Cochrane Library

Cochrane Database of Systematic Reviews

Topical antibiotics for treating bacterial keratitis: a network meta-analysis (Protocol)

Ting DSJ, Henein C, Bunce C, Qureshi R

Ting DSJ, Henein C, Bunce C, Qureshi R.
Topical antibiotics for treating bacterial keratitis: a network meta-analysis (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 12. Art. No.: CD015350.
DOI: 10.1002/14651858.CD015350.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Prototype Protocol]

Topical antibiotics for treating bacterial keratitis: a network meta-analysis

Darren SJ Ting[1,2], Christin Henein[3], Catey Bunce[4], Riaz Qureshi[5]

[1]Academic Ophthalmology, School of Medicine, University of Nottingham, Nottingham, NG7 2RD, UK. [2]Department of Ophthalmology, Queen's Medical Centre, Nottingham, UK. [3]National Institute for Health Research Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital and University College London Institute of Ophthalmology, London, UK. [4]The Royal Marsden National Health Service Foundation Trust, London, UK. [5]Department of Ophthalmology, University of Colorado Anschutz Medical Campus, Denver, Colorado, USA

Contact: Darren SJ Ting, ting.darren@gmail.com.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New, published in Issue 12, 2022.

Citation: Ting DSJ, Henein C, Bunce C, Qureshi R. Topical antibiotics for treating bacterial keratitis: a network meta-analysis (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 12. Art. No.: CD015350. DOI: 10.1002/14651858.CD015350.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (prototype). The objectives are as follows:

To compare the effectiveness and safety of topical antibiotics for treating BK and to rank different interventions through a systematic review and NMA.

BACKGROUND

Description of the condition

Infectious keratitis, more commonly known as corneal infection, is the leading cause of cornea-related blindness and visual impairment worldwide, affecting around six million of the world population (Ting 2021a). In addition, it accounts for 1.5 million to 2.0 million cases of monocular blindness each year (Ting 2021a). Based on large epidemiological studies, the incidence of infectious keratitis has been estimated at 2.5 to 799 cases per 100,000 population/year worldwide, with a disproportionately higher incidence and prevalence in low- and middle-income countries (LMICs) compared to high-income countries (HICs) and upper-middle-income countries (UMICs) (Green 2019; Ting 2021a; Ting 2021b; Ung 2019). The large variation in the incidence is mainly due to heterogeneity in population-based risk factors (e.g. trauma, contact lens wear, and agricultural activities), level of education, environmental and personal hygiene, and accessibility to healthcare systems (Ting 2021a).

Infectious keratitis can be caused by a wide range of organisms, including bacteria, fungi, viral, parasites, or a combination of these (Khoo 2020; Khor 2018; Shah 2011; Ting 2021c). Bacterial keratitis (BK) is the most common type of infectious keratitis in HICs and UMICs, accounting for 72% to 93% of all culture-proven infectious keratitis cases (Kowalski 2020; Tam 2017; Tan 2017; Tavassoli 2019; Ting 2018; Ting 2021a; Ting 2021b). BK not only causes significant ocular pain and visual impairment in affected people, but also negatively impacts on healthcare systems (due to the high need for hospitalization for intensive treatment) and work productivity (due to lost workdays) (Khor 2018; Ting 2021d). In addition, complications such as corneal melt, perforation, endophthalmitis, and loss of eye may occur despite timely intervention (Cabrera-Aguas 2021; Khor 2018; Ting 2021d).

A multitude of factors have been shown to affect the prognosis of infectious keratitis, including BK. These include the age of affected individuals, clinical severity of the disease, treatment regimen, causative pathogen with antimicrobial resistance, and presence of polymicrobial infection (Kaye 2010; Khoo 2020; Ting 2019a; Ting 2021d; Ting 2021e). Gaining a better understanding of these factors can enable clinicians to tailor treatment strategies during the management of BK, for example by modifying intensity, choice and duration of the antibiotic treatment, and evaluating the potential need for an adjuvant procedure or surgery. In addition, these factors have important implications for treatment outcome, and must be taken into consideration when analyzing and interpreting treatment effectiveness.

Description of the intervention

Broad-spectrum topical antibiotics are currently the mainstay of treatment for BK, although there is an emerging trend of antimicrobial resistance in corneal pathogens (Asbell 2020; Ting 2021a). In clinical practice, the choice of topical antibiotics for treating BK is influenced by region-specific microbiologic profiles, patterns of antimicrobial resistance, and clinicians' preferences and experience. Dual fortified antibiotic therapy (usually consisting of a cephalosporin and an aminoglycoside) and fluoroquinolone monotherapy (a second-, third-, or fourth-generation fluoroquinolone) are the most common treatments for BK. Alternative antibiotic options include combined cephalosporin-fluoroquinolone, vancomycin (a glycopeptide), polymyxin (a polypeptide), gramicidin (a cyclic peptide), and povidone-iodine (a commonly used and inexpensive antiseptic agent that plays an important role in LMICs). They are usually administered intensively during the initial phase (e.g. every one to two hours for the first 48 to 72 hours) then tapered off, with the regimen depending on the clinical course and treatment response. Medically refractory cases require surgical interventions such as therapeutic corneal cross-linking, amniotic membrane transplantation, corneal gluing, or keratoplasty (Hossain 2018; Said 2021; Ting 2019b; Ting 2021f).

Clinicians commonly prescribe topical corticosteroids as adjuvant therapy for treating BK, with the aim of reducing the associated inflammation and subsequent corneal scarring. The Steroids for Corneal Ulcers Trial (SCUT) has shown that the adjuvant use of topical corticosteroids could help improve visual outcomes in people with central and severe BK (Srinivasan 2012), but may worsen *Nocardia* keratitis (Lalitha 2012). However, one Cochrane Review found inadequate evidence as to the effect of topical corticosteroids compared with no topical corticosteroids on visual outcomes, infiltrate/scar size, or adverse events during the management of BK (Herretes 2014). In addition, therapeutic corneal cross-linking has emerged as an attractive adjuvant treatment for managing BK, though one Cochrane Review published in 2020 found only low-certainty evidence on the efficacy of this treatment on BK, due to small sample size and high clinical heterogeneity (Davis 2020).

In view of the potential heterogeneity introduced by the wide range of possible adjuvant therapies, our network meta-analysis (NMA) will focus exclusively on the effect of different types of antibiotics.

How the intervention might work

'Time is vision' is the underlying principle of infectious keratitis management, including BK management. Delay in the treatment of BK can cause severe corneal damage, melt, perforation, and scarring, leading to permanent visual impairment or blindness. The intensive topical antibiotics administered during the initial management of BK aim to rapidly eradicate the infection, limit corneal damage, and reduce the risk of complications. These antibiotics usually exhibit broad-spectrum activity (targeting both Gram-positive and Gram-negative bacteria), which is bactericidal rather than bacteriostatic. Depending on clinical severity and clinicians' preferences, the intensity, concentration, and duration of antibiotic treatment may vary from person to person, and can have important effects on the treatment efficacy.

Why it is important to do this review

BK is a major cause of corneal blindness worldwide. It has a significant impact on the vision and quality of life of affected people, on healthcare systems, and on the economy. One international survey published in 2017 highlighted the significant geographical variations in empirical antibiotic treatment regimens adopted by corneal specialists (Austin 2017). This heterogeneity hinders the analysis and direct comparison of the effectiveness and safety of different topical antibiotics in the treatment of BK. In 2014, McDonald and colleagues performed a systematic review and meta-analysis comparing the effectiveness of various topical antibiotics for BK (McDonald 2014). Although the review authors attempted multiple comparisons among different treatment groups, their analysis was limited because they did not use an NMA.

In addition, two further randomized controlled trials (RCTs) have been published since then, highlighting the need for an updated analysis (Isenberg 2017; Sharma 2016).

OBJECTIVES

To compare the effectiveness and safety of topical antibiotics for treating BK and to rank different interventions through a systematic review and NMA.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only RCTs. We will include parallel RCTs and exclude cross-over trials, as treatment for BK should take effect and influence the clinical course and outcome relatively quickly, rendering this particular condition and type of intervention unsuitable for cross-over trials. We will include trials that randomize at the participant level (i.e. all infected eyes receive the same treatment) as well as at the level of the eye (i.e. if both eyes are infected, eyes may receive different treatments). If we find multiple reports of a single study, we will treat the first or most complete report (e.g. earliest journal article) as the main report and all other linked sources (e.g. registration, conference abstract, secondary publications) as supplemental reports for that study. All reports may contribute information for a single study and if multiple sources are discrepant in the information, we will use the information contained in the most complete report.

Types of participants

We will include participants who are diagnosed (clinically or microbiologically) and treated for BK, with no restrictions related to age, gender, or ethnicity. We will exclude participants treated for other types of infectious keratitis such as fungal, viral, or parasitic infection, either separately or in conjunction with BK. For studies where only a subset of participants would be eligible for inclusion in the review, we will contact the authors to obtain individual participant data, and will only include this study if more than 50% of participants are eligible.

Types of interventions

We will only include studies that examine and compare different types of topical antibiotics. We will include trials with active controls and inactive controls (e.g. placebo) to maximize the amount of evidence in our review and strengthen the inferences (both direct and indirect) made through our NMA. We will consider all topical antibiotics – including those unspecified but identified in our search – to be our decision set (i.e. the interventions among which patients and health professionals choose in practice), and controls to be our supplementary set, included solely to increase the anticipated indirect evidence within our decision set (Chaimani 2017). Specific interventions for which we anticipate finding evidence include (but are not limited to) the following.

- Dual fortified antibiotic therapy (e.g. combined cephalosporin-aminoglycoside or combined cephalosporin-fluoroquinolone)
- Fluoroquinolone monotherapy (a second-, third-, or fourth-generation fluoroquinolone)
- Glycopeptides (e.g. vancomycin)
- Polypeptides (e.g. polymyxin)
- Cyclic peptides (e.g. gramicidin)
- Antiseptic agents (e.g. povidone-iodine)

Given that all interventions are of the same general type (i.e. topical antibiotics), with similar expected frequencies of administration, doses, and treatment durations, we assume the transitivity assumption will be met, and all interventions will be jointly randomizable for our population of interest (see 'Assessment of clinical heterogeneity and transitivity'; Caldwell 2005; Salanti 2012). The choice of antibiotics in practice is influenced by availability, affordability, and the microbiologic profile in the region; however, the antibiotics used usually provide broad-spectrum cover for most bacterial organisms, and we do not anticipate high prevalences of antimicrobial resistance in the included trials. Additionally, within all interventions, we will combine the various administration frequencies, doses, and durations, as we do not anticipate wide ranges within interventions, and we expect the transitivity assumption will hold for moderate variation in these clinical characteristics. We will exclude any treatment arm that involves primary surgical interventions, including intrastromal antibiotic injection, corneal cross-linking, amniotic membrane transplantation, or other types of surgery. We will list all treatment arms in the 'Characteristics of included studies' table, even if they are not used in the review. We will only include studies of topical antibiotics to avoid any potential confounding effect introduced by adjuvant therapy.

Types of outcome measures

Primary outcome

- Difference between interventions in the synthesis comparator set in mean number of days before complete corneal healing, defined as complete corneal re-epithelialization and clearance of infiltrate and hypopyon

Secondary outcomes

- Difference in mean size of epithelial defect (mm^2) at seven to 30 days and at final follow-up (three to six months)
- Difference in mean size of infiltrate (mm^2) at seven to 30 days and at final follow-up (three to six months)
- Difference in mean corrected distance visual acuity (CDVA) at one month and final follow-up (three to six months), expressed in LogMAR
- Difference in mean unaided distance visual acuity (UDVA) at one month and final follow-up (three to six months), expressed in LogMAR
- Difference in risk of specific prespecified adverse events at final follow-up (one to six months), defined as worsening infection or corneal melt or perforation requiring tectonic/therapeutic keratoplasty or evisceration
- Difference in risk of any other adverse events at final follow-up (one to six months)

We will conduct a random-effects NMA to synthesize all evidence for the primary outcome and the first four secondary outcomes and obtain a comprehensive ranking of all treatments for these five outcomes. We will focus an NMA approach to assessing the compound adverse event outcome 'difference in risk of specific adverse events by final follow-up', as we expect there will be data on this outcome for all interventions.

Search methods for identification of studies

Electronic searches

We will search the following electronic sources.

- Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Eyes and Vision Trials Register (latest issue);
- Ovid MEDLINE, Ovid MEDLINE E-pub Ahead of Print, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily (January 1946 to date of search)
- Embase (January 1947 to date of search)
- PubMed (1946 to date of search)
- Latin American and Caribbean Health Sciences Literature Database (LILACS; 1982 to date of search)
- ClinicalTrials.gov (www.clinicaltrials.gov)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/clinical-trials-registry-platform)

We will not apply any date or language restrictions in the electronic search for trials.

Details of search strategies are presented in Appendix 1 (CENTRAL), Appendix 2 (MEDLINE), Appendix 3 (Embase), Appendix 4 (PubMed), Appendix 5 (LILACS), Appendix 6 (ClinicalTrials.gov), and Appendix 7 (ICTRP).

Searching other resources

We will manually screen the reference lists of included RCTs to identify any further relevant studies. We will not search gray literature sources for this review as our target study type is RCT, and we expect these will all be identifiable in bibliographic or trial registry databases (Lefebvre 2011).

Data collection and analysis

Selection of studies

Based on pilot searching and other reviews, we expect to retrieve over 10,000 records from the various databases. For this reason, we will use a machine learning assisted web application designed for systematic reviews to help collate the potential studies and expedite the screening of abstracts and titles. Specifically, we will use PICO Portal, which uses a machine learning algorithm to prioritize records that are more likely to be included, based on initial screening patterns. Two review authors will independently screen the titles and abstracts until the system's prediction reaches 95% sensitivity and specificity for predicting eligibility of the remaining articles, at which point title and abstract screening will continue with a single review author until completion. Two review authors will independently screen the full-text articles to identify studies that fulfill our eligibility criteria, classifying each potentially eligible study as 'include', 'maybe', or 'exclude'. Discrepancies will be resolved by discussion or by consulting a third review author. We will use translators (e.g. Google Translate (translate.google.com) or native speakers) to assess the eligibility of records published in a language other than English.

Data extraction and management

Two review authors will use a standardized data collection form to extract study characteristics and outcome data. We will perform a pilot test on a few studies to ascertain the comprehensiveness, validity, and feasibility of this form.

Data to be extracted from included studies

- Study characteristics
  - Year of publication
  - Country of study
  - Number of study centers
  - Study design
- Participant data
  - Sample size
  - Inclusion and exclusion criteria
  - Diagnostic criteria
  - Method of randomization
  - Method of masking
  - Number of study arms
  - Number of participants
  - Demographic factors
    - Age
    - Gender
    - Ethnicity
    - Clinical severity of the condition
- Intervention data
  - Type of antibiotics
  - Frequency of administration
  - Dose
  - Duration of treatment
  - Concomitant medications
  - Excluded medications
- Outcome data
  - Primary and secondary outcomes
  - Duration of follow-up
  - Loss to follow-up
  - Intervals at which outcomes are assessed
- Additional information
  - Prospective registration of clinical trials in a publicly accessible database
  - Source of funding
  - Any notable conflicts of interest of trial authors

Where possible, for both primary and secondary outcomes, as well as risk of any adverse events, we will extract data at the arm level, not summary effects. If only summary effects are provided, we will contact the trial authors to request arm level data.

Assessment of risk of bias in included studies

Two review authors will independently assess the included studies for risk of bias with the revised Cochrane risk of bias tool (RoB 2; Higgins 2021; Sterne 2019). A third review author will adjudicate any disagreement. The review authors will not be masked to the authors of the studies during this assessment. We will primarily quantify the effect of adhering to the interventions as specified in the trial protocol (the per-protocol effect; Hernán 2017).

We will assess risk of bias for the following outcomes, including them in a summary of findings table (see 'Summary of findings and assessment of the certainty of the evidence').

- Difference between interventions in the synthesis comparator set in mean number of days before complete corneal healing, defined as complete corneal re-epithelialization and clearance of infiltrate and hypopyon
- Difference in mean size of epithelial defect (mm^2) at seven to 30 days and at final follow-up (three to six months)
- Difference in mean size of infiltrate (mm^2) at seven to 30 days and at final follow-up (three to six months)
- Difference in risk of specific adverse events at final follow-up (one to six months)

Using the signaling questions in RoB 2, we will make a risk of bias judgment ('high risk', 'some concern', or 'low risk') for the following domains (Higgins 2021; Sterne 2019).

- Randomization process
- Deviations from intended interventions
- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

We will summarize the risk of bias judgments across different studies for each of the domains for each outcome. The overall risk of bias for the outcome will be the least favorable assessment across the domains. We will record all answers to signaling questions (e.g. using the Excel tool on www.riskofbias.info) and make these available online on data repository websites.

Applying risk of bias assessments in this review

We will take into account the risk of bias in the studies for specific treatment effects (Schünemann 2021). We will perform sensitivity analyses as specified in the 'Sensitivity analysis' section below. The risk of bias results will inform the GRADE assessment and the summary of findings tables, and we will provide figures to illustrate the risk of bias.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review. We will report our completed NMA according to PRISMA and the NMA extension, as well as the standard guidance provided by Cochrane (Higgins 2019a; Hutton 2015; Liberati 2009).

Measures of treatment effect

We will measure dichotomous data as risk ratios (RRs) and continuous data as mean differences (MDs). We will obtain a comprehensive ranking of all treatments and will rank the competing interventions using mean or median ranks. We will use graphical tools such as rankograms to visually reflect the uncertainty in the ranking probabilities. Ranking will be avoided when there is considerable uncertainty in the effect estimates or when there are important differences in uncertainty across comparisons (Caldwell 2005; Chaimani 2017).

Unit of analysis issues

The unit of analysis will be the eye of individual participants. We anticipate that most trials will randomize and include only a single eye from each participant, and we will include all such trials in the analysis. Trials that include both eyes with the same treatment or two different treatments will be included in the qualitative synthesis, but excluded from the NMAs. These trials will be excluded from quantitative analyses because it is challenging to appropriately account for the intra-individual correlation between eyes when both are included in a trial without having access to the individual participant data from the trials.

Dealing with missing data

When data are unavailable due to loss to follow-up or dropouts, we will examine the prespecified outcomes of the individuals with complete data (i.e. complete case analysis), provided that the level of missing data and reasons for missing data are similar in each treatment arm. We will also contact study authors or study sponsors to verify key study characteristics and obtain missing outcome data. We will not impute missing outcome data ourselves.

Assessment of heterogeneity

Heterogeneity and inconsistency in the study populations and other study characteristics can invalidate meta-analysis. Assessing heterogeneity is especially important for NMAs – which can compare several different types of intervention – because too much clinical heterogeneity or inconsistency of effect may violate the transitivity assumption.

Assessment of clinical heterogeneity and transitivity

We will examine the overall characteristics of the studies – in particular the types of participants, clinical characteristics, and types of interventions – to assess clinical heterogeneity and transitivity. The clinical characteristics of particular relevance to the transitivity assumption include the following.

- Participant age
- Clinical severity of the condition
- Dose of antibiotic treatment
- Duration of antibiotic treatment

If the studies are sufficiently similar in their distributions of these characteristics, we will assume the transitivity assumption holds and that the interventions are jointly randomizable. If any particular trial differs considerably from the others in one of these characteristics, we may exclude it from the NMAs, although we may still include it in pair-wise meta-analyses (if it is sufficiently similar to other trials for relevant pair-wise analysis), and we will include it in all qualitative syntheses. Further, if multiple trials are found to differ in the distributions of these potential effect modifiers, we will explore the potential as effect modifiers in subgroup analyses (see 'Subgroup analysis and investigation of heterogeneity').

Assessment of statistical heterogeneity and inconsistency

For pair-wise comparison, we will assess the heterogeneity of the RCTs by careful review of the full-text articles, assessment of forest plots, and examination of the I^2 value with its 95% confidence interval (CI). For the pair-wise meta-analyses, we will review results of forest plots for consistency of the size and direction of effects, and we will estimate a different heterogeneity parameter for each

comparison. We will consider I^2 values above 80% indicative of substantial heterogeneity (Higgins 2019b). We will use a random-effects model for the pair-wise meta-analyses regardless of the degree of methodological and statistical heterogeneity, to be consistent with our random-effects NMAs. We will also consider the Chi^2 P value (with $P < 0.1$ representing statistical significance), as this has a low power when the number of studies is small (Higgins 2019b).

In our NMAs, we will assume a common estimate for the heterogeneity variance across all comparisons in the network. We will assess the statistical heterogeneity in the entire network based on the magnitude of the heterogeneity variance parameter (Tau^2) estimated from the NMA models. We will also examine incoherence in the NMA using both local and global approaches (Chaimani 2017). Specifically, we will use the SIDE (Separating Indirect from Direct Evidence) node-splitting approach to examine local incoherence by contrasting the direct and indirect estimates from all pair-wise comparisons. Global incoherence will be assessed with an incoherence model that allows intervention effects to vary when estimating directly and indirectly and testing the differences between incoherence factors using a Chi^2 statistic to ensure all are close to zero (Dias 2010). Both these local and global assessments are available in Stata, which we are using for all analyses (Statacorp; White 2015).

Assessment of reporting biases

If we identify more than 10 trials for any of our outcomes, we will use comparison-adjusted and contour-enhanced funnel plots to investigate the possibility of reporting bias for that outcome and explore whether results in imprecise trials differ from those in more precise trials (Egger 1997).

Data synthesis

As we expect all studies reporting our measures of interest to use the same scales (i.e. number of days, mm^2, LogMAR, and risk), we do not anticipate needing to standardize the measures. Thus, for each pair-wise comparison, we will synthesize data to obtain summary MDs for continuous outcomes or RRs for dichotomous outcomes, both with 95% CIs. We will check whether the continuous outcomes are normally distributed and apply a transformation before analysis if the data are heavily skewed. If the collected studies appear to be sufficiently similar with respect to the distribution of effect modifiers, we will conduct a random-effects NMA to synthesize all evidence for each outcome and obtain a comprehensive ranking of all treatments. We will use Stata to perform all analyses, including the pair-wise meta-analyses and any NMAs, ranking estimation, and funnel plots; and to generate any relevant graphics that are deemed appropriate for the analyses (e.g. forest plots and network graph) (Statacorp).

We will not conduct an NMA for any non-specified adverse events reported in the trials, as these are likely to be inconsistently reported across trials, and we do not expect to have enough data for each possible event to conduct a valid meta-analysis. Instead, we will descriptively summarize all harms reported in each trial and qualitatively synthesize any that occur in more than one included trial. We will not impose any selection criteria to the harms reported in the trials, and we will report all harms that we identify.

We will rank the interventions using the surface under the cumulative ranking curves (SUCRAs) approach. SUCRA ranges from 0% to 100% and represents the overall ranking for each intervention: the closer the SUCRA value to 100%, the higher the likelihood that particular therapy is in the top rank compared with other interventions (Mbuagbaw 2017; Salanti 2011). Additionally, to present the uncertainty in the ranking, we will create a rankogram for each NMA performed (Salanti 2011).

Summary of findings and assessment of the certainty of the evidence

For our NMA summary of findings table, we will consider the Confidence in Network Meta-Analysis (CINeMA) approach (Brignardello-Petersen 2018; Salanti 2014). We will create the summary of findings table using GRADEpro GDT software, including the three outcomes that are assessed for risk of bias (see 'Assessment of risk of bias in included studies'; GRADEpro GDT; Schünemann 2013). All RCTs will start with a rating of 'high-certainty' evidence and will be downgraded by one level for serious concerns (or by two levels for very serious concerns) regarding risk of bias, inconsistency, indirectness, imprecision, and publication bias (Yepes-Nuñez 2019). Two review authors will independently grade the certainty of evidence, consulting a third review author in case of disagreement.

Subgroup analysis and investigation of heterogeneity

We will not perform any subgroup analyses in this systematic review, provided that heterogeneity is low to moderate for our outcomes. However, if we find substantial heterogeneity for any outcomes, we will carry out the following subgroup analyses for those outcomes.

- Treatment frequency: low (trials with a frequency of four to six times a day) and high (trials with a frequency of every one to two hours)
- Treatment duration: short (trials with a duration of one month or less) and long (trials with a duration of more than one month)
- Age of participants: adult (trials with a mean age under 60 years) and older adult (trials with a mean age of 60 years or older)
- Clinical severity (Ting 2021d): mild or moderate (participants with small [3.0 mm or less] or moderate [3.1 mm to 6.0 mm] infiltrate) and severe (participants with large [6.0 mm or more] infiltrate)

Sensitivity analysis

We will perform sensitivity analysis by assessing the impact of including RCTs with high risk of bias for an outcome in one or more key domains. To do this, we will exclude each of those studies in turn to examine the influence of individual studies (with high risk of bias) on the overall pooled estimate.

Reaching conclusions

We will conduct the NMA based on this prespecified protocol. If we must deviate from the protocol due to lack of data, we will provide clear explanations in the published review.

ACKNOWLEDGEMENTS

We thank Lori Rosman, Information Specialist for Cochrane Eyes and Vision US Project (CEV@US), who created the electronic search strategies.

We also thank Sueko Ng, methodologist of CEV@US; Genie Han, Assistant Managing Editor of CEV@US; Anupa Shah, Managing Editor for CEV, for support and guidance in preparation of this protocol.

We would also like to thank the following peer reviewers for their comments on the review protocol: Renee Bovelle (Howard University) and Maria Petropoulou (Medical University of Freiburg).

This protocol was managed by CEV@US and was signed off for publication by Tianjing Li and Gianni Virgili.

REFERENCES

Additional references

Asbell 2020

Asbell PA, Sanfilippo CM, Sahm DF, DeCory HH. Trends in antibiotic resistance among ocular microorganisms in the United States from 2009 to 2018. *JAMA Ophthalmology* 2020;**138**(5):439-50.

Austin 2017

Austin A, Schallhorn J, Geske M, Mannis M, Lietman T, Rose-Nussbaumer J. Empirical treatment of bacterial keratitis: an international survey of corneal specialists. *BMJ Open Ophthalmology* 2017;**2**(1):e000047.

Brignardello-Petersen 2018

Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, Puhan MA. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *Journal of Clinical Epidemiology* 2018;**93**:36-44.

Cabrera-Aguas 2021

Cabrera-Aguas M, Khoo P, Watson SL. Presumed microbial keratitis cases resulting in evisceration and enucleation in Sydney, Australia. *Ocular Immunology and Inflammation* 2021;**December**:1-7.

Caldwell 2005

Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;**331**:897.

Chaimani 2017

Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G. Additional considerations are required when preparing a protocol for a systematic review with multiple interventions. *Journal of Clinical Epidemiology* 2017;**83**:65-74.

Davis 2020

Davis SA, Bovelle R, Han G, Kwagyan J. Corneal collagen cross-linking for bacterial infectious keratitis. *Cochrane Database of Systematic Reviews* 2020;**6**:CD014001.

Dias 2010

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010;**29**(7-8):932-44.

Egger 1997

Egger M, Smith GD, Schneider M, Christoph M. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Green 2019

Green M, Carnt N, Apel A, Stapleton F. Queensland Microbial Keratitis Database: 2005–2015. *British Journal of Ophthalmology* 2019;**103**(10):1481-6.

Hernán 2017

Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. *New England Journal of Medicine* 2017;**377**(14):1391-8.

Herretes 2014

Herretes S, Wang X, Reyes JM. Topical corticosteroids as adjunctive therapy for bacterial keratitis. *Cochrane Database of Systematic Reviews* 2014;**10**:CD005430.

Higgins 2019a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane handbook for systematic reviews of interventions. 2nd edition. Chichester (UK): John Wiley & Sons, 2019.

Higgins 2019b

Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. Draft version (29 January 2019). In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition. Chichester (UK): John Wiley & Sons, 2019.

Higgins 2021

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook/archive/v6.2/.

Hossain 2018

Hossain P, Tourkmani AK, Kazakos D, Jones M, Anderson D. Emergency corneal grafting in the UK: a 6-year analysis of the UK Transplant Registry. *British Journal of Ophthalmology* 2018;**102**(1):26-30.

Hutton 2015

Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of Internal Medicine* 2015;**162**(11):777-84.

Isenberg 2017

Isenberg SJ, Apt L, Valenton M, Sharma S, Garg P, Thomas PA, et al. Prospective, randomized clinical trial of povidone-iodine 1.25% solution versus topical antibiotics for treatment of bacterial keratitis. *American Journal of Ophthalmology* 2017;**176**:244-53.

Kaye 2010

Kaye S, Tuft S, Neal T, Tole D, Leeming J, Figueiredo F, et al. Bacterial susceptibility to topical antimicrobials and clinical outcome in bacterial keratitis. *Investigative Ophthalmology and Vision Science* 2010;**51**(1):362-8.

Khoo 2020

Khoo P, Cabrera-Aguas MP, Nguyen V, Lahra MM, Watson SL. Microbial keratitis in Sydney, Australia: risk factors, patient outcomes, and seasonal variation. *Graefes Archives for Clinical and Experimental Ophthalmology* 2020;**258**(8):1745-55.

Khor 2018

Khor WB, Prajna VN, Garg P, Mehta JS, Xie L, Liu Z, et al. The Asia cornea society infectious keratitis study: a prospective multicenter study of infectious keratitis in Asia. *American Journal of Ophthalmology* 2018;**195**:161-79.

Kowalski 2020

Kowalski RP, Nayyar SV, Romanowski EG, Shanks RM, Mammen A, Dhaliwal DK, et al. The prevalence of bacteria, fungi, viruses, and acanthamoeba from 3,004 cases of keratitis, endophthalmitis, and conjunctivitis. *Eye Contact Lens* 2020;**46**(5):265-8.

Lalitha 2012

Lalitha P, Srinivasan M, Rajaraman R, Ravindran M, Mascarenhas J, Priya JL, et al. Nocardia keratitis: clinical course and effect of corticosteroids. *American Journal of Ophthalmology* 2012;**154**(6):934-9.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLOS Medicine* 2009;**6**(7):e1000100.

Mbuagbaw 2017

Mbuagbaw L, Rochwerg B, Jaeschke R, Heels-Andsell D, Alhazzani W, Thabane L, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Systematic Reviews* 2017;**6**:79.

McDonald 2014

McDonald EM, Ram FS, Patel DV, McGhee CN. Topical antibiotics for the management of bacterial keratitis: an evidence-based review of high quality randomised controlled trials. *British Journal of Ophthalmology* 2014;**98**(11):1470-7.

Said 2021

Said DG, Rallis KI, Al-Aqaba MA, Ting DSJ, Dua HS. Surgical management of infectious keratitis. Ocular Surface 2021 Sep 27 [Epub ahead of print]. [DOI: 10.1016/j.jtos.2021.09.005]

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163-71.

Salanti 2012

Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis too. *Research Synthesis Methods* 2012;**3**(2):80-97.

Salanti 2014

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLOS One* 2014;**9**(7):e99682.

Schünemann 2013

Schünemann H, Brozek J, Guyatt G, Oxman A, editor(s). GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, 2013.

Schünemann 2021

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook/archive/v6.2/ 2021.

Shah 2011

Shah A, Sachdev A, Coggon D, Hossain P. Geographic variations in microbial keratitis: an analysis of the peer-reviewed literature. *British Journal of Ophthalmology* 2011;**95**(6):762-7.

Sharma 2016

Sharma N, Arora T, Jain V, Agarwal T, Jain R, Jain V, et al. Gatifloxacin 0.3% versus fortified tobramycin-cefazolin in treating nonperforated bacterial corneal ulcers: randomized, controlled trial. *Cornea* 2016;**35**(1):56-61.

Srinivasan 2012

Srinivasan M, Mascarenhas J, Rajaraman R, Ravindran M, Lalitha P, Glidden DV, et al. Corticosteroids for bacterial keratitis: the Steroids for Corneal Ulcers Trial (SCUT). *Archives of Ophthalmology* 2012;**130**(2):143-50.

Statacorp [Computer program]

Stata Statistical Software. Version 15. College Station, TX: StataCorp LLC, 2017.

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

Tam 2017

Tam AL, Côté E, Saldanha M, Lichtinger A, Slomovic AR. Bacterial keratitis in Toronto: a 16-year review of the

microorganisms isolated and the resistance patterns observed. *Cornea* 2017;**36**(12):1528-34.

Tan 2017

Tan SZ, Walkden A, Au L, Fullwood C, Hamilton A, Qamruddin A, et al. Twelve-year analysis of microbial keratitis trends at a UK tertiary hospital. *Eye (Lond.)* 2017;**31**(8):1229-36.

Tavassoli 2019

Tavassoli S, Nayar G, Darcy K, Grzeda M, Luck J, Williams OM, et al. An 11-year analysis of microbial keratitis in the South West of England using brain-heart infusion broth. *Eye (London, England)* 2019;**33**(10):1619-25.

Ting 2018

Ting DS, Settle C, Morgan SJ, Baylis O, Ghosh S. A 10-year analysis of microbiological profiles of microbial keratitis: the North East England Study. *Eye (London, England)* 2018;**32**(8):1416-7.

Ting 2019a

Ting DS, Bignardi G, Koerner R, Irion LD, Johnson E, Morgan SJ, et al. Polymicrobial keratitis with Cryptococcus curvatus, Candida parapsilosis, and Stenotrophomonas maltophilia after penetrating keratoplasty: a rare case report with literature review. *Eye Contact Lens* 2019;**45**(2):e5-10.

Ting 2019b

Ting DS, Henein C, Said DG, Dua HS. Photoactivated chromophore for infectious keratitis – corneal cross-linking (PACK-CXL): a systematic review and meta-analysis. *The Ocular Surface* 2019;**17**(4):624-34.

Ting 2021a

Ting DS, Ho CS, Deshmukh R, Said DG, Dua HS. Infectious keratitis: an update on epidemiology, causative microorganisms, risk factors, and antimicrobial resistance. *Eye (London, England)* 2021;**35**(4):1084-101.

Ting 2021b

Ting DS, Ho CS, Cairns J, Elsahn A, Al-Aqaba M, Boswell T, et al. 12-year analysis of incidence, microbiological profiles and in vitro antimicrobial susceptibility of infectious keratitis: the Nottingham Infectious Keratitis Study. *British Journal of Ophthalmology* 2021;**105**(3):328-33.

Ting 2021c

Ting DS, Ho CS, Cairns J, Gopal BP, Elsahn A, Al-Aqaba M, et al. Seasonal patterns of incidence, demographic factors and microbiological profiles of infectious keratitis: the Nottingham Infectious Keratitis Study. *Eye (London, England)* 2021;**35**(9):2543-9.

Ting 2021d

Ting DS, Cairns J, Gopal BP, Ho CS, Krstic L, Elsahn A, et al. Risk factors, clinical outcomes, and prognostic factors of bacterial keratitis: the Nottingham Infectious Keratitis Study. *Frontiers in Medicine (Lausanne)* 2021;**8**:715118.

Ting 2021e

Ting DS, Galal M, Kulkarni B, Elalfy MS, Lake D, Hamada S, et al. Clinical characteristics and outcomes of fungal keratitis in the United Kingdom 2011–2020: a 10-year study. *Journal of Fungi* 2021;**7**(11):966.

Ting 2021f

Ting DS, Henein C, Said DG, Dua HS. Amniotic membrane transplantation for infectious keratitis: a systematic review and meta-analysis. *Scientific Reports* 2021;**11**(1):13007.

Ung 2019

Ung L, Bispo PJ, Shanbhag SS, Gilmore MS, Chodosh J. The persistent dilemma of microbial keratitis: global burden, diagnosis, and antimicrobial resistance. *Survey of Ophthalmology* 2019;**64**(3):255-71.

White 2015

White IR. Network meta-analysis. *Stata Journal* 2015;**15**:951-85.

Yepes-Nuñez 2019

Yepes-Nuñez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the grading of recommendations assessment, development and evaluation (GRADE) summary of findings (SoF) table for network meta-analysis. *Journal of Clinical Epidemiology* 2019;**115**:1-13.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Keratitis] explode all trees
#2 (cornea* AND (melt* OR infection* OR microbial OR ulcer* OR inflammat*))
#3 (Keratiti* OR Keratoconjunctiviti* OR (Kerato NEXT/1 conjunctiviti*))
#4 #1 OR #2 OR #3
#5 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#6 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees
#7 MeSH descriptor: [Anti-Infective Agents] explode all trees
#8 antibiotic* OR (anti NEXT/1 biotic*) OR antibacterial* OR (anti NEXT/1 bacterial*) OR antimicrobial* OR (anti NEXT/1 microbial*) OR bacteriocidal* OR antiseptic* OR (anti NEXT/1 septic*) OR antiinfective* OR (anti NEXT1 infective*)
#9 MeSH descriptor: [Fluoroquinolones] explode all trees
#10 (fluoroquinolone* OR ciprofloxacin* OR fleroxacin* OR enoxacin* OR enrofloxacin* OR gatifloxacin* OR gemifloxacin* OR moxifloxacin* OR norfloxacin* OR ofloxacin* OR levofloxacin* OR pefloxacin*)
#11 MeSH descriptor: [Aminoglycosides] explode all trees

#12 (aminoglycoside* OR anthracycline* OR (butirosin NEXT/1 sulfate*) OR calicheamicin* OR gentamicin* OR "hygromycin b" OR kanamycin* OR metrizamide* OR neomycin* OR paromomycin* OR puromycin* OR spectinomycin* OR streptomycin* OR streptothricin* OR streptozocin*)
#13 MeSH descriptor: [Cephalosporins] explode all trees
#14 (cephalosporin* OR cefamandole* OR cefoperazone* OR cefazolin* OR cefdinir* OR cefepime* OR cefonicid* OR cefsulodin* OR ceftibuten* OR cefuroxime* OR cephacetrile* OR cefotaxime* OR cephalothin* OR cephapirin* OR cephalexin* OR cefaclor* OR cefadroxil* OR cephaloglycin* OR cephradine* OR cephaloridine* OR ceftazidime* OR cephamycin* OR cefmetazole* OR cefotetan* OR cefoxitin*)
#15 MeSH descriptor: [Glycopeptides] explode all trees
#16 (glycopeptide* OR bleomycin* OR peplomycin* OR phleomycin* OR lipoglycopeptide* OR teicoplanin* OR peptidoglycan* OR ristocetin* OR vancomycin*)
#17 MeSH descriptor: [Peptides] explode all trees
#18 MeSH descriptor: [Peptides, Cyclic] explode all trees
#19 (polypeptide* OR (cyclic NEXT/1 peptide*) OR alamethicin* OR amanitin* OR "alpha-amanitin" OR bacitracin* OR capreomycin* OR cyclosporin* OR cyclosporine* OR dactinomycin* OR daptomycin* OR depsipeptide* OR valinomycin* OR echinomycin* OR enterobactin* OR ferrichrome* OR microcystin* OR mycobacillin* OR nisin* OR octreotide* OR phalloidine* OR polymyxin* OR colistin* OR "polymyxin b" OR streptogramin* OR mikamycin* OR pristinamycin* OR "vernamycin b" OR virginiamycin* OR thiostrepton* OR tyrothricin* OR gramicidin* OR tyrocidine* OR viomycin* OR enviomycin*)
#20 MeSH descriptor: [Povidone-Iodine] explode all trees
#21 (povidone NEXT/1 iodine*) OR "PVP-I" OR (PVP NEXT/1 Iodine*) OR (polyvinylpyrrolidone NEXT/1 iodine*) OR betadine* OR providine* OR disadine* OR isodine* OR pharmadine* OR alphadine* OR betaisodona*
#22 {OR #5-#21}
#23 #4 AND #22 in Trials

Appendix 2. MEDLINE (Ovid) search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Keratitis/
13. (cornea* and (melt* or infection* or microbial or ulcer* or inflammat*)).tw.
14. (Keratiti* or Keratoconjunctiviti* or (Kerato adj1 conjunctiviti*)).tw.
15. 12 or 13 or 14
16. exp Anti-Bacterial Agents/
17. exp Antibiotic Prophylaxis/
18. exp Anti-Infective Agents/
19. (antibiotic* or "anti biotic*" or antibacterial* or "anti bacterial*" or antimicrobial* or "anti microbial*" or bacteriocidal* or antiseptic* or "anti septic*" or antiinfective* or "anti infective*").tw.
20. exp Fluoroquinolones/
21. (fluoroquinolone* or ciprofloxacin* or fleroxacin* or enoxacin* or enrofloxacin* or gatifloxacin* or gemifloxacin* or moxifloxacin* or norfloxacin* or ofloxacin* or levofloxacin* or pefloxacin*).tw.
22. exp Aminoglycosides/
23. (aminoglycoside* or anthracycline* or "butirosin sulfate*" or calicheamicin* or gentamicin* or "hygromycin b" or kanamycin* or metrizamide* or neomycin* or paromomycin* or puromycin* or spectinomycin* or streptomycin* or streptothricin* or streptozocin*).tw.
24. exp Cephalosporins/
25. (cephalosporin* or cefamandole* or cefoperazone* or cefazolin* or cefdinir* or cefepime* or cefonicid* or cefsulodin* or ceftibuten* or cefuroxime* or cephacetrile* or cefotaxime* or cephalothin* or cephapirin* or cephalexin* or cefaclor* or cefadroxil* or cephaloglycin* or cephradine* or cephaloridine* or ceftazidime* or cephamycin* or cefmetazole* or cefotetan* or cefoxitin*).tw.
26. exp Glycopeptides/
27. (glycopeptide* or bleomycin* or peplomycin* or phleomycin* or lipoglycopeptide* or teicoplanin* or peptidoglycan* or ristocetin* or vancomycin*).tw.
28. exp Peptides/
29. exp Peptides, Cyclic/
30. (polypeptide* or "cyclic peptide*" or alamethicin* or amanitin* or "alpha-amanitin" or bacitracin* or capreomycin* or cyclosporin* or cyclosporine* or dactinomycin* or daptomycin* or depsipeptide* or valinomycin* or echinomycin* or enterobactin* or ferrichrome*

or microcystin* or mycobacillin* or nisin* or octreotide* or phalloidine* or polymyxin* or colistin* or "polymyxin b" or streptogramin* or mikamycin* or pristinamycin* or "vernamycin b" or virginiamycin* or thiostrepton* or tyrothricin* or gramicidin* or tyrocidine* or viomycin* or enviomycin*).tw.
31. exp Povidone-Iodine/
32. ("povidone iodine*" OR "PVP-I" OR "PVP Iodine*" OR "polyvinylpyrrolidone iodine*" OR betadine* OR providine* OR disadine* OR isodine* OR pharmadine* OR alphadine* OR betaisodona*).tw.
33. or/16-32
34. 11 and 15 and 33

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

Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'keratitis'/exp
#34 cornea*:ab,ti,kw AND (melt*:ab,ti,kw OR infection*:ab,ti,kw OR microbial:ab,ti,kw OR ulcer*:ab,ti,kw OR inflammat*:ab,ti,kw)
#35 keratiti*:ab,ti,kw OR keratoconjunctiviti*:ab,ti,kw OR 'kerato conjunctiviti*':ab,ti,kw
#36 #33 OR #34 OR #35
#37 'antiinfective agent'/exp
#38 'antibiotic prophylaxis'/exp
#39 antibiotic*:ab,ti,kw OR 'anti biotic*':ab,ti,kw OR antibacterial*:ab,ti,kw OR 'anti bacterial*':ab,ti,kw OR antimicrobial*:ab,ti,kw OR 'anti microbial*':ab,ti,kw OR bacteriocidal*:ab,ti,kw OR antiseptic*:ab,ti,kw OR 'anti septic*':ab,ti,kw OR antiinfective*:ab,ti,kw OR 'anti infective*':ab,ti,kw
#40 fluoroquinolone*:ab,ti,kw,tn OR ciprofloxacin*:ab,ti,kw,tn OR fleroxacin*:ab,ti,kw,tn OR enoxacin*:ab,ti,kw,tn OR enrofloxacin*:ab,ti,kw,tn OR gatifloxacin*:ab,ti,kw,tn OR gemifloxacin*:ab,ti,kw,tn OR moxifloxacin*:ab,ti,kw,tn OR norfloxacin*:ab,ti,kw,tn OR ofloxacin*:ab,ti,kw,tn OR levofloxacin*:ab,ti,kw,tn OR pefloxacin*:ab,ti,kw,tn
#41 aminoglycoside*:ab,ti,kw,tn OR anthracycline*:ab,ti,kw,tn OR 'butirosin sulfate*':ab,ti,kw,tn OR calicheamicin*:ab,ti,kw,tn OR gentamicin*:ab,ti,kw,tn OR 'hygromycin b':ab,ti,kw,tn OR kanamycin*:ab,ti,kw,tn OR metrizamide*:ab,ti,kw,tn OR neomycin*:ab,ti,kw,tn OR paromomycin*:ab,ti,kw,tn OR puromycin*:ab,ti,kw,tn OR spectinomycin*:ab,ti,kw,tn OR streptomycin*:ab,ti,kw,tn OR streptothricin*:ab,ti,kw,tn OR streptozocin*:ab,ti,kw,tn

#42 'cephalosporin derivative'/exp
#43 cephalosporin*:ab,ti,kw,tn OR cefamandole*:ab,ti,kw,tn OR cefoperazone*:ab,ti,kw,tn OR cefazolin*:ab,ti,kw,tn OR cefdinir*:ab,ti,kw,tn OR cefepime*:ab,ti,kw,tn OR cefonicid*:ab,ti,kw,tn OR cefsulodin*:ab,ti,kw,tn OR ceftibuten*:ab,ti,kw,tn OR cefuroxime*:ab,ti,kw,tn OR cephacetrile*:ab,ti,kw,tn OR cefotaxime*:ab,ti,kw,tn OR cephalothin*:ab,ti,kw,tn OR cephapirin*:ab,ti,kw,tn OR cephalexin*:ab,ti,kw,tn OR cefaclor*:ab,ti,kw,tn OR cefadroxil*:ab,ti,kw,tn OR cephaloglycin*:ab,ti,kw,tn OR cephradine*:ab,ti,kw,tn OR cephaloridine*:ab,ti,kw,tn OR ceftazidime*:ab,ti,kw,tn OR cephamycin*:ab,ti,kw,tn OR cefmetazole*:ab,ti,kw,tn OR cefotetan*:ab,ti,kw,tn OR cefoxitin*:ab,ti,kw,tn
#44 'glycopeptide'/exp
#45 glycopeptide*:ab,ti,kw,tn OR bleomycin*:ab,ti,kw,tn OR peplomycin*:ab,ti,kw,tn OR phleomycin*:ab,ti,kw,tn OR lipoglycopeptide*:ab,ti,kw,tn OR teicoplanin*:ab,ti,kw,tn OR peptidoglycan*:ab,ti,kw,tn OR ristocetin*:ab,ti,kw,tn OR vancomycin*:ab,ti,kw,tn
#46 'polypeptide'/exp
#47 'cyclopeptide'/exp
#48 polypeptide*:ab,ti,kw,tn OR 'cyclic peptide*':ab,ti,kw,tn OR alamethicin*:ab,ti,kw,tn OR amanitin*:ab,ti,kw,tn OR 'alpha-amanitin':ab,ti,kw,tn OR bacitracin*:ab,ti,kw,tn OR capreomycin*:ab,ti,kw,tn OR cyclosporin*:ab,ti,kw,tn OR cyclosporine*:ab,ti,kw,tn OR dactinomycin*:ab,ti,kw,tn OR daptomycin*:ab,ti,kw,tn OR depsipeptide*:ab,ti,kw,tn OR valinomycin*:ab,ti,kw,tn OR echinomycin*:ab,ti,kw,tn OR enterobactin*:ab,ti,kw,tn OR ferrichrome*:ab,ti,kw,tn OR microcystin*:ab,ti,kw,tn OR mycobacillin*:ab,ti,kw,tn OR nisin*:ab,ti,kw,tn OR octreotide*:ab,ti,kw,tn OR phalloidine*:ab,ti,kw,tn OR polymyxin*:ab,ti,kw,tn OR colistin*:ab,ti,kw,tn OR 'polymyxin b':ab,ti,kw,tn OR streptogramin*:ab,ti,kw,tn OR mikamycin*:ab,ti,kw,tn OR pristinamycin*:ab,ti,kw,tn OR 'vernamycin b':ab,ti,kw,tn OR virginiamycin*:ab,ti,kw,tn OR thiostrepton*:ab,ti,kw,tn OR tyrothricin*:ab,ti,kw,tn OR gramicidin*:ab,ti,kw,tn OR tyrocidine*:ab,ti,kw,tn OR viomycin*:ab,ti,kw,tn OR enviomycin*:ab,ti,kw,tn
#49 'povidone iodine*':ab,ti,kw,tn OR 'pvp-i':ab,ti,kw,tn OR 'pvp iodine*':ab,ti,kw,tn OR 'polyvinylpyrrolidone iodine*':ab,ti,kw,tn OR betadine*:ab,ti,kw,tn OR providine*:ab,ti,kw,tn OR disadine*:ab,ti,kw,tn OR isodine*:ab,ti,kw,tn OR pharmadine*:ab,ti,kw,tn OR alphadine*:ab,ti,kw,tn OR betaisodona*:ab,ti,kw,tn
#50 #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#51 #32 AND #36 AND #50

Appendix 4. PubMed search strategy

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
#2 (cornea*[tw] AND (melt*[tw] OR infection*[tw] OR microbial[tw] OR ulcer*[tw] OR inflammat*[tw]))
#3 (Keratiti*[tw] OR Keratoconjunctiviti*[tw] OR Kerato conjunctiviti*[tw])
#4 #2 OR #3
#5 (antibiotic*[tw] OR "anti biotic*"[tw] OR antibacterial*[tw] OR "anti bacterial*"[tw] OR antimicrobial*[tw] OR "anti microbial*"[tw] OR bacteriocidal*[tw] OR antiseptic*[tw] OR "anti septic*"[tw] OR antiinfective*[tw] OR "anti infective*"[tw])
#6 (fluoroquinolone*[tw] OR ciprofloxacin*[tw] OR fleroxacin*[tw] OR enoxacin*[tw] OR enrofloxacin*[tw] OR gatifloxacin*[tw] OR gemifloxacin*[tw] OR moxifloxacin*[tw] OR norfloxacin*[tw] OR ofloxacin*[tw] OR levofloxacin*[tw] OR pefloxacin*[tw])
#7 (aminoglycoside*[tw] OR anthracycline*[tw] OR "butirosin sulfate*"[tw] OR calicheamicin*[tw] OR gentamicin*[tw] OR "hygromycin b"[tw] OR kanamycin*[tw] OR metrizamide*[tw] OR neomycin*[tw] OR paromomycin*[tw] OR puromycin*[tw] OR spectinomycin*[tw] OR streptomycin*[tw] OR streptothricin*[tw] OR streptozocin*[tw])
#8 (cephalosporin*[tw] OR cefamandole*[tw] OR cefoperazone*[tw] OR cefazolin*[tw] OR cefdinir*[tw] OR cefepime*[tw] OR cefonicid*[tw] OR cefsulodin*[tw] OR ceftibuten*[tw] OR cefuroxime*[tw] OR cephacetrile*[tw] OR cefotaxime*[tw] OR cephalothin*[tw] OR cephapirin*[tw] OR cephalexin*[tw] OR cefaclor*[tw] OR cefadroxil*[tw] OR cephaloglycin*[tw] OR cephradine*[tw] OR cephaloridine*[tw] OR ceftazidime*[tw] OR cephamycin*[tw] OR cefmetazole*[tw] OR cefotetan*[tw] OR cefoxitin*[tw])
#9 (glycopeptide*[tw] OR bleomycin*[tw] OR peplomycin*[tw] OR phleomycin*[tw] OR lipoglycopeptide*[tw] OR teicoplanin*[tw] OR peptidoglycan*[tw] OR ristocetin*[tw] OR vancomycin*[tw])
#10 (polypeptide*[tw] OR "cyclic peptide*"[tw] OR alamethicin*[tw] OR amanitin*[tw] OR "alpha-amanitin"[tw] OR bacitracin*[tw] OR capreomycin*[tw] OR cyclosporin*[tw] OR cyclosporine*[tw] OR dactinomycin*[tw] OR daptomycin*[tw] OR depsipeptide*[tw] OR valinomycin*[tw] OR echinomycin*[tw] OR enterobactin*[tw] OR ferrichrome*[tw] OR microcystin*[tw] OR mycobacillin*[tw] OR nisin*[tw] OR octreotide*[tw] OR phalloidine*[tw] OR polymyxin*[tw] OR colistin*[tw] OR "polymyxin b"[tw] OR streptogramin*[tw] OR mikamycin*[tw] OR pristinamycin*[tw] OR "vernamycin b"[tw] OR virginiamycin*[tw] OR thiostrepton*[tw] OR tyrothricin*[tw] OR gramicidin*[tw] OR tyrocidine*[tw] OR viomycin*[tw] OR enviomycin*[tw])
#11 "povidone iodine*"[tw] OR "PVP-I"[tw] OR "PVP Iodine*"[tw] OR "polyvinylpyrrolidone iodine*"[tw] OR betadine*[tw] OR providine*[tw] OR disadine*[tw] OR isodine*[tw] OR pharmadine*[tw] OR alphadine*[tw] OR betaisodona*[tw]
#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13 #1 AND #4 AND #12
#14 Medline[sb]
#15 #13 NOT #14

Appendix 5. LILACS search strategy

(MH:C11.204.564$ OR Keratiti$ OR Queratiti$ OR Ceratit$ OR MH:C11.187.183.394 OR Keratoconjunctiviti$ OR Queratoconjuntiviti$ OR Ceratoconjuntivit$ OR (cornea$ AND (melt$ OR infection$ OR microbial OR ulcer$ OR inflammat$))) AND (MH:D27.505.954.122.085$

OR MH:SP4.022.238.359$ OR MH:VS2.002.001.012$ OR MH:VS2.004.001.002.006$ OR MH:E02.319.162.150$ OR MH:E02.319.703.150$ OR MH:D27.505.954.122$ OR antibiotic$ OR "anti biotic" OR "anti biotics" OR antibacterial$ OR "anti bacterial" OR "anti bacterials" OR antimicrobial$ OR "anti microbial" OR "anti microbials" OR bacteriocidal$ OR antiseptic$ OR "anti septic" OR "anti septics" OR antiinfective$ OR "anti infective" OR "anti infectives" OR MH:D03.633.100.810.835.322$ OR fluoroquinolone$ OR ciprofloxacin$ OR fleroxacin$ OR enoxacin$ OR enrofloxacin$ OR gatifloxacin$ OR gemifloxacin$ OR moxifloxacin$ OR norfloxacin$ OR ofloxacin$ OR levofloxacin$ OR pefloxacin$ OR MH:D09.408.051$ OR aminoglycoside$ OR anthracycline$ OR "butirosin sulfate" OR "butirosin sulfates" OR calicheamicin$ OR gentamicin$ OR "hygromycin b" OR kanamycin$ OR metrizamide$ OR neomycin$ OR paromomycin$ OR puromycin $ OR spectinomycin$ OR streptomycin$ OR streptothricin$ OR streptozocin$ OR MH:D02.065.589.099.249$ OR MH:D02.886.665.074$ OR MH:D03.633.100.300.249$ OR cephalosporin$ OR cefamandole$ OR cefoperazone$ OR cefazolin$ OR cefdinir$ OR cefepime$ OR cefonicid $ OR cefsulodin$ OR ceftibuten$ OR cefuroxime$ OR cephacetrile$ OR cefotaxime$ OR cephalothin$ OR cephapirin$ OR cephalexin$ OR cefaclor$ OR cefadroxil$ OR cephaloglycin$ OR cephradine$ OR cephaloridine$ OR ceftazidime$ OR cephamycin$ OR cefmetazole$ OR cefotetan$ OR cefoxitin$ OR MH:D09.400.420$ OR MH:D12.644.233$ OR glycopeptide$ OR bleomycin$ OR peplomycin$ OR phleomycin $ OR lipoglycopeptide$ OR teicoplanin$ OR peptidoglycan$ OR ristocetin$ OR vancomycin$ OR MH:D12.644$ OR MH:D04.345.566$ OR MH:D12.644.641$ OR polypeptide$ OR "cyclic peptide" OR "cyclic peptides" OR alamethicin$ OR amanitin$ OR "alpha-amanitin" OR bacitracin$ OR capreomycin$ OR cyclosporin$ OR cyclosporine$ OR dactinomycin$ OR daptomycin$ OR depsipeptide$ OR valinomycin $ OR echinomycin$ OR enterobactin$ OR ferrichrome$ OR microcystin$ OR mycobacillin$ OR nisin$ OR octreotide$ OR phalloidine$ OR polymyxin$ OR colistin$ OR "polymyxin b" OR streptogramin$ OR mikamycin$ OR pristinamycin$ OR "vernamycin b" OR virginiamycin $ OR thiostrepton$ OR tyrothricin$ OR gramicidin$ OR tyrocidine$ OR viomycin$ OR enviomycin$ OR MH:D01.475.557.500$ OR MH:D02.455.326.271.884.533.710$ OR MH:D03.383.773.812.615.630$ OR MH:D05.750.716.721.838.745$ OR MH:D25.720.716.721.838.745$ OR MH:J01.637.051.720.716.721.838.745$ OR "povidone iodine" OR "PVP-I" OR "PVP Iodine" OR "polyvinylpyrrolidone iodine" OR betadine $ OR providine$ OR disadine$ OR isodine$ OR pharmadine$ OR alphadine$ OR betaisodona$)

Appendix 6. ClinicalTrials.gov search strategy

(Keratitis OR Keratoconjunctivitis OR ((cornea OR corneal) AND (melt OR infection OR microbial OR ulcer OR inflammation))) AND (antibiotic OR antibacterial OR antiseptic OR antiinfective OR fluoroquinolone OR ciprofloxacin OR fleroxacin OR enoxacin OR enrofloxacin OR gatifloxacin OR gemifloxacin OR moxifloxacin OR norfloxacin OR ofloxacin OR levofloxacin OR pefloxacin OR aminoglycoside OR anthracycline OR "butirosin sulfate" OR calicheamicin OR gentamicin OR "hygromycin b" OR kanamycin OR metrizamide OR neomycin OR paromomycin OR puromycin OR spectinomycin OR streptomycin OR streptothricin OR streptozocin OR cephalosporin OR cefamandole OR cefoperazone OR cefazolin OR cefdinir OR cefepime OR cefonicid OR cefsulodin OR ceftibuten OR cefuroxime OR cephacetrile OR cefotaxime OR cephalothin OR cephapirin OR cephalexin OR cefaclor OR cefadroxil OR cephaloglycin OR cephradine OR cephaloridine OR ceftazidime OR cephamycin OR cefmetazole OR cefotetan OR cefoxitin OR glycopeptide OR bleomycin OR peplomycin OR phleomycin OR lipoglycopeptide OR teicoplanin OR peptidoglycan OR ristocetin OR vancomycin OR polypeptide OR "cyclic peptide" OR alamethicin OR amanitin OR "alpha-amanitin" OR bacitracin OR capreomycin OR cyclosporin OR cyclosporine OR dactinomycin OR daptomycin OR depsipeptide OR valinomycin OR echinomycin OR enterobactin OR ferrichrome OR microcystin OR mycobacillin OR nisin OR octreotide OR phalloidine OR polymyxin OR colistin OR "polymyxin b" OR streptogramin OR mikamycin OR pristinamycin OR "vernamycin b" OR virginiamycin OR thiostrepton OR tyrothricin OR gramicidin OR tyrocidine OR viomycin OR enviomycin OR "povidone-iodine")

Appendix 7. ICTRP search strategy

Keratitis OR Keratoconjunctivitis OR cornea AND melt OR cornea AND infection OR cornea AND microbial OR cornea AND ulcer OR cornea AND inflammation OR corneal AND melt OR corneal AND infection OR corneal AND microbial OR corneal AND ulcer OR corneal AND inflammation

CONTRIBUTIONS OF AUTHORS

Study conceptualization: DT
Drafting the protocol: DT, RQ
Revising the protocol and approving it for submission: DT, CH, CB, RQ

DECLARATIONS OF INTEREST

DT: none
CH: none
CB: none
RQ: has done consulting work contributing to the development of PICO Portal (system to be used for screening).

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Medical Research Council / Fight for Sight Clinical Research Fellowship, UK

  D.S.J.T. acknowledges support from the Medical Research Council / Fight for Sight Clinical Research Fellowship (MR/T001674/1).
- National Eye Institute, National Institutes of Health, USA

  Cochrane Eyes and Vision US Project, supported by grant UG1EY020522 (PI: Tianjing Li, MD, MHS, PhD).
- Queen's University Belfast, UK

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