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Shorter versus longer durations of antibiotic treatment for patients with community-acquired pneumonia: a protocol for a systematic review and meta-analysis

Arnav Agarwal ,[1,2] Ya Gao ,[3] Luis Enrique Colunga Lozano,[4] Saad Asif,[5] Layla Bakaa,[6] Maryam Ghadimi,[2] John Basmaji,[7] Aninditee Das,[8] Mark Loeb,[2,5] Gordon Guyatt[2,5]

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For numbered affiliations see end of article.

Correspondence to
Professor Gordon Guyatt;
guyatt@mcmaster.ca

ABSTRACT

Introduction Community-acquired pneumonia (CAP), frequently encountered in both outpatient and inpatient settings, is the leading cause of infectious disease-related mortality. While equipoise regarding the optimal duration of antimicrobial therapy to treat CAP remains, recent studies suggest shorter durations of therapy may achieve optimal outcomes. We have therefore planned a systematic review and meta-analysis evaluating the impact of shorter versus longer durations of antibiotic therapy for patients with CAP.

Methods and analysis We searched Ovid MEDLINE, Embase, CINAHL and Cochrane Central Register of Controlled Trials from inception to September 2021 for randomised controlled trials evaluating shorter versus longer duration of antibiotics. Eligible studies will compare durations with a minimum difference of two days of antibiotic therapy, irrespective of antibiotic agent, class, route, frequency or dosage, and will report on any patient-important outcome of benefit or harm. Paired reviewers working independently will conduct title and abstract screening, full-text screening, data extraction and risk of bias (RoB) evaluation using a modified Cochrane RoB 2.0 tool. We will perform random-effects modelling for meta-analyses, with study weights generated using the inverse variance method, and will assess certainty in effect estimates using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) tool will inform assessments of credibility of subgroup effects based on severity of illness, drug class, duration of therapy, setting of CAP acquisition and RoB.

Ethics and dissemination The results will be of importance to general practitioners and internists managing CAP, and may directly inform international clinical guidance. Where concerns regarding antimicrobial resistance continue to grow internationally, this evidence summary may motivate new recommendations regarding shorter durations of therapy. We intend to disseminate our findings via national and international conferences, and publication in a peer-reviewed journal.

PROSPERO registration number CRD42021283990.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The planned systematic review will summarise all available evidence relevant to antibiotic duration for community-acquired pneumonia, irrespective of setting (outpatient or inpatient) and severity of illness, with a planned subgroup analysis to address possible effect modification by disease severity.
⇒ The review will use a comprehensive search strategy supplemented by reference list screening, will incorporate both published and unpublished data, and will have predefined frameworks for screening, extraction, statistical analysis and subgroup analysis.
⇒ The review will evaluate all patient-important outcomes with available data, and will not be limited to prespecified outcomes of interest.
⇒ The review will use a validated risk of bias tool, GRADE methodology to systematically evaluate certainty in effect estimates, and the ICEMAN tool to evaluate credibility of subgroup effects.
⇒ We have no plans to contact authors about issues of inadequate reporting or confirmation regarding our data abstraction or risk of bias assessments.

INTRODUCTION

Community-acquired pneumonia (CAP) is among the most common illnesses managed in the outpatient setting, frequently requires hospital admission, and constitutes one of the most common indications for antibiotic prescriptions.[1–4] It is the leading cause of infectious disease-related mortality in high-income countries.[5] There remains equipoise regarding the optimal duration of antimicrobial therapy to treat CAP in both inpatient and outpatient settings.

Although CAP has traditionally been treated for at least seven days,[6 7] clinicians are now considering shorter duration of therapy. Guidance from the American Thoracic

Society and Infectious Diseases Society of America published in 2019 provided a strong recommendation, based on moderate-quality evidence, for at least five days of therapy, and continuation of therapy until the patient achieves clinical stability[5] ; guidelines from the American College of Physicians published in 2021 recommended the same.[8] This shift is in keeping with evolving evidence over two decades, which has suggested optimal outcomes may require only five days of therapy.[9–11]

Recent randomised controlled trials (RCTs) have compared three versus eight days of therapy in both outpatients and those requiring hospital admission for CAP, and have reported satisfactory outcomes of clinical improvement and stability, improved adherence and fewer adverse effects in those receiving the shorter duration.[12–20] Whether these trials will motivate a change in recommendations remains uncertain.

