Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a systematic review and duration-effect meta-analysis (eAppendix)

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eAppendix 1. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: protocol for a systematic review and duration-effect network meta-analysis (protocol as of 15th August, 2021)

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INTRODUCTION

Community-acquired pneumonia (CAP) continues to be a leading cause of morbidity and mortality globally. (1) In the United States, for example, it is the second most common cause of hospitalization and the top infectious cause of death. (2,3) Clinical guidelines recommend starting several antibiotics empirically for non-severe pneumonia. (4) The optimal duration of antimicrobial therapy, however, remains unclear and controversial. Recent clinical guidelines suggest a minimum of five days of treatment before therapy discontinuation for patients achieving an afebrile state for 48 to 72 hours and meeting clinical stability criteria. (4) In clinical settings, however, a conventional ten to 14-day therapy is still used. (5,6) This may mean that many patients are receiving more antibiotics than necessary, which leads to an increased cost, time and also, higher probability of antimicrobial resistance. (7) Finding optimal duration of antibiotics is therefore meaningful not only for clinicians but also for policy-makers. A meta-analysis found that short-course therapy was not inferior to long-course therapy. (8) A major limitation of the method used in this meta-analysis is the arbitrary categorization of durations, when the original studies compared different durations, ranging from three to ten days. This resulted in categorizing a seven-day treatment in one trial to short-course and the same in another trial to long-course. We can overcome this limitation by using a novel method called dose-effect network meta-analysis (DE-NMA), which allows us to use the original duration in days and to examine the optimal duration with greater resolution of change points.

OBJECTIVES

To find the optimal treatment duration with antibiotics for CAP.

METHODS AND ANALYSIS

We follow PRISMA-P in reporting the protocol and will follow PRISMA(9) and PRISMA-NMA in reporting the DE-NMA results.

Data sources

Criteria for considering studies for this review

Types of studies

All randomized controlled studies. Quasi-randomized trials (such as those allocating by using alternate days of the week) will be excluded.

1. Cluster-randomized trials

Cluster-randomized trials will be included as long as proper adjustment for the intra-cluster correlation is conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.

2. Studies with multiple treatment groups

Where multiple trial arms are reported in a single trial, we will include only the relevant arms.

Types of participants

Patients of 18 years or older of both sexes with diagnosis of CAP as defined by the original authors. We will include both outpatients and inpatients. We will exclude patients who are admitted to intensive care unit. In order to focus on population without an elevated risk, we will exclude trials with 20% or more patients meeting one or more of the following criteria: having immunodeficiency; having been treated with another antibiotic within a month.

Types of interventions

We will include trials examining any of the antibiotics, administered orally or intravenously. As we can expect a limited number of studies to include, we will not be able to evaluate individual antibiotics. We will evaluate antibiotics as a class because clinical guidelines recommend treatment duration irrespective of the antibiotic used, (4) and because recent meta-analyses of antibiotics for CAP have not shown efficacy difference among antibiotics. (10,11) Oral and intravenous antibiotics will be merged, because they have been shown equally effective in many infectious conditions. (12–15) We will include trials comparing the same agents used in the same daily dosage but for different durations. We will use the predefined duration for fixed-duration arms and median duration for flexible-duration arms. If median duration is not reported, we will use mean duration. We will prioritize median duration because patients requiring longer duration may inflate the mean duration in flexible-duration arms.

Primary outcome and secondary outcomes

The primary outcome of interest in this study is clinical improvement as defined by the original authors at a time point as close to 15 days (range 7-45 days) as possible in each included study. (16) If equidistant, we will use the longer timeframe.

1 Clinical improvement at day 15 (range 7-45 days), as defined by the original study

Secondary outcomes of interest are the following outcomes.

2. All-cause mortality at day 15 (range 7-45 days)

3. Serious adverse events as defined by the original study at day 15 (range 7-45 days)

4. Clinical improvement, as defined by the original study, at day 30 (range 15-60)

We will use the number of randomized patients as the denominator for intention-to-treat (ITT) dataset and we will use per-protocol (PP) dataset as defined by the original study. Those who had been randomized but not accounted for in the original study will be assumed to have dropped out for some reason other than death or serious adverse events and without clinical

improvement. In case only one of PP or ITT can be obtained, we will use the same number for the other. We will use ITT for the primary analysis and PP for a sensitivity analysis. (17,18)

Search methods for identification of studies

Electronic searches

Searches for published studies will be undertaken in the following electronic bibliographic databases from inception to present (25 August, 2021): Ovid MEDLINE and Cochrane CENTRAL. We will use search terms for community acquired pneumonia in conjunction with the names of individual antibiotics as well as the names of antibiotic classes. We imposed no date, language or publication status restriction.

Search formula

Search strategy for Ovid MEDLINE is as follows

#1 randomized controlled trial.pt.
#2 controlled clinical trial.pt.
#3 randomized.ab.
#4 placebo.ab.
#5 drug therapy.fs.
#6 randomly.ab.
#7 trial.ab.
#8 groups.ab.
#9 or/#1-#8
#10 exp animals/ not humans.sh.
#11 #9 not #10
#12 exp Community-Acquired Infections/
#13 Pneumonia, Bacterial/dt [Drug Therapy]
#14 community acquired pneumonia.ab,ti.
#15 (#12 and #13) or #14
#16 ((short adj term) or (long adj term) or prolonged or (short adj course) or (long adj course) or day or days or duration or disconti*).mp.
#17 (beta-lactam* or macrolide* or quinolone* or tetracycline* or amikacin or amoxicillin or ampicillin or azithromycin or cefepim or cefotaxim* or ceftarolin or ceftazidim* or ceftibuten or ceftriaxon* or cefuroxim* or cethromycin or ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or co-amoxiclav or co-trimoxacol or doxycyclin* or ertapenem or erythromycin or fluoroquinolon* or fluorchinolon* or gemifloxacin or gentamicin or imipenem or levofloxacin or linezolide or meropenem or moxifloxacin or penicillin* or piperacillin or roxithromycin or sultamicillin or tazobactam or telithromycin or tetracyclin* or ticarcillin or tobramycin).mp.
#18 Anti-Bacterial Agents/ad [Administration & Dosage]

#19 #17 or #18

#20 #11 and #15 and #16 and #19

Reference lists and others

We will check the reference lists of all the included studies and review articles for additional references. We will also contact experts in the field to identify unpublished and on-going trials.

Data collection and analysis

Selection of studies

Two review authors will independently screen titles and abstracts of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full text study reports/publication and two review authors will independently screen the full text and identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, through consultation with a third review author. We will identify and exclude duplicates of the same study so that each study rather than each report is the unit of analysis in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and characteristics of excluded studies table.

Data items

We will use a standardized data collection form for study characteristics and outcome data which will have been piloted on at least one study in the review. Two review authors will extract data independently from the included studies. Any disagreement will be resolved through discussion, or discussed with a third person if necessary. We will abstract the following information.

1. Characteristics of the studies

Name of the study, year of publication, country, study site (single or multi-center), study design, patient characteristics (mean age, percentage of women, diagnostic criteria used), outcome (definition of clinical success), definition of clinical stability, timing of randomization, sponsorship (rated positive if the trial is directly sponsored by drug company or if any authors are employed by the drug company).

2. Risk of bias

We will use Cochrane Risk of Bias 2.0 tool (RoB2) (19). We will assess the effect of assignment to the interventions at baseline because we use the ITT population in our primary analysis.

3. Data to calculate effect sizes and conduct dose-effect network meta-analysis

Patients (number of participants randomized to each arm)

Interventions (placebo or name and the dose and duration of the drug used)

Outcomes (number of clinical success, mortality, adverse events).

Statistical analysis

Assessment of the network transitivity, consistency, heterogeneity and publication bias

We will evaluate

1) transitivity of the network by comparing potential effect modifiers (severity, comorbidity, age) across comparisons

2) consistency by global as well as local tests of inconsistency

3) heterogeneity by common tau

We decided not to draw a funnel plot, because there is no appropriate method to draw it in DE-NMA and even if there is, it would be uninterpretable.

Dose-effect network meta-analysis

We will then conduct a DE-NMA with the *MBNMAdose* package in R.(20,21) One advantage of the dose-effect network meta-analysis by *MBNMAdose* package is that we can connect nodes that might otherwise be disconnected, by linking up different durations via the duration-effect relationship.(20) Given the clinical and methodological heterogeneity likely present in the included studies, we will use the random effects model. We will use 3 knots, equally spaced across the duration range (25%, 50%, 75%), because we do not know a priori where the outcomes change. We will test different knot placements in sensitivity analyses. We will use odds ratio of each outcome to synthesize data. (22,23)

We will set 10 days as the reference, because it is the current practice. (5,6,24) We will test the non-inferiority of the shorter duration examined against 10 days using ITT dataset, with the non-inferiority margin of 10%, as previously proposed. (16) We will compare the margin and the 95% confidence interval. In case non-inferiority is shown, we will test the superiority of the shorter duration examined against 10 days.

Sensitivity analyses

In order to ascertain the robustness of the primary analyses, we will conduct the following sensitivity analysis and subgroup analysis.

1 To test the stability of the shape of the spline curves, using different numbers and locations of knots

2 To test the influence of trials included,

- 2.1 excluding trials with overall high risk of bias
- 2.2 excluding trials with inpatients

3 To test the robustness of the analytical method, using PP dataset

4 To test the influence of antibiotics examined, including only antibiotics recommended for empirical treatment of CAP by clinical guidelines: beta-lactam (amoxicillin, amoxicillin/clavulanate ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftraroline), macrolide (azithromycin , clarithromycin), doxycycline, respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin)

Patient and public involvement

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

Ethics and dissemination

This study uses published aggregate data and does not require ethical approval. Findings will be disseminated in a peer-reviewed journal.

Amendments

In case of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Abbreviations

AMR: antimicrobial resistance

CAP: community-acquired pneumonia

DE-NMA: dose-effect network meta-analysis

ITT: intention-to-treat

PP: per protocol

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

Reference

1 GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 2018;18:1191–210. doi:10.1016/s1473-3099(18)30310-4

2 Most Frequent Conditions in U.S. Hospitals, 2011. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf (accessed 15 Jul 2021).

3 Xu J, Murphy SL, Kochanek KD, et al. Deaths: Final Data for 2013. National Vital Statistics Reports Centers Dis Control Prev National Cent Heal Statistics National Vital Statistics Syst 2016;64:1–119.

4 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Resp Crit Care* 2019;200:e45–67. doi:10.1164/rccm.201908-1581st

5 Aliberti S, Blasi F, Zanaboni AM, et al. Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia. *Eur Respir J* 2009;36:128–34. doi:10.1183/09031936.00130909

6 Yi SH, Hatfield KM, Baggs J, et al. Duration of Antibiotic Use Among Adults With Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United States. *Clin Infect Dis* 2017;66:1333–41. doi:10.1093/cid/cix986

7 Guillemot D, Carbon C, Balkau B, et al. Low Dosage and Long Treatment Duration of β-Lactam: Risk Factors for Carriage of Penicillin-Resistant Streptococcus pneumoniae. *JAMA* 1998;279:365–70. doi:10.1001/jama.279.5.365

8 Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, et al. Short- versus Long-Course Antibacterial Therapy for Community-Acquired Pneumonia. *Drugs* 2008;68:1841–54. doi:10.2165/00003495-200868130-00004

9 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J* 2021;372:n71. doi:10.1136/bmj.n71

10 Montes-Andujar L, Tinoco E, Baez-Pravia O, et al. Empiric antibiotics for community-acquired pneumonia in adult patients: a systematic review and a network meta-analysis. *Thorax* 2021;:thoraxjnl-2019-214054. doi:10.1136/thoraxjnl-2019-214054

11 Pakhale S, Mulpuru S, Verheij TJ, et al. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane Db Syst Rev* 2014;10:CD002109. doi:10.1002/14651858.cd002109.pub4

12 Li HK, Agweyu A, English M, et al. An Unsupported Preference for Intravenous Antibiotics. *Plos Med* 2015;12:e1001825. doi:10.1371/journal.pmed.1001825

13 Keren R, Shah SS, Srivastava R, et al. Comparative Effectiveness of Intravenous vs Oral Antibiotics for Postdischarge Treatment of Acute Osteomyelitis in Children. *JAMA Pediatr* 2014;169:120. doi:10.1001/jamapediatrics.2014.2822

14 Li H-K, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. *New Engl J Med* 2019;380:425–36. doi:10.1056/nejmoa1710926

15 Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. *New Engl J Med* 2019;380:415–24. doi:10.1056/nejmoa1808312

16 Spellberg B, Talbot GH, Brass EP, et al. Position paper: recommended design features of future clinical trials of antibacterial agents for community-acquired pneumonia. *Clin Infect Dis* 2008;47 Suppl 3:S249-65.

17 Bai AD, Komorowski AS, Lo CKL, et al. Intention-to-treat analysis may be more conservative than per protocol analysis in antibiotic non-inferiority trials: a systematic review. *BMC Med Res Methodol* 2021;21:75. doi:10.1186/s12874-021-01260-7

18 Aberegg SK, Hersh AM, Samore MH. Empirical Consequences of Current Recommendations for the Design and Interpretation of Noninferiority Trials. *J Gen Intern Med* 2018;33:88–96. doi:10.1007/s11606-017-4161-4

19 Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Br Med J* 2019;366:l4898. doi:10.1136/bmj.l4898

20 Mawdsley D, Bennetts M, Dias S, Boucher M, Welton N. Model-Based Network Meta-Analysis: A Framework for Evidence Synthesis of Clinical Trial Data. *Cpt Pharmacometrics Syst Pharmacol.* 2016;5(8):393–401.

21 Team R. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2020. https://www.R-project.org/

22 Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth Methods* 2019;10:398–419. doi:10.1002/jrsm.1347

23 Doi SA, Furuya-Kanamori L, Xu C, et al. Questionable utility of the relative risk in clinical research: A call for change to practice. *J Clin Epidemiol* Published Online First: 2020. doi:10.1016/j.jclinepi.2020.08.019

24 Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A Multicenter Randomized Clinical Trial. *JAMA Intern Med* 2016;176:1257. doi:10.1001/jamainternmed.2016.3633

eAppendix 2. Search strings used for Ovid MEDLINE, Embase, and CENTRAL

2-1. Search strategy for Ovid MEDLINE

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 or/1-8
10 exp animals/ not humans.sh.
11 9 not 10
12 exp Community-Acquired Infections/
13 Pneumonia, Bacterial/dt [Drug Therapy]
14 community acquired pneumonia.ab,ti.
15 (12 and 13) or 14
16 ((short adj term) or (long adj term) or prolonged or (short adj course) or (long adj course) or day or days or duration or disconti*).mp.
17 (beta-lactam* or macrolide* or quinolone* or tetracycline* or amikacin or amoxicillin or ampicillin or azithromycin or cefepim or cefotaxim* or ceftarolin or ceftazidim* or ceftibuten or ceftriaxon* or cefuroxim* or cethromycin or ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or co-amoxiclav or co-trimoxacol or doxycyclin* or ertapenem or erythromycin or fluoroquinolon* or fluorchinolon* or gemifloxacin or gentamicin or imipenem or levofloxacin or linezolide or meropenem or moxifloxacin or penicillin* or piperacillin or roxithromycin or sultamicillin or tazobactam or telithromycin or tetracyclin* or ticarcillin or tobramycin).mp.
18 Anti-Bacterial Agents/ad [Administration & Dosage]
19 17 or 18
20 11 and 15 and 16 and 19

2-2. Search strategy for Embase

S1 (EMB.EXACT.EXPLODE("community acquired infection")) AND (EMB.EXACT("bacterial pneumonia -- drug therapy"))
S2 ab(community acquired pneumonia) OR ti(community acquired pneumonia)

S3 S2 OR S1

S4 ab((short near/1 term) OR (long near/1 term) OR prolonged OR (short near/1 course) OR (long near/1 course) OR day OR days OR duration or disconti*) OR ti((short near/1 term) OR (long near/1 term) OR prolonged OR (short near/1 course) OR (long near/1 course) OR day OR days OR duration or disconti*)

S5 ab(beta-lactam* OR macrolide* OR quinolone* OR tetracycline* OR amikacin OR amoxicillin OR ampicillin OR azithromycin OR cefepim OR cefotaxim* OR ceftarolin OR ceftazidim* OR ceftibuten OR ceftriaxon* OR cefuroxim* OR cethromycin OR ciprofloxacin OR clarithromycin OR clavulanic acid OR clindamycin OR co-amoxiclav OR co-trimoxacol OR doxycyclin* OR ertapenem OR erythromycin OR fluoroquinolon* OR fluorchinolon* OR gemifloxacin OR gentamicin OR imipenem OR levofloxacin OR linezolide OR meropenem OR moxifloxacin OR penicillin* OR piperacillin OR roxithromycin OR sultamicillin OR tazobactam OR telithromycin OR tetracyclin* OR ticarcillin OR tobramycin) OR ti(beta-lactam* OR macrolide* OR quinolone* OR tetracycline* OR amikacin OR amoxicillin OR ampicillin OR azithromycin OR cefepim OR cefotaxim* OR ceftarolin OR ceftazidim* OR ceftibuten OR ceftriaxon* OR cefuroxim* OR cethromycin OR ciprofloxacin OR clarithromycin OR clavulanic acid OR clindamycin OR co-amoxiclav OR co-trimoxacol OR doxycyclin* OR ertapenem OR erythromycin OR fluoroquinolon* OR fluorchinolon* OR gemifloxacin OR gentamicin OR imipenem OR levofloxacin OR linezolide OR meropenem OR moxifloxacin OR penicillin* OR piperacillin OR roxithromycin OR sultamicillin OR tazobactam OR telithromycin OR tetracyclin* OR ticarcillin OR tobramycin)

S6 (EMB.EXACT("antibiotic agent -- drug dose"))

S7 S6 OR S5

S8 S7 AND S4 AND S3

S9 (ab(random*) OR ti(random*)) OR (ab(placebo*) OR ti(placebo*)) OR (ab(double NEAR/1 blind*) OR ti(double NEAR/1 blind*))

S10 S9 AND S8

2-3. Search strategy for CENTRAL

#1 [mh "Community-Acquired Infections"]

#2 [mh "Pneumonia, Bacterial"]

#3 "community acquired pneumonia":ti,ab

#4 (#1 and #2) or #3

#5 (short:ti,ab,kw NEXT term:ti,ab,kw) OR (long:ti,ab,kw NEXT term:ti,ab,kw) OR prolonged:ti,ab,kw OR (short:ti,ab,kw NEXT course:ti,ab,kw) OR (long:ti,ab,kw NEXT course:ti,ab,kw) OR day:ti,ab,kw OR days:ti,ab,kw OR duration:ti,ab,kw OR disconti*:ti,ab,kw

#6 beta-lactam*:ti,ab,kw OR macrolide*:ti,ab,kw OR quinolone*:ti,ab,kw OR tetracycline*:ti,ab,kw OR amikacin:ti,ab,kw OR amoxicillin:ti,ab,kw OR ampicillin:ti,ab,kw OR azithromycin:ti,ab,kw OR cefepim:ti,ab,kw OR cefotaxim*:ti,ab,kw OR ceftarolin:ti,ab,kw OR ceftazidim*:ti,ab,kw OR ceftibuten:ti,ab,kw OR ceftriaxon*:ti,ab,kw OR cefuroxim*:ti,ab,kw OR cethromycin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR clarithromycin:ti,ab,kw OR "clavulanic

acid":ti,ab,kw OR clindamycin:ti,ab,kw OR co-amoxiclav:ti,ab,kw OR co-trimoxacol:ti,ab,kw OR doxycyclin*:ti,ab,kw OR ertapenem:ti,ab,kw OR erythromycin:ti,ab,kw OR fluoroquinolon*:ti,ab,kw OR fluorchinolon*:ti,ab,kw OR gemifloxacin:ti,ab,kw OR gentamicin:ti,ab,kw OR imipenem:ti,ab,kw OR levofloxacin:ti,ab,kw OR linezolide:ti,ab,kw OR meropenem:ti,ab,kw OR moxifloxacin:ti,ab,kw OR penicillin*:ti,ab,kw OR piperacillin:ti,ab,kw OR roxithromycin:ti,ab,kw OR sultamicillin:ti,ab,kw OR tazobactam:ti,ab,kw OR telithromycin:ti,ab,kw OR tetracyclin*:ti,ab,kw OR ticarcillin:ti,ab,kw OR tobramycin:ti,ab,kw

#7 [mh "Anti-Bacterial Agents"]

#8 #6 OR #7

#9 #4 AND #5 AND #8

eAppendix 3. Amendments from the protocol

We reconsidered data structure and realized that dose-effect meta-analysis, not *network* meta-analysis would be more suitable. We also realized that the small number of included studies would make using four or more knots inappropriate and decided not to conduct sensitivity analyses with different number of knots. We searched Embase via ProQuest in addition to MEDLINE and CENTRAL. (25th August, 2021, before starting formal screening)

We additionally extracted baseline severity data using Pneumonia Severity Index (10th October, 2021, after full text screening done, before data extraction started).

We planned to conduct a sensitivity analysis excluding trials with inpatients, but we found only one trial focusing on outpatients. We therefore decided to conduct a sensitivity analysis excluding trials with outpatients instead. (25th October, 2021, after data extraction)

We additionally conducted a sensitivity analysis excluding trials which randomised patients after achieving clinical stability. (27th October, 2021, after data extraction. Post hoc)

We additionally conducted pairwise meta-analyses comparing shorter treatment duration vs longer treatment duration and draw the forest plot and the funnel plot. (30th September, 2022, in response to the review)

We made a league table. (2th October 2022, in response to the review)

eAppendix 4. List of all included papers and table of characteristics of included studies

4.1. List of studies included in the analyses

Aliberti2017

- Aliberti S, Ramirez J, Giuliani F, et al. Individualizing duration of antibiotic therapy in community-acquired pneumonia. *Pulm Pharmacol Ther* 2017; 45: 191–201.
- NCT01492387

Dinh2021

- Dinh A, Ropers J, Duran C, et al. Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. *Lancet* 2021; 397: 1195–203.
- NCT01963442

ElMoussaoui2006

- El Moussaoui R, Borgie C, Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 2006; 332: 1355.

File2007

- File TM, Mandell LA, Tillotson G, et al. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. *J Antimicrob Chemoth* 2007; 60: 112–20.
- European Medicines Agency. Withdrawal assessment report for factive. 2009. (https://www.ema.europa.eu/en/documents/withdrawal-report/withdrawal-assessment-report-factive_en.pdf; Last accessed on 25 September 2022) *
- EUCTR2004-002619-10-CZ

Uranga2016

- Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A Multicenter Randomized Clinical Trial. *JAMA Intern Med*. 2016; 176: 1257.
- Uranga A, Artaraz A, Bilbao A, et al. Impact of reducing the duration of antibiotic treatment on the long-term prognosis of community acquired pneumonia. *BMC Pulm Med*. 2020;20(1):261.

Leophonte2002

- Léophonte P, Choutet P, Gaillat J, et al. Efficacité comparée de la ceftriaxone dans un traitement de dix jours versus un traitement raccourci de cinq jours des pneumonies aigues communautaires de l'adulte hospitalisé avec facteur de risque. *Médecine Et Maladies Infect* 2002; 32: 369–81.

Siegel1999

- Siegel RE, Alicea M, Lee A, Blaiklock R. Comparison of 7 Versus 10 Days of Antibiotic Therapy for Hospitalized Patients with Uncomplicated Community-Acquired Pneumonia. *Am J Ther* 1999; 6: 217–22.

Stralin2014

- Strålin K, Rubenson A, Lindroth H, et al. Betalactam treatment until no fever for 48 hours (at least 5 days) versus 10 days in community-acquired pneumonia: randomized, non-inferiority, open study. *Pneumonia* 2014; 3: 246–81.
- ISRCTN14523624

Tellier2004

- Tellier G, Niederman MS, Nusrat R, et al. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. *J Antimicrob Chemoth* 2004; 54: 515–23.
- Tellier G, Chang JR, Asche CV, Lavin B, Stewart J, Sullivan SD. Comparison of hospitalization rates in patients with community-acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. *Curr Med Res Opin*. 2004;20(5):739-747.

4.2. List of ongoing trials

NCT03609099

- NCT03609099. Adequate Duration of Antibiotic Treatment in Community-acquired Pneumonia With High Risk Class and Adequate Initial Clinical Response (2017-001406-15).

NCT04089787

- NCT04089787. Shortened Antibiotic Treatment of 5 Days in Community-Acquired Pneumonia (CAP5).

* found during web search using the sponsor's protocol code number.

4.3 Table of characteristics of included studies

Study	Age, mean, y	Age, SD, y	Female, %	PSI IV+V, %	Setting	Duration, day, median	Antibiotics	No. of participants	No. of clinical improvement on day 15	Measurement day for day 15	No. of death	No. of SAE	No. of clinical improvement on day 30	Measurement day for day 30
Siegel et al, 1999	61.1	15.1	NA	NA	Inpatient	7	CXM	25	21	42-44	1	-	21	42-44
						10		27	20		0	-	20	
Leophonte et al, 2002	64.0	18.7	25	NA	Inpatient	5	CRO	125	93	10	4	27	85	30
						10		119	85		5	32	75	
Tellier et al, 2004	45.8	18-87†	42	7	Both	5	TEL	193	154	17-21	1	9	154	17-21
						7		195	157		2	5	157	
El Moussaoui et al, 2006	57.2*	23.9*	40	12	Inpatient	3	AMX	57	50	10	1	0	47	28
						8		64	56		0	0	49	
File et al, 2007	45.4	16.8	42	3	Outpatient	5	GMI	256	240	7-9	0	8	237	24-30
						7		256	234		1	14	221	
Stralin et al, 2014	NA	NA	NA	NA	Inpatient	5	β-lactam	103	79	28	-	-	79	28
						10		104	81		-	-	81	
Uranga et al, 2016	65.4	18.3	37	39	Inpatient	5	Various	162	90	10	3	18	147	30
						10		150	71		3	19	132	
Aliberti et al, 2017	60.6*	24.8*	40	24	Inpatient	6	Various	125	111	30	4	-	111	30
						8		135	125		1	-	125	
Dinh et al, 2021	73.2*	21.0*	41	39	Inpatient	3	β-lactum + placebo	152	117	15	3	1	109	30
						8	β-lactum + AMC	151	102		2	1	109	

4.3 Characteristics of included studies (continued)

* = calculated using median and interquartile range; † = range

AMC = amoxicillin-clavulanic acid; AMX = amoxicillin; CRO = ceftriaxone; CXM = cefuroxime; GMI = gemifloxacin; PSI = pneumonia severity index; SAE = serious adverse events; SD = standard deviation; TEL = telithromycin

eAppendix 5. List of excluded studies

Name	Title	Comment
EUCTR2005-000105-65	Comparative study of the efficacy and tolerance of intravenously administered azithromycin (1.5 g) given either as a single dose or over a 3 day period in patients with community-acquired pneumonia	wrong intervention (dfferent drugs)
EUCTR2014-003137-25	Optimal duration of antibiotic treatment in patients with complicated parapneumonic pleural effusions or empyema	wrong intervention (dfferent drugs)
EUCTR2020-004452-15	ADMINISTRATION OF CLARITHROMYCIN IN COMMUNITY-ACQUIRED PNEUMONIA	wrong intervention (dfferent drugs)
Fekete2021	In moderately severe CAP stable after 3 d of beta-lactam, stopping therapy was noninferior to 5 additional d.	wrong design (comment)
File2007	No Title (Author's reply)	wrong design
Fine2003	Implementation of an evidence-based guideline to reduce duration of intravenous antibiotic therapy and length of stay for patients hospitalized with community-acquired pneumonia: a randomized controlled trial	wrong intervention (dfferent drugs)
JPRN-JapicCTI-163439	A Phase III study of Solithromycin in patients with community-acquired pneumonia	wrong intervention (dfferent drugs)
JPRN-UMIN000008677	Efficacy and Safety of treatment with Levofloxacin for Community-acquired Pneumonia	wrong design (single arm)
JPRN-UMIN000011835	Efficacy and safety of meropenem (3g/day) in the treatment of severe/refractory respiratory infections	wrong design (single arm)
JPRN-UMIN000011836	Efficacy and safety of azithromycin infusion in the treatment of mild/moderate community-acquired pneumonia	wrong design (observational)

Name	Title	Comment
Li2007	Efficacy of Short-Course Antibiotic Regimens for Community-Acquired Pneumonia: A Meta-analysis	wrong design (review)
Li2021	A multicenter randomized controlled study on the efficacy of moxifloxacin and garenoxacin for the treatment of adult community-acquired pneumonia	wrong intervention (dfferent drugs)
Lyttle2019	Dose and duration of antibiotic treatment in young children with community-acquired pneumonia	wrong participants
Malhotra-Kumar2016	Impact of amoxicillin therapy on resistance selection in patients with community-acquired lower respiratory tract infections: a randomized, placebo-controlled study	wrong participants
Melo2018	Shortening antibiotic duration for community acquired pneumonia.	wrong design (review)
Scalera2007	How long should we treat community-acquired pneumonia?.	wrong design (review)
Stralin2004	Short-course beta-lactam treatment for community-acquired pneumonia.	wrong design (review)
Uranga2015	Duration of Antibiotic Treatment in Community-Acquired Pneumonia.	wrong design (review)
Vetter2002	A prospective, randomized, double-blind multicenter comparison of parenteral ertapenem and ceftriaxone for the treatment of hospitalized adults with community-acquired pneumonia	wrong intervention (dfferent drugs)
Weber1987	Ampicillin versus cefamandole as initial therapy for community-acquired pneumonia	wrong intervention (dfferent drugs)
YangJ2020	The combined treatment of imipenem cilastatin and azithromycin for elderly patients with community-acquired pneumonia	wrong intervention (dfferent drugs)

eAppendix 6. Definitions of clinical improvement in each included study

Study	Definition
Siegel et al, 1999	"Patients were classified as a cure if the pneumonia was successfully treated within the constraints of the study protocol, including resolution of fever and leukocytosis and substantial improvement in chest radiograph by day 42"
Léophonte et al, 2002	"The main criteria defining success were apyrexia on D10 (temperature 37.5◦C) and no other antibiotic treatment before D10. The secondary criteria were absence of clinical signs on D10, cure (normalized clinical status and radiological imagery on D30/D45), and no other antibiotic treatment before D30/D45."
Tellier et al, 2004	"Clinical cure was defined as either the return to the pre-infection state (i.e. all pneumonia-related signs and symptoms had disappeared and chest X-ray findings had shown improvement) or improvement in related post-infectious stigmata, such that residual symptoms if any did not require additional treatment and were accompanied by improvement or lack of progression based on chest X-ray."
El Moussaoui et al, 2006	"Cure—resolution or improvement of symptoms and clinical signs related to pneumonia without the need for additional or alternative antibiotic therapy"
File et al, 2007	"Clinical response was based on subjective symptoms and objective signs of auscultatory findings (rales, rhonchi, wheezing and breath sounds) and was defined as success (sufficient improvement or resolution of the signs and symptoms of CAP recorded at baseline such that no additional antibacterial therapy was required at the end of therapy or follow-up)"
Strålin et al, 2014	"Clinical cure"
Uraga et al, 2014	"The primary outcomes were clinical success rate at day 10 and late follow-up (day 30) since admission, defined as resolution or improvement in signs and symptoms related to pneumonia without further antibiotics, and CAP-related symptoms at day 10 measured with the 18-item CAP symptom questionnaire, a specific and validated patient-reported outcome measure on which higher scores indicate more severe symptoms (range, 0-90)."
Aliberti et al, 2017	"Early failure was the primary composite study outcome occurring within 30 days following CAP diagnosis and including any of the following conditions: 1) pneumonia related complications (e.g., lung abscess, empyema); 2) clinical failure during hospitalization (definition in the online data supplement); 3) a new antibiotic course after discontinuation of antibiotic therapy prescribed for the pneumonia, 4) re-hospitalization from any reason; 5) death from any reason."
Dinh et al, 2021	"Cure was defined by the following criteria: apyrexia (temperature ≤37·8°C); resolution or improvement of clinical signs or symptoms (coughing frequency or severity, sputum production, dyspnoea, crackles); and no additional antibiotic treatment (for community-acquired pneumonia or any reason) since the last follow-up visit."

eAppendix 7. Risk of bias

	Risk of bias						
Study	**D1**	**D2**	**D3**	**D4**	**D5**	**Overall**	**Sponsored**
Siegel et al, 1999	L	H	H	L	S	H	Yes
Léophonte et al, 2002	S	L	L	S	H	H	Yes
Tellier et al, 2004	L	L	S	L	S	S	Yes
El Moussaoui et al, 2006	S	L	L	L	S	S	No
File et al, 2007	L	L	L	L	S	S	Yes
Strålin et al, 2014	H	H	H	H	H	H	No
Uranga et al, 2016	S	L	L	S	S	S	No
Aliberti et al, 2017	L	H	L	L	S	H	No
Dinh et al, 2021	L	L	L	L	L	L	No

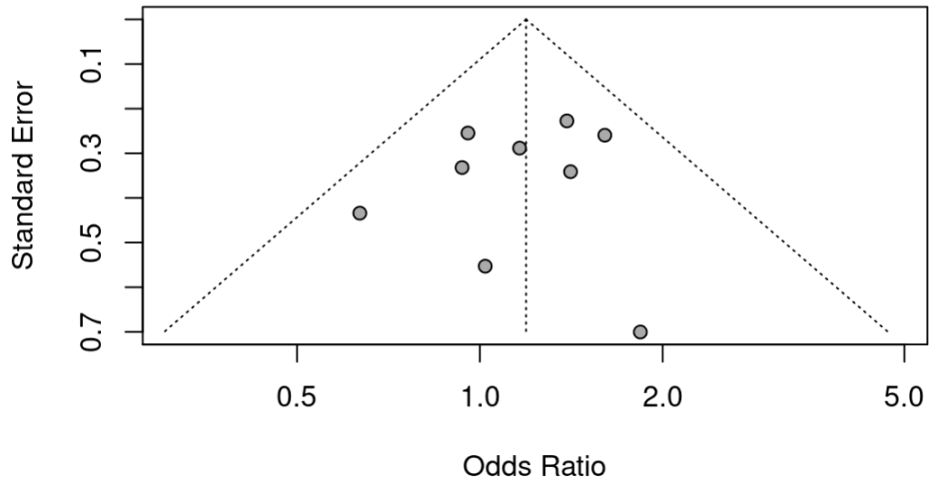
D1 = Bias due to randomisation; D2 = Bias due to deviations from intended intervention; D3 = Bias due to missing data; D4 = Bias due to outcome measurement; D5 = Bias due to selection of reported result; H = high; L = low; S = some concerns.

eAppendix 8. Heterogeneity: Variance partition coefficient for the primary outcome

VPC is computed for each non-referent arm of each study (those that have OR≠1). We included nine two-armed trials, and thus we have 9 VPC numbers. We present them below. It is generally interpreted as: VPC values below 25% low, 25-75% moderate and over 75% high.

```
>    vpc(mod1)
             2             4             6             8            10            12            14            16            18
1.059171e-10 1.102071e-09 3.592398e-09 4.059647e-09 2.000592e-09 8.322319e-10 1.771638e-09 1.071397e-10 1.843283e-08
```

eAppendix 9. Funnel plot



eAppendix 10. League table

3-day	–	–	–	–	1.48 (0.93-2.34)	–	–
1.09 (0.95-1.25)	**4-day**	–	–	–	–	–	–
1.19 (0.90-1.57)	1.09 (0.95-1.25)	**5-day**	–	1.10 (0.74-1.64)	–	–	1.21 (0.89-1.64)
1.29 (0.86-1.93)	1.18 (0.91-1.54)	1.08 (0.96-1.23)	**6-day**	–	0.63 (0.27-1.49)	–	–
1.36 (0.86-2.15)	1.25 (0.91-1.72)	1.15 (0.96-1.38)	1.06 (1.00-1.13)	**7-day**	–	–	1.84 (0.47-7.25)
1.39 (0.93-2.09)	1.28 (0.97-1.69)	1.18 (1.00-1.38)	1.08 (0.97-1.21)	1.02 (0.92-1.13)	**8-day**	–	–
1.42 (0.99-2.03)	1.30 (1.01-1.68)	1.19 (0.97-1.46)	1.10 (0.88-1.38)	1.04 (0.83-1.30)	1.01 (0.89-1.15)	**9-day**	–
1.44 (1.01-2.05)	1.32 (0.98-1.77)	1.21 (0.90-1.63)	1.12 (0.79-1.58)	1.05 (0.74-1.50)	1.03 (0.80-1.33)	1.01 (0.89-1.15)	**10-day**

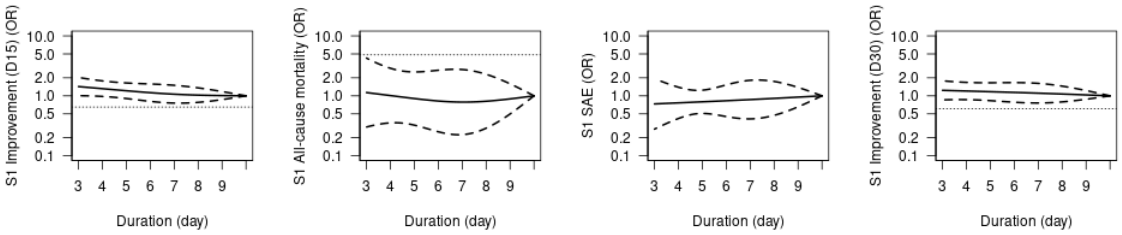
Results of the duration-effect meta-analysis are shown in the bottom-left area. Results of the pairwise meta-analyses of direct comparisons are shown in the upper-right area. Data are odds ratios (95% confidence interval) of the upper-left treatment duration compared with the bottom-right treatment duration. Non-inferior results (lower bound of the 95% confidence interval higher than 0.65) are shown in light green colour.

eAppendix 11. Sensitivity analyses

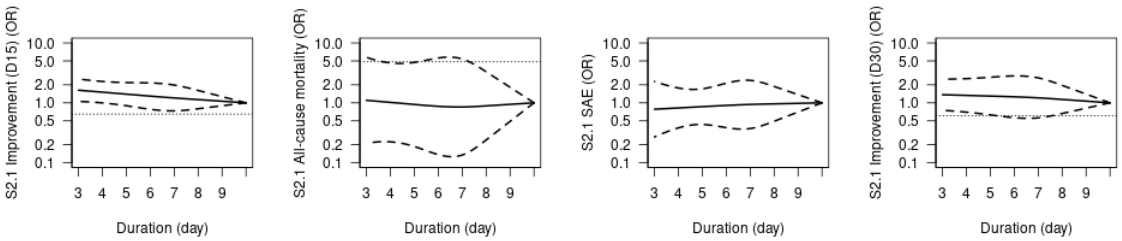
Duration-effect relationship of secondary outcomes could not be computed due to missing data in some cases.

