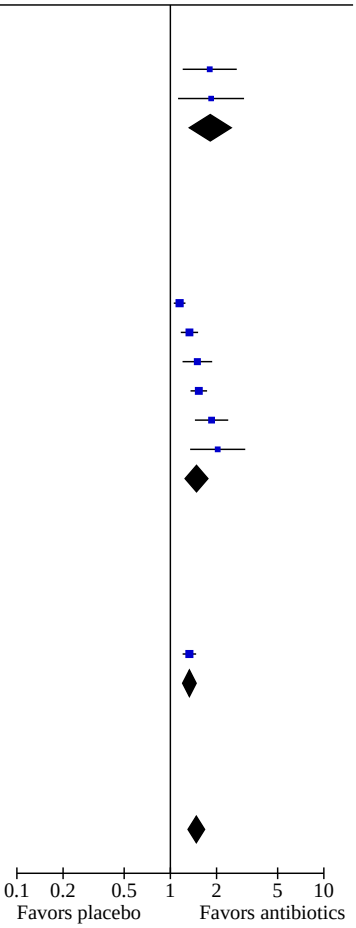
(1) Day 8, fusidic acid gel
(2) Up to day 6, gatifloxacin 0.5%
(3) Day 4, moxifloxacin 0.5%, mixed pediatric and adult participants (including children < 1 years)
(4) Day 4 or 5, besifloxacin 0.6%
(5) Day 8 to 10, polymyxin + bacitracin, only pediatric participants (including children < 1 years), end-of-therapy visit
(6) Day 6, gatifloxacin 0.5%
(7) Day 5, moxifloxacin 0.5%, mixed pediatric and adult participants (including children < 1 years)
(8) Day 4, moxifloxacin 0.5%, two intervention groups and two vehicle groups were combined separately
(9) Day 5, besifloxacin 0.6%
(10) Day or 5, besifloxacin 0.6%

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 2: Microbiological efficacy at end of therapy - mITT population, excluding age < 1 month or no reporting of age limit

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Minimum age: 18 years						
Miller 1992 (1)	43	76	21	67	6.1%	1.81 [1.20 , 2.71]
Rietveld 2005 (2)	16	21	12	29	4.6%	1.84 [1.12 , 3.02]
Subtotal (95% CI)		**97**		**96**	**10.7%**	**1.82 [1.33 , 2.49]**
Total events:	59		33			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.74 (P = 0.0002)						
2.2.2 Minimum age: one year						
NCT00518089 (3)	153	166	134	167	16.2%	1.15 [1.05 , 1.25]
Abelson 2008 (4)	115	130	99	149	14.8%	1.33 [1.17 , 1.52]
DeLeon 2012 (5)	89	135	62	141	11.2%	1.50 [1.20 , 1.87]
Tepedino 2009 (6)	182	199	114	191	15.0%	1.53 [1.35 , 1.73]
Malhotra 2013 (7)	172	206	36	80	10.3%	1.86 [1.45 , 2.38]
NCT01740388 (5)	17	18	13	28	5.9%	2.03 [1.35 , 3.08]
Subtotal (95% CI)		**854**		**756**	**73.5%**	**1.48 [1.25 , 1.76]**
Total events:	728		458			
Heterogeneity: Tau² = 0.03; Chi² = 33.09, df = 5 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 4.51 (P < 0.00001)						
2.2.3 Minimum age: one month						
Tauber 2011 (8)	316	424	237	423	15.8%	1.33 [1.20 , 1.47]
Subtotal (95% CI)		**424**		**423**	**15.8%**	**1.33 [1.20 , 1.47]**
Total events:	316		237			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.53 (P < 0.00001)						
Total (95% CI)		**1375**		**1275**	**100.0%**	**1.48 [1.30 , 1.67]**
Total events:	1103		728			
Heterogeneity: Tau² = 0.02; Chi² = 35.58, df = 8 (P < 0.0001); I² = 78%						
Test for overall effect: Z = 6.17 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.07, df = 2 (P = 0.13), I² = 50.9%						

