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

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TITLE PAGE

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

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ABSTRACT (299<300 words)

Objectives: To find the optimal treatment duration with antibiotics for community-acquired pneumonia (CAP) in adults.

Design: Systematic review and duration-effect meta-analysis. We systematically searched MEDLINE, Embase and CENTRAL from inception to present (25 August, 2021) to find all randomized controlled trials comparing the same antibiotics used at the same daily dosage but for different durations for CAP in adults. We conducted random-effects, one-stage duration-effect meta-analysis with restricted cubic splines. We tested the non-inferiority with the pre-specified non-inferiority margin of 10% examined against 10 days using intention-to-treat dataset.

Setting and Participants: Both outpatients and inpatients but not those admitted to intensive care unit.

Interventions: Any antibiotics, administered orally or intravenously.

Primary and Secondary Outcome Measures: The primary outcome was clinical improvement at day 15 (range 7-45 days). Secondary outcomes were all-cause mortality, serious adverse events, and clinical improvement at day 30 (15-60 days). We calculated odds ratios.

Results: We included 9 trials (2399 patients with a mean [SD] age of 61.2 [22.1]; 39% women). The duration-effect curve was monotonic with longer duration leading to lower probability of improvement, and the lower 95%CI curve was constantly above the prespecified non-inferiority margin. Harmful outcome curves indicated no association. The average percentage of clinical improvement rate at day 15 in the 10-day treatment arms was 68%. Using that average, we computed the absolute clinical improvement rates at the following durations: a 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day treatment 69% (61 to 76%).

Conclusions: Shorter treatment duration probably achieves the optimal balance between efficacy and treatment burden for treating CAP in adults. However, the small number of included studies and the overall moderate to high risk of bias may compromise the certainty of the results. Further research focusing on the shorter duration range is required.

Registration: PROSPERO (CRD 42021273357).

Strengths and Limitations

- To our knowledge, this is the first systematic review and duration-effect meta-analysis to examine the optimal duration of antibiotic treatment for community-acquired pneumonia in adults by day.
- This study may lead to efficient antibiotics use, which is critical to curbing antimicrobial resistance.
- Limited number of included studies and the overall moderate to high risk of bias may compromise the certainty of the results.

Keywords

Community-acquired pneumonia; antibiotic; treatment duration; dose-response meta-analysis

MAIN TEXT (2497<3000 words)

BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality globally, especially among the elderly.[1] In the United States, it is the second most common cause of hospitalization and the top infectious cause of death.[2,3] The initial treatment for CAP is empirical, with guidelines recommending starting several antibiotics depending on patients' severity and risk factors for certain pathogens.[4–6]

The optimal duration of antimicrobial therapy remains unclear and controversial. The American and British guidelines recommend a minimum of five days of treatment before therapy discontinuation for patients achieving clinical stability.[4,5] The European guideline states that the duration of treatment should not exceed 8 days in responding patients.[6] In clinical practice, however, antibiotics for pneumonia are often prescribed for 10 up to 14 days.[7,8] This may mean that many patients may be receiving more antibiotics than necessary, with a consequent increase in costs and a higher probability of antimicrobial resistance.[9] Finding optimal duration of antibiotics can facilitate reducing antimicrobial use efficiently. A pair-wise meta-analysis published in

2008 found that short-course therapy was non-inferior to long-course therapy regarding clinical success at end-of-therapy, clinical success at late follow-up, microbiological success, relapses, mortality and adverse events.[10] Since then, at least two trials have been reported,[11,12] which warrants update of the systematic review and meta-analysis. A major limitation of the method used in the previous pair-wise 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 other two trials to long-course.[13–15] We overcame this limitation by using a novel method called dose-effect meta-analysis.[16] It has been used, for example, to examine the effects of potassium intake or sodium reduction for blood pressure[17,18]. Unlike conventional categorization-based meta-analyses[19], dose-effect meta-analysis can reveal more fine-grained optimal dose[20]. By treating duration as dose, we aimed to apply this method to obtain a more specific optimal treatment duration.

METHODS

We summarized the currently available evidence to find the optimal treatment duration of antibiotics for CAP in adults. We followed the Preferred Reporting Items for Systematic

reviews and Meta-Analyses (PRISMA 2020) [21]. The protocol has been prospectively registered in PROSPERO (CRD 42021273357) and can be found in the appendix (eAppendix1).

Patient and Public Involvement

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

Data sources

Criteria for considering studies for this review

Types of studies

To examine the duration-effect relationship, we included all trials that compared two or more different durations of the same antibiotic treatment for CAP.

Types of participants

Patients were eligible if they were 18 years or older of both genders with a diagnosis of CAP as defined by the original authors. We included both outpatients and inpatients. We excluded patients who were admitted to intensive care unit. In order to focus on individuals at low to medium risk, we excluded 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 included trials examining any antibiotics, administered orally or intravenously. We evaluated antibiotics as a class because clinical guidelines recommend treatment duration irrespective of the antibiotic used,[4–6] and because recent meta-analyses of antibiotics for CAP have not shown efficacy differences among antibiotics.[22,23] Oral and intravenous antibiotics were merged because they have been shown equally effective in many infectious conditions within the same time frame.[24–26] We included trials comparing the same agents used at the same daily dosage but for different durations. We used the predefined duration for fixed-duration arms. If some studies did not prespecified the duration (eg. left it to clinicians' judgment[11]), we used the median duration.

Primary outcome and secondary outcomes

The primary outcome of interest in this study was 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.[27] Secondary outcomes of interest were: all-cause mortality at day 15 (range

7-45 days), serious adverse events as defined by the original study at day 15 (range 7-45 days), and clinical improvement as defined by the original study at day 30 (range 15-60). We used the number of randomized patients as the denominator for intention-to-treat (ITT) dataset. When only clinical failure was reported, clinical improvement was calculated by subtracting clinical failure from the total number randomized. We used ITT for the primary analysis and per-protocol (PP) dataset for a sensitivity analysis.[28,29] We used odds ratio (OR) of each outcome to synthesize data. [30,31]

Search methods for identification of studies

Electronic searches

We systematically searched the following electronic bibliographic databases from inception to present (25 August, 2021): MEDLINE, Embase and CENTRAL. We used search terms for community acquired pneumonia in conjunction with the names of individual antibiotics as well as the names of antibiotic classes. Detailed search formulas are presented in the appendix (eAppendix2). We imposed no date, language or publication status restriction.

Reference lists

We checked the reference lists of all the included studies and review articles for additional references.

Data collection and analysis

Selection of studies

Two review authors independently screened and selected the included studies (YF and one of AO, EO, SF or YL). Two review authors extracted data independently from the included studies (YF and one of AO, EO, SF or YL). We used the Cochrane risk of bias tool Version 2 [32] to assess and summarize the risk of bias. Disagreements were resolved through discussion.

Statistical analysis

To perform our analyses, we used the *dosresmeta* package (Version 2.0.1) and *meta* package (Version 5.0-1) for *R* (Version 4.1.0. R foundation, Wien, Austria).[33–35]

Assessment of heterogeneity

We investigated the heterogeneity between studies by the variance partition coefficient (VPC). [16] VPC represents the percentage of variation attributed to heterogeneity rather than sampling error and can be interpreted similarly to the I^2.

Dose-effect meta-analysis

Given the clinical and methodological heterogeneity likely present in the included studies, we used the random effects model. We used 3 knots, equally spaced across the duration range (25%, 50%, 75%). We set 10 days as the reference because it can be regarded as the current practice.[7,8,11] We tested the non-inferiority with the non-inferiority margin of 10%, as previously proposed,[27] and the superiority of the shorter duration examined against 10 days using ITT dataset.

Sensitivity analyses

In order to ascertain the robustness of the primary analyses, we conducted the following sensitivity analyses. To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%). To test the influence of trials included, we conducted sensitivity analyses excluding trials with an overall high risk of bias and excluding trials

with outpatients. To test the robustness of the analytical method, we used the PP dataset. To test the influence of antibiotics examined, we conducted sensitivity analyses restricting eligible antibiotics only to those recommended by clinical guidelines for empirical treatment of CAP.[4,5] In addition to the pre-defined sensitivity analyses, we conducted exploratory sensitivity analyses including only trials that randomized before the initial antibiotic treatment to test the influence of randomization timing.

Amendments

We report amendments with the date and the rationale in the appendix (eAppendix3).

RESULTS

We identified 1,994 records via database and one record via searching websites, which revealed that some different records refer to the same clinical trial. We assessed 38 full-text records for eligibility and included 11 eligible studies. (Fig1) Of these, 8 were published,[11–15,36–38] 1 was unpublished[39] and 2 studies were still ongoing,[40,41] resulting in 9 trials for the primary outcome analysis. The lists of included and excluded studies are provided in the appendix (eAppendix4 and 5). The 9 studies with 2,399 participants in total included 18

eligible arms. Treatment duration ranged from 3 to 10 days. The study year ranged between 1999 and 2021. Table 1 presents the characteristics of the included studies.

The included studies were all parallel-group and individually randomized. Seven out of nine were reported as non-inferiority trial. In total, 1,199 participants were randomly assigned to the shorter duration arm and 1,200 to the longer duration arm. The mean age was 61.2 years (standard deviation 22.1); 831 (39%) of 2,140 reported were women. Six were conducted in a single European country, one in the US, and the two were cross-continental. CAP was defined as newly confirmed clinical symptoms (eg, dyspnoea, cough, purulent sputum, or crackles), and radiological findings. Clinical stability was often defined as apyrexia (temperature ≤37.8 C) for 48 hours, heart rate below 100 beats per min, respiratory rate below 24 breaths per min, arterial oxygen saturation of 90% or higher, systolic blood pressure of 90 mm Hg or higher, and normal mental status.[42] Percentage of pneumonia severity index class IV or V was on average 19% (362 of 1,896 reported; ranging from 2 to 41%). Seven studies focused on inpatients, whereas one study focused on outpatients and one included both. Antibiotics used included β-lactam (amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, ceftazidime, ceftriaxone, cefuroxime, piperacillin/tazobactam), macrolide (azithromycin, clarithromycin), quinolone

(ciprofloxacin, gemifloxacin, levofloxacin, telithromycin), amikacin, doxycycline, and meropenem. Pharmaceutical companies funded four studies.[13–15,36] Four studies had a high overall risk of bias, four some concerns, and only one had low overall risk of bias. (Table 1)

Table 1 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 at day 15	Risk of bias D1	D2	D3	D4	D5	Overall	Sponsored
Siegel et al, 1999	61.1	15.1	NA	NA	Inpatient	7 10	CXM	25 27	21 20	L	H	H	L	S	H	Yes
Leophonte et al, 2002	64.0	18.7	25	NA	Inpatient	5 10	CRO	125 119	93 85	S	L	L	S	H	H	Yes
Tellier et al, 2004	45.8	18-87†	42	7	Both	5 7	TEL	193 195	154 157	L	L	S	L	S	S	Yes
El Moussaoui et al, 2006	57.2*	23.9*	40	12	Inpatient	3 8	AMX	57 64	50 56	S	L	L	L	S	S	No
File et al, 2007	45.4	16.8	42	3	Outpatient	5 7	GMI	256 256	240 234	L	L	L	L	S	S	Yes
Stralin et al, 2014	NA	NA	NA	NA	Inpatient	5 10	β-lactam	103 103.5	79 81	H	H	H	H	H	H	No
Uranga et al, 2016	65.4	18.3	37	39	Inpatient	5 10	Various	162 150	90 71	S	L	L	S	S	S	No
Aliberti et al, 2017	60.6*	24.8*	40	24	Inpatient	6 8	Various	125 135	111 125	L	H	L	L	S	H	No
Dinh et al, 2021	73.2*	21.0*	41	39	Inpatient	3 8	β-lactum + placebo β-lactum + AMC	152 151	117 102	L	L	L	L	L	L	No

Table 1 Characteristics of included studies (continued)

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

AMC = amoxicillin-clavulanic acid; AMX = amoxicillin; CRO = ceftriaxone; CXM = cefuroxime; D1 = Bias due to randomization; 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: GMI = gemifloxacin; H = high; L = low; PSI = pneumonia severity index; S = some concerns; SD = standard deviation; TEL = telithromycin

Assessment of heterogeneity

We assessed the heterogeneity in efficacy outcome across duration range (9 studies). VPC values were constantly below 10% which suggests low levels of heterogeneity. However, these assessments need to be carefully interpreted due to the small number of included studies. (eAppendix6)

Dose-effect meta-analysis

We present the duration-effect curves in Figure 2 and Figure 3, and the tabulation of results in Table 2. The x-axis of the figures represents the treatment duration in days and the y-axis represents the odds ratio of the outcome. The thin solid horizontal line represents the odds ratio = 1 and the thin dotted horizontal line in the clinical improvement figures corresponds to the non-inferiority margin translated into OR. (The average percentage of clinical improvement rate at day 15 in the 10-day treatment arms was 68%. Non-inferiority margin was therefore 58% and the corresponding OR was 0.65. For clinical improvement at day 30, the numbers were 77%, 67% and OR 0.61, respectively.) The thick solid line represents the dose-effect curve and the thick dotted lines represent its 95% CI. The duration-effect curve is monotonic with longer duration leading to lower probability of improvement. The

lower 95%CI curve was constantly above the prespecified non-inferiority margin, meaning that a shorter treatment duration (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days). It was slightly above the OR = 1 line around 3 days, suggesting 3-day treatment may be superior to 10-day treatment. Secondary outcomes had wider confidence interval curves. Harmful outcome curves (all-cause mortality and severe adverse events) were almost flat and 95%CI curves did not cross the OR = 1 line, indicating no association. Clinical improvement at day 30 showed a similar trend with the primary outcome with the lower 95%CI curve constantly above the prespecified non-inferiority margin. The average percentage of clinical improvement rate at day 15 in the 10-day treatment arms was 68% (based on a meta-analysis of the included studies). Using that average, we computed the absolute clinical improvement rates at the following durations: a 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day treatment 69% (61 to 76%).

Table 2 Primary and secondary outcomes for 3, 5, 7 and 10-day treatment

Outcome		Treatment duration (days)							
		3		5		7		10	(Reference)
Clinical improvement	OR	1.44	[1.01-2.05]	1.21	[0.90-1.63]	1.05	[0.74-1.50]	1.00	(reference)
at day 15	Rate	75%	[68-81%]	72%	[66-78%]	69%	[61-76%]	68%	(4 arms)
All-cause mortality	OR	1.11	[0.28-4.35]	0.93	[0.34-2.58]	0.84	[0.23-3.09]	1.00	(reference)
	Rate	3%	[1-11%]	3%	[1-7%]	2%	[1-8%]	3%	(3 arms)
Serious adverse	OR	0.73	[0.27-1.96]	0.80	[0.51-1.24]	0.86	[0.40-1.85]	1.00	(reference)
events	Rate	15%	[6-31%]	16%	[11-22%]	17%	[9-30%]	19%	(2 arms)
Clinical improvement	OR	1.24	[0.86-1.78]	1.16	[0.82-1.63]	1.09	[0.74-1.60]	1.00	(reference)
at day 30	Rate	81%	[74-86%]	80%	[74-85%]	79%	[73-84%]	77%	(4 arms)

Sensitivity analyses

Sensitivity analyses were in line with the primary analyses. (eAppendix7. Figures S1, using different locations of knots; S2.1, excluding trials with overall high risk of bias; S2.2, excluding trials with outpatients; S3, using PP dataset; S4 including only antibiotics recommended for empirical treatment of CAP by clinical guidelines). Exploratory sensitivity analyses showed that non-inferiority of the shorter duration was more likely to be the case in studies that randomized patients who had reached clinical stability early (eAppendix7. Figures S5.1, S5.2).

DISCUSSION

To our knowledge, this is the first systematic review and duration-effect meta-analysis of antibiotics treatment for CAP in adults. The results showed that a shorter treatment duration (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for CAP in adults. There may be no significant difference in all-cause mortality or serious adverse events. A shorter range probably achieves the optimal balance between efficacy and treatment burden.

This is in line with the previous pair-wise meta-analysis that showed shorter duration was non-inferior to longer duration.[10] Methodological limitations in a previous meta-analysis restricted authors from recommending a specific treatment duration. We overcame this limitation by examining the duration of antibiotic treatment range in days and found that a 3 to 9-day treatment is likely to be non-inferior to a 10-day treatment. Our results are in line with the guidelines for CAP recommending antibiotics to be prescribed for a duration shorter (5-8 days) than current clinical standard practice (10 days).[4–6] Our results suggest that an even shorter duration (3-5 days) may be considered, which is in line with the trials that found 3-day treatment was non-inferior to 8-day treatment.[12,37]

Limitations

Our study has several limitations. First, most of the included studies presented with moderate to high overall risk of bias. Second, the number of studies was small, leaving confidence intervals for secondary outcomes wide. Third, original studies excluded patients with complications of CAP and therefore the results of this study may not be generalizable to those patients. Forth, baseline severity of the included studies varied. However, the overall heterogeneity was low.

Strengths

First, we did a comprehensive systematic review and found 4 studies that were not included the previous systematic reviews. Second, we treated duration as a continuous variable, which allowed us to estimate the duration-effect relationship with greater resolution of change points. Third, we examined impacts of treatment duration not only for clinical improvement but also for all-cause mortality and severe adverse events and made sure that a shorter treatment duration would not translate into more harmful events. Finally, the very nature of shortened duration treatment offers a unique opportunity for interpretation. Shorter treatment durations have been examined by non-inferiority trials. The underlying assumption has been that there was a trade-off between a loss in efficacy of standard treatment duration and other benefits of a shortened duration, [43,44] such as less time, less cost and probably a diminished rate of antimicrobial resistance. This study suggests that there may be even no trade-off for antibiotic treatments of 3 to 5 days. Shorter treatment duration reduces the burden on patients, the healthcare system and the risk of antimicrobial resistance and might even offer better clinical outcomes at the same time.