A priori sensitivity analyses

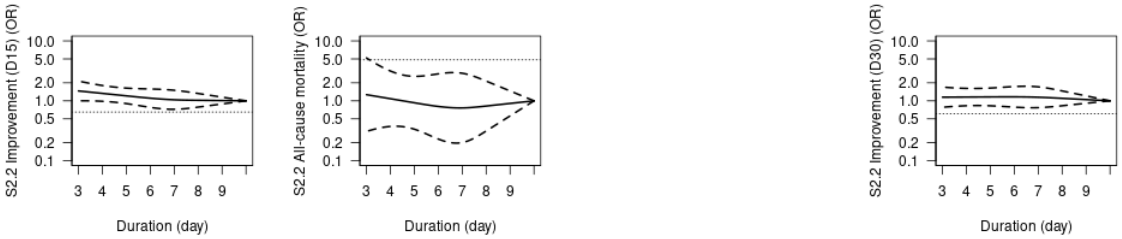
##S1 To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%).



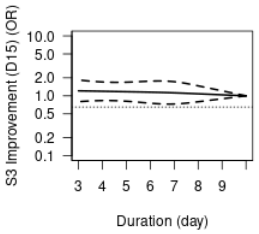
##S2.1 To test the influence of trials included, we conducted sensitivity analyses excluding trials with overall high risk of bias (excluding Siegel1999, Leophonte2002, Stralin2014, Aliberti2017)

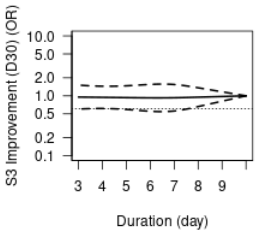


##S2.2 To test the influence of trials included, we conducted sensitivity analyses excluding trials with outpatients (excluding Tellier2004, File2007. SAE not computable)

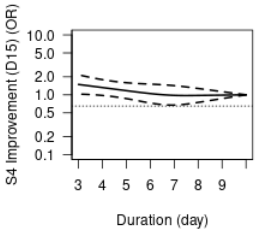


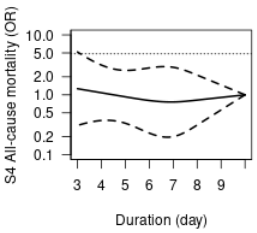
##S3 To test the robustness of the analytical method, we used PP dataset. (All-cause mortality and SAE not computable)

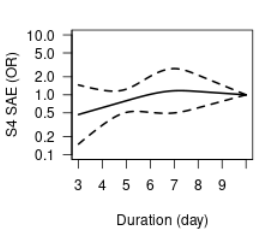


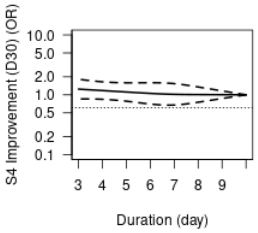


##S4 To test the influence of antibiotics examined, we conducted sensitivity analyses including only antibiotics recommended for empirical treatment of CAP by clinical guidelines. (excluding Siegel1999, Tellier2004. We included trials that used various antibiotics)



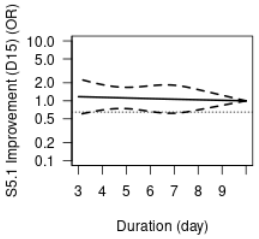


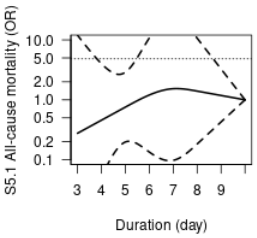


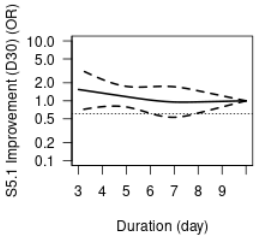


Post-hoc, exploratory sensitivity analyses

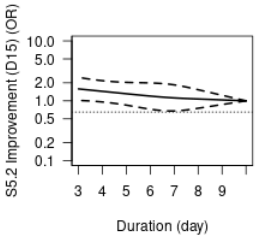
##S5.1 Randomization before the initial antibiotic treatment (including Siegel1999, Leophonete2002, Tellier2004, File2007, Stralin2014. SAE not computable)

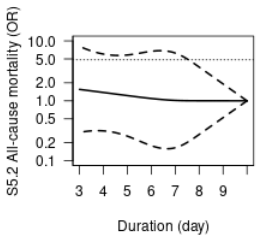


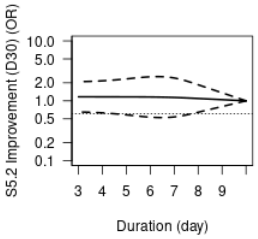




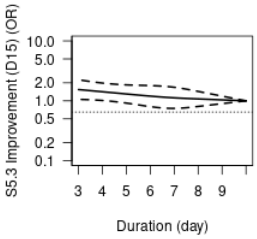
##S5.2 Randomization after several days or clinical stability achieved (including ElMoussaoui2006, Uranga2016, Aliberti2017, Dinh2021. SAE not computable)

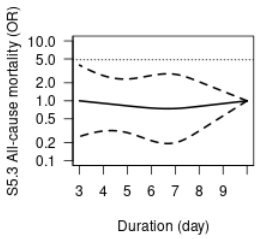


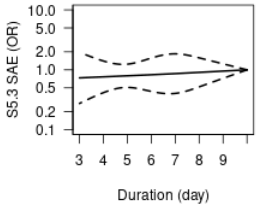




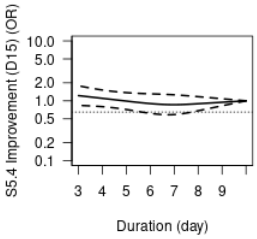
##S5.3 To test the influence of trials with large deviation from the day 15 measurement time (excluding Siegel1999, Stralin2014, Aliberti2017. Clinical improvement on day 30 not applicable.)

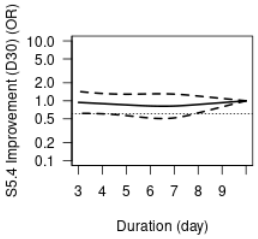






##S5.4 To test the influence of handling missing data as not improved (counting missing data as clinically improved)





eAppendix 12. Pairwise meta-analysis of the included trials