Shortened duration of antimicrobial therapy may reduce the emergence of antimicrobial resistance, individual and healthcare system-related costs, antibiotic-related side effects and risk of bacterial superinfection. Short courses may, however, be associated with recurrent or refractory illness, and relatedly greater individual and healthcare system-related costs.[21]

Although previous systematic reviews, and overviews of reviews, have examined shorter versus longer duration of therapy for CAP,[10 11 22–26] they have not evaluated durations less than five days,[11 23 25] or are limited to a comparison of two durations with the same drug across arms.[26] A recent review by Tansarli and colleagues in 2018 found no significant difference in clinical cure, fewer adverse events and lower mortality associated with shorter (≤six days) versus longer courses of therapy (≥seven days), irrespective of patient setting or severity of pneumonia. Subgroup analyses comparing three versus five days of therapy found no significant difference in clinical cure or relapse rates.[10]

An updated synthesis of evidence may motivate a change in evidence-based clinical guidance. We therefore plan to conduct a systematic review and meta-analysis evaluating the impact of shorter versus longer durations of antibiotic therapy for patients with CAP, including recent RCT evidence comparing durations less than five days with longer courses of treatment.

METHODS AND ANALYSIS

This protocol adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-Protocols standards. We will adhere to the PRISMA checklist for reporting our systematic review and meta-analysis (online supplemental material 1). Our protocol has been registered on PROSPERO (CRD42021283990).

Search strategy

With the aid of a medical librarian, we have conducted a systematic search of the published literature in four electronic databases from inception to present: Ovid MEDLINE (1946–September 2021), Embase (1947–September 2021), CINAHL (1982–September 2021) and the Cochrane Central Register of Controlled Trials (1991–September 2021).

Search terms include a combination of keywords and medical subject heading terms: “duration of therapy”, “vs”, “days”, “extended”, “limited”, “shorter”, “longer”, “pneumonia, “respiratory tract infection”, “antibiotic”, “randomized controlled trial” (online supplemental material 2). We did not apply language restrictions in our search.

We will supplement our search by reviewing bibliographies of review articles and eligible trials for additional studies not identified by the electronic searches.

Eligibility criteria

We will include parallel arm RCTs or quasi-randomised studies.

Studies including adults aged 18 years of age or older with a diagnosis of CAP will be eligible. We will accept investigator-defined definitions of CAP, including clinical (confirmed based on signs and symptoms) and radiologically established diagnoses. All severities of CAP will be eligible, including mild, moderate, severe and critical illness. We will not limit eligibility to ‘uncomplicated’ or ‘complicated’ pneumonia, regardless of definition. Studies undertaken in the outpatient setting, and those in hospitalised patients, will both be eligible. Studies involving patients with immunocompromise or other comorbidities will be eligible. We will not limit to specific implicated organisms, and will include both typical and atypical pneumonias and both empirical and pathogen-directed therapies. Pneumonia acquired in other congregate settings such as long-term care facilities and retirement homes will be eligible.

We will exclude studies addressing hospital-acquired pneumonia and those enrolling only patients with Pneumocystis pneumonia. We will include studies enrolling patients we do not consider eligible (eg, under 18 years, having Pneumocystis pneumonia) if the proportion of such patients is 20% or less, or if authors report separately on our population of interest.

We will include studies with at least one arm with antibiotics for a shorter duration, compared with at least one arm with antibiotics for a longer duration. Eligible studies will involve a minimum difference of two days in duration of therapy between two or more arms, without requirement that the shorter and longer duration arms use the same antibiotic regimens, and without restriction regarding frequency, dosage or route of administration.

Eligible studies will report at least one patient-important outcome including, but not limited to, clinical cure or response, overall and pneumonia-related mortality, need for and duration of hospitalisation, need for and duration of intensive care unit admission, hospital readmission, invasive ventilation, relapse, serious adverse events leading to discontinuation and all adverse events.