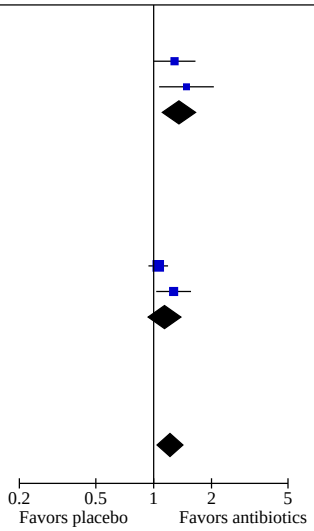


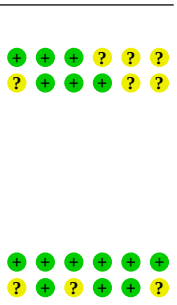
Footnotes

(1) Day 7 or 8, norfloxacin 0.3%, end-of-therapy visit
(2) Day 8, fusidic acid gel, end-of-therapy visit
(3) Up to day 6, gatifloxacin 0.5%, end-of-therapy visit
(4) Day 6 or 7, azithromycin 1%, end-of-therapy visit
(5) Day 4 or 5, besifloxacin 0.6%, end-of-therapy visit
(6) Day 5, besifloxacin 0.6%, end-of-therapy visit
(7) Day 8 or 9, besifloxacin 0.6%, end-of-therapy visit
(8) Day 4, moxifloxacin 0.5%, end-of-therapy visit, mixed pediatric and adult participants (including children < 1 years)

Analysis 2.3. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 3: Clinical cure at test of cure - mITT population, excluding Karpecki 2009

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Fluoroquinolone						
Hwang 2003 (1)	46	59	34	56	21.3%	1.28 [1.00 , 1.65]
Gross 2003 (2)	25	27	15	24	15.3%	1.48 [1.07 , 2.06]
Subtotal (95% CI)		**86**		**80**	**36.6%**	**1.35 [1.11 , 1.65]**
Total events:	71		49			
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 2.98 (P = 0.003)						
2.3.2 Non-fluoroquinolone						
Rose 2005 (3)	101	119	94	117	37.7%	1.06 [0.94 , 1.19]
Abelson 2008 (4)	82	130	74	149	25.7%	1.27 [1.03 , 1.56]
Subtotal (95% CI)		**249**		**266**	**63.4%**	**1.14 [0.94 , 1.39]**
Total events:	183		168			
Heterogeneity: Tau² = 0.01; Chi² = 2.79, df = 1 (P = 0.09); I² = 64%						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**335**		**346**	**100.0%**	**1.22 [1.04 , 1.42]**
Total events:	254		217			
Heterogeneity: Tau² = 0.01; Chi² = 6.49, df = 3 (P = 0.09); I² = 54%						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: Chi² = 1.47, df = 1 (P = 0.23), I² = 32.0%						





Footnotes

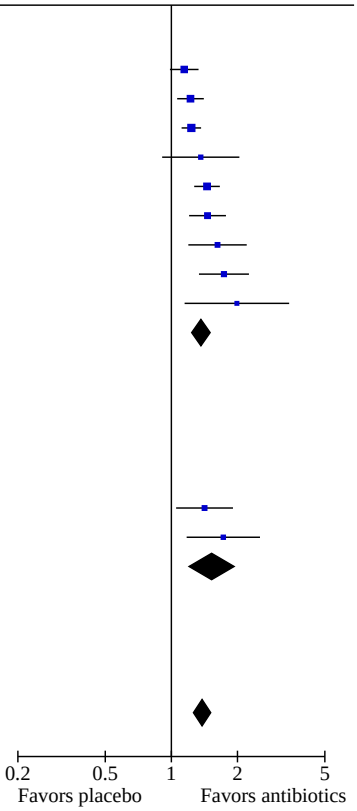
(1) Day 6 to 10, levofloxacin 0.5%
(2) Day 7, moxifloxacin 0.5%
(3) Day 7, chloramphenicol 0.3%, only pediatric participants (including children < 1 years)
(4) Day 6 or 7, azithromycin 1%