CONCLUSIONS

Shorter treatment duration (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for adults with CAP if they achieved clinical stability. A shorter range (3-5 days) probably results in an optimal balance between efficacy and treatment burden. However, the small number of included studies and the overall moderate to high risk of bias may compromise the certainty of the results. Further research focusing on the shorter duration range is required.

Abbreviations

CAP: community-acquired pneumonia
ITT: intention-to-treat
PP: per protocol
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
VPC: variance partition coefficient

DECLARATIONS

Ethics approval and consent to participate

This study uses published aggregate data and did not require ethical approval.

Consent for publication

Not applicable.

Availability of data and materials

Data and code used for analyses are available from the corresponding author on reasonable request.

Competing interests

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YF, TH declare no conflicts of interest.

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Author Contributions

YF: Conceptualization, Methodology, Software, Validation, Formal analysis, Data Curation, Writing – Original Draft, Visualization, Supervision, Project administration
YL: Conceptualization, Methodology, Data Curation, Validation, Writing – Review & Editing,
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EGO: Conceptualization, Methodology, Data Curation, Validation, Writing – Review & Editing,
TH: Methodology, Software, Formal analysis, Visualization, Validation, Writing – Review & Editing,
TAF: Conceptualization, Methodology, Writing – Review & Editing, Supervision,
YK: Conceptualization, Methodology, Writing – Review & Editing, Supervision
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FIGURE LEGENDS

Figure 1 PRISMA flow diagram

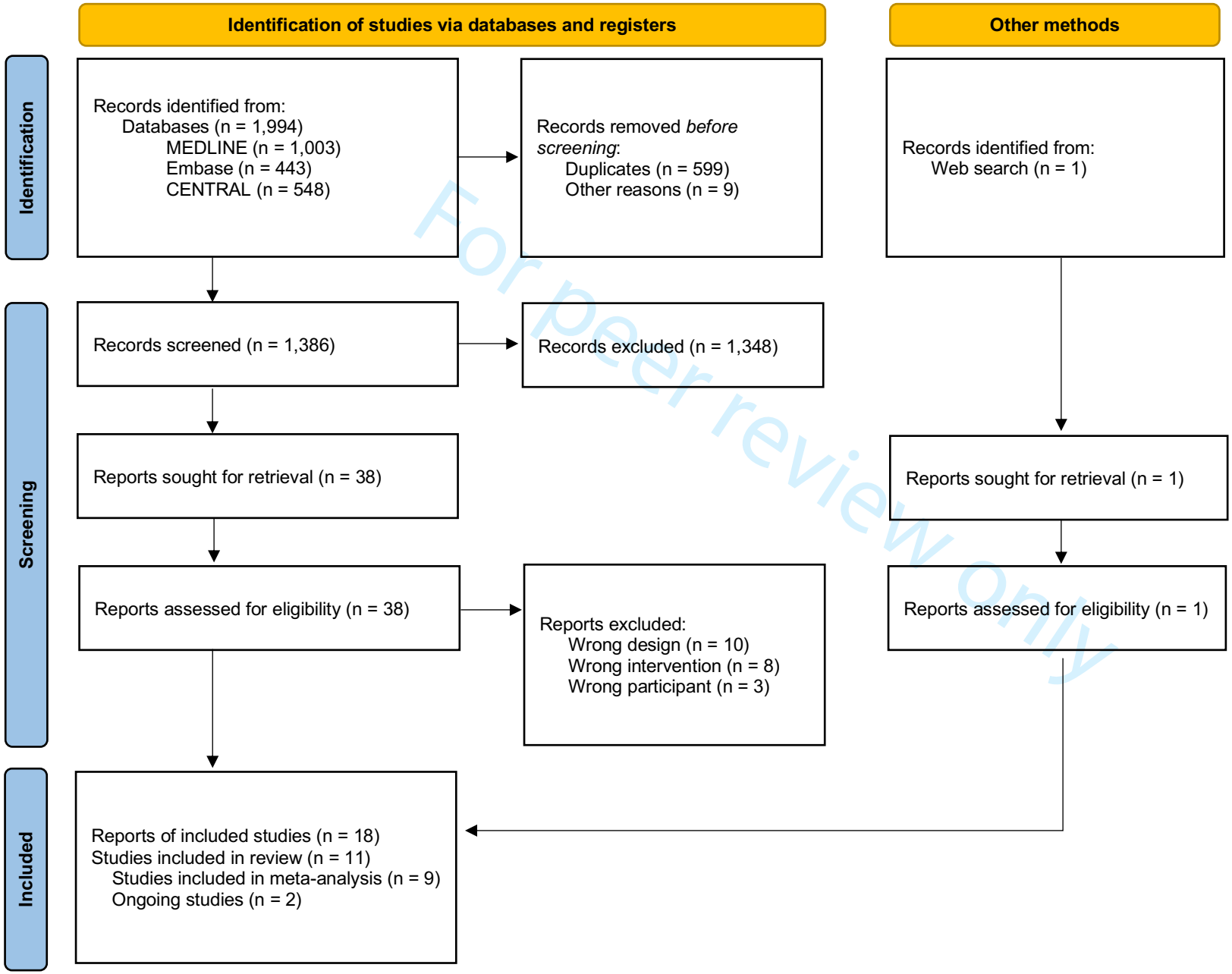
Figure 2 Duration–effect relationship of antibiotics for CAP in adults. Clinical improvement at day 15.

OR=odds ratio. The dotted lines represent 95% confidence intervals. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the average event rate of 68%

Figure 3 Duration–effect relationships of antibiotics for CAP in adults. (a) All-cause mortality. (b) Severe adverse events. (c) Clinical improvement at day 30.

OR=odds ratio. The dotted lines represent 95% confidence intervals. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the average event rate of 77%

Figure 1 PRISMA flow diagram



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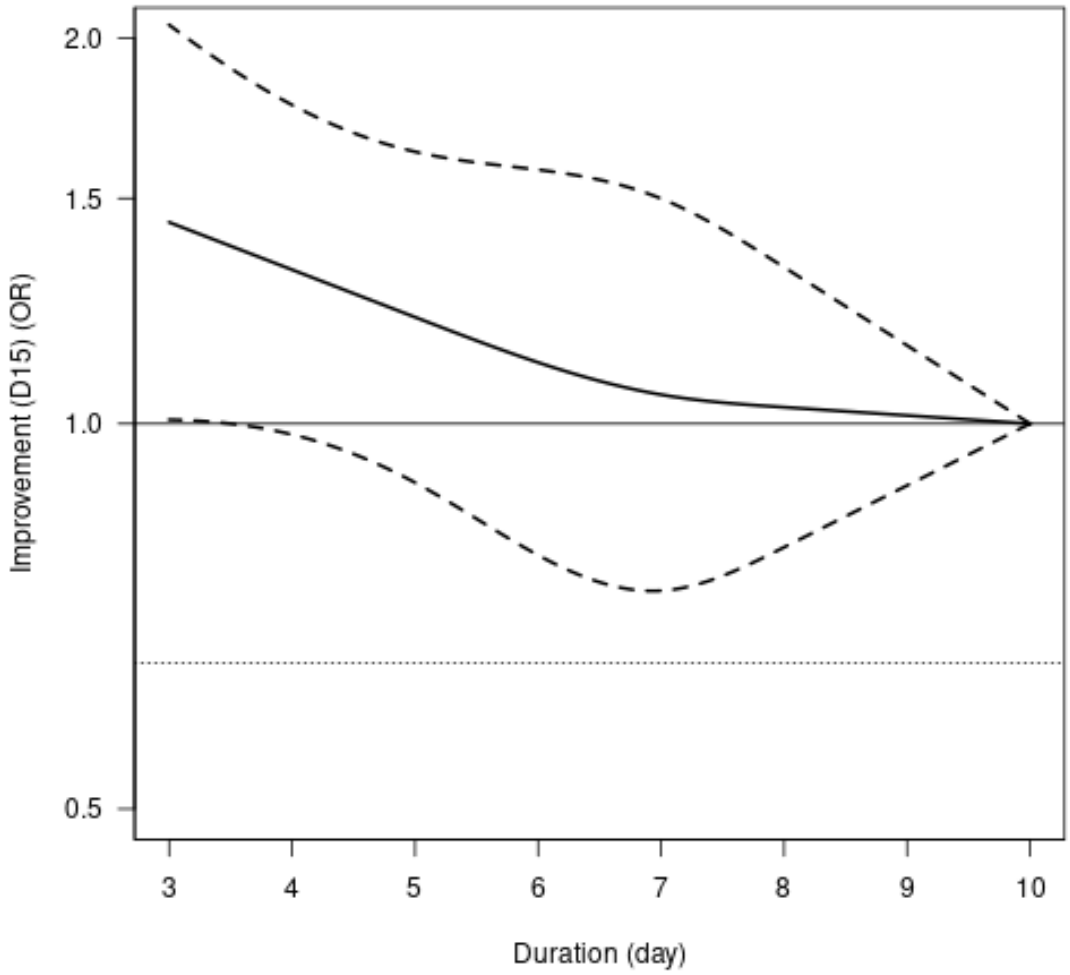

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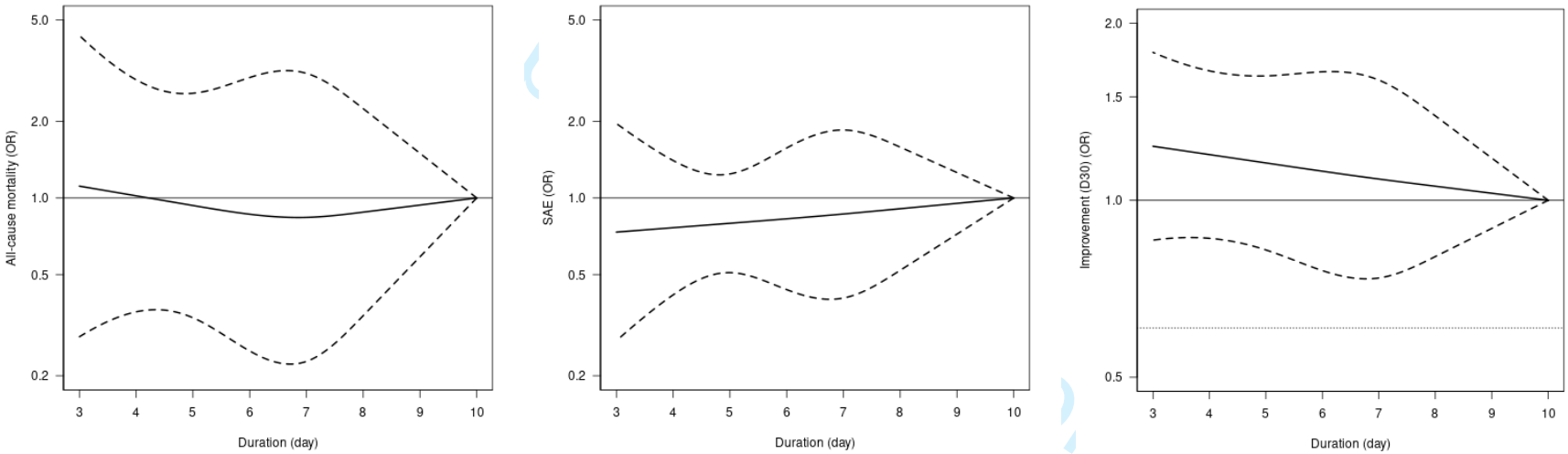

Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a systematic review and duration-effect meta-analysis (eAppendix)

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

1. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: protocol for a systematic review and duration-effect meta-analysis (protocol as of 15th August, 2021)
2. Search strings used for Ovid MEDLINE, Embase, and CENTRAL.
3. Amendments from the protocol
4. List of all included papers
5. List of excluded studies
6. Heterogeneity: Variance partition coefficient for the primary outcome
7. Sensitivity analyses

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)

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

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).

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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

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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

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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

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

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 randomized patients after achieving clinical stability. (27th October, 2021, after data extraction. Post hoc)

4. List of all included papers

- 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.
- 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.
- 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.
- 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.
- 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.
- Strålin K, Rubenson A, Lindroth H, et al. BETALACTAM TREATMENT UNTIL NO FEVER FOR 48HOURS (AT LEAST 5 DAYS) VERSUS 10 DAYS IN COMMUNITY-ACQUIRED PNEUMONIA: RANDOMISED, NON-INFERIORITY, OPEN STUDY. *Pneumonia* 2014; 3: 246–81.
- 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.
- Aliberti S, Ramirez J, Giuliani F, et al. Individualizing duration of antibiotic therapy in community-acquired pneumonia. *Pulm Pharmacol Ther* 2017; 45: 191–201.
- 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.

Ongoing trials

- NCT03609099. Adequate Duration of Antibiotic Treatment in Community-acquired Pneumonia With High Risk Class and Adequate Initial Clinical Response (2017-001406-15). Available from: https://clinicaltrials.gov/ct2/show/NCT03609099
- NCT04089787. Shortened Antibiotic Treatment of 5 Days in Community-Acquired Pneumonia (CAP5). Available from: https://clinicaltrials.gov/ct2/show/NCT04089787

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)

6. 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.

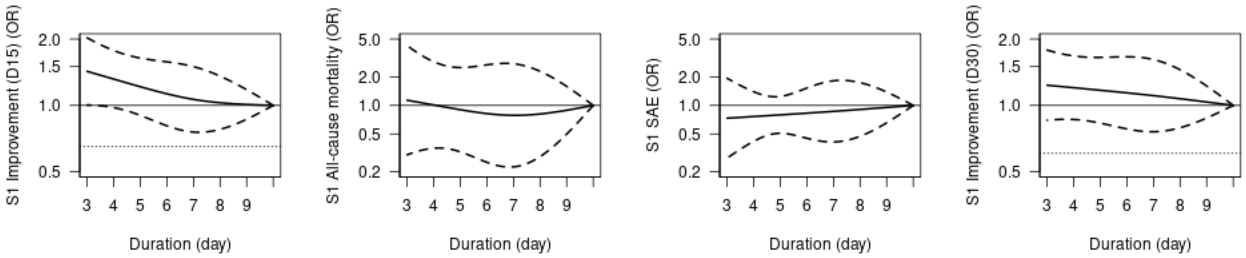
```
>   vpc(mod1)
          2           4           6           8          10          12          14          16          18
1.059171e-10 1.102071e-09 3.592398e-09 4.059647e-09 2.000592e-10 8.322319e-10 1.771638e-09 1.071397e-10 1.843283e-08
```

7. Sensitivity analyses

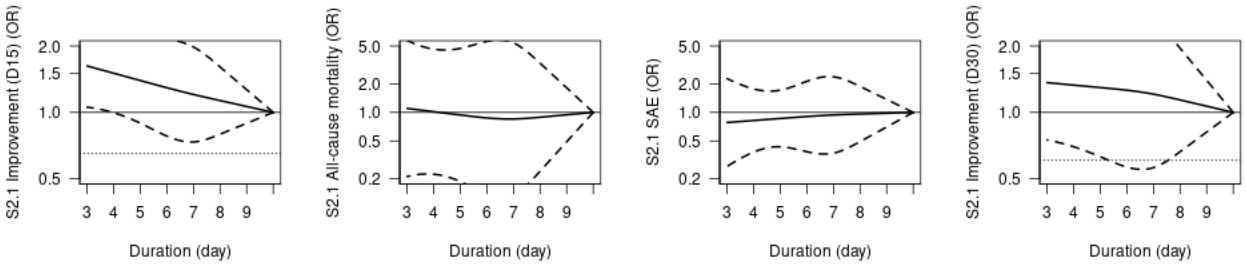
Duration-effect relationship of secondary outcomes could not be computed due to missing data in some cases.

A priori sensitivity analyses

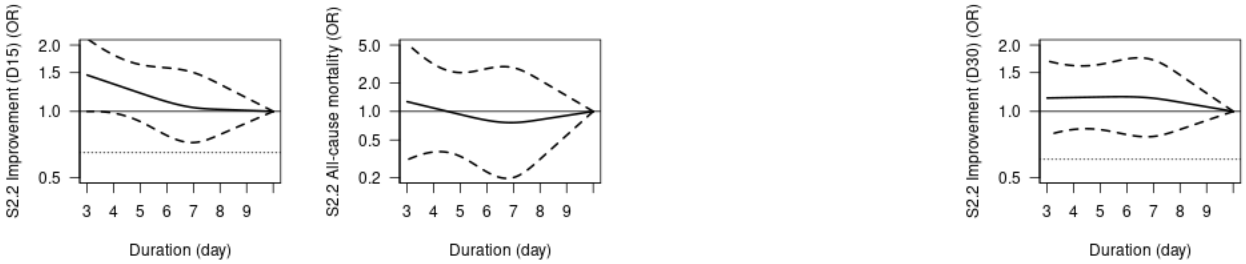
##S1 To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%).