We will include articles meeting eligibility criteria, irrespective of publication status; specifically, we will include grey literature and conference abstracts.

Study selection

Paired reviewers will independently conduct title and abstract and full-text screening using pretested, standardised screening forms with accompanying instructions. Reviewers will resolve disagreements by discussion; as necessary, a third reviewer (AA) will adjudicate. We will use Covidence (https://covidence.org/) for screening.

Data extraction and risk of bias

Paired reviewers will independently extract data and evaluate risk of bias using pretested, standardised extraction forms with accompanying instructions, resolving disagreements by discussion; if necessary, a third reviewer (AA) will adjudicate.

We will extract data on population, interventions, comparators and outcomes of interest. For population, extracted data will include: setting (outpatient vs admission to hospital at baseline); initial severity of illness (mild vs moderate vs severe vs critical); cointerventions; antibiotic administered; dosing, route of administration and frequency; compliance with therapy; radiographic findings and sputum culture positivity.

We will evaluate risk of bias using the modified Cochrane risk of bias 2.0, with judgements classified as 'low', 'probably low', 'probably high' or 'high' for the following domains: bias due to randomisation, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result and bias due to competing risks. We will assess risk of bias by outcome.

Certainty of the evidence

We will consider the overall certainty in evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, based on the following domains: risk of bias, imprecision, inconsistency, indirectness and publication bias. Overall certainty of evidence will be rated as 'very low', 'low', 'moderate' or 'high'. We will consider rating down the certainty of evidence for risk of bias based on lack of blinding for subjective outcomes only.[27–29] We will address missing data as part of risk of bias assessments based on a previously published approach.[30]

Statistical analysis

Given significant variation in patients and interventions may be present, we plan to conduct random-effects modelling for our primary meta-analyses (Cochrane Collaboration, Oxford). In instances where random effects give counterintuitive results, in particular large differences between small and larger studies, we will switch to fixed-effect modelling. All analyses will be performed in RevMan version 5.3 (Cochrane Collaboration, Oxford).

Study weights will be generated using the inverse variance method. We will present dichotomous outcomes as risk ratios, with absolute effects calculated to facilitate interpretation. Baseline risk will be inferred from median values for a given outcome from the control group. We will present continuous outcomes as mean differences or standardised mean differences, all with 95% CIs. We will assume a normal distribution for continuous outcomes, and will convert IQRs to SDs as per guidance from the Cochrane Collaboration. We will assess heterogeneity between studies using the χ^2 test for homogeneity, I^2 measure and visual inspection of the forest plots.

If sufficient data are available, we will plan the following subgroup analyses:

1. Severity of illness: mild versus moderate versus severe versus critical (hypothesis: larger benefit in the longer duration group with increasingly severe disease).
2. Drug class: comparisons in which arms receive agents belonging to the same drug class versus comparisons in which arms receive agents belonging to different drug classes (hypothesis: differences will be greater when the drug classes differ between arms).
3. Shorter durations of therapy: 1 day vs 3 days vs 5 days vs 7 days (all compared with longer durations) (hypothesis: differences will be greater with comparisons involving shorter duration in the shorter duration arm).
4. Setting: nursing home-acquired pneumonia versus pneumonia acquired in other community settings (hypothesis: differences will be greater in studies including patients with nursing home-acquired pneumonia).
5. Risk of bias: low versus high risk of bias studies (hypothesis: differences will be greater in high risk of bias studies).

We will classify patients requiring hospitalisation without intensive care unit-level care as severe illness, and those requiring intensive care unit-level care, vasopressors and/or mechanical ventilation as critical illness.

We will rate the credibility of effect modification analyses using the Instrument for assessing the Credibility of Effect Modification Analyses tool.[31]

Ethics and dissemination

Ethics approval is not required for this systematic review. We plan to disseminate our results through national and international clinical and methods conferences. We also plan to publish our findings in a peer-reviewed journal widely accessed by general practitioners and internists.

Patient and public involvement

The research question was developed with a focus on all patient-important outcomes. Patients and members of the public were not directly involved in the design of this review.

DISCUSSION

The publication of multiple RCTs evaluating three days of antibiotic therapy compared with longer durations

for the treatment of CAP warrants an updated evidence synthesis to inform guideline recommendations and clinical practice.

Our planned systematic review has a number of strengths. First, we will summarise evidence relevant to CAP irrespective of whether treatment is initiated in the outpatient or inpatient setting. Our evaluation will therefore address the effectiveness of shorter versus longer duration across the spectrum of mild to critical illness, with a planned subgroup analysis to address possible effect modification by disease severity. Second, our analysis will account for both interclass and intraclass antibiotic comparisons. Third, we will evaluate all patient-important outcomes and will not limit our analysis *a priori* to specific outcomes, maximising the available information to guide clinical practice. Fourth, we have used a comprehensive search strategy developed with the aid of a medical librarian, have incorporated both published and unpublished data, and have predefined screening, extraction, statistical analysis and subgroup analysis plans. To ensure comprehensive identification of all eligible literature, we will screen the reference lists of previously conducted systematic reviews. We intend to use a validated risk of bias tool and GRADE methodology to systematically evaluate certainty in effect estimates.

In conclusion, this protocol describes the detailed methodology of a planned systematic review and meta-analysis addressing shorter versus longer durations of antibiotic therapy for CAP. The results will be of importance to general practitioners and internists managing CAP, and may directly inform international clinical guidance. Particularly, given growing concerns regarding antimicrobial resistance, should shorter and longer courses prove similar in their impact on patient-important outcomes, the new evidence may result in new recommendations for shorter durations of therapy.

Author affiliations
[1]Division of General Internal Medicine, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[2]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[3]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu, China
[4]Department of Clinical Medicine, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico
[5]Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[6]Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, Ontario, Canada
[7]Division of Critical Care, Department of Medicine, Western University, London, Ontario, Canada
[8]Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

Twitter Arnav Agarwal @DrArnavAgarwal

Contributors AA and GG drafted the protocol. All coauthors (AA, YG, LECL, SA, LB, MG, JB, AD, ML and GG) reviewed the protocol, provided critical revisions and approved the final version. GG is the guarantor of the review.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Arnav Agarwal http://orcid.org/0000-0001-5780-725X
Ya Gao http://orcid.org/0000-0002-9280-4457

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Supplement 1: PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	-
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	51
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-23
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	243-245
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	246-247
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	246-247
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	-
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	69-102
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	102-104

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	123-150
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	112-116
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	117-122
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	151-155
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	151-155
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	156-164
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	156-164
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	144-148
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	165-176
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	-
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	177-190
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	191-209
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	☒	☐	170-176

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	170-176

Supplement 2: Search strategy

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:
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1 exp Drug Administration Schedule/
2 ad.fs.
3 "Duration of Therapy"/
4 (versus or vs).ti.
5 (?day or day or days).ti.
6 (extended or limited or shortened or short or long or longer or course or duration).ti,ab.
7 or/1-6
8 exp Pneumonia/
9 Respiratory Tract Infections/
10 Pneumonia, Pneumococcal/
11 Pleuropneumonia/
12 (pneumon* or bronchopneumon* or pleuropneumon*) mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13 (respiratory adj2 infection*).mp.
14 or/8-13
15 exp Anti-Bacterial Agents/
16 (antimicrobial or antibiotic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17 Tetracycline/ or tetracycline*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18 exp Lincosamides/ or lincosamide*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
19 exp Macrolides/ or macrolide*.mp.
20 Ketolides/ or Ketolide*.mp.
21 exp Aminoglycosides/ or Aminoglycoside*.mp.
22 exp Oxazolidinones/ or Oxazolidinone*.mp.
23 exp Glycopeptides/ or Glycopeptide*.mp.
24 exp beta-Lactams/ or Beta-lactam*.mp.