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 4: Microbiological efficacy at test of cure - mITT population, excluding Karpecki 2009

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Fluoroquinolone						
DeLeon 2012 (1)	103	135	94	141	13.3%	1.14 [0.99 , 1.33]
C-00-55 (2)	112	136	93	138	14.0%	1.22 [1.06 , 1.41]
Tepedino 2009 (3)	176	199	137	191	16.6%	1.23 [1.11 , 1.37]
NCT01740388 (1)	14	18	16	28	4.0%	1.36 [0.91 , 2.04]
NCT00509873 (4)	149	167	97	158	14.4%	1.45 [1.27 , 1.66]
Malhotra 2013 (5)	169	200	48	83	10.7%	1.46 [1.20 , 1.77]
C-00-02 (6)	43	53	25	50	6.2%	1.62 [1.19 , 2.20]
Hwang 2003 (7)	54	59	29	55	7.6%	1.74 [1.34 , 2.26]
Gross 2003 (6)	21	27	9	23	2.4%	1.99 [1.15 , 3.44]
Subtotal (95% CI)		**994**		**867**	**89.2%**	**1.36 [1.24 , 1.50]**
Total events:	841		548			
Heterogeneity: Tau² = 0.01; Chi² = 17.97, df = 8 (P = 0.02); I² = 55%						
Test for overall effect: Z = 6.30 (P < 0.00001)						
2.4.2 Non-fluoroquinolone						
Yang 2013 (8)	24	28	23	38	6.4%	1.42 [1.05 , 1.91]
Rose 2005 (9)	50	125	29	125	4.4%	1.72 [1.17 , 2.53]
Subtotal (95% CI)		**153**		**163**	**10.8%**	**1.52 [1.20 , 1.93]**
Total events:	74		52			
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 3.51 (P = 0.0004)						
Total (95% CI)		**1147**		**1030**	**100.0%**	**1.38 [1.26 , 1.51]**
Total events:	915		600			
Heterogeneity: Tau² = 0.01; Chi² = 20.46, df = 10 (P = 0.03); I² = 51%						
Test for overall effect: Z = 6.99 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.74, df = 1 (P = 0.39), I² = 0%						

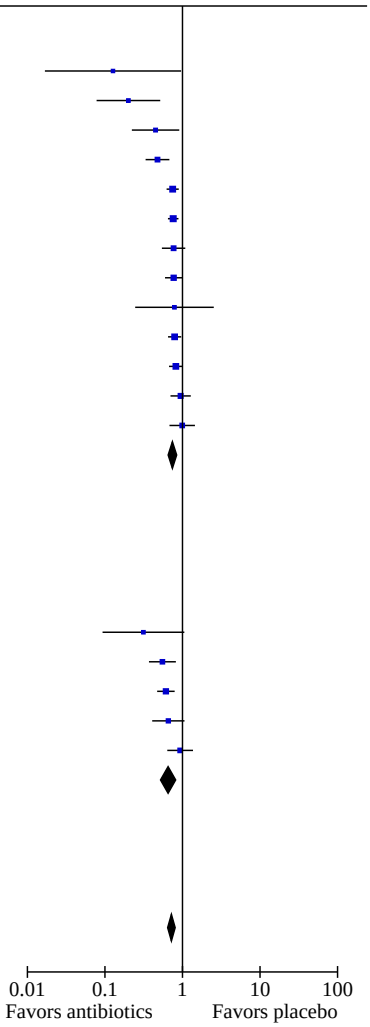


Footnotes

(1) Day 6 to 8, besifloxacin 0.6%
(2) Day 9, moxifloxacin 0.5%, mixed pediatric and adult participants (including children < 1 years)
(3) Day 8 or 9, besifloxacin 0.6%
(4) Day 6 or later, gatifloxacin 0.5%
(5) Day 10 to 12, besifloxacin 0.6%
(6) Day 7, moxifloxacin 0.5%
(7) day 6 to 10, levofloxacin 0.5%
(8) Day 8 or 9, azithromycin 1%, test-of-cure visit
(9) Day 7, chloramphenicol 0.3%, only pediatric participants (including children < 1 years)