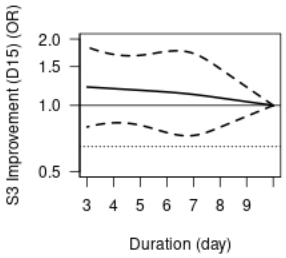
##S2.1 To test the influence of trials included, we conducted sensitivity analyses excluding trials with overall high risk of bias (excluding Siegel1999, Leophonte2002, Stralin2014, Aliberti2017)

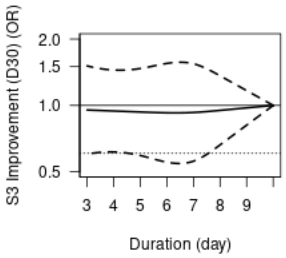


##S2.2 To test the influence of trials included, we conducted sensitivity analyses excluding trials with outpatients (excluding Tellier2004, File2007. SAE not computable)

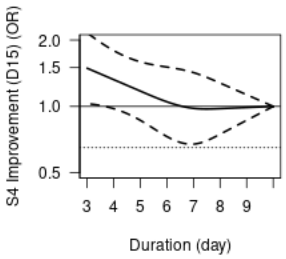


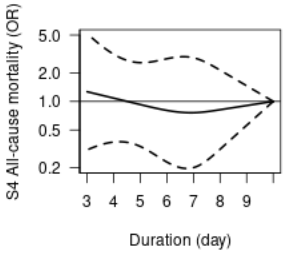
##S3 To test the robustness of the analytical method, we used PP dataset. (All-cause mortality and SAE not computable)

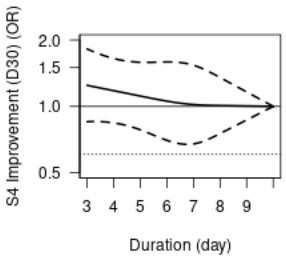




##S4 To test the influence of antibiotics examined, we conducted sensitivity analyses including only antibiotics recommended for empirical treatment of CAP by clinical guidelines. (excluding Siegel1999, Tellier2004. SAE not computable.We included trials that used various antibiotics)

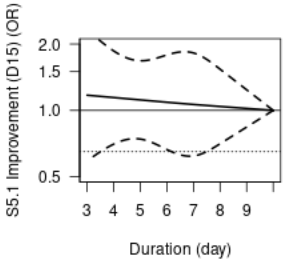


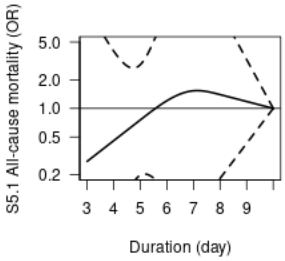


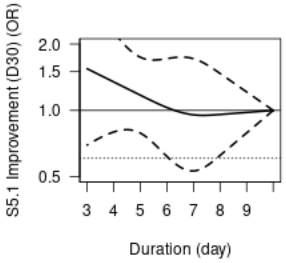


Post-hoc, exploratory sensitivity analyses

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

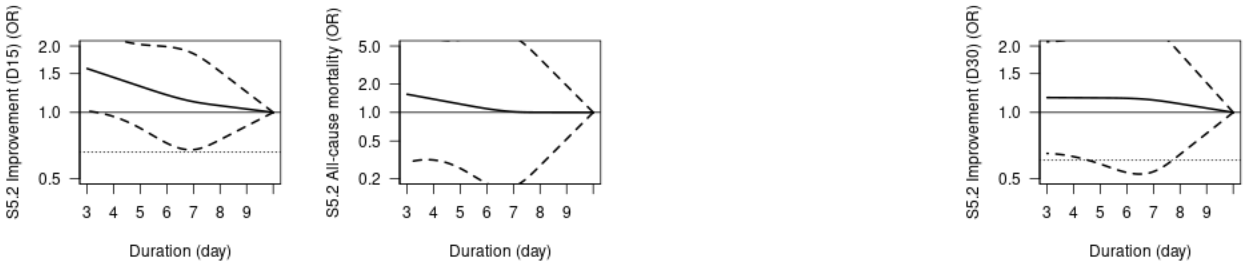






##S5.2 Randomization after several days or clinical stability achieved (including ElMoussaoui2006, Uranga2016, Aliberti2017, Dinh2021. SAE not computable)

437



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

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1, Line 3-4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Page 3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 6, Line 97-124
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 7, Line 127-128
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 8, Line 134-157
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 10, Line 171-176
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 10, Line 173-177, eAppendix2

Topic	No.	Item	Location where item is reported
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11, Line 182-188
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 11, Line 182-188
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 9-10, Line 159-168, eAppendix1 (protocol) > METHODS AND ANALYSES > Data items
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	eAppendix1 (protocol) > METHODS AND ANALYSES > Data items
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11, Line 185-187
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 10, Line 168

Topic	No.	Item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 10, Line 167-168
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 12, Line 199-205
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 12, Line 199-205
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 12, Line 206-216
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			

Topic	No.	Item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 13, Line 220-224, Fig1 (flow diagram)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	eAppendix4
Study characteristics	17	Cite each included study and present its characteristics.	Table1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 16, Table1 (primary outcome)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA (not presented for each synthesis)
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 18-20, Line 264-287, Fig2 and 3, Table2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 21, Line 291-298, eAppendix7

Topic	No.	Item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 21, Line 300-306
	23b	Discuss any limitations of the evidence included in the review.	Page 22, Line 317-323
	23c	Discuss any limitations of the review processes used.	NA
	23d	Discuss implications of the results for practice, policy, and future research.	Page 24, Line 341-347
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 8, Line 130
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	eAppendix1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	eAppendix3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 26, Line 406-408

Topic	No.	Item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Page 24, Line 365-387
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 24, Line 362-364

PRISMA 2020 Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No (stated in main text)
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes

Topic	No.	Item	Reported?
OTHER			
Funding	11	Specify the primary source of funding for the review.	No (stated in main text)
Registration	12	Provide the register name and registration number.	Yes

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061023.R1
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TITLE PAGE

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

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ABSTRACT (300 words)

Objectives: To find the optimal treatment duration with antibiotics for community-acquired pneumonia (CAP) in adults.

Design: Systematic review and duration-effect meta-analysis.

Data sources: MEDLINE, Embase and CENTRAL through 25 August 2021.

Eligibility criteria: All randomised controlled trials comparing the same antibiotics used at the same daily dosage but for different durations for CAP in adults. Both outpatients and inpatients were included but not those admitted to intensive care units. We imposed no date, language or publication status restriction.

Data extraction and synthesis: Data extraction by two independent reviewers. We conducted a random-effects, one-stage duration-effect meta-analysis with restricted cubic splines. We tested the non-inferiority with the pre-specified non-inferiority margin of 10% examined against 10 days using. The primary outcome was clinical improvement on day 15 (range 7-45 days). Secondary outcomes: all-cause mortality, serious adverse events, and clinical improvement on day 30 (15-60 days).

Results: We included 9 trials (2,399 patients with a mean [SD] age of 61.2 [22.1]; 39% women). The duration-effect curve was monotonic with longer duration leading to a lower probability of improvement, and shorter treatment duration (3-9 days) was likely to be non-inferior to 10-day treatment. Harmful outcome curves indicated no association. The weighted average percentage of the primary outcome in the 10-day treatment arms was 68%. Using that average, the absolute clinical improvement rates of the following durations were: 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day treatment 69% (61 to 76%).

Conclusions: Shorter treatment duration (3-5 days) probably offers the optimal balance between efficacy and treatment burden for treating CAP in adults if they achieved clinical stability. However, the small number of included studies and the overall moderate to high risk of bias may compromise the certainty of the results. Further research on the shorter duration range is required.

Registration: PROSPERO (CRD 42021273357).

Strengths and limitations of this study

- We conducted a comprehensive and up-to-date systematic literature review.
- The duration-effect meta-analysis treated duration as a continuous variable, which allowed us to estimate the duration-effect relationship with greater resolution than the conventional pairwise meta-analysis that dichotomised duration arbitrarily.
- The small number of trials included limited the precision of some study results.
- Most of the trials had a moderate to high overall risk of bias.
- About 80% of the patients had pneumonia severity index class III or less and thus the results may not be generalisable to severely ill patients.

Keywords

Community-acquired pneumonia; antibiotic; treatment duration; dose-response meta-analysis

MAIN TEXT (3259 words)

BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality globally, especially among the elderly.[1] In the United States, it is the second most common cause of hospitalisation and the top infectious cause of death.[2,3] The initial treatment for CAP is empirical, with guidelines recommending starting several antibiotics depending on patients' severity and risk factors for certain pathogens.[4–6]

The optimal duration of antimicrobial therapy remains unclear and controversial. The American and British guidelines recommend a minimum of five days of treatment before therapy discontinuation for patients achieving clinical stability.[4,5] The European guideline states that the duration of treatment should not exceed eight days in responding patients.[6] In clinical practice, however, antibiotics for pneumonia are often prescribed for 10 up to 14 days.[7,8] This may mean that many patients are receiving more antibiotics than necessary, with a consequent increase in costs and a higher probability of antimicrobial resistance.[9] Finding the optimal duration of antibiotics can facilitate reducing antimicrobial use efficiently. Several meta-analyses have been reported on this topic.[10–12] A major limitation of the method used in the previous pairwise meta-analyses

is the arbitrary categorisation of duration when the original studies compared different duration, ranging from three to ten days. A pairwise meta-analysis published in 2008, [10] for example, categorised a seven-day treatment arm in one trial as short-course and the same in other two trials as long-course. [13–15] Another pairwise meta-analysis in 2018 excluded a trial comparing seven-day against ten-day treatment because they defined long-course as seven days or longer.[11] The duration range of short course therapy defined by a systematic review of systematic reviews and guidelines with pairwise meta-analyses in 2019 was wide (three to seven days) and the duration-effect relationship within that range remains unclear.[12] We overcame the limitation of arbitrary dichotomisation of duration by using a novel method called dose-effect meta-analysis.[16] It has been used, for example, to examine the effects of potassium intake or sodium reduction on blood pressure[17,18]. Unlike conventional categorisation-based meta-analyses[19], dose-effect meta-analysis can reveal more fine-grained optimal dose[20]. By treating duration as dose, we aimed to apply this method to obtain a more specific optimal treatment duration.

METHODS

We summarised the currently available evidence to find the optimal treatment duration of antibiotics for CAP in adults. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) [21]. The protocol has been prospectively registered in PROSPERO (CRD 42021273357) and can be found in the appendix (eAppendix1).

Patient and Public Involvement

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

Data sources

Criteria for considering studies for this review

Types of studies

To examine the duration-effect relationship, we included all trials that compared two or more different durations of the same antibiotic treatment for CAP.

Types of participants

Patients were eligible if they were 18 years or older of both genders with a diagnosis of CAP as defined by the original authors. We included both outpatients and inpatients. We

excluded patients who were admitted to the intensive care unit. To focus on individuals at low to medium risk, we excluded 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 included trials examining any antibiotics, administered orally or intravenously. We evaluated antibiotics as a class because clinical guidelines recommend treatment duration irrespective of the antibiotic used,[4–6] and because recent meta-analyses of antibiotics for CAP have not shown efficacy differences among antibiotics.[22,23] Oral and intravenous antibiotics were merged because they have been shown equally effective in many infectious conditions within the same time frame.[24–26] We included trials comparing the same agents used at the same daily dosage but for different durations. We used the predefined duration for fixed-duration arms. If some studies did not prespecified the duration (eg. left it to clinicians' judgment[27]), we used the median duration.

Primary outcome and secondary outcomes

The primary outcome of interest in this study was the 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.[28] Secondary outcomes of interest were: all-cause mortality on day 15 (range 7-45 days), serious adverse events as defined by the original study on day 15 (range 7-45 days), and clinical improvement as defined by the original study on day 30 (range 15-60). We used the number of randomised patients as the denominator for the intention-to-treat (ITT) dataset. When only clinical failure was reported, clinical improvement was calculated by subtracting clinical failure from the total number randomised. We used ITT for the primary analysis and the per-protocol (PP) dataset for a sensitivity analysis.[29,30] We used the odds ratio (OR) of each outcome to synthesise data. [31,32]

Search methods for identification of studies

Electronic searches

We systematically searched the following electronic bibliographic databases from inception through 25 August 2021: MEDLINE, Embase and CENTRAL. We used search terms for community-acquired pneumonia in conjunction with the names of individual antibiotics as

well as the names of antibiotic classes. Detailed search formulas are presented in the appendix (eAppendix2). We imposed no date, language or publication status restriction.

Reference lists

We checked the reference lists of all the included studies and review articles for additional references.

Data collection and analysis

Selection of studies

Two review authors independently screened and selected the included studies (YF and one of AO, EO, SF or YL). Two review authors extracted data independently from the included studies (YF and one of AO, EO, SF or YL). We used the Cochrane risk of bias tool Version 2 [33] to assess and summarise the risk of bias. Disagreements were resolved through discussion.

Statistical analysis

To perform our analyses, we used the *dosresmeta* package (Version 2.0.1) and *meta* package (Version 5.0-1) for *R* (Version 4.1.0. R foundation, Wien, Austria).[34–36]

Assessment of heterogeneity

We investigated the heterogeneity between studies by the variance partition coefficient (VPC). [16] VPC represents the percentage of variation attributed to heterogeneity rather than sampling error and can be interpreted similarly to the I^2.

Duration-effect meta-analysis

In the duration-effect meta-analysis, we assumed that the relative efficacy of a certain treatment duration ($duration_i$) against another ($duration_j$) can be expressed in the log-odds ratio ($\log OR_{ij}$) and that it is a function of both durations ($\log OR_{ij} = f(duration_i; duration_j)$). We fitted restricted cubic splines with three knots to the dataset obtained by the systematic review because this model has shown sufficient flexibility to capture different shapes.[37] Given the clinical and methodological heterogeneity likely present in the included studies, we used the random effects model. We used three knots, equally spaced across the duration range (25%, 50%, 75%). Typically, in dose-effect meta-analyses, the reference dose is assigned to the zero or the minimal dose to make interpretation easier.[37] As this duration-effect meta-analysis aimed to test the non-

inferiority of the shorter treatment duration, we decided to use the maximum duration as the reference to make interpretation easier. Also, the reference we set (10-day treatment) can be regarded as the current practice.[7,8,27] We tested the non-inferiority with the non-inferiority margin of 10%, as previously proposed,[28] and the superiority of the shorter duration examined against 10-day treatment using the ITT dataset.

Sensitivity analyses

To ascertain the robustness of the primary analyses, we conducted the following sensitivity analyses. To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%). To test the influence of trials included, we conducted sensitivity analyses excluding trials with an overall high risk of bias and excluding trials with outpatients. To test the robustness of the analytical method, we used the PP dataset. To test the influence of antibiotics examined, we conducted sensitivity analyses restricting eligible antibiotics only to those recommended by clinical guidelines for empirical treatment of CAP.[4,5] In addition to the pre-defined sensitivity analyses, we conducted exploratory sensitivity analyses including only trials that randomised before the initial antibiotic treatment to test the influence of randomisation timing.

Amendments

We report amendments with the date and the rationale in the appendix (eAppendix3).

RESULTS

We identified 1,994 records via database and one record via searching websites, which revealed that some different records refer to the same clinical trial. We assessed 38 full-text records for eligibility and included 11 eligible studies. (Fig1) Of these, eight were published,[13–15,27,38–41] one was unpublished[42] and two studies were still ongoing,[43,44] resulting in nine trials for the primary outcome analysis. The lists of included and excluded studies are provided in the appendix (eAppendix4 and 5). The nine studies with 2,399 participants in total included 18 eligible arms. Treatment duration ranged from three to ten days. The study year ranged between 1999 and 2021. Table 1 presents the characteristics of the included studies.

The included studies were all parallel-group and individually randomised. Seven out of nine were reported as non-inferiority trials. In total, 1,199 participants were randomly assigned to the shorter duration arm and 1,200 to the longer duration arm. The mean age was 61.2 years (standard deviation 22.1); 831 (39%) of 2,140 reported were women. Six

were conducted in a single European country, one in the US, and the two were cross-continental. CAP was defined as newly confirmed clinical symptoms (eg, dyspnoea, cough, purulent sputum, or crackles), and radiological findings. Antibiotic treatment was discontinued when the patient was clinically stable and the pre-determined treatment period was completed. Clinical stability was often defined as apyrexia (temperature ≤37.8 C) for 48 hours, heart rate below 100 beats per min, a respiratory rate below 24 breaths per min, arterial oxygen saturation of 90% or higher, systolic blood pressure of 90 mmHg or higher, and normal mental status.[45] Clinical improvement was often described as "clinical cure" or "clinical success" and was often defined as the resolution of fever and improvement of symptoms related to pneumonia without further antibiotics. More detailed definitions of clinical improvement in each included study are listed in the appendix. (eAppendix6) The percentage of pneumonia severity index class IV or V was on average 19% (362 of 1,896 reported; ranging from 2 to 41%). Seven studies focused on inpatients, whereas one study focused on outpatients and one included both. Antibiotics used included β-lactams (amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, ceftazidime, ceftriaxone, cefuroxime, piperacillin/tazobactam), macrolides (azithromycin, clarithromycin), quinolones (ciprofloxacin, gemifloxacin, levofloxacin, telithromycin), amikacin,

doxycycline, and meropenem. Pharmaceutical companies funded four studies.[13–15,38] Four studies had a high overall risk of bias, four some concerns, and only one had a low overall risk of bias. (Table 1)

Table 1 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	Risk of bias D1	D2	D3	D4	D5	Overall	Sponsored
Siegel et al, 1999	61.1	15.1	NA	NA	Inpatient	7 10	CXM	25 27	21 20	L	H	H	L	S	H	Yes
Léophonte et al, 2002	64.0	18.7	25	NA	Inpatient	5 10	CRO	125 119	93 85	S	L	L	S	H	H	Yes
Tellier et al, 2004	45.8	18-87†	42	7	Both	5 7	TEL	193 195	154 157	L	L	S	L	S	S	Yes
El Moussaoui et al, 2006	57.2*	23.9*	40	12	Inpatient	3 8	AMX	57 64	50 56	S	L	L	L	S	S	No
File et al, 2007	45.4	16.8	42	3	Outpatient	5 7	GMI	256 256	240 234	L	L	L	L	S	S	Yes
Strålin et al, 2014	NA	NA	NA	NA	Inpatient	5 10	β-lactam	103 104	79 81	H	H	H	H	H	H	No
Uranga et al, 2016	65.4	18.3	37	39	Inpatient	5 10	Various	162 150	90 71	S	L	L	S	S	S	No
Aliberti et al, 2017	60.6*	24.8*	40	24	Inpatient	6 8	Various	125 135	111 125	L	H	L	L	S	H	No
Dinh et al, 2021	73.2*	21.0*	41	39	Inpatient	3 8	β-lactam + placebo β-lactam + AMC	152 151	117 102	L	L	L	L	L	L	No

Table 1 Characteristics of included studies (continued)

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

AMC = amoxicillin-clavulanic acid; AMX = amoxicillin; CRO = ceftriaxone; CXM = cefuroxime; 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: GMI = gemifloxacin; H = high; L = low; PSI = pneumonia severity index; S = some concerns; SD = standard deviation; TEL = telithromycin

Assessment of heterogeneity and publication bias

We assessed the heterogeneity in the efficacy outcome across the duration range (9 studies). VPC values were constantly below 10% which suggests low levels of heterogeneity. Visual inspection of the funnel plot suggested no significant publication bias. However, these assessments need to be carefully interpreted due to the small number of included studies. (eAppendix8 and 9)

Duration-effect meta-analysis

We present the duration-effect curves in Figure 2 and Figure 3, and the tabulation of results in Table 2. The x-axis of the figures represents the treatment duration in days. The y-axis represents the odds ratio of the outcome on a logarithmic scale, just as in the forest plot of conventional pairwise meta-analysis using binary outcomes. The thin dotted horizontal line in the clinical improvement figures and the all-cause mortality figure corresponds to the non-inferiority margin translated into OR. (The weighted average percentage of clinical improvement rate on day 15 in the 10-day treatment arms was 68%. The non-inferiority margin was therefore 58% and the corresponding OR was 0.65. For all-cause mortality, the numbers were 3%, 13% and OR 4.8, respectively. For clinical improvement on day 30, the

numbers were 77%, 67% and OR 0.61, respectively. We did not show the non-inferiority margin in the figures for severe adverse events, because the position paper did not provide any margin for this outcome.[28]) The thick solid line represents the ~~dose~~ duration-effect curve and the thick dotted lines represent its 95% CI. The 95% CI band becomes narrower when the duration range was examined by many trials or when it gets closer to the reference point. For the beneficial outcomes (clinical improvement), OR > 1 means more effective. For the harmful outcomes (all-cause mortality and serious adverse events), OR < 1 means safer.

