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Head-to-head oral prophylactic antibiotics therapy for chronic obstructive pulmonary disease (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Head-to-head oral prophylactic antibiotics therapy for chronic obstructive pulmonary disease

Christopher JD Threapleton[1], Rebecca Normansell[2], Emma H Baker[1]

[1]Clinical Pharmacology, St George's, University of London, London, UK. [2]Cochrane Airways, Population Health Research Institute, St George's, University of London, London, UK

Contact address: Rebecca Normansell, Cochrane Airways, Population Health Research Institute, St George's, University of London, London, SW17 0RE, UK. rnormans@sgul.ac.uk, r_normansell@hotmail.com.

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ABSTRACT

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

To examine the effect of different classes of antibiotics for prophylaxis of exacerbations in patients with COPD.

BACKGROUND

Description of the condition

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (GOLD 2018). Diagnosis is established by typical symptoms, risk factors and spirometry. Typical symptoms consist of dyspnoea, cough with sputum production and recurrent lower respiratory tract infections. The most prevalent risk factor is tobacco smoke; other environmental risk factors include smoke from home cooking and heating fuels, and occupational dust; host factors include genetic conditions such as alpha1 antitrypsin deficiency. The spirometric criterion for COPD is a post-bronchodilator fixed ratio of forced expiratory volume in one second/forced vital capacity (FEV1/FVC) < 0.70 (GOLD 2018).

The impact of COPD on world health is substantial. The number of cases of COPD worldwide has increased from approximately 227.3 million in 1990 to 384 million in 2010, with a global prevalence rising from 10.7% to 11.7% (Adeloye 2015). It is the fourth leading cause of death and is predicted to rise to third place by 2020 (GOLD 2018), or 2030 (WHO 2018). COPD is characterised by frequent exacerbations and lower respiratory tract infections, which further increase the risk of mortality (Schmidt 2014; Suissa 2012). Exacerbations also impact on exercise tolerance, quality of life and muscle strength; and are associated with a faster decline in lung function (Cote 2007; Donaldson 2008; Kessler 2006; Miravitlles 2004; Niewoehner 2006; Seemungal 1998; Wüst 2007). Exacerbations are associated with systemic, upper and lower airway inflammation (Hurst 2006). It is likely that the aetiology of exacerbations is multifactorial, with inflammation caused by bacteria, viruses and environmental pollutants (Beasley 2012). The aetiology of a particular exacerbation is not

always clear. Whilst antibiotics are frequently used to treat COPD exacerbations, and bacterial pathogens are isolated from approximately half of patients with an exacerbation (Kuwal 2018, Llor 2006, Sethi 2004), they are also commonly isolated in patients with stable COPD (Sethi 2008). A network analysis of the lung microbiome of COPD patients demonstrated that a reduction in microbial diversity and the proliferation of a single organism were associated with exacerbation events (Wang 2016). It has been hypothesised that lungs of people with COPD are more susceptible to bacteria, which are not normally present in healthy lungs (Rosell 2005). This chronic bacterial presence contributes to a vicious cycle of inflammation, enhances mucus secretion and worsens ciliary activity, leading to further epithelial damage (Matkovic 2013; Sethi 2008).

Description of the intervention

There are a number of strategies available that are effective at reducing COPD exacerbations, including patient self-management training (Zwerink 2014); pulmonary rehabilitation (McCarthy 2015; Puhan 2016); inhaled corticosteroids (Yang 2012); inhaled long-acting muscarinic antagonists (Chong 2012); and roflumilast, a phosphodiesterase 4 inhibitor (Chong 2013). An additional treatment consideration in an attempt to reduce the frequency of exacerbations of COPD, and reverse this potential 'vicious circle' of inflammation is the use of long-term antibiotics as prophylaxis. Prophylatic antibiotics are usually given by mouth, but may also be delivered via other routes, including inhalation. This review will examine the use of head-to-head oral antibiotics only. Depending on the type of antibiotic, regimens include daily, three times a week or 'pulsed' (e.g. daily administration for several days followed by a break) administration (BNF).

A Cochrane Review analysed 3170 patients in seven RCTs published between 2001 and 2011 (Herath 2013). The authors investigated the effects of macrolides (azithromycin, erythromycin, clarithromycin) and moxifloxacin (a fourth-generation synthetic fluoroquinolone) compared with placebo. The use of long-term prophylactic antibiotics was associated with significantly fewer patients who experienced an exacerbation of COPD (odds ratio 0.55) compared with those receiving placebo. However patients on prophylactic antibiotics were more likely to experience adverse effects, such as hearing loss with azithromycin and gastrointestinal symptoms with moxifloxacin.

How the intervention might work

The effect of prophylactic antibiotics is not completely understood. Antibiotics may offer both anti-bacterial and anti-inflammatory effects (Martinez 2008), and therefore may reduce both bacterial load and inflammation as a result of exacerbations from bacteria, viruses and environmental pollution. Choice of prophylactic antibiotic may be guided by factors including clinician and patient preference and prior experience, previously isolated bacteria and side effect profile. Organisms isolated from exacerbating patients include *Haemophilus influenzae* (11% of all patients), *Streptococcus pneumoniae* (10%), *Moraxella catarrhalis* (10%), *Haemophilus parainfluenzae* (10%), and *Pseudomonas aeruginosa* (4%) (Sapey 2006).

Prophylactic antibiotics may be of greatest benefit in a subset of patients (Miravittles 2015). A 2011 study by Albert and colleagues suggests that compared to placebo, azithromycin (a macrolide antibiotic) reduces exacerbations most markedly in older patients, non-smokers and those not using oral or inhaled steroids at baseline, which may reflect sub-optimal treatment (Albert 2011). We have specified several subgroup analyses which we will conduct to explore this in the context of head-to-head antibiotics, if we identify sufficient evidence to do so.

Why it is important to do this review

COPD represents a huge burden, to both the patient (Cote 2007; Kessler 2006) and healthcare services (López-Campos 2016; Mannino 2015; Punekar 2014). Therefore it is important to assess treatments that may reduce the risk of exacerbations and improve quality and longevity of life of patients with COPD.

This review builds upon a Cochrane Review comparing prophylactic antibiotics with placebo (Herath 2013), currently being updated, and will be complemented by a network meta-analysis which is under development. Whilst there is evidence that antibiotic prophylaxis is efficacious in people with COPD, there remains a large concern over the risk of antibiotic resistance (Miravittles 2017; Thurston 2013). It is therefore imperative to identify which antibiotic provides the best prophylaxis against exacerbations of COPD and least evidence of antibiotic resistance and adverse effects.

OBJECTIVES

To examine the effect of different classes of antibiotics for prophylaxis of exacerbations in patients with COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include cross-over trials providing there is an adequate wash-out period (at least three months) and cluster randomised trials. We will include studies reported in full text, those published as an abstract only and unpublished data.

Types of participants

We will include adults (older than 18 years of age) with a diagnosis of COPD according to established criteria (e.g. European Respiratory Society (ERS), American Thoracic Society (ATS) or GOLD criteria). We will exclude participants with the following co-morbidities/characteristics: bronchiectasis; asthma; or genetic diseases such as cystic fibrosis or primary ciliary dyskinesia. However, we recognise that disease definitions change over time and if older studies are identified we will consider the directness of the evidence when applying GRADE. If we identify trials in which only a subset of the participants have COPD we will include them providing disaggregated data is provided or can be obtained from the trial authors. We will include participants irrespective of vaccination status (e.g. pneumococcal vaccination), providing vaccination is not part of the randomised treatment.

Types of interventions

We will include studies comparing one prophylactic oral antibiotic with another. We will exclude studies where the comparison group receive a placebo or usual care not involving a prophylactic antibiotic. To be eligible, studies must randomise participants to receive the antibiotic for at least 12 weeks, either continuously or pulsed. Pulsed antibiotics must be given for a minimum of five consecutive days every eight weeks. We will exclude studies which deliver antibiotics via a nebuliser, inhaler, intravenously or intramuscularly.

We will include the following co-interventions provided they are not part of the randomised treatment: short- and long-acting bronchodilators, inhaled corticosteroids, oral corticosteroids, oxygen, pulmonary rehabilitation, smoking cessation interventions or any other standard treatment for COPD.

We will consider the following comparisons.

1. Macrolides (e.g. azithromycin) versus other antibiotic classes
2. Quinolones (e.g. moxifloxacin) versus other antibiotics classes
3. Macrolides versus quinolones
4. Macrolides versus penicillins (e.g. amoxicillin)
5. Macrolides versus tetracyclines (e.g. doxycycline)

If we identify studies comparing different regimens of the same prophylactic antibiotic (e.g. azithromycin 250 mg daily versus azithromycin 500 mg three times/week) we will include these studies but consider them separately from the above comparisons. Similarly, if we identify studies that compare two antibiotics within the same class (e.g. moxifloxacin versus ciprofloxacin, both quinolones) we will include them but consider them separately from the above comparisons.

Types of outcome measures

Primary outcomes

1. Exacerbations (as defined by trialists and grouped by exacerbation severity where possible, e.g. those requiring hospitalisation versus those requiring ambulatory management only). Depending on the available data, we will extract either the number of participants experiencing one or more exacerbation, or the exacerbation rate, or both.
2. Quality of life (validated scales such as the St George's Respiratory Questionnaire preferred)
3. Drug resistance/microbial sensitivity (as reported by trialists), including emergence of atypical bacteria
4. Serious adverse events

Primary outcomes are considered to be the most important to patients, health care providers and policy makers. Specific adverse events reported by trialists (e.g. episodes of *Clostridium difficile*, tendon rupture, hearing difficulties) will be extracted and summarised narratively.

Secondary outcomes

1. Lung function (FEV1 and FVC)
2. Mortality (respiratory and all-cause mortality will be analysed separately where possible)
3. Hospitalisations
4. Adverse events/side effects
5. Number of participants colonised with *Pseudomonas aeruginosa*

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review.

If outcomes are reported at multiple time points, the latest reported time point/end-of-treatment data will be extracted. We will group outcomes reported at 3 months or more to less than 6 months; 6 months to less than 12 months; and 12 months or more. If post-treatment follow-up is reported this will be extracted and analysed separately.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group.

The Cochrane Airways Trials Register contains studies identified from several sources, as follows.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org).
2. Weekly searches of MEDLINE Ovid SP 1946 to date.
3. Weekly searches of Embase Ovid SP 1974 to date.
4. Monthly searches of PsycINFO Ovid SP 1967 to date.
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date.
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine).
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We will search the following trials registries.

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov).
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will search the Cochrane Airways Trials Register and additional sources from inception to present, with no restriction on language of publication.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for study information.

We will search for errata or retractions from included studies published in full text on PubMed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (CT and RN) will screen the titles and abstracts of the search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (CT and RN) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (EB). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (CT) will extract the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported. We will seek and record definitions used to diagnose an exacerbation.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (CT and RN) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (EB). One review author (CT) will transfer data into the Review Manager file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (RN) will spot-check study characteristics for accuracy against the study report.

We will produce a table summarising the key characteristics of each study, including region, baseline characteristics of participants, size of study, antibiotic regimens investigated and the reported effect, thus facilitating comparison across studies.

Assessment of risk of bias in included studies

Two review authors (CT and RN) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (EB). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.

7. Other bias.

We will judge each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported quality-of-life scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). If data from rating scales are combined in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement). We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus drug B and drug C versus drug B) are combined in the same meta-analysis, we will either combine the 'active' arms or halve the 'control' group to avoid double-counting.

If adjusted analyses are available (ANOVA or ANCOVA) we will use these as a preference in our meta-analyses. If both 'change from baseline' and endpoint scores are available for continuous data then we will use 'change from baseline', as correlation is expected between measurements in individuals. If a study reports outcomes at multiple time points, we will use the latest reported time point in meta-analysis.

We will use intention-to-treat (ITT) or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, if rate ratios are reported in a study (e.g. for exacerbations), we will analyse them on this basis. We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted), to account for the clustering. We will enter data from cross-over trials using generic inverse variance and with the help of a statistician.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We will use a random-effects model and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: exacerbations of COPD, quality of life, serious adverse events, mortality, lung function (FEV1), hospitalisations, antibiotic resistance. We will use the five GRADE considerations (risk of bias; consistency of effect; imprecision; indirectness; and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Exacerbation history: trials recruiting participants with a group mean of less than one versus one to two versus more than two exacerbations in the preceding year
2. COPD severity: participants classed as predominantly GOLD group 1 or 2 versus those predominantly GOLD group 3 or 4
3. Studies with more than 70% on LABA/LAMA/ICS at baseline versus those with less than 70% on LABA/LAMA/ICS at baseline

We will use the following outcomes in subgroup analyses.

1. Participants having one or more exacerbation
2. Quality of life
3. Serious adverse events

We will use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses, removing the following from the primary outcome analyses.

1. Studies judged to be at high risk of bias in one or more domains
2. Cross-over trials

We will compare the results from a fixed-effect model with the random-effects model.

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Ian Yang was the Editor for this review and commented critically on the review.

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Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012;**67**:957–63. DOI: 10.1136/thoraxjnl-2011-201518

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group's Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly

(*Continued*)

PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify studies for the CAGR

Condition search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/

14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15
17. exp Aspergillosis, Allergic Bronchopulmonary/
18. lung diseases, fungal/
19. aspergillosis/
20. 18 and 19
21. (bronchopulmonar$ adj3 aspergillosis).mp.
22. 17 or 20 or 21
23. 16 or 22
24. Lung Diseases, Obstructive/
25. exp Pulmonary Disease, Chronic Obstructive/
26. emphysema$.mp.
27. (chronic$ adj3 bronchiti$).mp.
28. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
29. COPD.mp.
30. COAD.mp.
31. COBD.mp.
32. AECB.mp.
33. or/24-32
34. exp Bronchiectasis/
35. bronchiect$.mp.
36. bronchoect$.mp.
37. kartagener$.mp.
38. (ciliary adj3 dyskinesia).mp.
39. (bronchial$ adj3 dilat$).mp.
40. or/34-39
41. exp Sleep Apnea Syndromes/
42. (sleep$ adj3 (apnea$ or apnoea$)).mp.
43. (hypopnoea$ or hypopnoea$).mp.
44. OSA.mp.
45. SHS.mp.
46. OSAHS.mp.
47. or/41-46
48. Lung Diseases, Interstitial/
49. Pulmonary Fibrosis/
50. Sarcoidosis, Pulmonary/
51. (interstitial$ adj3 (lung$ or disease$ or pneumon$)).mp.
52. ((pulmonary$ or lung$ or alveoli$) adj3 (fibros$ or fibrot$)).mp.
53. ((pulmonary$ or lung$) adj3 (sarcoid$ or granulom$)).mp.
54. or/48-53
55. 23 or 33 or 40 or 47 or 54

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised 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. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify studies in other electronic databases.

Appendix 2. Search strategy to identify relevant studies from the Cochrane Airways Trials Register

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MESH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL
#8 antibiotic* NEAR prophyla*
#9 continuous NEAR antibiotic*
#10 antibiotic*
#11 penicillin
#12 phenoxymethylpenicillin
#13 phenethicillin
#14 amoxicillin
#15 amoxycillin
#16 clavulanic acid
#17 tetracycline
#18 oxytetracycline
#19 doxycycline
#20 quinolone
#21 ciprofloxacin
#22 moxifloxacin
#23 macrolide*
#24 erythromycin
#25 roxithromycin
#26 azithromycin
#27 sulphonamide
#28 co-trimoxazole
#29 sulphaphenazole
#30 trimethoprim
#31 sigmamycin
#32 tetracycline AND oleandomycin
#33 sulfamethoxazole
#34 sulfaphenazole
#35 sulfonamide
#36 anti-bacteri* or antibacteri*
#37 ceph*
#38 sulpha*
#39 {OR #7-#38}
#40 #39 AND #6

CONTRIBUTIONS OF AUTHORS

CT: drafting of background and methods of protocol. Sifting, data extraction, risk of bias assessment and write-up of full review.

RN: drafting of background and methods of protocol. Sifting, data extraction, risk of bias assessment and write-up of full review.

EB: conceptual and clinical advice on protocol. Arbitrating conflicts, analysis and interpretation, approval of final draft of full review.

DECLARATIONS OF INTEREST

CT is employed part-time by an NIHR Programme Grant to complete work on this review and is an academic clinical fellow in pharmacology.

RN is employed part-time by an NIHR Programme Grant to complete work on this review and is a qualified general practitioner.

EB is a consultant clinical pharmacologist.

SOURCES OF SUPPORT

Internal sources

- Christopher Threapleton, UK.

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