Analysis 2.5. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 5: Persistent clinical infection, excluding Karpecki 2009

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Fluoroquinolone						
Gross 2003 (1)	1	27	7	24	0.3%	0.13 [0.02 , 0.96]
C-01-66	5	265	25	266	1.3%	0.20 [0.08 , 0.52]
Hwang 2003 (2)	9	59	19	56	2.1%	0.45 [0.22 , 0.91]
DeLeon 2012 (3)	31	135	68	141	5.8%	0.48 [0.33 , 0.68]
Tepedino 2009 (4)	95	199	122	191	10.2%	0.75 [0.62 , 0.90]
Tauber 2011 (5)	159	424	209	423	11.0%	0.76 [0.65 , 0.89]
C-00-02 (5)	31	74	36	66	5.9%	0.77 [0.54 , 1.09]
Miller 1992 (6)	57	143	73	141	8.0%	0.77 [0.60 , 1.00]
NCT00509873 (7)	5	167	6	158	0.9%	0.79 [0.25 , 2.53]
C-00-55 (8)	103	270	132	274	9.8%	0.79 [0.65 , 0.96]
NCT00518089 (9)	80	166	98	167	9.6%	0.82 [0.67 , 1.01]
NCT01740388 (3)	14	18	23	28	6.9%	0.95 [0.70 , 1.28]
Malhotra 2013 (10)	64	206	26	83	5.4%	0.99 [0.68 , 1.45]
Subtotal (95% CI)		**2153**		**2018**	**77.1%**	**0.74 [0.65 , 0.84]**
Total events:	654		844			
Heterogeneity: Tau² = 0.02; Chi² = 25.11, df = 12 (P = 0.01); I² = 52%						
Test for overall effect: Z = 4.65 (P < 0.00001)						
2.5.2 Non-fluoroquinolone						
Gigliotti 1984 (11)	3	34	9	32	0.8%	0.31 [0.09 , 1.06]
Yang 2013 (12)	21	68	51	91	5.0%	0.55 [0.37 , 0.82]
Abelson 2008 (13)	48	130	90	149	7.9%	0.61 [0.47 , 0.79]
Rose 2005 (14)	23	163	35	163	3.9%	0.66 [0.41 , 1.06]
Rietveld 2005 (15)	28	73	37	90	5.3%	0.93 [0.64 , 1.37]
Subtotal (95% CI)		**468**		**525**	**22.9%**	**0.65 [0.52 , 0.82]**
Total events:	123		222			
Heterogeneity: Tau² = 0.02; Chi² = 5.71, df = 4 (P = 0.22); I² = 30%						
Test for overall effect: Z = 3.73 (P = 0.0002)						
Total (95% CI)		**2621**		**2543**	**100.0%**	**0.72 [0.64 , 0.80]**
Total events:	777		1066			
Heterogeneity: Tau² = 0.02; Chi² = 33.50, df = 17 (P = 0.010); I² = 49%						
Test for overall effect: Z = 5.79 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² = 0%						