The duration-effect curve is monotonic with a longer duration leading to a lower probability of improvement. The lower 95%CI curve was constantly above the prespecified non-inferiority margin, meaning that a shorter treatment duration (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days). It was slightly above the OR = 1 around 3-day treatment, suggesting 3-day treatment may be superior to 10-day treatment. Harmful outcome curves (all-cause mortality and severe adverse events) were almost flat and 95%CI curves did not cross the OR = 1, indicating no association. Although the confidence interval curves were wide for all-cause mortality, shorter treatment duration (3-9 days) was likely to be non-inferior to 10-day treatment. Clinical improvement on day 30

showed a similar trend with the primary outcome with the lower 95%CI curve constantly above the prespecified non-inferiority margin. We made a league table (eAppendix10), which showed that shorter treatment duration was likely to be non-inferior to longer treatment duration, regardless of the reference duration.

Odds ratios need to be translated into absolute event rates so that the results can be interpreted from the clinical point of view. The weighted average percentage of clinical improvement rate on day 15 in the 10-day treatment arms was 68%, based on a single proportion meta-analysis of the included studies. Using this average, we computed the absolute clinical improvement rates at the following durations as follows: 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day treatment 69% (61 to 76%). (Table 2)

Table 2 Primary and secondary outcomes for 3, 5, 7 and 10-day treatment

Outcome		Treatment duration (days)							
		3		5		7		10	(Reference)
Clinical improvement on day 15	OR	1.44	[1.01-2.05]	1.21	[0.90-1.63]	1.05	[0.74-1.50]	1.00	(reference)
	Rate	75%	[68-81%]	72%	[66-78%]	69%	[61-76%]	68%	-
All-cause mortality	OR	1.11	[0.28-4.35]	0.93	[0.34-2.58]	0.84	[0.23-3.09]	1.00	(reference)
	Rate	3%	[1-11%]	3%	[1-7%]	2%	[1-8%]	3%	-
Serious adverse events	OR	0.73	[0.27-1.96]	0.80	[0.51-1.24]	0.86	[0.40-1.85]	1.00	(reference)
	Rate	15%	[6-31%]	16%	[11-22%]	17%	[9-30%]	19%	-
Clinical improvement on day 30	OR	1.24	[0.86-1.78]	1.16	[0.82-1.63]	1.09	[0.74-1.60]	1.00	(reference)
	Rate	81%	[74-86%]	80%	[74-85%]	79%	[73-84%]	77%	-

Sensitivity analyses

Sensitivity analyses were in line with the primary analyses. Sensitivity analyses using different locations of knots confirmed the stability of the shape of the spline curves. (eAppendix11, Figures S1) Sensitivity analyses excluding trials with an overall high risk of bias were also in agreement with the primary analyses. (eAppendix11, Figure S2.1) Sensitivity analyses excluding trials with outpatients also confirmed the main findings, suggesting the results are generalisable to inpatients, except for those admitted to the intensive care unit. (eAppendix11, Figure S2.2) Sensitivity analyses using the per protocol dataset and those including only trials that used antibiotics recommended for empirical treatment of CAP by clinical guidelines also confirmed the results. (eAppendix11, Figure S3 and S4) Exploratory sensitivity analyses showed that non-inferiority of the shorter duration was more likely to be the case in studies that randomised patients who had reached clinical stability early (eAppendix11, FigureS5)

DISCUSSION

To our knowledge, this is the first systematic review and duration-effect meta-analysis of antibiotics treatment for CAP in adults. The results showed that shorter treatment duration

(3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for CAP in adults if they achieved clinical stability. There may be no significant difference in all-cause mortality or serious adverse events. Shorter treatment duration (3-5 days) probably achieves the optimal balance between efficacy and treatment burden. Multiple sensitivity analyses confirmed the primary findings.

This is in line with the previous pairwise meta-analyses that showed shorter duration was non-inferior to longer duration.[10–12] We updated the systematic review and found four trials that were not included in the previous studies. This allowed us to focus on trials that used the same antibiotics with the same daily dosage. The previous studies included trials using different antibiotics or different daily dosages, so the results may not have reflected the differences in treatment durations alone. Moreover, they subcategorised the treatment durations and may have thus lost some statistical power to detect meaningful differences among durations. We overcame this limitation by examining the duration of antibiotic treatment range in days as a continuous variable and found that three to nine-day treatment is likely to be non-inferior to 10-day treatment. Our results are in line with the guidelines for CAP recommending antibiotics to be prescribed for a duration shorter (5-8 days) than current clinical standard practice (10 days).[4–6] Our results suggest that an

even shorter duration (3-5 days) may be considered, which is in line with the trials that found 3-day treatment was non-inferior to 8-day treatment.[39,41] Possibility of 3-day treatment being superior to 10-day treatment should be carefully interpreted, as none of the included trials, previous meta-analyses[11,12] or the pairwise meta-analysis of the included trials (eAppendix7, post hoc analysis) showed the superiority of shorter treatment duration. This could be explained by the fact that most of the combinations of treatment durations examined (7 days vs 10 days, 5 days vs 10 days, 5 days vs 7 days, 3 days vs 8 days) suggested better efficacy of shorter durations, if not statistically significant alone. (eAppendix7, post hoc analysis) The duration-effect meta-analysis combined these findings, leading to the possible superiority of the shortest duration examined (3 days) over the longest duration examined (10 days). Further research focusing on the shorter duration range is warranted to confirm this finding.

Limitations

Our study has several limitations. First, most of the included studies presented a moderate to high overall risk of bias, which compromises the validity of this meta-analysis. Second,

the number of studies was small, leaving confidence intervals for secondary outcomes wide. Third, original studies excluded patients with complications of CAP and therefore the results of this study may not be generalisable to those patients. Forth, baseline severity of the included studies varied. We included both the outpatients and inpatients, which may have concealed important heterogeneity in the study results. However, sensitivity analyses excluding trials with outpatients generally confirmed the primary analyses (eAppendix11) and the overall statistical heterogeneity was low. Fifth, we did not include patients admitted to the intensive care units and the results of this study may not be generalisable to those patients.

Strengths

First, we did a comprehensive systematic review and found four studies that were not included in the previous systematic reviews. Second, we treated duration as a continuous variable, which allowed us to estimate the duration-effect relationship with greater resolution of change points. Third, we examined the impacts of treatment duration not only for clinical improvement but also for all-cause mortality and severe adverse events and made sure that a shorter treatment duration would not translate into more harmful events.

Finally, the very nature of shortened duration treatment offers a unique opportunity for interpretation. Shorter treatment duration has been examined by non-inferiority trials. The underlying assumption has been that there was a trade-off between a loss in the efficacy of standard treatment duration and other benefits of shortened treatment duration, [46,47] such as less time, less cost and probably a diminished rate of antimicrobial resistance. This study suggests that there may be even no trade-off for antibiotic treatments of three to five days. The shorter treatment duration reduces the burden on patients, the healthcare system and the risk of antimicrobial resistance and might even offer better clinical outcomes at the same time.

CONCLUSIONS

Short treatment duration (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for adults with CAP if they achieved clinical stability. Shorter range (3-5 days) probably results in an optimal balance between efficacy and treatment burden. However, the small number of included studies and the overall moderate to high risk of bias may compromise the certainty of the results. Further research focusing on the shorter duration range is required.

Abbreviations

CAP: community-acquired pneumonia
CI: confidence interval
ITT: intention-to-treat
OR: odds ratio
PP: per protocol
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
SD: standard deviation
VPC: variance partition coefficient

DECLARATIONS

Ethics approval and consent to participate

This study uses published aggregate data and did not require ethical approval.

Consent for publication

Not applicable.

Availability of data and materials

Data and code used for analyses are available from the corresponding author upon reasonable request.

Competing interests

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Author Contributions

All authors had full access to all of the data (including statistical reports and tables) in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: YF, YL, SF, AO, EGO, TAF, YK. Analysis and interpretation of the data: YF, YL, SF, AO, EGO, TH, TAF, YK. Drafting of the article: YF. Critical revision of the article for important intellectual content: YL, SF, AO, EGO, TH, TAF, YK. Final approval of the article: YF, YL, SF, AO, EGO, TH, TAF, YK. Obtaining of funding: none. Administrative, technical or logistic support: YF, TH. Collection and assembly of data: YF, YL, SF, AO, EGO. Guarantor: YF. Transparency declaration: As guarantor, YF affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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FIGURE LEGENDS

Figure 1 PRISMA flow diagram

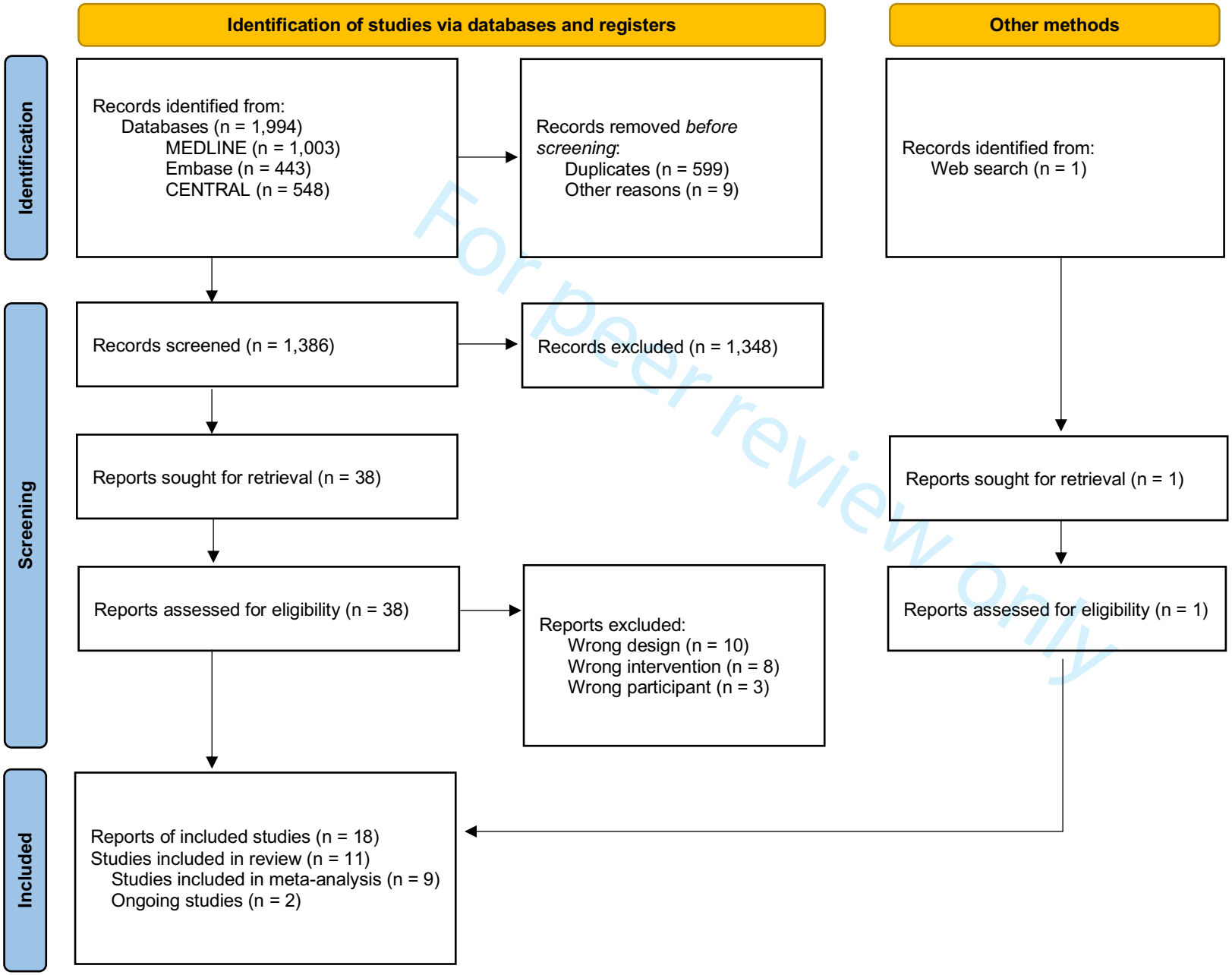
Figure 2 Duration–effect relationship of antibiotics for CAP in adults. Clinical improvement on day 15.

OR=odds ratio. D15=day 15. The dotted lines represent 95% confidence intervals. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the control event rate of 68% (OR 0.65). ORs greater than the non-inferiority threshold signifies that the treatment is non-inferior to the 10-day treatment.

Figure 3 Duration–effect relationships of antibiotics for CAP in adults. (a) All-cause mortality. (b) Severe adverse events. (c) Clinical improvement on day 30.

OR=odds ratio. D30=day 30. The dotted lines represent 95% confidence intervals. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the control event rate of 3% (OR 4.8) in all-cause mortality and 77% (OR 0.61) in clinical improvement on day 30.

Figure 1 PRISMA flow diagram



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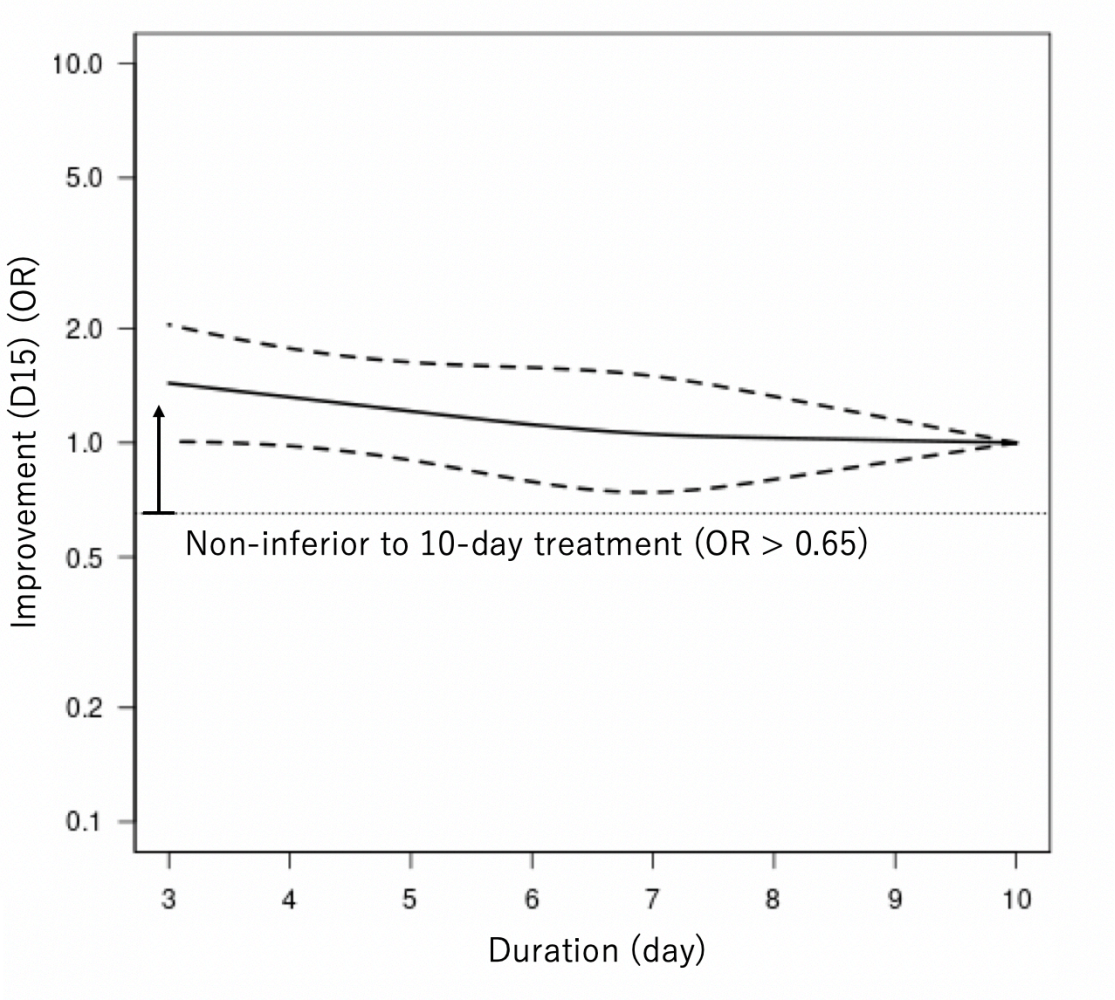

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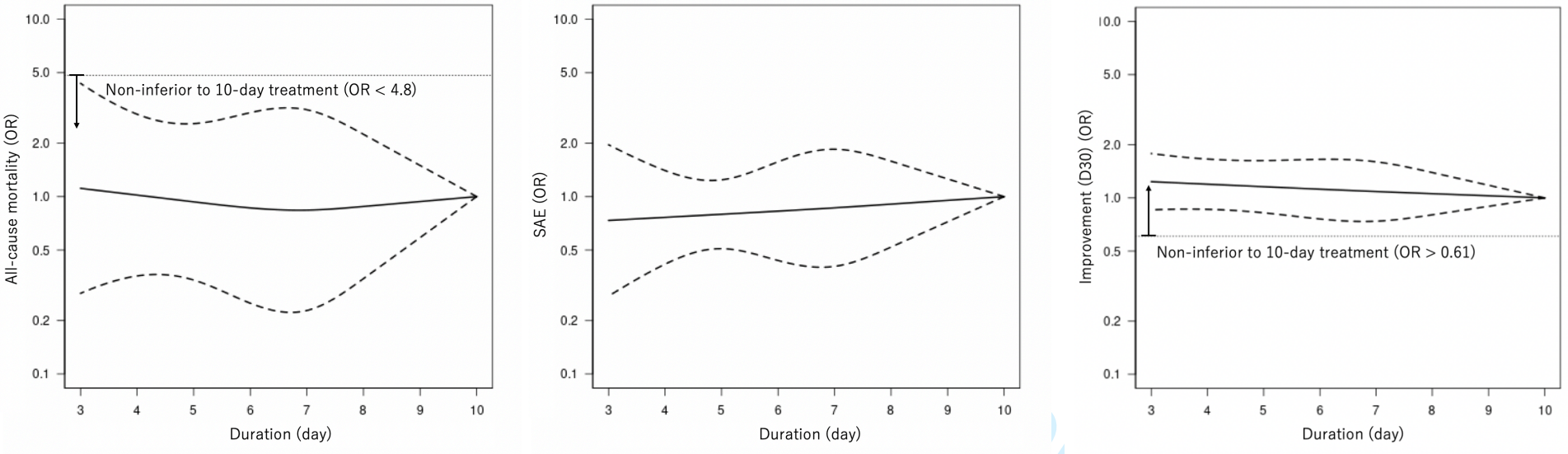

Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a systematic review and duration-effect meta-analysis (eAppendix)

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

1. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: protocol for a systematic review and duration-effect meta-analysis (protocol as of 15th August, 2021)
2. Search strings used for Ovid MEDLINE, Embase, and CENTRAL.
3. Amendments from the protocol
4. List of all included papers
5. List of excluded studies
6. Definitions of clinical improvement in each included study
7. Pairwise meta-analysis of the included trials
8. Funnel plot
9. Heterogeneity: Variance partition coefficient for the primary outcome
10. League table
11. Sensitivity analyses

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)

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

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.

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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

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)

4. List of all included papers

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.

5. List of excluded studies

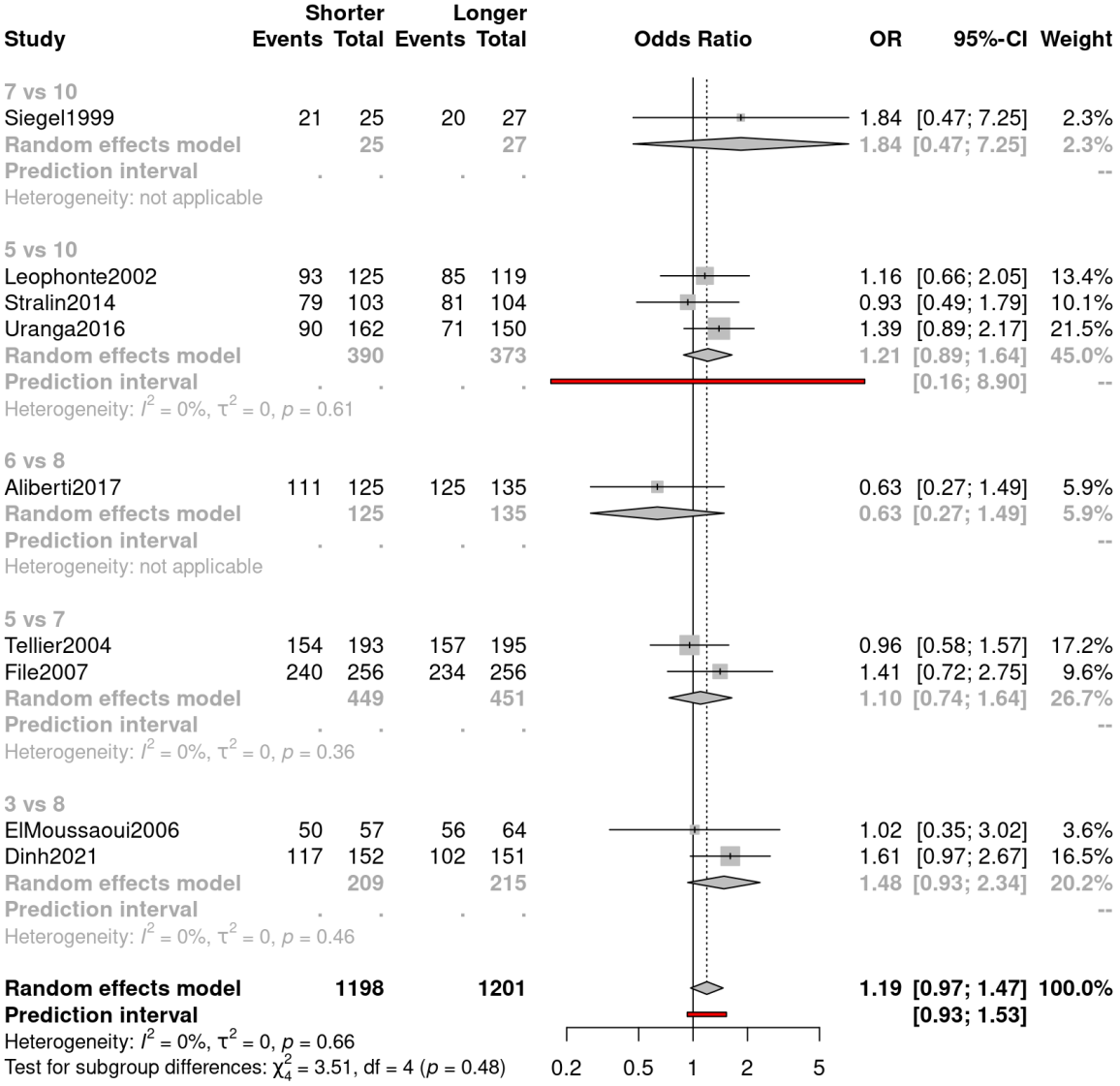
Name	Title	Comment
EUCTR2005-000105-65	Comparative study of the efficacy and tolerance of intravenously administered azithromycin (1.5 g) given either as a single dose or over a 3 day period in patients with community-acquired pneumonia	wrong intervention (dfferent drugs)
EUCTR2014-003137-25	Optimal 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)

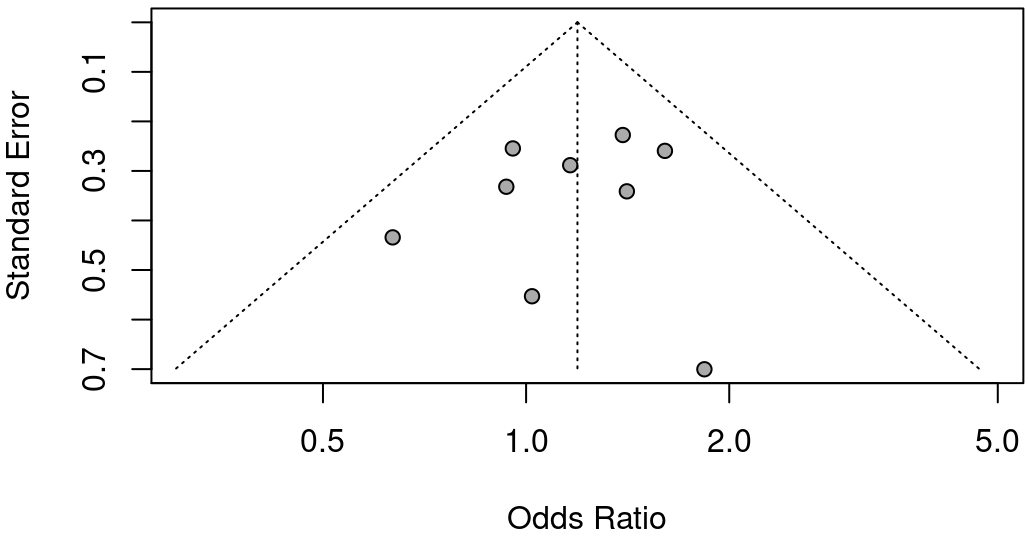
6. Definitions of clinical improvement in each included study

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."

7. Pairwise meta-analysis of the included trials



8. Funnel plot



9. 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
```

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**

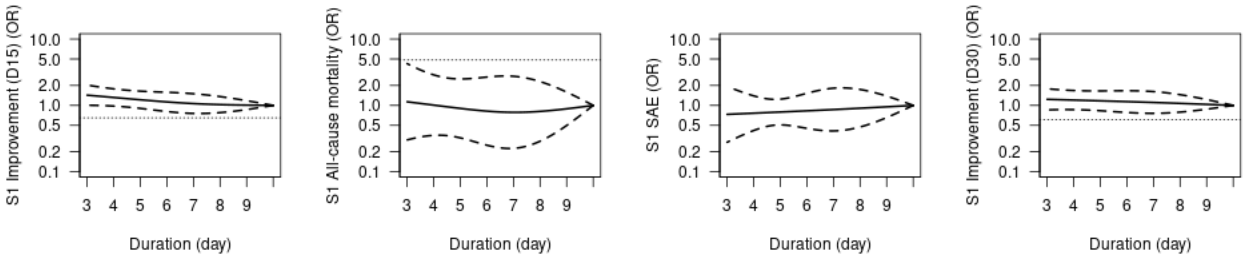
Results of the duration-effect meta-analysis are shown in the bottom-left area. Results of the pairwise meta-analyses of direct comparisons are shown in the upper-right area. Data are odds ratios (95% confidence interval) of the upper-left treatment duration compared with the bottom-right treatment duration.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

11. Sensitivity analyses

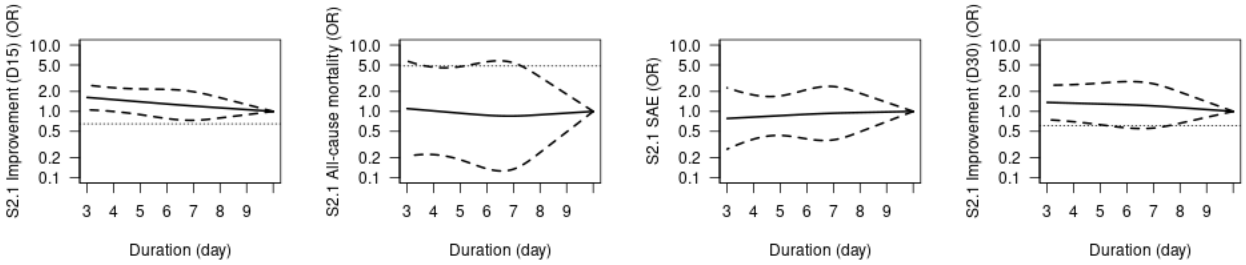
Duration-effect relationship of secondary outcomes could not be computed due to missing data in some cases.

A priori sensitivity analyses

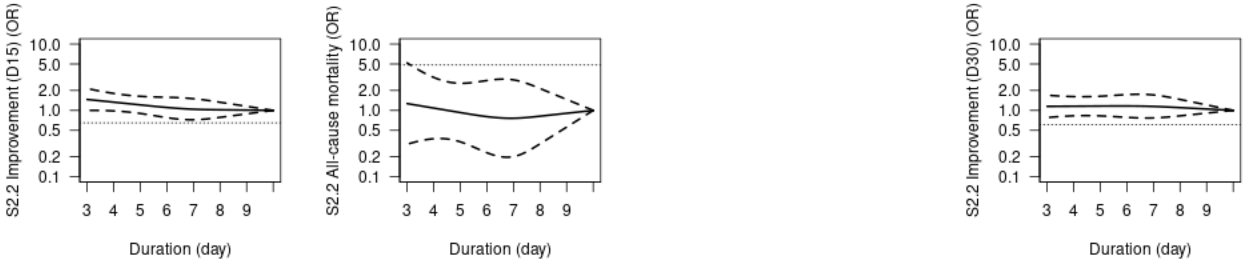
##S1 To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%).



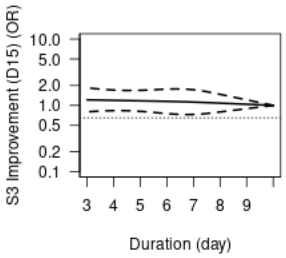
##S2.1 To test the influence of trials included, we conducted sensitivity analyses excluding trials with overall high risk of bias (excluding Siegel1999, Leophonte2002, Stralin2014, Aliberti2017)

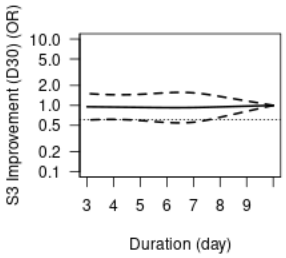


##S2.2 To test the influence of trials included, we conducted sensitivity analyses excluding trials with outpatients (excluding Tellier2004, File2007. SAE not computable)

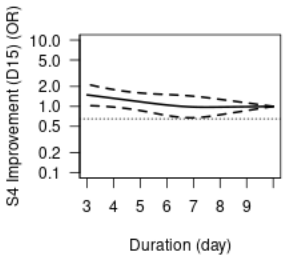


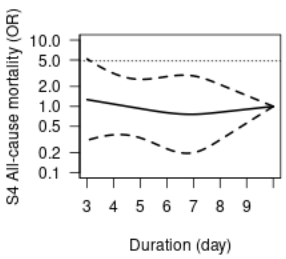
##S3 To test the robustness of the analytical method, we used PP dataset. (All-cause mortality and SAE not computable)

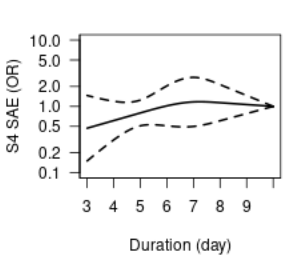


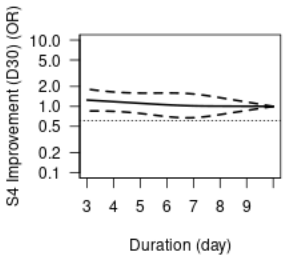


##S4 To test the influence of antibiotics examined, we conducted sensitivity analyses including only antibiotics recommended for empirical treatment of CAP by clinical guidelines. (excluding Siegel1999, Tellier2004. We included trials that used various antibiotics)



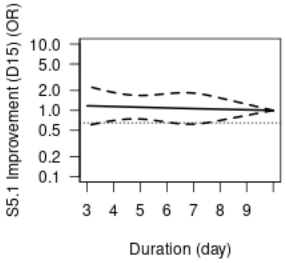


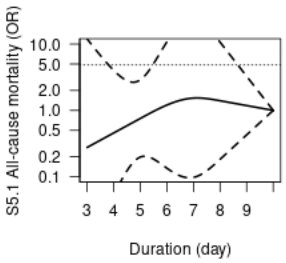


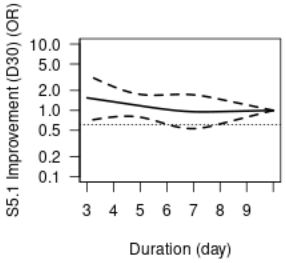


Post-hoc, exploratory sensitivity analyses

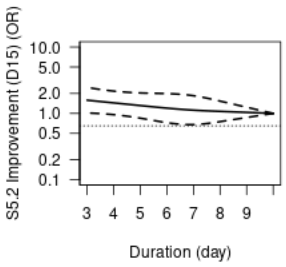
##S5.1 Randomization before the initial antibiotic treatment (including Siegel1999, Leophonete2002, Tellier2004, File2007, Stralin2014. SAE not computable)

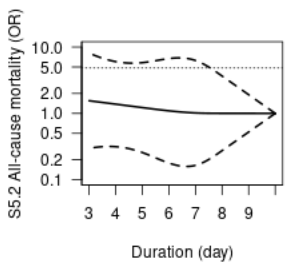


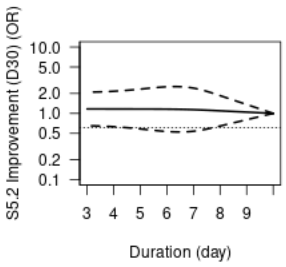




##S5.2 Randomization after several days or clinical stability achieved (including ElMoussaoui2006, Uranga2016, Aliberti2017, Dinh2021. SAE not computable)







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

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1, Line 3-4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Page 3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 6, Line 97-124
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 7, Line 127-128
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 8, Line 134-157
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 10, Line 171-176
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 10, Line 173-177, eAppendix2

Topic	No.	Item	Location where item is reported
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11, Line 182-188
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 11, Line 182-188
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 9-10, Line 159-168, eAppendix1 (protocol) > METHODS AND ANALYSES > Data items
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	eAppendix1 (protocol) > METHODS AND ANALYSES > Data items
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11, Line 185-187
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 10, Line 168

Topic	No.	Item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 10, Line 167-168
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 12, Line 199-205
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 12, Line 199-205
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 12, Line 206-216
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			

Topic	No.	Item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 13, Line 220-224, Fig1 (flow diagram)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	eAppendix4
Study characteristics	17	Cite each included study and present its characteristics.	Table1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 16, Table1 (primary outcome)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA (not presented for each synthesis)
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 18-20, Line 264-287, Fig2 and 3, Table2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 21, Line 291-298, eAppendix7

Topic	No.	Item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 21, Line 300-306
	23b	Discuss any limitations of the evidence included in the review.	Page 22, Line 317-323
	23c	Discuss any limitations of the review processes used.	NA
	23d	Discuss implications of the results for practice, policy, and future research.	Page 24, Line 341-347
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 8, Line 130
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	eAppendix1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	eAppendix3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 26, Line 406-408

Topic	No.	Item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Page 24, Line 365-387
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 24, Line 362-364

PRISMA 2020 Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No (stated in main text)
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes

Topic	No.	Item	Reported?
OTHER			
Funding	11	Specify the primary source of funding for the review.	No (stated in main text)
Registration	12	Provide the register name and registration number.	Yes

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

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Primary Subject Heading:	Infectious diseases
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Keywords:	BACTERIOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory infections < THORACIC MEDICINE

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TITLE PAGE

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

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Word count
3367 words

ABSTRACT (300 words)

Objectives: To find the optimal treatment duration with antibiotics for community-acquired pneumonia (CAP) in adults.

Design: Systematic review and duration-effect meta-analysis.

Data sources: MEDLINE, Embase and CENTRAL through 25 August 2021.

Eligibility criteria: All randomised controlled trials comparing the same antibiotics used at the same daily dosage but for different durations for CAP in adults. Both outpatients and inpatients were included but not those admitted to intensive care units. We imposed no date, language or publication status restriction.

Data extraction and synthesis: Data extraction by two independent reviewers. We conducted a random-effects, one-stage duration-effect meta-analysis with restricted cubic splines. We tested the non-inferiority with the pre-specified non-inferiority margin of 10% examined against 10 days using. The primary outcome was clinical improvement on day 15 (range 7-45 days). Secondary outcomes: all-cause mortality, serious adverse events, and clinical improvement on day 30 (15-60 days).

Results: We included 9 trials (2,399 patients with a mean [SD] age of 61.2 [22.1]; 39% women). The duration-effect curve was monotonic with longer duration leading to a lower probability of improvement, and shorter treatment duration (3-9 days) was likely to be non-inferior to 10-day treatment. Harmful outcome curves indicated no association. The weighted average percentage of the primary outcome in the 10-day treatment arms was 68%. Using that average, the absolute clinical improvement rates of the following durations were: 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day treatment 69% (61 to 76%).

Conclusions: Shorter treatment duration (3-5 days) probably offers the optimal balance between efficacy and treatment burden for treating CAP in adults if they achieved clinical stability. However, the small number of included studies and the overall moderate to high risk of bias may compromise the certainty of the results. Further research on the shorter duration range is required.

Registration: PROSPERO (CRD 42021273357).

Strengths and limitations of this study

- We conducted a comprehensive and up-to-date systematic literature review.
- The duration-effect meta-analysis treated duration as a continuous variable, which allowed us to estimate the duration-effect relationship with greater resolution than the conventional pairwise meta-analysis that dichotomised duration arbitrarily.
- The small number of trials included limited the precision of some study results.
- Most of the trials had a moderate to high overall risk of bias.
- About 80% of the patients had pneumonia severity index class III or less and thus the results may not be generalisable to severely ill patients.

Keywords

Community-acquired pneumonia; antibiotic; treatment duration; dose-response meta-analysis

MAIN TEXT (3367 words)

BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality globally, especially among the elderly.[1] In the United States, it is the second most common cause of hospitalisation and the top infectious cause of death.[2,3] The initial treatment for CAP is empirical, with guidelines recommending starting several antibiotics depending on patients' severity and risk factors for certain pathogens.[4–6]

The optimal duration of antimicrobial therapy remains unclear and controversial. The American and British guidelines recommend a minimum of five days of treatment before therapy discontinuation for patients achieving clinical stability.[4,5] The European guideline states that the duration of treatment should not exceed eight days in responding patients.[6] In clinical practice, however, antibiotics for pneumonia are often prescribed for 10 up to 14 days.[7,8] This may mean that many patients are receiving more antibiotics than necessary, with a consequent increase in costs and a higher probability of antimicrobial resistance.[9] Finding the optimal duration of antibiotics can facilitate reducing antimicrobial use efficiently. Several meta-analyses have been reported on this topic.[10–12] A major limitation of the method used in the previous pairwise meta-analyses

is the arbitrary categorisation of duration when the original studies compared different duration, ranging from three to ten days. A pairwise meta-analysis published in 2008, [10] for example, categorised a seven-day treatment arm in one trial as short-course and the same in other two trials as long-course. [13–15] Another pairwise meta-analysis in 2018 excluded a trial comparing seven-day against ten-day treatment because they defined long-course as seven days or longer.[11] The duration range of short course therapy defined by a systematic review of systematic reviews and guidelines with pairwise meta-analyses in 2019 was wide (three to seven days) and the duration-effect relationship within that range remains unclear.[12] We overcame the limitation of arbitrary dichotomisation of duration by using a novel method called dose-effect meta-analysis.[16] It has been used, for example, to examine the effects of potassium intake or sodium reduction on blood pressure[17,18]. Unlike conventional categorisation-based meta-analyses[19], dose-effect meta-analysis can reveal more fine-grained optimal dose[20]. By treating duration as dose, we aimed to apply this method to obtain a more specific optimal treatment duration.

METHODS

We summarised the currently available evidence to find the optimal treatment duration of antibiotics for CAP in adults. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) [21]. The protocol has been prospectively registered in PROSPERO (CRD 42021273357) and can be found in the appendix (eAppendix1).

Patient and Public Involvement

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

Data sources

Criteria for considering studies for this review

Types of studies

To examine the duration-effect relationship, we included all trials that compared two or more different durations of the same antibiotic treatment for CAP.

Types of participants

Patients were eligible if they were 18 years or older of both genders with a diagnosis of CAP as defined by the original authors. We included both outpatients and inpatients. We

excluded patients who were admitted to the intensive care unit. To focus on individuals at low to medium risk, we excluded 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 included trials examining any antibiotics, administered orally or intravenously. We evaluated antibiotics as a class because clinical guidelines recommend treatment duration irrespective of the antibiotic used,[4–6] and because recent meta-analyses of antibiotics for CAP have not shown efficacy differences among antibiotics.[22,23] Oral and intravenous antibiotics were merged because they have been shown equally effective in many infectious conditions within the same time frame.[24–26] We included trials comparing the same agents used at the same daily dosage but for different durations. We used the predefined duration for fixed-duration arms. If some studies did not prespecified the duration (eg. left it to clinicians' judgment[27]), we used the median duration.

Primary outcome and secondary outcomes

The primary outcome of interest in this study was the 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.[28] Secondary outcomes of interest were: all-cause mortality on day 15 (range 7-45 days), serious adverse events as defined by the original study on day 15 (range 7-45 days), and clinical improvement as defined by the original study on day 30 (range 15-60). We used the number of randomised patients as the denominator for the intention-to-treat (ITT) dataset. When only clinical failure was reported, clinical improvement was calculated by subtracting clinical failure from the total number randomised. We used ITT for the primary analysis and the per-protocol (PP) dataset for a sensitivity analysis.[29,30] We used the odds ratio (OR) of each outcome to synthesise data. [31,32]

Search methods for identification of studies

Electronic searches

We systematically searched the following electronic bibliographic databases from inception through 25 August 2021: MEDLINE, Embase and CENTRAL. We used search terms for community-acquired pneumonia in conjunction with the names of individual antibiotics as

well as the names of antibiotic classes. Detailed search formulas are presented in the appendix (eAppendix2). We imposed no date, language or publication status restriction.

Reference lists

We checked the reference lists of all the included studies and review articles for additional references.

Data collection and analysis

Selection of studies

Two review authors independently screened and selected the included studies (YF and one of AO, EO, SF or YL). Two review authors extracted data independently from the included studies (YF and one of AO, EO, SF or YL). We used the Cochrane risk of bias tool Version 2 [33] to assess and summarise the risk of bias. Disagreements were resolved through discussion.

Statistical analysis

To perform our analyses, we used the *dosresmeta* package (Version 2.0.1) and *meta* package (Version 5.0-1) for *R* (Version 4.1.0. R foundation, Wien, Austria).[34–36]

Assessment of heterogeneity

We investigated the heterogeneity between studies by the variance partition coefficient (VPC). [16] VPC represents the percentage of variation attributed to heterogeneity rather than sampling error and can be interpreted similarly to the I^2.

Duration-effect meta-analysis

In the duration-effect meta-analysis, we assumed that the relative efficacy of a certain treatment duration ($duration_i$) against another ($duration_j$) can be expressed in the log-odds ratio ($\log OR_{ij}$) and that it is a function of both durations ($\log OR_{ij} = f(duration_i; duration_j)$). We fitted restricted cubic splines with three knots to the dataset obtained by the systematic review because this model has shown sufficient flexibility to capture different shapes.[37] Given the clinical and methodological heterogeneity likely present in the included studies, we used the random effects model. We used three knots, equally spaced across the duration range (25%, 50%, 75%). Typically, in dose-effect meta-analyses, the reference dose is assigned to the zero or the minimal dose to make interpretation easier.[37] As this duration-effect meta-analysis aimed to test the non-

inferiority of the shorter treatment duration, we decided to use the maximum duration as the reference to make interpretation easier. Also, the reference we set (10-day treatment) can be regarded as the current practice.[7,8,27] We tested the non-inferiority with the non-inferiority margin of 10%, as previously proposed,[28] and the superiority of the shorter duration examined against 10-day treatment using the ITT dataset.

Sensitivity analyses

To ascertain the robustness of the primary analyses, we conducted the following sensitivity analyses. To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%). To test the influence of trials included, we conducted sensitivity analyses excluding trials with an overall high risk of bias and excluding trials with outpatients. To test the robustness of the analytical method, we used the PP dataset. To test the influence of antibiotics examined, we conducted sensitivity analyses restricting eligible antibiotics only to those recommended by clinical guidelines for empirical treatment of CAP.[4,5] In addition to the pre-defined sensitivity analyses, we conducted exploratory sensitivity analyses including only trials that randomised before the initial antibiotic treatment to test the influence of randomisation timing. We further conducted sensitivity

analyses excluding trials with substantial deviation from the day 15 measurement time and analyses imputing missing data as improved outcomes.

Amendments

We report amendments with the date and the rationale in the appendix (eAppendix3).

RESULTS

We identified 1,994 records via database and one record via searching websites, which revealed that some different records refer to the same clinical trial. We assessed 38 full-text records for eligibility and included 11 eligible studies. (Fig1) Of these, eight were published,[13–15,27,38–41] one was unpublished[42] and two studies were still ongoing,[43,44] resulting in nine trials for the primary outcome analysis. The lists of included and excluded studies are provided in the appendix (eAppendix4 and 5). The nine studies with 2,399 participants in total included 18 eligible arms. Treatment duration ranged from three to ten days. The study year ranged between 1999 and 2021. Table 1 presents the characteristics of the included studies. (more details can be found in eAppendix4)

The included studies were all parallel-group and individually randomised. Seven out of nine were reported as non-inferiority trials. In total, 1,199 participants were randomly

assigned to the shorter duration arm and 1,200 to the longer duration arm. The mean age was 61.2 years (standard deviation 22.1); 831 (39%) of 2,140 reported were women. Six were conducted in a single European country, one in the US, and the two were cross-continental. CAP was defined as newly confirmed clinical symptoms (eg, dyspnoea, cough, purulent sputum, or crackles), and radiological findings. Antibiotic treatment was discontinued when the patient was clinically stable, and the pre-determined treatment period was completed. Clinical stability was often defined as apyrexia (temperature ≤37.8 C) for 48 hours, heart rate below 100 beats per min, a respiratory rate below 24 breaths per min, arterial oxygen saturation of 90% or higher, systolic blood pressure of 90 mmHg or higher, and normal mental status.[45] Clinical improvement was often described as “clinical cure” or “clinical success” and was often defined as the resolution of fever and improvement of symptoms related to pneumonia without further antibiotics. More detailed definitions of clinical improvement in each included study are listed in the appendix. (eAppendix6) The percentage of pneumonia severity index class IV or V was on average 19% (362 of 1,896 reported; ranging from 2 to 41%). Seven studies focused on inpatients, whereas one study focused on outpatients and one included both. Antibiotics used included β-lactams (amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, ceftazidime,

ceftriaxone, cefuroxime, piperacillin/tazobactam), macrolides (azithromycin, clarithromycin), quinolones (ciprofloxacin, gemifloxacin, levofloxacin, telithromycin), amikacin, doxycycline, and meropenem. Pharmaceutical companies funded four studies.[13–15,38] Four studies had a high overall risk of bias, four some concerns, and only one had a low overall risk of bias. (eAppendix 7)

Table 1 Characteristics of included studies

Study	Age, mean (SD), y	Female, %	PSI IV+V, %	Setting	Duration, day, median	Antibiotics	No. of participants	No. of clinical improvement on day 15
Siegel et al, 1999	61.1 (15.1)	NA	NA	Inpatient	7	CXM	25	21
					10		27	20
Leophonte et al, 2002	64.0 (18.7)	25	NA	Inpatient	5	CRO	125	93
					10		119	85
Tellier et al, 2004	45.8 (18-87†)	42	7	Both	5	TEL	193	154
					7		195	157
El Moussaoui et al, 2006	57.2* (23.9*)	40	12	Inpatient	3	AMX	57	50
					8		64	56
File et al, 2007	45.4 (16.8)	42	3	Outpatient	5	GMI	256	240
					7		256	234
Stralin et al, 2014	NA (NA)	NA	NA	Inpatient	5	β-lactam	103	79
					10		103.5	81
Uranga et al, 2016	65.4 (18.3)	37	39	Inpatient	5	Various	162	90
					10		150	71
Aliberti et al, 2017	60.6* (24.8*)	40	24	Inpatient	6	Various	125	111
					8		135	125
Dinh et al, 2021	73.2* (21.0*)	41	39	Inpatient	3	β-lactum + placebo	152	117
					8	β-lactum + AMC	151	102

Table 1 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

Assessment of heterogeneity and publication bias

We assessed the heterogeneity in the efficacy outcome across the duration range (9 studies). VPC values were constantly below 10% which suggests low levels of heterogeneity. Visual inspection of the funnel plot suggested no significant publication bias. However, these assessments need to be carefully interpreted due to the small number of included studies. (eAppendix8 and 9)

Duration-effect meta-analysis

We present the duration-effect curves in Figure 2 and Figure 3, and the tabulation of results in Table 2. The x-axis of the figures represents the treatment duration in days. The y-axis represents the odds ratio of the outcome on a logarithmic scale, just as in the forest plot of conventional pairwise meta-analysis using binary outcomes. The thin dotted horizontal line in the clinical improvement figures and the all-cause mortality figure corresponds to the non-inferiority margin translated into OR. (The weighted average percentage of clinical improvement rate on day 15 in the 10-day treatment arms was 68%. The non-inferiority margin was therefore 58% and the corresponding OR was 0.65. For all-cause mortality, the numbers were 3%, 13% and OR 4.8, respectively. For clinical improvement on day 30, the

numbers were 77%, 67% and OR 0.61, respectively. We did not show the non-inferiority margin in the figures for severe adverse events, because the position paper did not provide any margin for this outcome.[28]) The thick solid line represents the duration-effect curve and the thick dotted lines represent its 95% CI. The 95% CI band becomes narrower when the duration range was examined by many trials or when it gets closer to the reference point. For the beneficial outcomes (clinical improvement), OR > 1 means more effective. For the harmful outcomes (all-cause mortality and serious adverse events), OR < 1 means safer.

The duration-effect curve is monotonic with a longer duration leading to a lower probability of improvement. The lower 95%CI curve was constantly above the prespecified non-inferiority margin, meaning that a shorter treatment duration (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days). It was slightly above the OR = 1 around 3-day treatment, suggesting 3-day treatment may be superior to 10-day treatment. Harmful outcome curves (all-cause mortality and severe adverse events) were almost flat and 95%CI curves did not cross the OR = 1, indicating no association. Although the confidence interval curves were wide for all-cause mortality, shorter treatment duration (3-9 days) was likely to be non-inferior to 10-day treatment. Clinical improvement on day 30

showed a similar trend with the primary outcome with the lower 95%CI curve constantly above the prespecified non-inferiority margin. We made a league table (eAppendix10), which showed that shorter treatment duration was likely to be non-inferior to longer treatment duration, regardless of the reference duration.

Odds ratios need to be translated into absolute event rates so that the results can be interpreted from the clinical point of view. The weighted average percentage of clinical improvement rate on day 15 in the 10-day treatment arms was 68%, based on a single proportion meta-analysis of the included studies. Using this average, we computed the absolute clinical improvement rates at the following durations as follows: 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day treatment 69% (61 to 76%). (Table 2)

Table 2 Primary and secondary outcomes for 3, 5, 7 and 10-day treatment

Outcome		Treatment duration (days)						
		3		5		7		10
Clinical improvement on day 15	OR	1.44	[1.01-2.05]	1.21	[0.90-1.63]	1.05	[0.74-1.50]	1.00
	Rate	75%	[68-81%]	72%	[66-78%]	69%	[61-76%]	68%
All-cause mortality	OR	1.11	[0.28-4.35]	0.93	[0.34-2.58]	0.84	[0.23-3.09]	1.00
	Rate	3%	[1-11%]	3%	[1-7%]	2%	[1-8%]	3%
Serious adverse events	OR	0.73	[0.27-1.96]	0.80	[0.51-1.24]	0.86	[0.40-1.85]	1.00
	Rate	15%	[6-31%]	16%	[11-22%]	17%	[9-30%]	19%
Clinical improvement on day 30	OR	1.24	[0.86-1.78]	1.16	[0.82-1.63]	1.09	[0.74-1.60]	1.00
	Rate	81%	[74-86%]	80%	[74-85%]	79%	[73-84%]	77%

Sensitivity analyses

Sensitivity analyses were in line with the primary analyses. Sensitivity analyses using different locations of knots confirmed the stability of the shape of the spline curves. (eAppendix11, Figures S1) Sensitivity analyses excluding trials with an overall high risk of bias were also in agreement with the primary analyses. (eAppendix11, FigureS2.1) Sensitivity analyses excluding trials with outpatients also confirmed the main findings, suggesting the results are generalisable to inpatients, except for those admitted to the intensive care unit. (eAppendix11, Figures S2.2) Sensitivity analyses using the per protocol dataset and those including only trials that used antibiotics recommended for empirical treatment of CAP by clinical guidelines also confirmed the results. (eAppendix11, Figures S3 and S4) Exploratory sensitivity analyses showed that non-inferiority of the shorter duration was more likely to be the case in studies that randomised patients who had reached clinical stability early. (eAppendix11, Figures S5.1 and S5.2) Furthermore, post-hoc sensitivity analyses which excluded trials with substantial deviation from the day 15 measurement time (eAppendix11, Figures S5.3) and those which imputed missing data as clinically improved (eAppendix11, and S5.4) also aligned with the primary analyses.

DISCUSSION

To our knowledge, this is the first systematic review and duration-effect meta-analysis of antibiotics treatment for CAP in adults. The results showed that shorter treatment duration (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for CAP in adults if they achieved clinical stability. There may be no significant difference in all-cause mortality or serious adverse events. Shorter treatment duration (3-5 days) probably achieves the optimal balance between efficacy and treatment burden. Multiple sensitivity analyses confirmed the primary findings.

This is in line with the previous pairwise meta-analyses that showed shorter duration was non-inferior to longer duration.[10–12] We updated the systematic review and found four trials that were not included in the previous studies. This allowed us to focus on trials that used the same antibiotics with the same daily dosage. The previous studies included trials using different antibiotics or different daily dosages, so the results may not have reflected the differences in treatment durations alone. Moreover, they subcategorised the treatment durations and may have thus lost some statistical power to detect meaningful differences among durations. We overcame this limitation by examining the duration of antibiotic treatment range in days as a continuous variable and found that three to nine-day treatment is likely to be non-inferior to 10-day treatment. Our results are in line with the

guidelines for CAP recommending antibiotics to be prescribed for a duration shorter (5-8 days) than current clinical standard practice (10 days).[4–6] Our results suggest that an even shorter duration (3-5 days) may be considered, which is in line with the trials that found 3-day treatment was non-inferior to 8-day treatment.[39,41] Possibility of 3-day treatment being superior to 10-day treatment should be carefully interpreted, as none of the included trials, previous meta-analyses[11,12] or the pairwise meta-analysis of the included trials (eAppendix12, post hoc analysis) showed the superiority of shorter treatment duration. This could be explained by the fact that most of the combinations of treatment durations examined (7 days vs 10 days, 5 days vs 10 days, 5 days vs 7 days, 3 days vs 8 days) suggested better efficacy of shorter durations, if not statistically significant alone. (eAppendix12, post hoc analysis) The duration-effect meta-analysis combined these findings, leading to the possible superiority of the shortest duration examined (3 days) over the longest duration examined (10 days). Further research focusing on the shorter duration range is warranted to confirm this finding.

Limitations

Our study has several limitations. First, most of the included studies presented a moderate to high overall risk of bias, which compromises the validity of this meta-analysis. Second, the number of studies was small, leaving confidence intervals for secondary outcomes wide. Third, original studies excluded patients with complications of CAP and therefore the results of this study may not be generalisable to those patients. Forth, baseline severity of the included studies varied. We included both the outpatients and inpatients, which may have concealed important heterogeneity in the study results. However, sensitivity analyses excluding trials with outpatients generally confirmed the primary analyses (eAppendix11) and the overall statistical heterogeneity was low. Fifth, we did not include patients admitted to the intensive care units and the results of this study may not be generalisable to those patients. Sixth, the actual measurement day for the primary outcome in each included study varied (7 to 44 days) and this may have introduced between-study heterogeneity. However, post-hoc sensitivity analyses excluding trials with large deviation from the day 15 measurement time were in line with the primary analyses.

Strengths

First, we did a comprehensive systematic review and found four studies that were not included in the previous systematic reviews. Second, we treated duration as a continuous variable, which allowed us to estimate the duration-effect relationship with greater resolution of change points. Third, we examined the impacts of treatment duration not only for clinical improvement but also for all-cause mortality and severe adverse events and made sure that a shorter treatment duration would not translate into more harmful events. Finally, the very nature of shortened duration treatment offers a unique opportunity for interpretation. Shorter treatment duration has been examined by non-inferiority trials. The underlying assumption has been that there was a trade-off between a loss in the efficacy of standard treatment duration and other benefits of shortened treatment duration, [46,47] such as less time, less cost and probably a diminished rate of antimicrobial resistance. This study suggests that there may be even no trade-off for antibiotic treatments of three to five days. The shorter treatment duration reduces the burden on patients, the healthcare system and the risk of antimicrobial resistance and might even offer better clinical outcomes at the same time.

CONCLUSIONS

Short treatment duration (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for adults with CAP if they achieved clinical stability. Shorter range (3-5 days) probably results in an optimal balance between efficacy and treatment burden. However, the small number of included studies and the overall moderate to high risk of bias may compromise the certainty of the results. Further research focusing on the shorter duration range is required.

Abbreviations

CAP: community-acquired pneumonia
CI: confidence interval
ITT: intention-to-treat
OR: odds ratio
PP: per protocol
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
SAE: serious adverse events
SD: standard deviation
VPC: variance partition coefficient

DECLARATIONS

Ethics approval and consent to participate

This study uses published aggregate data and did not require ethical approval.

Consent for publication

Not applicable.

Availability of data and materials

Data and code used for analyses are available from the corresponding author upon reasonable request.

Competing interests

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YF, TH declare no conflicts of interest.

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Author Contributions

All authors had full access to all of the data (including statistical reports and tables) in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: YF, YL, SF, AO, EGO, TAF, YK. Analysis and interpretation of the data: YF, YL, SF, AO, EGO, TH, TAF, YK. Drafting of the article: YF. Critical revision of the article for important intellectual content: YL, SF, AO, EGO, TH, TAF, YK. Final approval of the article: YF, YL, SF, AO, EGO, TH, TAF, YK. Obtaining of funding: none. Administrative, technical or logistic support: YF, TH. Collection and assembly of data: YF, YL, SF, AO, EGO. Guarantor: YF. Transparency declaration: As guarantor, YF affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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FIGURE LEGENDS

Figure 1 PRISMA flow diagram

Figure 2 Duration–effect relationship of antibiotics for CAP in adults. Clinical improvement on day 15.

OR=odds ratio. D15=day 15. The dotted lines represent 95% confidence intervals. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the control event rate of 68% (OR 0.65). ORs greater than the non-inferiority threshold signifies that the treatment is non-inferior to the 10-day treatment.

Figure 3 Duration–effect relationships of antibiotics for CAP in adults. (a) All-cause mortality. (b) Severe adverse events. (c) Clinical improvement on day 30.

OR=odds ratio. D30=day 30. The dotted lines represent 95% confidence intervals. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the control event rate of 3% (OR 4.8) in all-cause mortality and 77% (OR 0.61) in clinical improvement on day 30.

Figure 1 PRISMA flow diagram

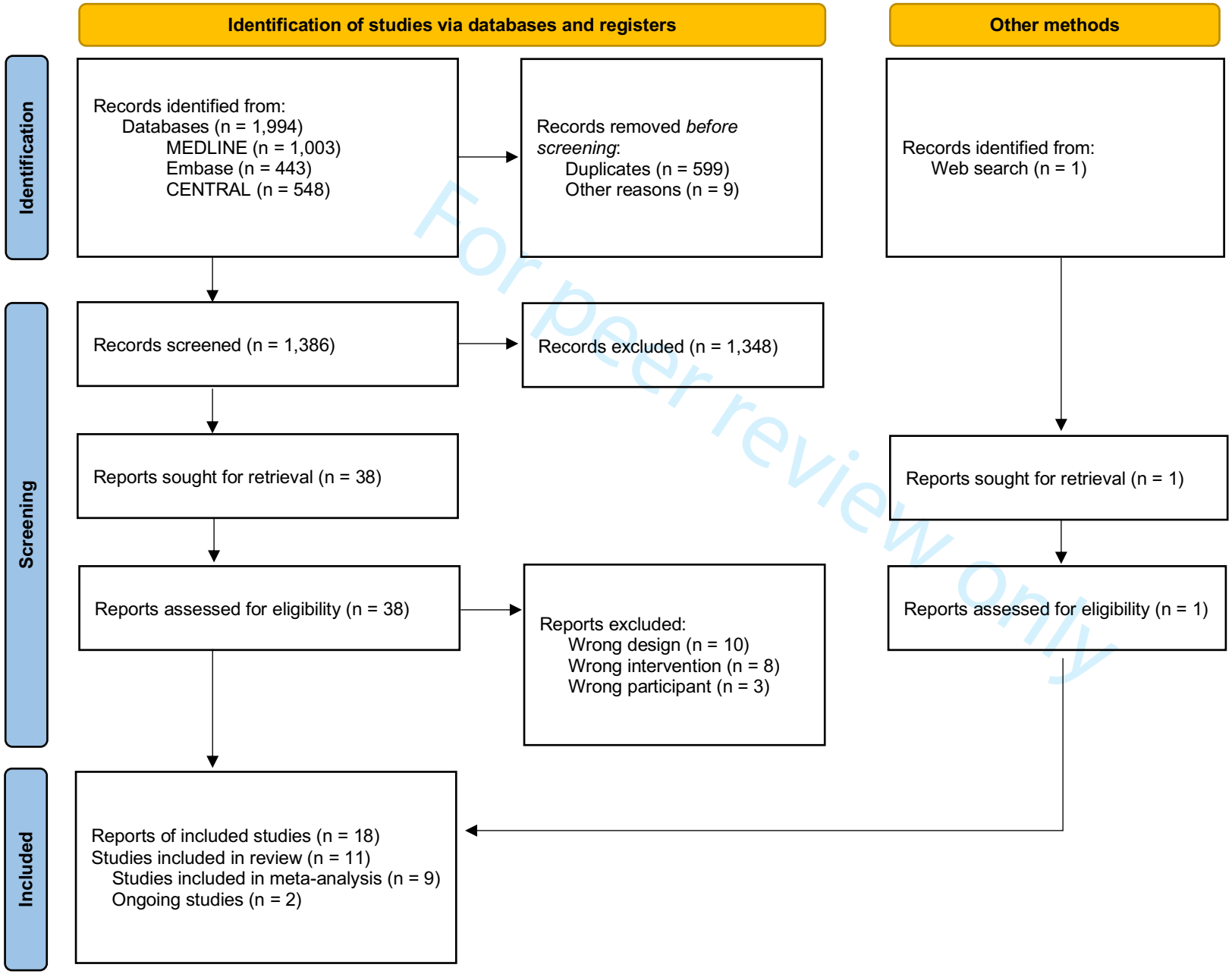


Figure 2 Duration–effect relationship of antibiotics for CAP in adults. Clinical improvement on day 15.

OR=odds ratio. D15=day 15. The dotted lines represent 95% confidence intervals. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the control event rate of 68% (OR 0.65). ORs greater than the non-inferiority threshold signifies that the treatment is non-inferior to the 10-day treatment.

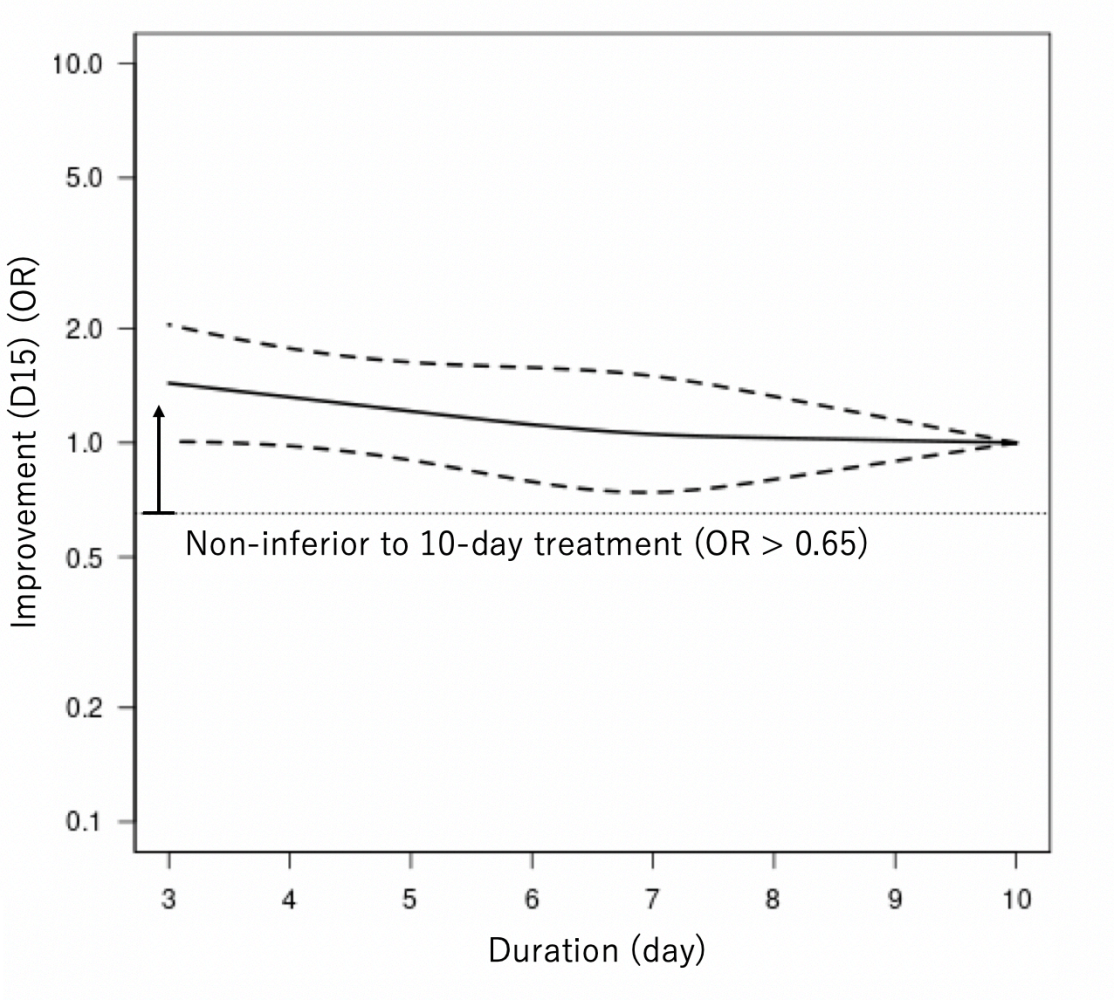
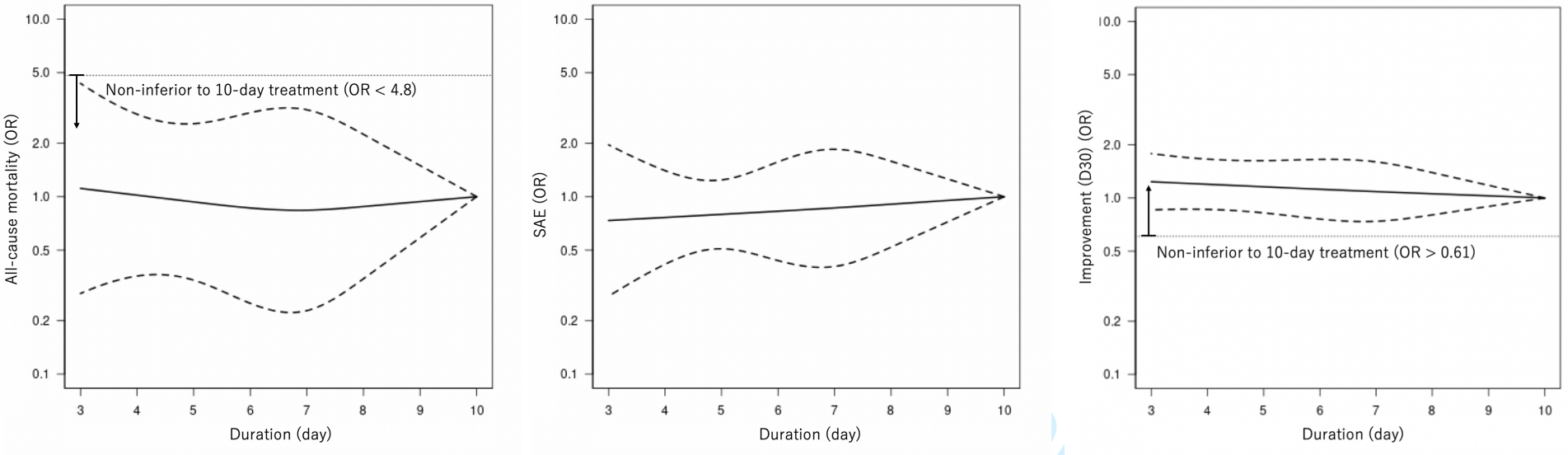


Figure 3 Duration–effect relationships of antibiotics for CAP in adults. (a) All-cause mortality. (b) Severe adverse events. (c) Clinical improvement on day 30.

OR=odds ratio. D30=day 30. The dotted lines represent 95% confidence intervals. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the control event rate of 3% in all-cause mortality (OR 4.8) and 77% in clinical improvement on day 30 (OR 0.61).



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

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

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)

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

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

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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

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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

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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.

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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.

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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		103.5	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

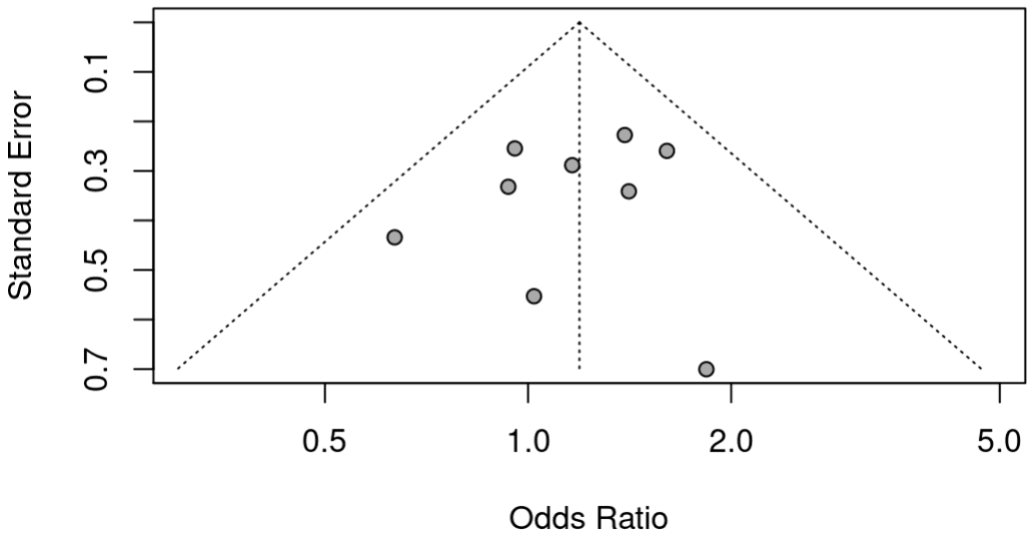
VPC is computed for each non-referent arm of each study (those that have OR≠1). We included nine two-armed trials, and thus we have 9 VPC numbers. We present them below. It is generally interpreted as: VPC values below 25% low, 25-75% moderate and over 75% high.

```
>    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**

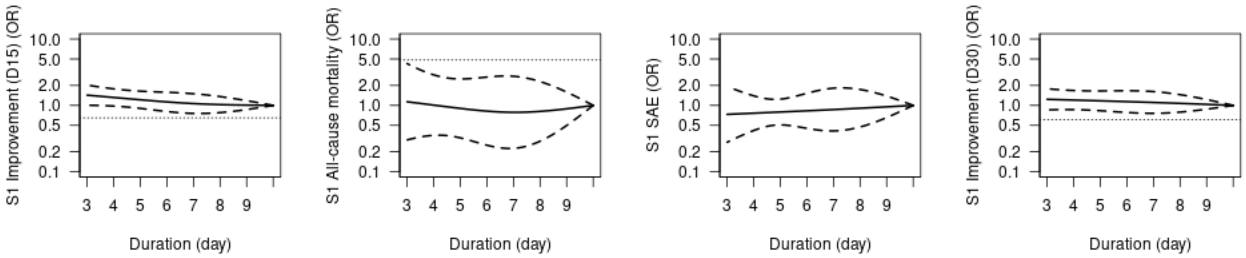
Results of the duration-effect meta-analysis are shown in the bottom-left area. Results of the pairwise meta-analyses of direct comparisons are shown in the upper-right area. Data are odds ratios (95% confidence interval) of the upper-left treatment duration compared with the bottom-right treatment duration.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

eAppendix 11. Sensitivity analyses

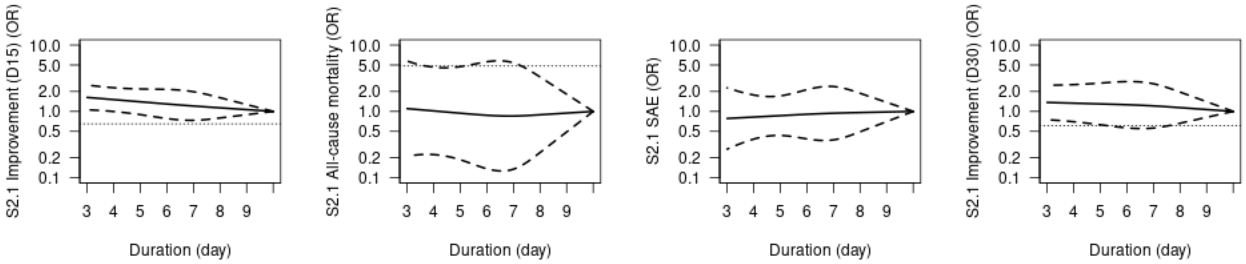
Duration-effect relationship of secondary outcomes could not be computed due to missing data in some cases.

A priori sensitivity analyses

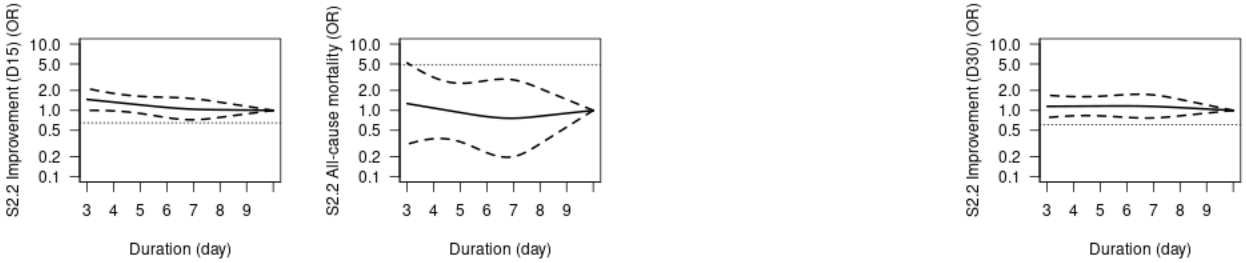
##S1 To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%).



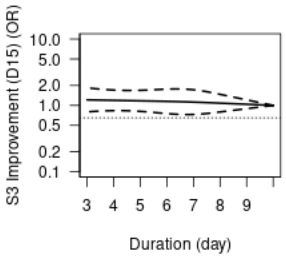
##S2.1 To test the influence of trials included, we conducted sensitivity analyses excluding trials with overall high risk of bias (excluding Siegel1999, Leophonte2002, Stralin2014, Aliberti2017)

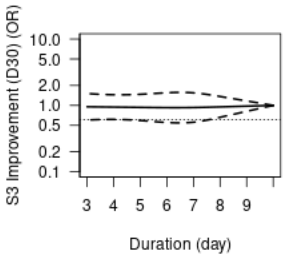


##S2.2 To test the influence of trials included, we conducted sensitivity analyses excluding trials with outpatients (excluding Tellier2004, File2007. SAE not computable)

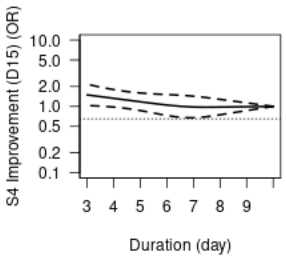


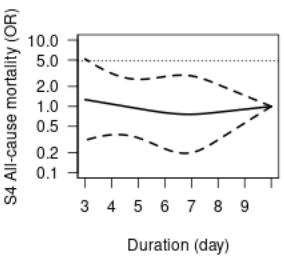
##S3 To test the robustness of the analytical method, we used PP dataset. (All-cause mortality and SAE not computable)

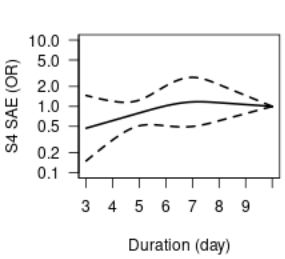


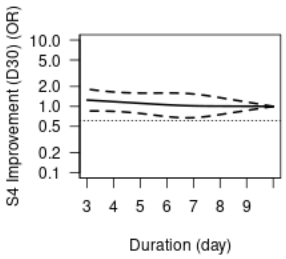


##S4 To test the influence of antibiotics examined, we conducted sensitivity analyses including only antibiotics recommended for empirical treatment of CAP by clinical guidelines. (excluding Siegel1999, Tellier2004. We included trials that used various antibiotics)



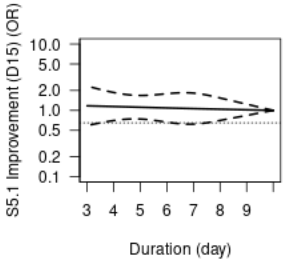


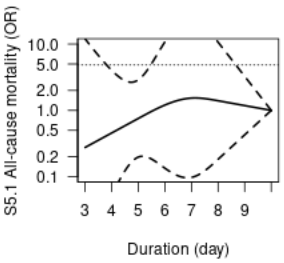


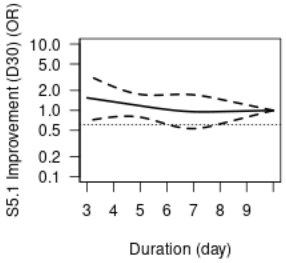


Post-hoc, exploratory sensitivity analyses

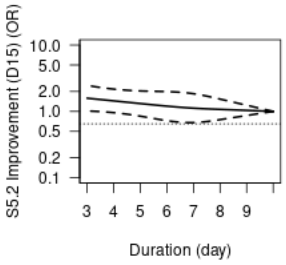
##S5.1 Randomization before the initial antibiotic treatment (including Siegel1999, Leophonete2002, Tellier2004, File2007, Stralin2014. SAE not computable)

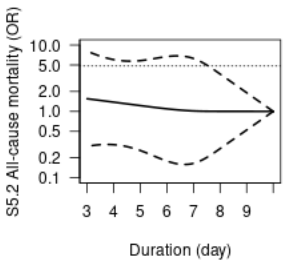


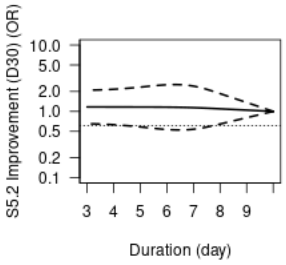




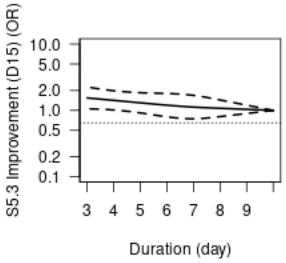
##S5.2 Randomization after several days or clinical stability achieved (including ElMoussaoui2006, Uranga2016, Aliberti2017, Dinh2021. SAE not computable)

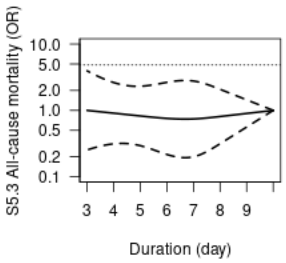


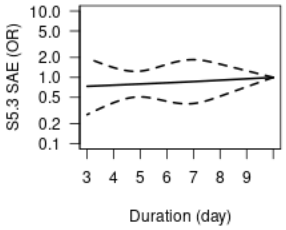




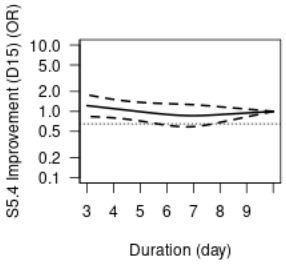
##S5.3 To test the influence of trials with large deviation from the day 15 measurement time (excluding Siegel1999, Stralin2014, Aliberti2017. Clinical improvement on day 30 not applicable.)

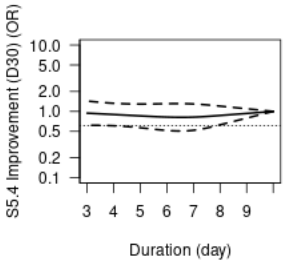




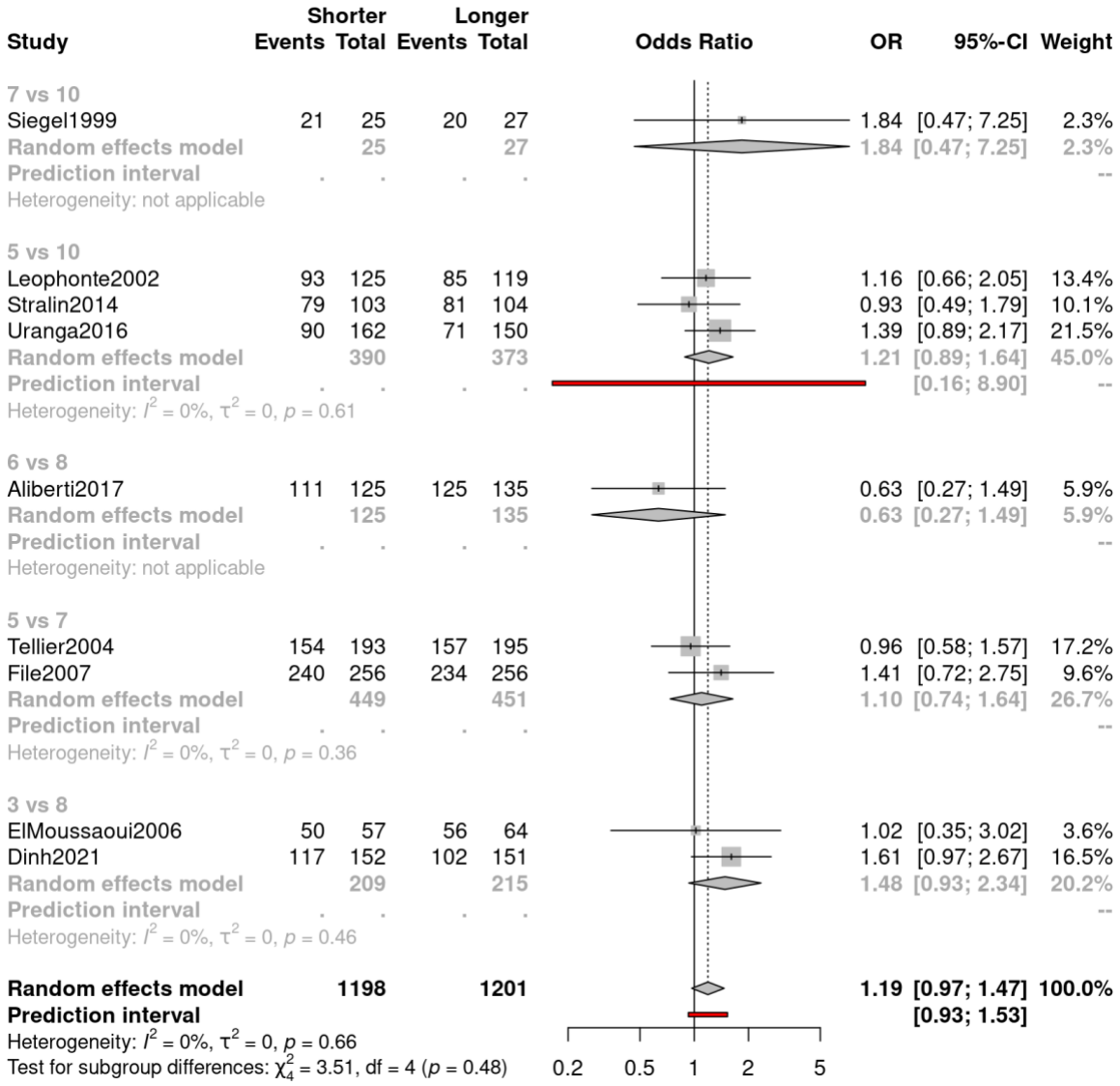


##S5.4 To test the influence of handling missing data as not improved (counting missing data as clinically improved)





eAppendix 12. Pairwise meta-analysis of the included trials



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

Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki Kataoka

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1, Line 3-4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Page 3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 6, Line 97-124
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 7, Line 127-128
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 8, Line 134-157
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 10, Line 171-176
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 10, Line 173-177, eAppendix2

Topic	No.	Item	Location where item is reported
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11, Line 182-188
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 11, Line 182-188
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 9-10, Line 159-168, eAppendix1 (protocol) > METHODS AND ANALYSES > Data items
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	eAppendix1 (protocol) > METHODS AND ANALYSES > Data items
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11, Line 185-187
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 10, Line 168

Topic	No.	Item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 10, Line 167-168
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 12, Line 199-205
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 12, Line 199-205
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 12, Line 206-216
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			

Topic	No.	Item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 13, Line 220-224, Fig1 (flow diagram)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	eAppendix4
Study characteristics	17	Cite each included study and present its characteristics.	Table1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 16, Table1 (primary outcome)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA (not presented for each synthesis)
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 18-20, Line 264-287, Fig2 and 3, Table2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 21, Line 291-298, eAppendix7

Topic	No.	Item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 21, Line 300-306
	23b	Discuss any limitations of the evidence included in the review.	Page 22, Line 317-323
	23c	Discuss any limitations of the review processes used.	NA
	23d	Discuss implications of the results for practice, policy, and future research.	Page 24, Line 341-347
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 8, Line 130
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	eAppendix1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	eAppendix3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 26, Line 406-408

Topic	No.	Item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Page 24, Line 365-387
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 24, Line 362-364

PRISMA 2020 Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No (stated in main text)
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes

Topic	No.	Item	Reported?
OTHER			
Funding	11	Specify the primary source of funding for the review.	No (stated in main text)
Registration	12	Provide the register name and registration number.	Yes