25 exp Penicillins/ or Penicillin*.mp.
26 Carbapenem*.mp. or exp Carbapenems/
27 exp Cephalosporins/ or Cephalosporin*.mp.
28 exp Monobactams/ or Monobactam*.mp.
29 exp Folic Acid Antagonists/ or Antifolate*.mp.
30 exp sulfonamide/ or Sulfonamide*.mp.
31 exp Fluoroquinolones/ or Fluoroquinolone*.mp.
32 (Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
33 (Aztreonam or Aztreonam-avibactam or Lefamulin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
34 (Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or Cefozopran or Cefpirome or Ceftobiprole or Ceftolozane or Carumonam or Nocardicin A).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
35 (Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

36 (levofloxacin or Ciprofloxacin or Moxifloxacin or Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
37 (Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
38 (Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
39 (Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin orMidecamycin or Miocamycin or Rokitamycin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
40 (Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
41 (Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
42 (Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword

heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
43 (Metronidazole or Tinidazole or Ornidazole).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
44 (Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
45 (Rifampicin or Rifabutin or Rifapentine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
46 or/15-45
47 7 and 14 and 46
48 randomized controlled trial.pt.
49 controlled clinical trial.pt.
50 random:.tw. or placebo:.mp. or double-blind:.tw.
51 ((treatment or control) adj3 group*).ab.
52 (allocat* adj5 group*).ab.
53 ((clinical or control*) adj3 trial).ti,ab,kw.
54 or/48-53
55 exp animals/ not humans.sh.
56 54 not 55
57 47 and 56

EMBASE (OVID)

Search Strategy:

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1 drug dose/ or dosage schedule comparison/ or drug dose comparison/ or drug dose titration/ or optimal drug dose/
2 treatment duration/
3 cm.fs.
4 ct.fs.
5 cb.fs.
6 (duration or course or extended or limited or shortened or shot or long or longer).ti,ab.
7 (versus or vs).ti.
8 (?day or day or days).ti.
9 or/1-8
10 *pneumonia/
11 pneumonia.ti.
12 10 or 11
13 9 and 12
14 tetracycline/ or tetracycline*.mp.
15 lincosamide/ or lincosamide*.mp.
16 exp macrolide/ or macrolide*.mp.
17 exp ketolide/ or Ketolide*.mp.
18 aminoglycoside/ or Aminoglycoside*.mp.
19 oxazolidinone derivative/ or Oxazolidinone*.mp.
20 exp glycopeptide/ or Glycopeptide*.mp.
21 exp beta lactam antibiotic/ or Beta-lactam*.mp.
22 Penicillin*.mp. or exp penicillin derivative/
23 carbapenem derivative/ or Carbapenem*.mp.
24 exp cephalosporin derivative/ or Cephalosporin*.mp.
25 exp monobactam derivative/ or Monobactam*.mp.
26 exp folic acid antagonist/
27 sulfonamide/ or Sulfonamide*.mp.
28 Fluoroquinolone*.mp.
29 (Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

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43 (antibiotic or anti biotic or antimicrobial).mp.
44 exp antibiotic agent/
45 or/14-44
46 13 and 45
47 randomized controlled trial/
48 Controlled clinical study/
49 random$.ti,ab.
50 randomization/
51 intermethod comparison/
52 placebo.ti,ab.
53 (compare or compared or comparison).ti.
54 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
55 (open adj label).ti,ab.
56 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

57 double blind procedure/
58 parallel group$1.ti,ab.
59 (crossover or cross over).ti,ab.
60 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
61 (assigned or allocated).ti,ab.
62 (controlled adj7 (study or design or trial)).ti,ab.
63 (volunteer or volunteers).ti,ab.
64 human experiment/
65 trial.ti.
66 or/47-65
67 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
68 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
69 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
70 (Systematic review not (trial or study)).ti.
71 (nonrandom$ not random$).ti,ab.
72 "Random field$".ti,ab.
73 (random cluster adj3 sampl$).ti,ab.
74 (review.ab. and review.pt.) not trial.ti.
75 "we searched".ab. and (review.ti. or review.pt.)
76 "update review".ab.
77 (databases adj4 searched).ab.
78 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
79 Animal experiment/ not (human experiment/ or human/)
80 or/67-79
81 66 not 80
82 46 and 81

CINAHL

#	Query
S47	S30 AND S46
S46	S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45
S45	AB (CLUSTER W3 RCT)
S44	MH (CROSSOVER DESIGN) OR MH (COMPARATIVE STUDIES)
S43	AB (CONTROL W5 GROUP)
S42	PT (randomized controlled trial)
S41	MH (placebos)
S40	MH (sample size) AND AB (assigned OR allocated OR control)
S39	TI (trial)
S38	AB (random*)
S37	TI (randomised OR randomized)
S36	MH cluster sample
S35	MH pretest-posttest design
S34	MH random assignment
S33	MH single-blind studies
S32	MH double-blind studies
S31	MH randomized controlled trials
S30	S11 AND S29
S29	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S28	TI Rifampicin or Rifabutin or Rifapentine
S27	TX Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin
S26	TI Metronidazole or Tinidazole or Ornidazole
S25	TX Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or

	Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim
S24	TX Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin
S23	TX Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline
S22	TX Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin orMidecamycin or Miocamycin or Rokitamycin
S21	TX Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid
S20	TX Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin
S19	TX levofloxacin or Ciprofloxacin or Moxifloxacin Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin
S18	TX Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem
S17	TX Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin

	or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or Cefozopran or Cefpirome or Ceftobiprole or Ceftolozane or Carumonam or Nocardicin A
S16	TX Aztreonam or Aztreonam-avibactam or Lefamulin
S15	TX Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate
S14	TX tetracycline or lincosamide or macrolide or Ketolide* or Aminoglycoside* or Oxazolidinone* or Glycopeptide or Beta-lactam* or Penicillin* or Carbapenem* or Cephalosporin* or Monobactam* or Folic Acid Antagonists or Antifolate* or Sulfonamide* or Fluoroquinolone*
S13	TI (antibiotic or anti biotic or antimicrobial) OR TI (antibiotic or anti biotic or antimicrobial)
S12	(MH "Antibiotics+")
S11	S6 AND S10
S10	S7 OR S8 OR S9
S9	TI (pneumon* or bronchopneumon* or pleuropneumon*) OR AB (pneumon* or bronchopneumon* or pleuropneumon*)
S8	(MH "Respiratory Tract Infections")
S7	(MH "Pneumonia+")
S6	S1 OR S2 OR S3 OR S4 OR S5
S5	TI day or days
S4	TI versus or vs
S3	TI (duration or course or extended or limited or shortened or shot or long or longer) OR AB (duration or course or extended or limited or shortened or shot or long or longer)
S2	(MH "Treatment Duration")
S1	(MH "Drug Administration Schedule")

Cochrane Library

ID Search Hits
#1 MeSH descriptor: [Drug Administration Schedule] explode all trees
#2 MeSH descriptor: [Duration of Therapy] explode all trees
#3 (versus or vs):ti (Word variations have been searched)
#4 (day or days):ti (Word variations have been searched)
#5 (extended or limited or shortened or short or long or longer or course or duration):ti,ab,kw (Word variations have been searched)
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Pneumonia] explode all trees
#8 MeSH descriptor: [Respiratory Tract Infections] this term only
#9 MeSH descriptor: [Pneumonia, Pneumococcal] explode all trees
#10 MeSH descriptor: [Pleuropneumonia] explode all trees
#11 (pneumon* or bronchopneumon* or pleuropneumon*):ti,ab,kw (Word variations have been searched)
#12 respiratory near/2 infection*
#13 #7 or #8 or #9 or #10 or #11 or #12
#14 #6 and #13
#15 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#16 (antibiotic or anti biotic or antimicrobial):ti,ab,kw (Word variations have been searched)
#17 tetracycline or lincosamide or macrolide or Ketolide* or Aminoglycoside* or Oxazolidinone* or Glycopeptide or Beta-lactam* or Penicillin* or Carbapenem* or Cephalosporin* or Monobactam* or Folic Acid Antagonists or Antifolate* or Sulfonamide* or Fluoroquinolone*
#18 Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate
#19 Aztreonam or Aztreonam-avibactam or Lefamulin
#20 Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or

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#21 Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem
#22 levofloxacin or Ciprofloxacin or Moxifloxacin Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin
#23 Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin
#24 Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid
#25 Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin orMidecamycin or Miocamycin or Rokitamycin
#26 Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline
#27 Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin
#28 Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim
#29 Metronidazole or Tinidazole or Ornidazole
#30 Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin
#31 Rifampicin or Rifabutin or Rifapentine
#32 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#33 #14 and #32 in Trials