Footnotes

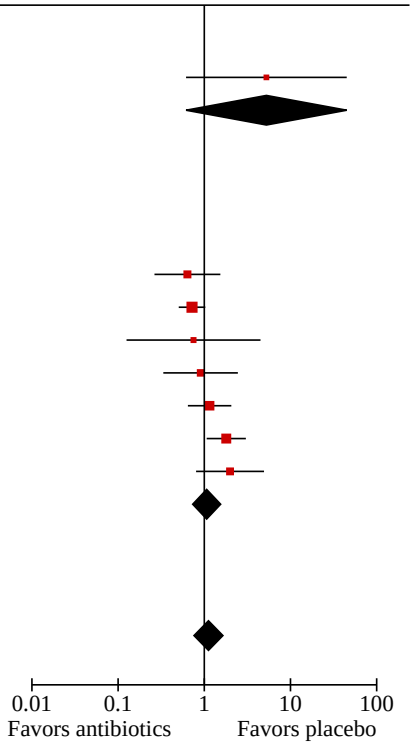
(1) Day 7, moxifloxacin 0.5%, test-of-cure visit
(2) Day 6 to 10, levofloxacin 0.5%, test-of-cure visit
(3) Day 4 or 5, besifloxacin 0.6%, end-of-therapy visit
(4) Day 5, besifloxacin 0.6%, end-of-therapy visit
(5) Day 4, moxifloxacin 0.5%, end-of-therapy visit
(6) Day 7 or 8, Norfloxacin 0.3%, end-of-therapy visit
(7) Day 6, gatifloxacin 0.5%, test-of-cure visit
(8) Day 5, moxifloxacin 0.5%, end-of-therapy visit
(9) Day 6, gatifloxacin 0.5%, end-of-therapy visit
(10) Day 8, besifloxacin 0.6%, end-of-therapy visit
(11) Day 8 to 10, polymycin + bacitracin, end-of-therapy visit
(12) Day 8 or 9, azithromycin 1%, end-of-therapy visit
(13) Day 6 or 7, azithromycin 1%, test-of-cure visit
(14) Day 7, chloramphenicol 0.3%, end-of-study visit
(15) Day 8, fusidic acid gel, end-of-therapy visit

Analysis 2.5. (Continued)

(15) Day 8, fusidic acid gel, end-of-therapy visit

Analysis 2.6. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 6: Treatment-related ocular adverse events - rate ratio, excluding Karpecki 2009

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
2.6.1 Non-fluoroquinolone				
Abelson 2008 (1)	1.659	1.095	2.9%	5.25 [0.61 , 44.93]
Subtotal (95% CI)			**2.9%**	**5.25 [0.61 , 44.93]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.52 (P = 0.13)				
2.6.2 Fluoroquinolone				
DeLeon 2012 (2)	-0.451	0.449	11.6%	0.64 [0.26 , 1.54]
Tepedino 2009 (2)	-0.328	0.181	23.6%	0.72 [0.51 , 1.03]
NCT01740388 (2)	-0.288	0.913	4.0%	0.75 [0.13 , 4.49]
Malhotra 2013 (2)	-0.099	0.508	9.9%	0.91 [0.33 , 2.45]
Hwang 2003 (3)	0.142	0.296	17.7%	1.15 [0.65 , 2.06]
C-00-55 (4)	0.587	0.267	19.1%	1.80 [1.07 , 3.04]
NCT00518089 (5)	0.688	0.463	11.2%	1.99 [0.80 , 4.93]
Subtotal (95% CI)			**97.1%**	**1.07 [0.73 , 1.55]**
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 11.70$, df = 6 (P = 0.07); $I^2 = 49\%$				
Test for overall effect: Z = 0.33 (P = 0.74)				
Total (95% CI)			**100.0%**	**1.12 [0.76 , 1.64]**
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 13.97$, df = 7 (P = 0.05); $I^2 = 50\%$				
Test for overall effect: Z = 0.57 (P = 0.57)				
Test for subgroup differences: $Chi^2 = 2.06$, df = 1 (P = 0.15), $I^2 = 51.5\%$				

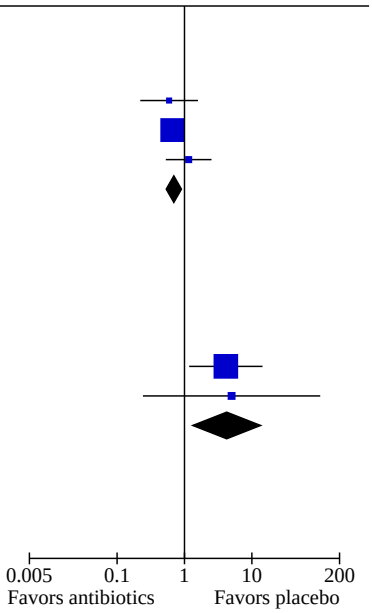


Footnotes

(1) Azithromycin 1%
(2) Besifloxacin 0.6%
(3) Levofloxacin 0.5%
(4) Moxifloxacin 0.5%
(5) Gatifloxacin 0.5%

Analysis 2.7. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 7: Treatment-related ocular adverse events - risk ratio, excluding Comstock 2012

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo/vehicle Events	Placebo/vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Fluoroquinolone						
Tauber 2011 (1)	0	593	0	586		Not estimable
Miller 1992 (2)	6	143	10	141	7.0%	0.59 [0.22 , 1.58]
Tepedino 2009 (3)	68	741	106	760	81.9%	0.66 [0.49 , 0.88]
DeLeon 2012 (4)	12	228	12	263	11.1%	1.15 [0.53 , 2.52]
Subtotal (95% CI)		**1705**		**1750**	**100.0%**	**0.70 [0.54 , 0.90]**
Total events:	86		128			
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
2.7.2 Non-fluoroquinolone						
Rietveld 2005 (5)	10	73	3	90	85.4%	4.11 [1.17 , 14.38]
Rose 2005	2	163	0	163	14.6%	5.00 [0.24 , 103.35]
Subtotal (95% CI)		**236**		**253**	**100.0%**	**4.23 [1.33 , 13.46]**
Total events:	12		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 2.44 (P = 0.01)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

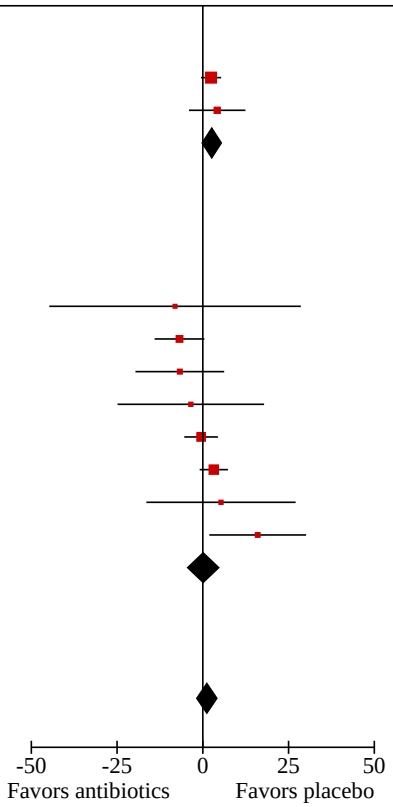


Footnotes

(1) Moxifloxacin 0.5%, reporting threshold 5%
(2) Norfloxacin 0.3%
(3) Besifloxacin 0.6%, unit of analysis was eye, reporting threshold 0.5%
(4) Bdesifloxacin 0.6%, reporting threshold 0.5%
(5) Fusidic acid gel

Analysis 2.8. Comparison 2: Antibiotics vs placebo - sensitivity analysis and post hoc subgroup analysis, Outcome 8: Treatment-related ocular adverse events - rate difference per 1000 person-days, excluding Comstock 2012

Study or Subgroup	Rate difference	SE	Weight	Rate difference IV, Random, 95% CI
2.8.1 Non-fluoroquinolone				
Abelson 2008 (1)	2.4	1.5	27.3%	2.40 [-0.54 , 5.34]
Gigliotti 1984 (2)	4.2	4.2	9.4%	4.20 [-4.03 , 12.43]
Subtotal (95% CI)			**36.7%**	**2.60 [-0.17 , 5.37]**
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%				
Test for overall effect: Z = 1.84 (P = 0.07)				
2.8.2 Fluoroquinolone				
Karpecki 2009 (3)	-8.1	18.7	0.6%	-8.10 [-44.75 , 28.55]
Tepedino 2009 (3)	-6.8	3.7	11.3%	-6.80 [-14.05 , 0.45]
DeLeon 2012 (3)	-6.7	6.6	4.4%	-6.70 [-19.64 , 6.24]
NCT01740388 (3)	-3.5	10.9	1.8%	-3.50 [-24.86 , 17.86]
Malhotra 2013 (3)	-0.5	2.5	18.2%	-0.50 [-5.40 , 4.40]
NCT00518089 (4)	3.2	2.1	21.5%	3.20 [-0.92 , 7.32]
Hwang 2003 (5)	5.3	11.1	1.7%	5.30 [-16.46 , 27.06]
C-00-55 (6)	16	7.2	3.8%	16.00 [1.89 , 30.11]
Subtotal (95% CI)			**63.3%**	**0.11 [-4.39 , 4.60]**
Heterogeneity: Tau² = 14.00; Chi² = 12.06, df = 7 (P = 0.10); I² = 42%				
Test for overall effect: Z = 0.05 (P = 0.96)				
Total (95% CI)			**100.0%**	**1.17 [-1.73 , 4.07]**
Heterogeneity: Tau² = 5.76; Chi² = 13.29, df = 9 (P = 0.15); I² = 32%				
Test for overall effect: Z = 0.79 (P = 0.43)				
Test for subgroup differences: Chi² = 0.86, df = 1 (P = 0.35), I² = 0%				



Footnotes

(1) Azithromycin 1%
(2) Polymyxin + bacitracin
(3) Besifloxacin 0.6%
(4) Gatifloxacin 0.5%
(5) Levofloxacin 0.5%
(6) Moxifloxacin 0.5%

APPENDICES

Appendix 1. CENTRAL search strategy

1 MeSH descriptor Conjunctivitis, Bacterial
#2 conjunctiv* near (acute or infect* or bacteria*)
#3 (#1 OR #2)
#4 MeSH descriptor Anti-Bacterial Agents
#5 antibiotic*
#6 (#4 OR #5)
#7 (#3 AND #6)

Appendix 2. MEDLINE (OvidSP) 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 conjunctivitis,bacterial/
14. ((acute or infect$ or bacteria$) adj4 conjunctiv$).tw.
15. or/13-14
16. exp anti-bacterial agent/
17. antibiotic$.tw.
18. or/16-17
19. 15 and 18
20. 12 and 19

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. Embase (OvidSP) 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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. bacterial conjunctivitis/
34. ((acute or infect$ or bacteria$) adj4 conjunctiv$).tw.
35. or/33-34
36. exp antibiotic agent/
37. antibiotic$.tw.
38. or/36-37
39. 35 and 38

40. 32 and 39

Appendix 4. Open Grey search strategy

bacterial conjunctivitis

Appendix 5. *meta*Register of Controlled Trials search strategy

(bacterial conjunctivitis) and antibiotic

Appendix 6. ClinicalTrials.gov search strategy

Bacterial Conjunctivitis AND Antibiotic

Appendix 7. ICTRP search strategy

Bacterial Conjunctivitis = Condition AND Antibiotic = Intervention

WHAT'S NEW

Date	Event	Description
24 April 2023	Amended	A typo in Summary of findings table was corrected.

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 1999

Date	Event	Description
13 March 2023	New citation required but conclusions have not changed	The current update synthesized the evidence based on a different perspective from the previous review in defininng 'clinical efficacy' and 'microbiological efficacy', considering the varying length of treatment duration; the conclusion remained the same.
3 November 2022	New search has been performed	Updated search yielded seven eligible new trials.
11 May 2022	New search has been performed	Updated searches conducted.
1 August 2012	New citation required and conclusions have changed	Issue 9, 2012: The conclusion of the previous version of this review was that antibiotics resulted in significantly improved rates of early remission; these benefits were more modest in relation to later resolution. This updated version confirms these early benefits but also more clearly points to benefits with later resolution.
1 August 2012	New search has been performed	Issue 9, 2012: Updated searches yielded six new trials (Abelson 2008; Gross 2003; Karpecki 2009; Silverstein 2011; Tauber 2011; Tepedino 2009) that met the inclusion criteria and were included in the review. One new author, Ulugbek Nurmatov, joined the review team and took the lead in updating the review.
30 October 2008	Amended	Converted to new review format.
30 January 2008	New search has been performed	Issue 2 2008: Updated searches did not yield any new trials.

Date	Event	Description
23 January 2006	New citation required and conclusions have changed	Substantive amendment. Updated searches identified two new RCTs (Rose 2005 and Rietveld 2005), which have been incorporated into the review.
26 May 2001	Feedback has been incorporated	Feedback incorporated.

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the conception and design of the study, participated in study selection, data extraction, and/or analysis, drafted portions of the review, commented on drafts critically regarding intellectual content, and approved the final version for publication.

DECLARATIONS OF INTEREST

Yu-Yen Chen: declared no conflicts of interest.
Su-Hsun Liu: reported a grant from the National Eye Institute, National Institutes of Health, USA; payment to institution.
Onno CP van Schayck: no declaration of interest to be reported
Ulugbek Nurmatov: no declaration of interest to be reported
Irene C Kuo: reported partial salary support from the National Eye Institute, National Institutes of Health, for her editorial work for the Cochrane review.

SOURCES OF SUPPORT

Internal sources

- None, Other

  No internal source of support.

External sources

- Maastricht University, Netherlands

  The work of Professor van Schayck is supported by Maastricht University, the Netherlands.
- National Eye Institute, National Institutes of Health, USA

  Cochrane Eyes and Vision US Project, supported by grant UG1EY020522 (PI: Tianjing Li, MD, MHS, PhD)
- Public Health Agency, UK

  The HSC Research and Development (R&D) Division of the Public Health Agency funds the Cochrane Eyes and Vision editorial base at Queen's University Belfast.
- Queen's University Belfast, UK

  The work of Gianni Virgili, Co-ordinating Editor for Cochrane Eyes and Vision, is funded by the Centre for Public Health, Queen's University of Belfast, Northern Ireland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Subsections in the Methods section have been updated to the current reporting standard (MECIR Standards 2022).
2. All authors of the current update agreed to exclude OpenGrey from the updated searches.
3. Review outcomes were revised to improve clarity as described below:
   a. 'Time-to-clinical cure' was rephrased to '**clinical efficacy**', which was measured by proportion of participants (or eyes) with clinical resolution of signs or symptoms of acute conjunctivitis) after one course of treatment, the duration of which depended upon the original trials;
   b. 'Time-to-microbiological cure' was rephrased to '**microbiological efficacy**', which was quantified by proportion of participants (or eyes) with microbiological clearance after one course of treatment, the duration of which depended upon the original trials;
   c. 'Recurrence of infection within four weeks' was removed;
   d. '**Cost-effectiveness of treatment**' was redefined as those quantified by previously-published measures;

e. 'Compliance of participants' was rephrased as '**treatment incompletion**';
f. 'Complications of acute bacterial conjunctivitis' and 'adverse outcomes' were combined and re-phrased into two separate adverse outcomes: '**treatment-associated ocular complications'** and '**treatment-associated systemic complications.**'

4. The author team also chose to apply Cochrane's RoB 2 tool for risk of bias assessment in each newly identified trial as well as previously included trials that had reported on 'clinical efficacy'.
5. One additional post hoc sensitivity analysis excluded trials that enrolled infants yonger than 1-month-old or trials that did not report the minimum age of participants.
6. For trials that did not provide subject-level, proportion data, we estimated event rates by taking into account the numbers of different complications observed and the person-time at risk. Because a few trials reported zero numbers of ocular AEs, we reported both absolute rate differences and rate ratios as effect measures when comparing effects of antibiotics with placebo.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anti-Bacterial Agents [adverse effects]; *Conjunctivitis, Bacterial [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans