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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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6 **1 TITLE PAGE**

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9 **3 Title: Optimal duration of antibiotic treatment for community-acquired pneumonia in**
10 **4 adults: a systematic review and duration-effect meta-analysis**

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22 46 **Word count**

23 47 2515 words

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5
6 **49 ABSTRACT (299<300 words)**
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9 **50 Objectives:** To find the optimal treatment duration with antibiotics for community-
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13 **51** acquired pneumonia (CAP) in adults.
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15 **52 Design:** Systematic review and duration-effect meta-analysis. We systematically searched
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18 **53** MEDLINE, Embase and CENTRAL from inception to present (25 August, 2021) to find all
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21 **54** randomized controlled trials comparing the same antibiotics used at the same daily dosage
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24 **55** but for different durations for CAP in adults. We conducted random-effects, one-stage
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27 **56** duration-effect meta-analysis with restricted cubic splines. We tested the non-inferiority
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30 **57** with the pre-specified non-inferiority margin of 10% examined against 10 days using
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33 **58** intention-to-treat dataset.
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36 **59 Setting and Participants:** Both outpatients and inpatients but not those admitted to
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39 **60** intensive care unit.
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42 **61 Interventions:** Any antibiotics, administered orally or intravenously.
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45 **62 Primary and Secondary Outcome Measures:** The primary outcome was clinical
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48 **63** improvement at day 15 (range 7-45 days). Secondary outcomes were all-cause mortality,
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51 **64** serious adverse events, and clinical improvement at day 30 (15-60 days). We calculated
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54 **65** odds ratios.
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7 66 **Results:** We included 9 trials (2399 patients with a mean [SD] age of 61.2 [22.1]; 39%
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9 67 women). The duration-effect curve was monotonic with longer duration leading to lower
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11 68 probability of improvement, and the lower 95%CI curve was constantly above the
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15 69 prespecified non-inferiority margin. Harmful outcome curves indicated no association. The
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18 70 average percentage of clinical improvement rate at day 15 in the 10-day treatment arms was
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21 71 68%. Using that average, we computed the absolute clinical improvement rates at the
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24 72 following durations: a 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66
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27 73 to 78%), and 7-day treatment 69% (61 to 76%).

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30 74 **Conclusions:** Shorter treatment duration probably achieves the optimal balance between
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33 75 efficacy and treatment burden for treating CAP in adults. However, the small number of
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36 76 included studies and the overall moderate to high risk of bias may compromise the certainty
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39 77 of the results. Further research focusing on the shorter duration range is required.

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42 78 **Registration:** PROSPERO (CRD 42021273357).

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7 **82 Strengths and Limitations**

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9 **83** - To our knowledge, this is the first systematic review and duration-effect meta-analysis to
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12 **84** examine the optimal duration of antibiotic treatment for community-acquired pneumonia in
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15 **85** adults by day.

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18 **86** - This study may lead to efficient antibiotics use, which is critical to curbing antimicrobial
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21 **87** resistance.

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24 **88** - Limited number of included studies and the overall moderate to high risk of bias may
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27 **89** compromise the certainty of the results.

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30 **90**

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33 **91 Keywords**

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36 **92** Community-acquired pneumonia; antibiotic; treatment duration; dose-response meta-
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39 **93** analysis
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6 **95 MAIN TEXT (2497<3000 words)**

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9 **96**

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12 **97 BACKGROUND**

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15 **98** Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality
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18 **99** globally, especially among the elderly.¹ In the United States, it is the second most common
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21 **100** cause of hospitalization and the top infectious cause of death.^{2,3} The initial treatment for
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24 **101** CAP is empirical, with guidelines recommending starting several antibiotics depending on
25
26
27 **102** patients' severity and risk factors for certain pathogens.⁴⁻⁶

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30 **103** The optimal duration of antimicrobial therapy remains unclear and
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33 **104** controversial. The American and British guidelines recommend a minimum of five days of
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36 **105** treatment before therapy discontinuation for patients achieving clinical stability.^{4,5} The
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39 **106** European guideline states that the duration of treatment should not exceed 8 days in
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42 **107** responding patients.⁶ In clinical practice, however, antibiotics for pneumonia are often
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45 **108** prescribed for 10 up to 14 days.^{7,8} This may mean that many patients may be receiving
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48 **109** more antibiotics than necessary, with a consequent increase in costs and a higher
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51 **110** probability of antimicrobial resistance.⁹ Finding optimal duration of antibiotics can
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54 **111** facilitate reducing antimicrobial use efficiently. A pair-wise meta-analysis published in

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6 112 2008 found that short-course therapy was non-inferior to long-course therapy regarding
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9 113 clinical success at end-of-therapy, clinical success at late follow-up, microbiological
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12 114 success, relapses, mortality and adverse events.¹⁰ Since then, at least two trials have been
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15 115 reported,^{11,12} which warrants update of the systematic review and meta-analysis. A major
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18 116 limitation of the method used in the previous pair-wise meta-analysis is the arbitrary
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21 117 categorization of durations when the original studies compared different durations, ranging
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24 118 from three to ten days. This resulted in categorizing a seven-day treatment in one trial to
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27 119 short-course and the same in other two trials to long-course.^{13–15} We overcame this
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30 120 limitation by using a novel method called dose-effect meta-analysis.¹⁶ It has been used, for
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33 121 example, to examine the effects of potassium intake or sodium reduction for blood
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36 122 pressure^{17,18}. Unlike conventional categorization-based meta-analyses¹⁹, dose-effect meta-
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39 123 analysis can reveal more fine-grained optimal dose²⁰. By treating duration as dose, we
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42 124 aimed to apply this method to obtain a more specific optimal treatment duration.
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126 **METHODS**

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

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6 129 reviews and Meta-Analyses (PRISMA 2020)²¹. The protocol has been prospectively
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9 130 registered in PROSPERO (CRD 42021273357) and can be found in the appendix
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12 131 (eAppendix1).

132 ***Patient and Public Involvement***

133 Patients or the public were not involved in the design, conduct, reporting or dissemination
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21 134 plans of this research.

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25 26 27 136 **Data sources**

28 29 30 137 **Criteria for considering studies for this review**

31 32 33 138 ***Types of studies***

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36 139 To examine the duration-effect relationship, we included all trials that compared two or
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39 140 more different durations of the same antibiotic treatment for CAP.

40 41 42 141 ***Types of participants***

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45 142 Patients were eligible if they were 18 years or older of both genders with a diagnosis of
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48 143 CAP as defined by the original authors. We included both outpatients and inpatients. We
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51 144 excluded patients who were admitted to intensive care unit. In order to focus on individuals
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54 145 at low to medium risk, we excluded trials with 20% or more patients meeting one or more
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6 146 of the following criteria: having immunodeficiency; having been treated with another
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9 147 antibiotic within a month.

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12 148 ***Types of interventions***

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15 149 We included trials examining any antibiotics, administered orally or intravenously. We
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18 150 evaluated antibiotics as a class because clinical guidelines recommend treatment duration
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21 151 irrespective of the antibiotic used,⁴⁻⁶ and because recent meta-analyses of antibiotics for
22
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24 152 CAP have not shown efficacy differences among antibiotics.^{22,23} Oral and intravenous
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27 153 antibiotics were merged because they have been shown equally effective in many infectious
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30 154 conditions within the same time frame.²⁴⁻²⁶ We included trials comparing the same agents
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33 155 used at the same daily dosage but for different durations. We used the predefined duration
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36 156 for fixed-duration arms. If some studies did not prespecified the duration (eg. left it to
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39 157 clinicians' judgment¹¹), we used the median duration.

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45 159 **Primary outcome and secondary outcomes**

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48 160 The primary outcome of interest in this study was clinical improvement as defined by the
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51 161 original authors at a time point as close to 15 days (range 7-45 days) as possible in each
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54 162 included study.²⁷ Secondary outcomes of interest were: all-cause mortality at day 15 (range

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6 163 7-45 days), serious adverse events as defined by the original study at day 15 (range 7-45
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9 164 days), and clinical improvement as defined by the original study at day 30 (range 15-60).
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12 165 We used the number of randomized patients as the denominator for intention-to-treat (ITT)
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15 166 dataset. When only clinical failure was reported, clinical improvement was calculated by
16
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18 167 subtracting clinical failure from the total number randomized. We used ITT for the primary
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21 168 analysis and per-protocol (PP) dataset for a sensitivity analysis.^{28,29} We used odds ratio
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24 169 (OR) of each outcome to synthesize data.^{30,31}
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30 171 **Search methods for identification of studies**

33 172 *Electronic searches*

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36 173 We systematically searched the following electronic bibliographic databases from inception
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39 174 to present (25 August, 2021): MEDLINE, Embase and CENTRAL. We used search terms
40
41
42 175 for community acquired pneumonia in conjunction with the names of individual antibiotics
43
44
45 176 as well as the names of antibiotic classes. Detailed search formulas are presented in the
46
47
48 177 appendix (eAppendix2). We imposed no date, language or publication status restriction.
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51 178 *Reference lists*

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6 179 We checked the reference lists of all the included studies and review articles for additional
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9 180 references.

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13 14 15 182 **Data collection and analysis**

16 17 18 183 **Selection of studies**

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21 184 Two review authors independently screened and selected the included studies (YF and one
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24 185 of AO, EO, SF or YL). Two review authors extracted data independently from the included
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26
27 186 studies (YF and one of AO, EO, SF or YL). We used the Cochrane risk of bias tool Version
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30 187 2³² to assess and summarize the risk of bias. Disagreements were resolved through
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33 188 discussion.

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37 38 39 190 **Statistical analysis**

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42 191 To perform our analyses, we used the *dosresmeta* package (Version 2.0.1) and *meta*
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45 192 package (Version 5.0-1) for *R* (Version 4.1.0. R foundation, Wien, Austria).^{33–35}

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49 50 51 194 ***Assessment of heterogeneity***

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7 195 We investigated the heterogeneity between studies by the variance partition coefficient
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9 196 (VPC).¹⁶ VPC represents the percentage of variation attributed to heterogeneity rather than
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12 197 sampling error and can be interpreted similarly to the I^2 .
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18 199 *Dose-effect meta-analysis*

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21 200 Given the clinical and methodological heterogeneity likely present in the included studies,
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24 201 we used the random effects model. We used 3 knots, equally spaced across the duration
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27 202 range (25%, 50%, 75%). We set 10 days as the reference because it can be regarded as the
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30 203 current practice.^{7,8,11} We tested the non-inferiority with the non-inferiority margin of 10%,
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33 204 as previously proposed,²⁷ and the superiority of the shorter duration examined against 10
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36 205 days using ITT dataset.
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42 207 *Sensitivity analyses*

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45 208 In order to ascertain the robustness of the primary analyses, we conducted the following
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48 209 sensitivity analyses. To test the stability of the shape of the spline curves, we used different
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51 210 locations of knots (10%, 50%, 90%). To test the influence of trials included, we conducted
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54 211 sensitivity analyses excluding trials with an overall high risk of bias and excluding trials
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7 212 with outpatients. To test the robustness of the analytical method, we used the PP dataset. To
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9 213 test the influence of antibiotics examined, we conducted sensitivity analyses restricting
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11 214 eligible antibiotics only to those recommended by clinical guidelines for empirical
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15 215 treatment of CAP.^{4,5} In addition to the pre-defined sensitivity analyses, we conducted
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18 216 exploratory sensitivity analyses including only trials that randomized before the initial
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21 217 antibiotic treatment to test the influence of randomization timing.
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23 24 218 **Amendments**

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27 219 We report amendments with the date and the rationale in the appendix (eAppendix3).
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31 32 33 221 **RESULTS**

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36 222 We identified 1,994 records via database and one record via searching websites, which
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39 223 revealed that some different records refer to the same clinical trial. We assessed 38 full-text
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42 224 records for eligibility and included 11 eligible studies. (Fig1) Of these, 8 were published,¹¹⁻
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45 225 ^{15,36-38} 1 was unpublished³⁹ and 2 studies were still ongoing,^{40,41} resulting in 9 trials for the
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48 226 primary outcome analysis. The lists of included and excluded studies are provided in the
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51 227 appendix (eAppendix4 and 5). The 9 studies with 2,399 participants in total included 18
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6 228 eligible arms. Treatment duration ranged from 3 to 10 days. The study year ranged between
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9 229 1999 and 2021. Table 1 presents the characteristics of the included studies.
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12 230 The included studies were all parallel-group and individually randomized. Seven out of
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15 231 nine were reported as non-inferiority trial. In total, 1,199 participants were randomly
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18 232 assigned to the shorter duration arm and 1,200 to the longer duration arm. The mean age
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21 233 was 61.2 years (standard deviation 22.1); 831 (39%) of 2,140 reported were women. Six
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24 234 were conducted in a single European country, one in the US, and the two were cross-
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27 235 continental. CAP was defined as newly confirmed clinical symptoms (eg, dyspnoea, cough,
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30 236 purulent sputum, or crackles), and radiological findings. Clinical stability was often defined
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33 237 as apyrexia (temperature ≤ 37.8 C) for 48 hours, heart rate below 100 beats per min,
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36 238 respiratory rate below 24 breaths per min, arterial oxygen saturation of 90% or higher,
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39 239 systolic blood pressure of 90 mm Hg or higher, and normal mental status.⁴² Percentage of
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42 240 pneumonia severity index class IV or V was on average 19% (362 of 1,896 reported;
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45 241 ranging from 2 to 41%). Seven studies focused on inpatients, whereas one study focused on
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48 242 outpatients and one included both. Antibiotics used included β -lactam (amoxicillin,
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51 243 amoxicillin/clavulanate, ampicillin/sulbactam, ceftazidime, ceftriaxone, cefuroxime,
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54 244 piperacillin/tazobactam), macrolide (azithromycin, clarithromycin), quinolone
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6 245 (ciprofloxacin, gemifloxacin, levofloxacin, telithromycin), amikacin, doxycycline, and
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9 246 meropenem. Pharmaceutical companies funded four studies.^{13–15,36} Four studies had a high
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12 247 overall risk of bias, four some concerns, and only one had low overall risk of bias. (Table 1)
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248 **Table 1 Characteristics of included studies**

| Study | Age, | | Female, % | PSI | | Duration, | | No. of partici pants | No. of clinical improvement | | Risk of bias | | | | | Ove rall | Spon sored |
|--------------------------|-------------|---------------|--------------|-------------|------------|----------------|--------------------------------------|----------------------------|--------------------------------|----|--------------|----|----|----|---|-------------|---------------|
| | mean , y | Age, SD, y | | IV+V , % | Setting | day, median | Antibiotics | | at day 15 | D1 | D2 | D3 | D4 | D5 | | | |
| 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

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258 **Assessment of heterogeneity**

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

263

264 **Dose-effect meta-analysis**

265 We present the duration-effect curves in Figure 2 and Figure 3, and the tabulation of results
266 in Table 2. The x-axis of the figures represents the treatment duration in days and the y-axis
267 represents the odds ratio of the outcome. The thin solid horizontal line represents the odds
268 ratio = 1 and the thin dotted horizontal line in the clinical improvement figures corresponds
269 to the non-inferiority margin translated into OR. (The average percentage of clinical
270 improvement rate at day 15 in the 10-day treatment arms was 68%. Non-inferiority margin
271 was therefore 58% and the corresponding OR was 0.65. For clinical improvement at day
272 30, the numbers were 77%, 67% and OR 0.61, respectively.) The thick solid line represents
273 the dose-effect curve and the thick dotted lines represent its 95% CI. The duration-effect
274 curve is monotonic with longer duration leading to lower probability of improvement. The

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6 275 lower 95%CI curve was constantly above the prespecified non-inferiority margin, meaning
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9 276 that a shorter treatment duration (3-9 days) was likely to be non-inferior to the standard
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12 277 treatment duration (10 days). It was slightly above the OR = 1 line around 3 days,
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14
15 278 suggesting 3-day treatment may be superior to 10-day treatment. Secondary outcomes had
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18 279 wider confidence interval curves. Harmful outcome curves (all-cause mortality and severe
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21 280 adverse events) were almost flat and 95%CI curves did not cross the OR = 1 line, indicating
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24 281 no association. Clinical improvement at day 30 showed a similar trend with the primary
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27 282 outcome with the lower 95%CI curve constantly above the prespecified non-inferiority
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30 283 margin. The average percentage of clinical improvement rate at day 15 in the 10-day
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33 284 treatment arms was 68% (based on a meta-analysis of the included studies). Using that
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36 285 average, we computed the absolute clinical improvement rates at the following durations: a
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39 286 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day
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42 287 treatment 69% (61 to 76%).
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288 **Table 2 Primary and secondary outcomes for 3, 5, 7 and 10-day treatment**

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| Outcome | Treatment duration (days) | | | | | | | | |
|--------------------------------|---------------------------|------|-------------|------|-------------|------|-------------|------|-------------|
| | | 3 | | 5 | | 7 | | 10 | (Reference) |
| Clinical improvement at 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% | (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 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% | (2 arms) |
| Clinical improvement at 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% | (4 arms) |

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7 **291 Sensitivity analyses**

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9 **292** Sensitivity analyses were in line with the primary analyses. (eAppendix7. Figures S1, using
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12 **293** different locations of knots; S2.1, excluding trials with overall high risk of bias; S2.2,
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15 **294** excluding trials with outpatients; S3, using PP dataset; S4 including only antibiotics
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18 **295** recommended for empirical treatment of CAP by clinical guidelines). Exploratory
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21 **296** sensitivity analyses showed that non-inferiority of the shorter duration was more likely to
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24 **297** be the case in studies that randomized patients who had reached clinical stability early
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27 **298** (eAppendix7. Figures S5.1, S5.2).

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33 **300 DISCUSSION**

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36 **301** To our knowledge, this is the first systematic review and duration-effect meta-analysis of
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39 **302** antibiotics treatment for CAP in adults. The results showed that a shorter treatment duration
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42 **303** (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for
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45 **304** CAP in adults. There may be no significant difference in all-cause mortality or serious
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48 **305** adverse events. A shorter range probably achieves the optimal balance between efficacy
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51 **306** and treatment burden.

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7 307 This is in line with the previous pair-wise meta-analysis that showed shorter
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9 308 duration was non-inferior to longer duration.¹⁰ Methodological limitations in a previous
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11 309 meta-analysis restricted authors from recommending a specific treatment duration. We
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15 310 overcame this limitation by examining the duration of antibiotic treatment range in days
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18 311 and found that a 3 to 9-day treatment is likely to be non-inferior to a 10-day treatment. Our
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21 312 results are in line with the guidelines for CAP recommending antibiotics to be prescribed
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24 313 for a duration shorter (5-8 days) than current clinical standard practice (10 days).⁴⁻⁶ Our
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27 314 results suggest that an even shorter duration (3-5 days) may be considered, which is in line
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30 315 with the trials that found 3-day treatment was non-inferior to 8-day treatment.^{12,37}

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317 **Limitations**

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

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9 325 **Strengths**

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12 326 First, we did a comprehensive systematic review and found 4 studies that were not included

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15 327 the previous systematic reviews. Second, we treated duration as a continuous variable,

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18 328 which allowed us to estimate the duration-effect relationship with greater resolution of

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21 329 change points. Third, we examined impacts of treatment duration not only for clinical

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24 330 improvement but also for all-cause mortality and severe adverse events and made sure that

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27 331 a shorter treatment duration would not translate into more harmful events. Finally, the very

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30 332 nature of shortened duration treatment offers a unique opportunity for interpretation.

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33 333 Shorter treatment durations have been examined by non-inferiority trials. The underlying

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36 334 assumption has been that there was a trade-off between a loss in efficacy of standard

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39 335 treatment duration and other benefits of a shortened duration,^{43,44} such as less time, less

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42 336 cost and probably a diminished rate of antimicrobial resistance. This study suggests that

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45 337 there may be even no trade-off for antibiotic treatments of 3 to 5 days. Shorter treatment

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48 338 duration reduces the burden on patients, the healthcare system and the risk of antimicrobial

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51 339 resistance and might even offer better clinical outcomes at the same time.

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6 **341 CONCLUSIONS**

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9 **342** Shorter treatment duration (3-9 days) was likely to be non-inferior to the standard treatment
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12 **343** duration (10 days) for adults with CAP if they achieved clinical stability. A shorter range
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15 **344** (3-5 days) probably results in an optimal balance between efficacy and treatment burden.
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18 **345** However, the small number of included studies and the overall moderate to high risk of bias
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21 **346** may compromise the certainty of the results. Further research focusing on the shorter
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24 **347** duration range is required.

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29 **350 Abbreviations**

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31 **351** CAP: community-acquired pneumonia

32 **352** ITT: intention-to-treat

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34 **353** PP: per protocol

35 **354** PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

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37 **355** VPC: variance partition coefficient

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39 **356**

40 **357 DECLARATIONS**

41 **358 Ethics approval and consent to participate**

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43 **359** This study uses published aggregate data and did not require ethical approval.

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45 **360 Consent for publication**

46 **361** Not applicable.

47
48 **362 Availability of data and materials**

49 **363** Data and code used for analyses are available from the corresponding author on reasonable
50
51 **364** request.

52 **365 Competing interests**

53 **366** YL is receiving a Grant-in-Aid for JSPS Fellow (KAKENHI Grant Number 21J15050).
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30
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6 391 **Author Contributions**

7 392 **YF:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data
8 393 Curation, Writing – Original Draft, Visualization, Supervision, Project administration

9 394 **YL:** Conceptualization, Methodology, Data Curation, Validation, Writing – Review &
10 395 Editing,

11 396 **SF:** Conceptualization, Methodology, Data Curation, Validation, Writing – Review &
12 397 Editing,

13 398 **AO:** Conceptualization, Methodology, Data Curation, Validation, Writing – Review &
14 399 Editing,

15 400 **EGO:** Conceptualization, Methodology, Data Curation, Validation, Writing – Review &
16 401 Editing,

17 402 **TH:** Methodology, Software, Formal analysis, Visualization, Validation, Writing – Review
18 403 & Editing,

19 404 **TAF:** Conceptualization, Methodology, Writing – Review & Editing, Supervision,

20 405 **YK:** Conceptualization, Methodology, Writing – Review & Editing, Supervision

21 406 All authors have read and approved the manuscript

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28 413 1. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional,
29 414 and national morbidity, mortality, and aetiologies of lower respiratory infections in 195
30 415 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.
31 416 *Lancet Infect Dis.* 2018;18(11):1191-1210. doi:10.1016/s1473-3099(18)30310-4

32 417 2. Most Frequent Conditions in U.S. Hospitals, 2011. Accessed December 8, 2021.
33 418 <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf>

34 419 3. Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final Data for 2013. *Natl Vital*
35 420 *Stat Rep.* 2016;64(2):1-119.

- 1
2
3
4
5
6 421 4. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with
7 422 Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American
8 423 Thoracic Society and Infectious Diseases Society of America. *Am J Resp Crit Care*.
9 424 2019;200(7):e45-e67. doi:10.1164/rccm.201908-1581st
- 12 425 5. National Institute of Health and Care Excellence (NICE). Pneumonia (community-
13 426 acquired): antimicrobial prescribing. Accessed December 8, 2021.
14 427 <https://www.nice.org.uk/guidance/NG138>
- 18 428 6. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower
19 429 respiratory tract infections - Full version. *Clin Microbiol Infec*. 2011;17(s6):E1-E59.
20 430 doi:10.1111/j.1469-0691.2011.03672.x
- 24 431 7. Aliberti S, Blasi F, Zanaboni AM, et al. Duration of antibiotic therapy in hospitalised
25 432 patients with community-acquired pneumonia. *Eur Respir J*. 2009;36(1):128-134.
26 433 doi:10.1183/09031936.00130909
- 29 434 8. Yi SH, Hatfield KM, Baggs J, et al. Duration of Antibiotic Use Among Adults With
30 435 Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United
31 436 States. *Clin Infect Dis*. 2017;66(9):1333-1341. doi:10.1093/cid/cix986
- 35 437 9. Guillemot D, Carbon C, Balkau B, et al. Low Dosage and Long Treatment Duration of β -
36 438 Lactam: Risk Factors for Carriage of Penicillin-Resistant *Streptococcus pneumoniae*.
37 439 *JAMA*. 1998;279(5):365-370. doi:10.1001/jama.279.5.365
- 41 440 10. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, Grammatikos AP, Athanassa Z,
42 441 Falagas ME. Short- versus Long-Course Antibacterial Therapy for Community-Acquired
43 442 Pneumonia. *Drugs*. 2008;68(13):1841-1854. doi:10.2165/00003495-200868130-00004
- 46 443 11. Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-
47 444 Acquired Pneumonia: A Multicenter Randomized Clinical Trial. *JAMA Intern Med*.
48 445 2016;176(9):1257. doi:10.1001/jamainternmed.2016.3633
- 52 446 12. Dinh A, Ropers J, Duran C, et al. Discontinuing β -lactam treatment after 3 days for
53 447 patients with community-acquired pneumonia in non-critical care wards (PTC): a double-

- 1
2
3
4
5
6 448 blind, randomised, placebo-controlled, non-inferiority trial. *Lancet*. 2021;397(10280):1195-
7 449 1203. doi:10.1016/s0140-6736(21)00313-5
8
9
10 450 13. Siegel RE, Alicea M, Lee A, Blaiklock R. Comparison of 7 Versus 10 Days of
11 451 Antibiotic Therapy for Hospitalized Patients with Uncomplicated Community-Acquired
12 452 Pneumonia. *Am J Ther*. 1999;6(4):217-222. doi:10.1097/00045391-199907000-00007
13
14
15 453 14. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological
16 454 efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10
17 455 day regimen of clarithromycin twice daily in patients with mild to moderate community-
18 456 acquired pneumonia. *J Antimicrob Chemoth*. 2004;54(2):515-523. doi:10.1093/jac/dkh356
19
20
21
22 457 15. File TM, Mandell LA, Tillotson G, Kostov K, Georgiev O. Gemifloxacin once daily for
23 458 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized,
24 459 multicentre, double-blind study. *J Antimicrob Chemoth*. 2007;60(1):112-120.
25 460 doi:10.1093/jac/dkm119
26
27
28
29 461 16. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response
30 462 meta-analysis for aggregated data. *Stat Methods Med Res*. 2019;28(5):1579-1596.
31 463 doi:10.1177/0962280218773122
32
33
34
35 464 17 Filippini T, Naska A, Kasdagli M, et al. Potassium Intake and Blood Pressure: A
36 465 Dose-Response Meta-Analysis of Randomized Controlled Trials. *J Am Hear Assoc*
37 466 2020;9(12):e015719. doi:10.1161/jaha.119.015719
38
39
40
41 467 18. Filippini T, Malavolti M, Whelton PK, Naska A, Orsini N, Vinceti M. Blood Pressure
42 468 Effects of Sodium Reduction. *Circulation*. 2021;143(16):1542-1567.
43 469 doi:10.1161/circulationaha.120.050371
44
45
46
47 470 19. Højlund M, Kemp AF, Haddad PM, Neill JC, Correll CU. Standard versus reduced
48 471 dose of antipsychotics for relapse prevention in multi-episode schizophrenia: a systematic
49 472 review and meta-analysis of randomised controlled trials. *Lancet Psychiatry*.
50 473 2021;8(6):471-486. doi:10.1016/s2215-0366(21)00078-x
51
52
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55
56
57
58
59
60

- 1
2
3
4
5
6 474 20. Leucht S, Bauer S, Sifakis S, et al. Examination of Dosing of Antipsychotic Drugs for
7 475 Relapse Prevention in Patients With Stable Schizophrenia. *JAMA Psychiat.* 2021;78(11).
8 476 doi:10.1001/jamapsychiatry.2021.2130
- 10
11 477 21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated
12 478 guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. doi:10.1136/bmj.n71
- 14
15 479 22. Montes-Andujar L, Tinoco E, Baez-Pravia O, et al. Empiric antibiotics for community-
16 480 acquired pneumonia in adult patients: a systematic review and a network meta-analysis.
17 481 *Thorax.* Published online 2021:thoraxjnl-2019-214054. doi:10.1136/thoraxjnl-2019-214054
- 20
21 482 23. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for
22 483 community-acquired pneumonia in adult outpatients. *Cochrane Db Syst Rev.*
23 484 2014;10(10):CD002109. doi:10.1002/14651858.cd002109.pub4
- 26
27 485 24. Keren R, Shah SS, Srivastava R, et al. Comparative Effectiveness of Intravenous vs
28 486 Oral Antibiotics for Postdischarge Treatment of Acute Osteomyelitis in Children. *JAMA*
29 487 *Pediatr.* 2014;169(2):120. doi:10.1001/jamapediatrics.2014.2822
- 31
32 488 25. Li HK, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone
33 489 and Joint Infection. *New Engl J Med.* 2019;380(5):425-436. doi:10.1056/nejmoa1710926
- 35
36 490 26. Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic
37 491 Treatment of Endocarditis. *New Engl J Med.* 2019;380(5):415-424.
38 492 doi:10.1056/nejmoa1808312
- 41
42 493 27. Spellberg B, Talbot GH, Brass EP, et al. Position paper: recommended design features
43 494 of future clinical trials of antibacterial agents for community-acquired pneumonia. *Clin*
44 495 *Infect Dis.* 2008;47 Suppl 3:S249-65.
- 47
48 496 28. Bai AD, Komorowski AS, Lo CKL, et al. Intention-to-treat analysis may be more
49 497 conservative than per protocol analysis in antibiotic non-inferiority trials: a systematic
50 498 review. *BMC Med Res Methodol.* 2021;21(1):75. doi:10.1186/s12874-021-01260-7
- 52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 499 29. Aberegg SK, Hersh AM, Samore MH. Empirical Consequences of Current
7 500 Recommendations for the Design and Interpretation of Noninferiority Trials. *J Gen Intern*
8 501 *Med.* 2018;33(1):88-96. doi:10.1007/s11606-017-4161-4
9
10
11 502 30. Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in
12 503 meta-analysis. *Res Synth Methods.* 2019;10(3):398-419. doi:10.1002/jrsm.1347
13
14
15 504 31. Doi SA, Furuya-Kanamori L, Xu C, Lin L, Chivese T, Thalib L. Questionable utility of
16 505 the relative risk in clinical research: A call for change to practice. *J Clin Epidemiol.*
17 506 Published online 2020. doi:10.1016/j.jclinepi.2020.08.019
18
19
20
21 507 32. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in
22 508 randomised trials. *BMJ.* 2019;366:l4898. doi:10.1136/bmj.l4898
23
24
25 509 33. Team RC. R: A Language and Environment for Statistical Computing. R Foundation
26 510 for Statistical Computing.; 2020. <https://www.R-project.org/>
27
28
29 511 34. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a
30 512 practical tutorial. *Évid Based Ment Heal.* 2019;22(4):153. doi:10.1136/ebmental-2019-
31 513 300117
32
33
34
35 514 35. Crippa A, Orsini N. Multivariate Dose-Response Meta-Analysis: The dosresmeta R
36 515 Package. Published online 2016. doi:doi.org/10.18637/jss.v072.c01
37
38
39 516 36. Léophonte P, Choutet P, Gaillat J, et al. Efficacité comparée de la ceftriaxone dans un
40 517 traitement de dix jours versus un traitement raccourci de cinq jours des pneumonies aiguës
41 518 communautaires de l'adulte hospitalisé avec facteur de risque. *Médecine Et Maladies*
42 519 *Infect.* 2002;32(7):369-381. doi:10.1016/s0399-077x(02)00384-0
43
44
45
46 520 37. Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, et al.
47 521 Effectiveness of discontinuing antibiotic treatment after three days versus eight days in
48 522 mild to moderate-severe community acquired pneumonia: randomised, double blind study.
49 523 *BMJ.* 2006;332(7554):1355. doi:10.1136/bmj.332.7554.1355
50
51
52
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54
55
56
57
58
59
60

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2
3
4
5
6 524 38. Aliberti S, Ramirez J, Giuliani F, et al. Individualizing duration of antibiotic therapy in
7 525 community-acquired pneumonia. *Pulm Pharmacol Ther.* 2017;45:191-201.
8
9 526 doi:10.1016/j.pupt.2017.06.008
10
11 527 39. Strålin K, Rubenson A, Lindroth H, et al. BETA LACTAM TREATMENT UNTIL
12 528 NO FEVER FOR 48 HOURS (AT LEAST 5 DAYS) VERSUS 10 DAYS IN
13
14 529 COMMUNITY-ACQUIRED PNEUMONIA: RANDOMISED, NON-INFERIORITY,
15
16 530 OPEN STUDY. In: Vol 3. *Pneumonia.* ; 2014:246-281. doi:10.1007/bf03399446
17
18 531 40. NCT03609099. Adequate Duration of Antibiotic Treatment in Community-acquired
19
20 532 Pneumonia With High Risk Class and Adequate Initial Clinical Response (2017-001406-
21
22 533 15). <https://clinicaltrials.gov/ct2/show/NCT03609099>
23
24 534 41. NCT04089787. Shortened Antibiotic Treatment of 5 Days in Community-Acquired
25
26 535 Pneumonia (CAP5). <https://clinicaltrials.gov/ct2/show/NCT04089787>
27
28 536 42. Halm EA, Fine MJ, Marrie TJ, et al. Time to Clinical Stability in Patients Hospitalized
29
30 537 With Community-Acquired Pneumonia: Implications for Practice Guidelines. *JAMA.*
31
32 538 1998;279(18):1452-1457. doi:10.1001/jama.279.18.1452
33
34 539 43. Mulla SM, Scott IA, Jackevicius CA, You JJ, Guyatt GH. How to Use a Noninferiority
35
36 540 Trial: Users' Guides to the Medical Literature. *JAMA.* 2012;308(24):2605-2611.
37
38 541 doi:10.1001/2012.jama.11235
39
40 542 44. Acuna SA, Chesney TR, Baxter NN. Incorporating Patient Preferences in
41
42 543 Noninferiority Trials. *JAMA.* 2019;322(4):305-306. doi:10.1001/jama.2019.7059
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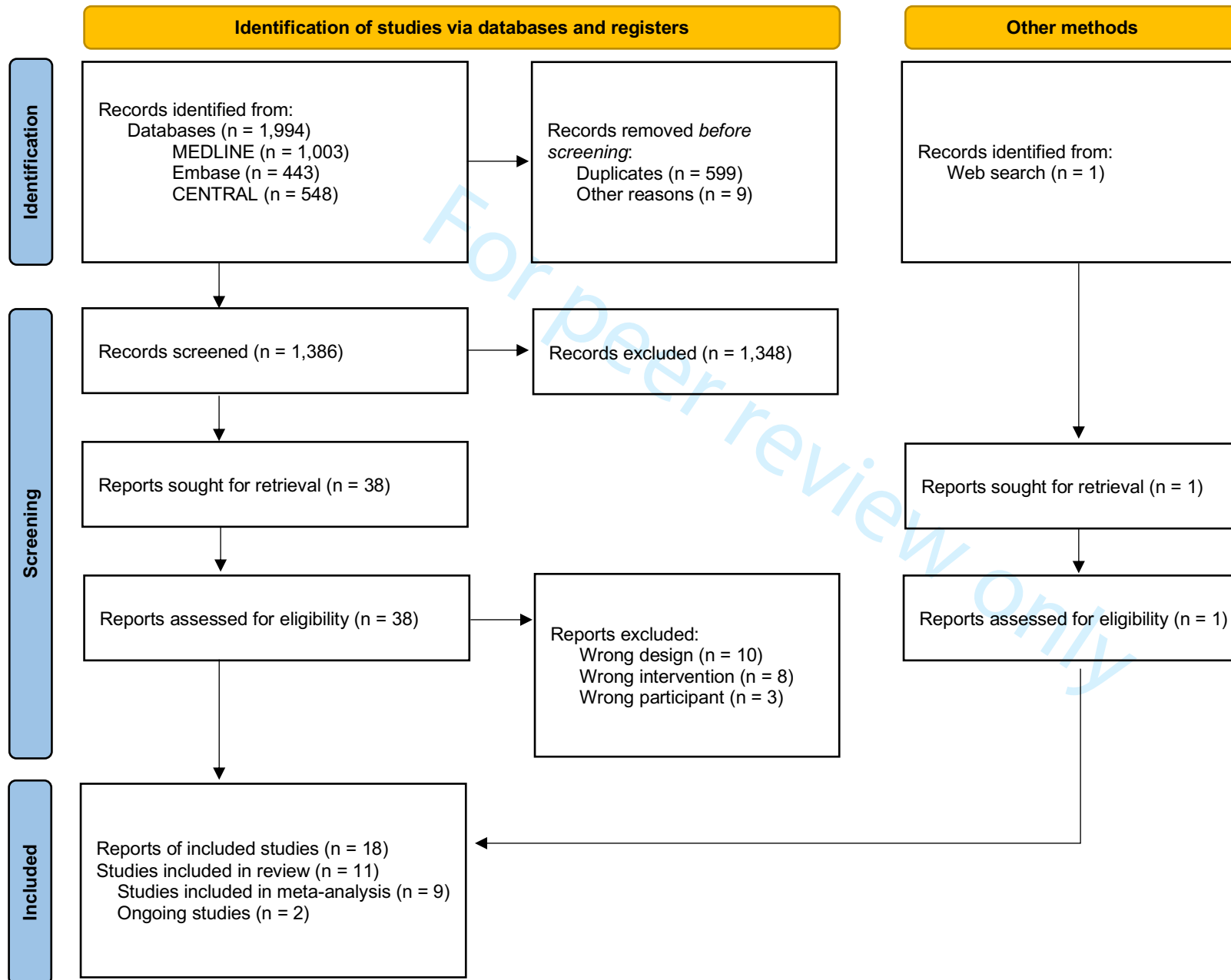
FIGURE LEGENDS**Figure 1 PRISMA flow diagram****Figure 2 Duration–effect relationship of antibiotics for CAP in adults. Clinical improvement at day 15.**

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

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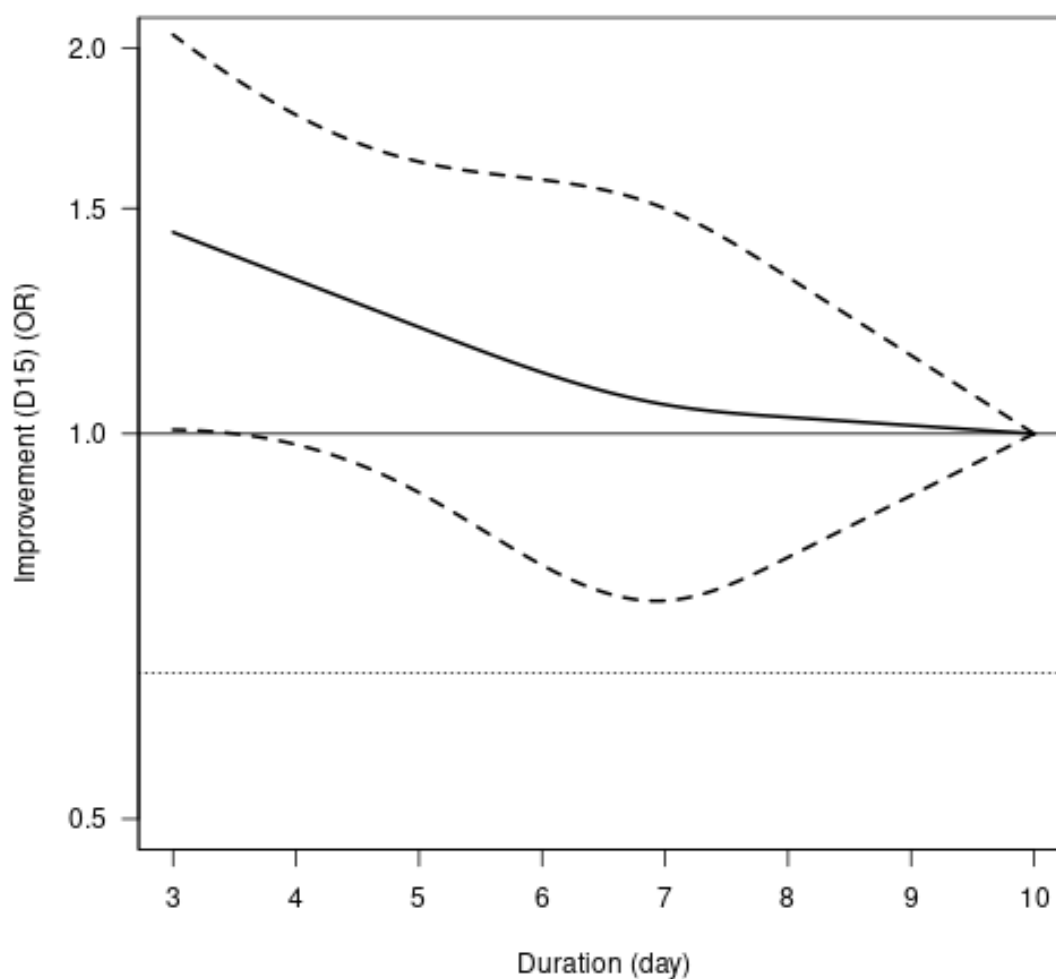
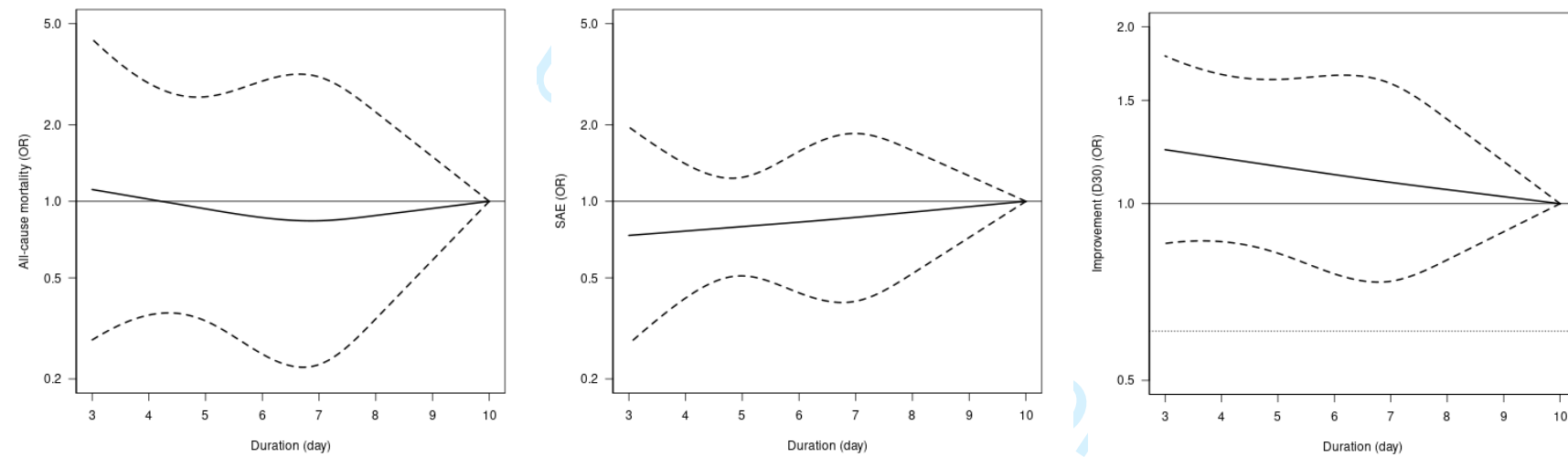


Figure 3 Duration–effect relationships of antibiotics for CAP in adults. (a) All-cause mortality. (b) Severe adverse events. (c) Clinical improvement at day 30.

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%.



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3 **1 Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a**
4 **2 systematic review and duration-effect meta-analysis (eAppendix)**
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8 **4** Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A
9 **5** Furukawa, Yuki Kataoka
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11 **6**

12 **7** 1. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: protocol for a
13 **8** systematic review and duration-effect meta-analysis (protocol as of 15th August, 2021)

14 **9** 2. Search strings used for Ovid MEDLINE, Embase, and CENTRAL.
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16 **10**

17 **11** 3. Amendments from the protocol

18 **12** 4. List of all included papers

19 **13** 5. List of excluded studies

20 **14** 6. Heterogeneity: Variance partition coefficient for the primary outcome

21 **15** 7. Sensitivity analyses
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4 17 **1. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults:**
5 18 **protocol for a systematic review and duration-effect network meta-analysis (protocol as of 15th**
6 19 **August, 2021)**
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9 21 Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A Furukawa, Yuki
10 22 Kataoka
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14 24 **INTRODUCTION**

15 25 Community-acquired pneumonia (CAP) continues to be a leading cause of morbidity and mortality globally. (1) In the United
16 26 States, for example, it is the second most common cause of hospitalization and the top infectious cause of death. (2,3)
17 27 Clinical guidelines recommend starting several antibiotics empirically for non-severe pneumonia. (4) The optimal duration of
18 28 antimicrobial therapy, however, remains unclear and controversial. Recent clinical guidelines suggest a minimum of five
19 29 days of treatment before therapy discontinuation for patients achieving an afebrile state for 48 to 72 hours and meeting
20 30 clinical stability criteria. (4) In clinical settings, however, a conventional ten to 14-day therapy is still used. (5,6) This may
21 31 mean that many patients are receiving more antibiotics than necessary, which leads to an increased cost, time and also, higher
22 32 probability of antimicrobial resistance. (7) Finding optimal duration of antibiotics is therefore meaningful not only for
23 33 clinicians but also for policy-makers. A meta-analysis found that short-course therapy was not inferior to long-course therapy.
24 34 (8) A major limitation of the method used in this meta-analysis is the arbitrary categorization of durations, when the original
25 35 studies compared different durations, ranging from three to ten days. This resulted in categorizing a seven-day treatment in
26 36 one trial to short-course and the same in another trial to long-course. We can overcome this limitation by using a novel
27 37 method called dose-effect network meta-analysis (DE-NMA), which allows us to use the original duration in days and to
28 38 examine the optimal duration with greater resolution of change points.
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38 40 **OBJECTIVES**

39 41 To find the optimal treatment duration with antibiotics for CAP.
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41 43 **METHODS AND ANALYSIS**

42 44 We follow PRISMA-P in reporting the protocol and will follow PRISMA(9) and PRISMA-NMA in reporting the DE-NMA
43 45 results.
44 46
45 47

46 48 **Data sources**

47 49 **Criteria for considering studies for this review**

48 50 *Types of studies*

49 51 All randomized controlled studies. Quasi-randomized trials (such as those allocating by using alternate days of the week) will
50 52 be excluded.
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52 53 1. Cluster-randomized trials
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53 Cluster-randomized trials will be included as long as proper adjustment for the intra-cluster correlation is conducted in
54 accordance with the Cochrane Handbook for Systematic Reviews of Interventions.

55 2. Studies with multiple treatment groups

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

57 *Types of participants*

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

62
63 *Types of interventions*

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

73
74 **Primary outcome and secondary outcomes**

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

77
78 1 Clinical improvement at day 15 (range 7-45 days), as defined by the original study

79
80 Secondary outcomes of interest are the following outcomes.

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

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

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

84
85 We will use the number of randomized patients as the denominator for intention-to-treat (ITT) dataset and we will use
86 per-protocol (PP) dataset as defined by the original study. Those who had been randomized but not accounted for in the
87 original study will be assumed to have dropped out for some reason other than death or serious adverse events and without

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3 88 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
4
5 89 ITT for the primary analysis and PP for a sensitivity analysis. (17,18)

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8 91 **Search methods for identification of studies**

9 92 *Electronic searches*

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11 93 Searches for published studies will be undertaken in the following electronic bibliographic databases from inception to
12 94 present (25 August, 2021): Ovid MEDLINE and Cochrane CENTRAL. We will use search terms for community acquired
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14 95 pneumonia in conjunction with the names of individual antibiotics as well as the names of antibiotic classes. We imposed no
15 96 date, language or publication status restriction.

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17 97 *Search formula*

18 98 Search strategy for Ovid MEDLINE is as follows

19 99
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21 100 #1 randomized controlled trial.pt.

22
23 101 #2 controlled clinical trial.pt.

24 102 #3 randomized.ab.

25
26 103 #4 placebo.ab.

27 104 #5 drug therapy.fs.

28
29 105 #6 randomly.ab.

30 106 #7 trial.ab.

31
32 107 #8 groups.ab.

33 108 #9 or/#1-#8

34
35 109 #10 exp animals/ not humans.sh.

36 110 #11 #9 not #10

37
38 111 #12 exp Community-Acquired Infections/

39 112 #13 Pneumonia, Bacterial/dt [Drug Therapy]

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41 113 #14 community acquired pneumonia.ab,ti.

42 114 #15 (#12 and #13) or #14

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44 115 #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
45 116 disconti*).mp.

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47 117 #17 (beta-lactam* or macrolide* or quinolone* or tetracycline* or amikacin or amoxicillin or ampicillin or azithromycin or
48 118 cefepim or cefotaxim* or ceftarolin or ceftazidim* or ceftibuten or ceftriaxon* or cefuroxim* or cethromycin or
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50 119 ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or co-amoxiclav or co-trimoxacol or doxycyclin* or

51 120 ertapenem or erythromycin or fluoroquinolon* or fluorochinolon* or gemifloxacin or gentamicin or imipenem or levofloxacin
52
53 121 or linezolid or meropenem or moxifloxacin or penicillin* or piperacillin or roxithromycin or sultamicillin or tazobactam or
54 122 telithromycin or tetracyclin* or ticarcillin or tobramycin).mp.

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56 123 #18 Anti-Bacterial Agents/ad [Administration & Dosage]

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124 #19 #17 or #18

125 #20 #11 and #15 and #16 and #19

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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 *MBNMA* package in R.(20,21) One advantage of the dose-effect network meta-analysis by *MBNMA* 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, ceftaroline), 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.

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Ethics and dissemination

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

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Amendments

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

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Abbreviations

AMR: antimicrobial resistance

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CAP: community-acquired pneumonia

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DE-NMA: dose-effect network meta-analysis

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ITT: intention-to-treat

209

PP: per protocol

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

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Reference

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

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

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

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

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

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

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

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

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- 231 9 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic
232 reviews. *Br Med J* 2021;372:n71. doi:10.1136/bmj.n71
- 233 10 Montes-Andujar L, Tinoco E, Baez-Pravia O, et al. Empiric antibiotics for community-acquired pneumonia in adult
234 patients: a systematic review and a network meta-analysis. *Thorax* 2021;;thoraxjnl-2019-214054.
235 doi:10.1136/thoraxjnl-2019-214054
- 236 11 Pakhale S, Mulpuru S, Verheij TJ, et al. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane*
237 *Db Syst Rev* 2014;10:CD002109. doi:10.1002/14651858.cd002109.pub4
- 238 12 Li HK, Agweyu A, English M, et al. An Unsupported Preference for Intravenous Antibiotics. *Plos Med* 2015;12:e1001825.
239 doi:10.1371/journal.pmed.1001825
- 240 13 Keren R, Shah SS, Srivastava R, et al. Comparative Effectiveness of Intravenous vs Oral Antibiotics for Postdischarge
241 Treatment of Acute Osteomyelitis in Children. *JAMA Pediatr* 2014;169:120. doi:10.1001/jamapediatrics.2014.2822
- 242 14 Li H-K, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. *New Engl J Med*
243 2019;380:425–36. doi:10.1056/nejmoa1710926
- 244 15 Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. *New Engl J*
245 *Med* 2019;380:415–24. doi:10.1056/nejmoa1808312
- 246 16 Spellberg B, Talbot GH, Brass EP, et al. Position paper: recommended design features of future clinical trials of
247 antibacterial agents for community-acquired pneumonia. *Clin Infect Dis* 2008;47 Suppl 3:S249-65.
- 248 17 Bai AD, Komorowski AS, Lo CKL, et al. Intention-to-treat analysis may be more conservative than per protocol analysis
249 in antibiotic non-inferiority trials: a systematic review. *BMC Med Res Methodol* 2021;21:75.
250 doi:10.1186/s12874-021-01260-7
- 251 18 Aberegg SK, Hersh AM, Samore MH. Empirical Consequences of Current Recommendations for the Design and
252 Interpretation of Noninferiority Trials. *J Gen Intern Med* 2018;33:88–96. doi:10.1007/s11606-017-4161-4
- 253 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*
254 2019;366:14898. doi:10.1136/bmj.14898
- 255 20 Mawdsley D, Bennetts M, Dias S, Boucher M, Welton N. Model-Based Network Meta-Analysis: A Framework for
256 Evidence Synthesis of Clinical Trial Data. *Cpt Pharmacometrics Syst Pharmacol.* 2016;5(8):393–401.
- 257 21 Team R. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2020.
258 <https://www.R-project.org/>
- 259 22 Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth Methods*
260 2019;10:398–419. doi:10.1002/jrsm.1347
- 261 23 Doi SA, Furuya-Kanamori L, Xu C, et al. Questionable utility of the relative risk in clinical research: A call for change to
262 practice. *J Clin Epidemiol* Published Online First: 2020. doi:10.1016/j.jclinepi.2020.08.019
- 263 24 Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A
264 Multicenter Randomized Clinical Trial. *JAMA Intern Med* 2016;176:1257. doi:10.1001/jamainternmed.2016.3633

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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 ceftazolidin 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 fluorochinolon* or gemifloxacin or gentamicin or imipenem or levofloxacin
or linezolid 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(communitary acquired pneumonia) OR ti(communitary acquired pneumonia)

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3 302 S3 S2 OR S1
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5 303 S4 ab((short near/1 term) OR (long near/1 term) OR prolonged OR (short near/1 course) OR (long near/1 course) OR
6 304 day OR days OR duration or disconti*) OR ti((short near/1 term) OR (long near/1 term) OR prolonged OR (short near/1
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8 305 course) OR (long near/1 course) OR day OR days OR duration or disconti*)
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10 306 S5 ab(beta-lactam* OR macrolide* OR quinolone* OR tetracycline* OR amikacin OR amoxicillin OR ampicillin OR
11 307 azithromycin OR cefepim OR cefotaxim* OR ceftarolin OR ceftazidim* OR ceftibuten OR ceftriaxon* OR cefuroxim* OR
12 308 cethromycin OR ciprofloxacin OR clarithromycin OR clavulanic acid OR clindamycin OR co-amoxiclav OR co-trimoxacol
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14 309 OR doxycyclin* OR ertapenem OR erythromycin OR fluoroquinolon* OR fluorchinolon* OR gemifloxacin OR gentamicin
15 310 OR imipenem OR levofloxacin OR linezolid OR meropenem OR moxifloxacin OR penicillin* OR piperacillin OR
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17 311 roxithromycin OR sultamicillin OR tazobactam OR telithromycin OR tetracyclin* OR ticarcillin OR tobramycin) OR
18 312 ti(beta-lactam* OR macrolide* OR quinolone* OR tetracycline* OR amikacin OR amoxicillin OR ampicillin OR
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20 313 azithromycin OR cefepim OR cefotaxim* OR ceftarolin OR ceftazidim* OR ceftibuten OR ceftriaxon* OR cefuroxim* OR
21 314 cethromycin OR ciprofloxacin OR clarithromycin OR clavulanic acid OR clindamycin OR co-amoxiclav OR co-trimoxacol
22
23 315 OR doxycyclin* OR ertapenem OR erythromycin OR fluoroquinolon* OR fluorchinolon* OR gemifloxacin OR gentamicin
24 316 OR imipenem OR levofloxacin OR linezolid OR meropenem OR moxifloxacin OR penicillin* OR piperacillin OR
25
26 317 roxithromycin OR sultamicillin OR tazobactam OR telithromycin OR tetracyclin* OR ticarcillin OR tobramycin)
27 318 S6 (EMB.EXACT("antibiotic agent -- drug dose"))
28
29 319 S7 S6 OR S5
30 320 S8 S7 AND S4 AND S3
31
32 321 S9 (ab(random*) OR ti(random*)) OR (ab(placeholder*) OR ti(placeholder*)) OR (ab(double NEAR/1 blind*) OR ti(double
33 322 NEAR/1 blind*))
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35 323 S10 S9 AND S8
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38 325 2-3. Search strategy for CENTRAL
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41 327 #1 [mh "Community-Acquired Infections"]
42 328 #2 [mh "Pneumonia, Bacterial"]
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44 329 #3 "community acquired pneumonia":ti,ab
45 330 #4 (#1 and #2) or #3
46
47 331 #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
48 332 (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
49
50 333 duration:ti,ab,kw OR disconti*:ti,ab,kw
51 334 #6 beta-lactam*:ti,ab,kw OR macrolide*:ti,ab,kw OR quinolone*:ti,ab,kw OR tetracycline*:ti,ab,kw OR
52 335 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
53 336 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
54 337 cefuroxim*:ti,ab,kw OR cethromycin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR clarithromycin:ti,ab,kw OR "clavulanic
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3 338 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
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5 339 ertapenem:ti,ab,kw OR erythromycin:ti,ab,kw OR fluoroquinolon*:ti,ab,kw OR fluorquinolon*:ti,ab,kw OR
6
7 340 gemifloxacin:ti,ab,kw OR gentamicin:ti,ab,kw OR imipenem:ti,ab,kw OR levofloxacin:ti,ab,kw OR linezolid:ti,ab,kw OR
8 341 meropenem:ti,ab,kw OR moxifloxacin:ti,ab,kw OR penicillin*:ti,ab,kw OR piperacillin:ti,ab,kw OR roxithromycin:ti,ab,kw
9
10 342 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
11 343 OR tobramycin:ti,ab,kw

12 344 #7 [mh "Anti-Bacterial Agents"]

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14 345 #8 #6 OR #7

15 346 #9 #4 AND #5 AND #8

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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

- 362 ● Siegel RE, Alicea M, Lee A, Blaiklock R. Comparison of 7 Versus 10 Days of Antibiotic Therapy for Hospitalized
363 Patients with Uncomplicated Community-Acquired Pneumonia. *Am J Ther* 1999; 6: 217–22.
- 364 ● Léophonte P, Choutet P, Gaillat J, et al. Efficacité comparée de la ceftriaxone dans un traitement de dix jours versus un
365 traitement raccourci de cinq jours des pneumonies aiguës communautaires de l'adulte hospitalisé avec facteur de risque.
366 *Médecine Et Maladies Infect* 2002; 32: 369–81.
- 367 ● Tellier G, Niederman MS, Nusrat R, et al. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of
368 telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to
369 moderate community-acquired pneumonia. *J Antimicrob Chemoth* 2004; 54: 515–23.
- 370 ● El Moussaoui R, Borgie C, Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus
371 eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 2006;
372 332: 1355.
- 373 ● File TM, Mandell LA, Tillotson G, et al. Gemifloxacin once daily for 5 days versus 7 days for the treatment of
374 community-acquired pneumonia: a randomized, multicentre, double-blind study. *J Antimicrob Chemoth* 2007; 60: 112–
375 20.
- 376 ● Strålin K, Rubenson A, Lindroth H, et al. BETALACTAM TREATMENT UNTIL NO FEVER FOR 48HOURS (AT
377 LEAST 5 DAYS) VERSUS 10 DAYS IN COMMUNITY-ACQUIRED PNEUMONIA: RANDOMISED,
378 NON-INFERIORITY, OPEN STUDY. *Pneumonia* 2014; 3: 246–81.
- 379 ● Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A
380 Multicenter Randomized Clinical Trial. *JAMA Intern Med* 2016; 176: 1257.
- 381 ● Aliberti S, Ramirez J, Giuliani F, et al. Individualizing duration of antibiotic therapy in community-acquired pneumonia.
382 *Pulm Pharmacol Ther* 2017; 45: 191–201.
- 383 ● Dinh A, Ropers J, Duran C, et al. Discontinuing β -lactam treatment after 3 days for patients with community-acquired
384 pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial.
385 *Lancet* 2021; 397: 1195–203.

Ongoing trials

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

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3 395 **5. List of excluded studies**
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| 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 (different drugs) |
| EUCTR2014-003137-25 | Optimal duration of antibiotic treatment in patients with complicated parapneumonic pleural effusions or empyema | wrong intervention (different drugs) |
| EUCTR2020-004452-15 | ADMINISTRATION OF CLARITHROMYCIN IN COMMUNITY-ACQUIRED PNEUMONIA | wrong intervention (different 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 (different drugs) |
| JPRN-JapicCTI-163439 | A Phase III study of Solithromycin in patients with community-acquired pneumonia | wrong intervention (different 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) |

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| 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 (different 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 (different drugs) |
| Weber1987 | Ampicillin versus cefamandole as initial therapy for community-acquired pneumonia | wrong intervention (different drugs) |
| YangJ2020 | The combined treatment of imipenem cilastatin and azithromycin for elderly patients with community-acquired pneumonia | wrong intervention (different drugs) |

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6. Heterogeneity: Variance partition coefficient for the primary outcome

VPC is computed for each non-referent arm of each study (those that have $OR \neq 1$). 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
```

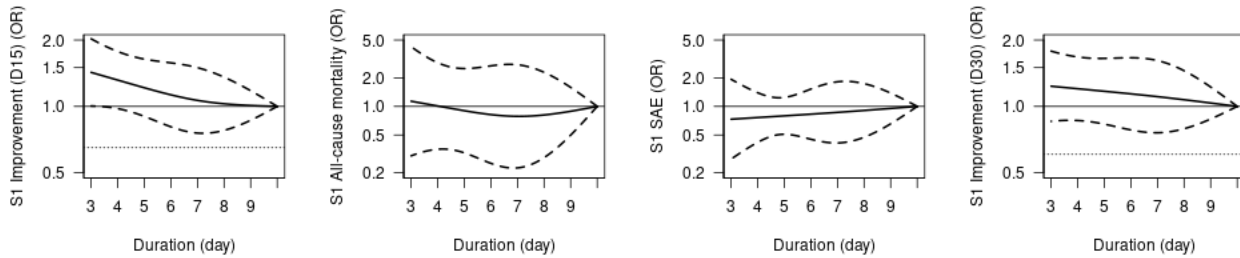
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7. Sensitivity analyses

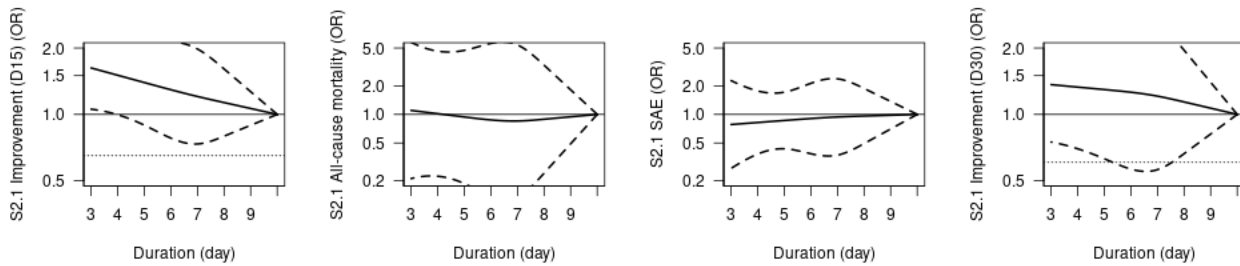
Duration-effect relationship of secondary outcomes could not be computed due to missing data in some cases.

A priori sensitivity analyses

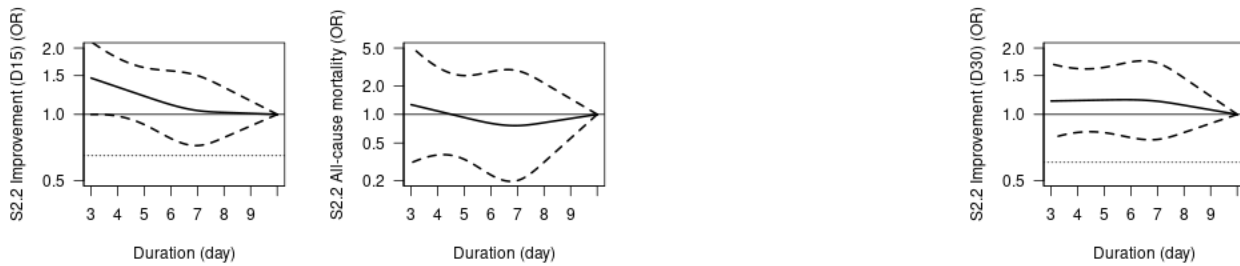
##S1 To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%).



##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)

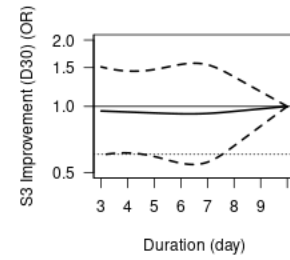
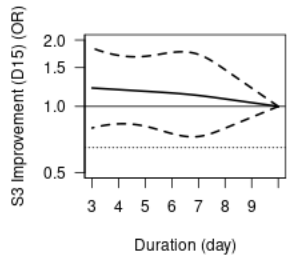


##S2.2 To test the influence of trials included, we conducted sensitivity analyses excluding trials with outpatients (excluding Tellier2004, File2007. SAE not computable)

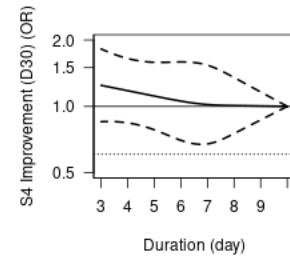
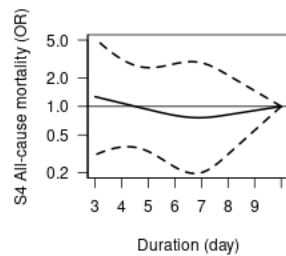
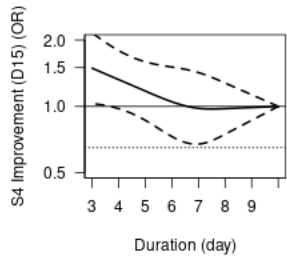


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425 ##S3 To test the robustness of the analytical method, we used PP dataset. (All-cause mortality and SAE not computable)

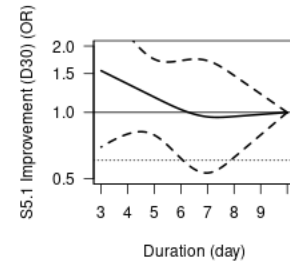
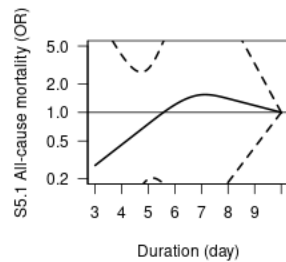
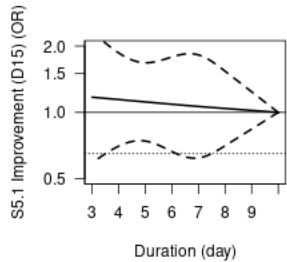


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427 ##S4 To test the influence of antibiotics examined, we conducted sensitivity analyses including only antibiotics
428 recommended for empirical treatment of CAP by clinical guidelines. (excluding Siegel1999, Tellier2004. SAE not
429 computable.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

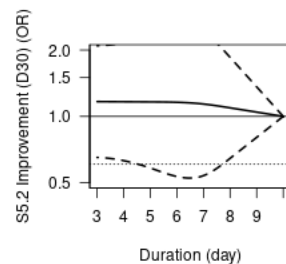
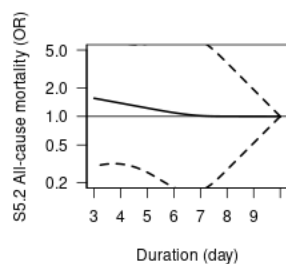
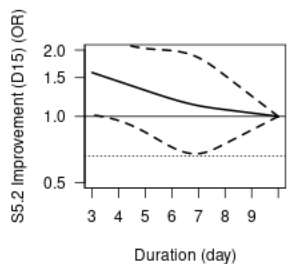


430 # Post-hoc, exploratory sensitivity analyses

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



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



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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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BMJ Open

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

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-061023.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 07-Oct-2022 |
| Complete List of Authors: | FURUKAWA, YUKI; Tokyo Musashino Hospital, Department of Psychiatry; University of Tokyo Hospital, Department of Neuropsychiatry Luo, Yan; Kyoto University Graduate School of Medicine, Department of Health Promotion and Human Behavior Funada, Satoshi; Kyoto University, Urology; Kyoto University, Health Promotion and Human Behavior Onishi, Akira; Graduate School of Medicine, Kyoto University, Department of Advanced Medicine for Rheumatic diseases Ostinelli, Edoardo; University of Oxford, Department of Psychiatry Hamza, Tasnim; University of Bern, Institute of Social and Preventive Medicine Furukawa, Toshi; Kyoto University, Graduate School of Medicine and School of Public Health Kataoka, Yuki; Kyoto Min-Iren Asukai Hospital, Department of Internal Medicine; Kyoto University Graduate School of Medicine Faculty of Medicine, Department of Community Medicine |
| Primary Subject Heading: | Infectious diseases |
| Secondary Subject Heading: | Evidence based practice, Infectious diseases, Respiratory medicine |
| Keywords: | BACTERIOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory infections < THORACIC MEDICINE |
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6 **1 TITLE PAGE**

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9 **3 Title: Optimal duration of antibiotic treatment for community-acquired pneumonia in**
10 **4 adults: a systematic review and duration-effect meta-analysis**

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24 46 **Word count**

25 47 **3259 words**

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6 49 **ABSTRACT** (300 words)

7 50 **Objectives:** To find the optimal treatment duration with antibiotics for community-
8
9 51 acquired pneumonia (CAP) in adults.

10 52 **Design:** Systematic review and duration-effect meta-analysis.

11 53 **Data sources:** MEDLINE, Embase and CENTRAL through 25 August 2021.

12 54 **Eligibility criteria:** All randomised controlled trials comparing the same antibiotics used at
13
14 55 the same daily dosage but for different durations for CAP in adults. Both outpatients and
15
16 56 inpatients were included but not those admitted to intensive care units. We imposed no
17
18 57 date, language or publication status restriction.

19 58 **Data extraction and synthesis:** Data extraction by two independent reviewers. We
20
21 59 conducted a random-effects, one-stage duration-effect meta-analysis with restricted cubic
22
23 60 splines. We tested the non-inferiority with the pre-specified non-inferiority margin of 10%
24
25 61 examined against 10 days using. The primary outcome was clinical improvement on day 15
26
27 62 (range 7-45 days). Secondary outcomes: all-cause mortality, serious adverse events, and
28
29 63 clinical improvement on day 30 (15-60 days).

30 64 **Results:** We included 9 trials (2,399 patients with a mean [SD] age of 61.2 [22.1]; 39%
31
32 65 women). The duration-effect curve was monotonic with longer duration leading to a lower
33
34 66 probability of improvement, and shorter treatment duration (3-9 days) was likely to be non-
35
36 67 inferior to 10-day treatment. Harmful outcome curves indicated no association. The
37
38 68 weighted average percentage of the primary outcome in the 10-day treatment arms was
39
40 69 68%. Using that average, the absolute clinical improvement rates of the following durations
41
42 70 were: 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-
43
44 71 day treatment 69% (61 to 76%).

45 72 **Conclusions:** Shorter treatment duration (3-5 days) probably offers the optimal balance
46
47 73 between efficacy and treatment burden for treating CAP in adults if they achieved clinical
48
49 74 stability. However, the small number of included studies and the overall moderate to high
50
51 75 risk of bias may compromise the certainty of the results. Further research on the shorter
52
53 76 duration range is required.

54
55 77 **Registration:** PROSPERO (CRD 42021273357).
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6 **79 Strengths and limitations of this study**

- 7 80 - We conducted a comprehensive and up-to-date systematic literature review.
8
9 81 - The duration-effect meta-analysis treated duration as a continuous variable, which
10 82 allowed us to estimate the duration-effect relationship with greater resolution than the
11 83 conventional pairwise meta-analysis that dichotomised duration arbitrarily.
12
13 84 - The small number of trials included limited the precision of some study results.
14
15 85 - Most of the trials had a moderate to high overall risk of bias.
16
17 86 - About 80% of the patients had pneumonia severity index class III or less and thus the
18 87 results may not be generalisable to severely ill patients.
19
20 88

21 **89 Keywords**

22 90 Community-acquired pneumonia; antibiotic; treatment duration; dose-response meta-
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24 91 analysis
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6 93 **MAIN TEXT** (3259 words)

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8
9 95 **BACKGROUND**

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12 96 Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality

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15 97 globally, especially among the elderly.[1] In the United States, it is the second most

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18 98 common cause of hospitalisation and the top infectious cause of death.[2,3] The initial

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21 99 treatment for CAP is empirical, with guidelines recommending starting several antibiotics

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24 100 depending on patients' severity and risk factors for certain pathogens.[4–6]

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27 101 The optimal duration of antimicrobial therapy remains unclear and

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30 102 controversial. The American and British guidelines recommend a minimum of five days of

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33 103 treatment before therapy discontinuation for patients achieving clinical stability.[4,5] The

34
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36 104 European guideline states that the duration of treatment should not exceed eight days in

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39 105 responding patients.[6] In clinical practice, however, antibiotics for pneumonia are often

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41
42 106 prescribed for 10 up to 14 days.[7,8] This may mean that many patients are receiving more

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45 107 antibiotics than necessary, with a consequent increase in costs and a higher probability of

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48 108 antimicrobial resistance.[9] Finding the optimal duration of antibiotics can facilitate

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51 109 reducing antimicrobial use efficiently. Several meta-analyses have been reported on this

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54 110 topic.[10–12] A major limitation of the method used in the previous pairwise meta-analyses

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6 111 is the arbitrary categorisation of duration when the original studies compared different
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9 112 duration, ranging from three to ten days. A pairwise meta-analysis published in 2008, [10]
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12 113 for example, categorised a seven-day treatment arm in one trial as short-course and the
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15 114 same in other two trials as long-course. [13–15] Another pairwise meta-analysis in 2018
16
17
18 115 excluded a trial comparing seven-day against ten-day treatment because they defined long-
19
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21 116 course as seven days or longer.[11] The duration range of short course therapy defined by a
22
23
24 117 systematic review of systematic reviews and guidelines with pairwise meta-analyses in
25
26
27 118 2019 was wide (three to seven days) and the duration-effect relationship within that range
28
29
30 119 remains unclear.[12] We overcame the limitation of arbitrary dichotomisation of duration
31
32
33 120 by using a novel method called dose-effect meta-analysis.[16] It has been used, for
34
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36 121 example, to examine the effects of potassium intake or sodium reduction on blood
37
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39 122 pressure[17,18]. Unlike conventional categorisation-based meta-analyses[19], dose-effect
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42 123 meta-analysis can reveal more fine-grained optimal dose[20]. By treating duration as dose,
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45 124 we aimed to apply this method to obtain a more specific optimal treatment duration.
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126 **METHODS**

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7 127 We summarised the currently available evidence to find the optimal treatment duration of
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9 128 antibiotics for CAP in adults. We followed the Preferred Reporting Items for Systematic
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12 129 reviews and Meta-Analyses (PRISMA 2020) [21]. The protocol has been prospectively
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14
15 130 registered in PROSPERO (CRD 42021273357) and can be found in the appendix
16
17
18 131 (eAppendix1).

132 ***Patient and Public Involvement***

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

135

136 **Data sources**

137 **Criteria for considering studies for this review**

138 ***Types of studies***

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

141 ***Types of participants***

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

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6 144 excluded patients who were admitted to the intensive care unit. To focus on individuals at
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9 145 low to medium risk, we excluded trials with 20% or more patients meeting one or more of
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12 146 the following criteria: having immunodeficiency; having been treated with another
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15 147 antibiotic within a month.

18 148 *Types of interventions*

20
21 149 We included trials examining any antibiotics, administered orally or intravenously. We
22
23
24 150 evaluated antibiotics as a class because clinical guidelines recommend treatment duration
25
26
27 151 irrespective of the antibiotic used,[4–6] and because recent meta-analyses of antibiotics for
28
29
30 152 CAP have not shown efficacy differences among antibiotics.[22,23] Oral and intravenous
31
32
33 153 antibiotics were merged because they have been shown equally effective in many infectious
34
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36 154 conditions within the same time frame.[24–26] We included trials comparing the same
37
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39 155 agents used at the same daily dosage but for different durations. We used the predefined
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41
42 156 duration for fixed-duration arms. If some studies did not prespecified the duration (eg. left
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45 157 it to clinicians' judgment[27]), we used the median duration.

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51 159 **Primary outcome and secondary outcomes**

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7 160 The primary outcome of interest in this study was the clinical improvement as defined by
8
9 161 the original authors at a time point as close to 15 days (range 7-45 days) as possible in each
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12 162 included study.[28] Secondary outcomes of interest were: all-cause mortality on day 15
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15 163 (range 7-45 days), serious adverse events as defined by the original study on day 15 (range
16
17
18 164 7-45 days), and clinical improvement as defined by the original study on day 30 (range 15-
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20
21 165 60). We used the number of randomised patients as the denominator for the intention-to-
22
23
24 166 treat (ITT) dataset. When only clinical failure was reported, clinical improvement was
25
26
27 167 calculated by subtracting clinical failure from the total number randomised. We used ITT
28
29
30 168 for the primary analysis and the per-protocol (PP) dataset for a sensitivity analysis.[29,30]
31
32
33 169 We used the odds ratio (OR) of each outcome to synthesise data. [31,32]
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39 171 **Search methods for identification of studies**

42 172 *Electronic searches*

44
45 173 We systematically searched the following electronic bibliographic databases from inception
46
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48 174 through 25 August 2021: MEDLINE, Embase and CENTRAL. We used search terms for
49
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51 175 community-acquired pneumonia in conjunction with the names of individual antibiotics as
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6 176 well as the names of antibiotic classes. Detailed search formulas are presented in the
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8
9 177 appendix (eAppendix2). We imposed no date, language or publication status restriction.

12 178 ***Reference lists***

15 179 We checked the reference lists of all the included studies and review articles for additional
16
17
18 180 references.

21 181

24 182 **Data collection and analysis**

27 183 **Selection of studies**

30 184 Two review authors independently screened and selected the included studies (YF and one
31
32
33 185 of AO, EO, SF or YL). Two review authors extracted data independently from the included
34
35
36 186 studies (YF and one of AO, EO, SF or YL). We used the Cochrane risk of bias tool Version
37
38
39 187 2 [33] to assess and summarise the risk of bias. Disagreements were resolved through
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41
42 188 discussion.

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48 190 **Statistical analysis**

51 191 To perform our analyses, we used the *dosresmeta* package (Version 2.0.1) and *meta*
52
53
54 192 package (Version 5.0-1) for *R* (Version 4.1.0. R foundation, Wien, Austria).[34–36]
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9 194 ***Assessment of heterogeneity***

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12 195 We investigated the heterogeneity between studies by the variance partition coefficient
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15 196 (VPC). [16] VPC represents the percentage of variation attributed to heterogeneity rather
16
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18 197 than sampling error and can be interpreted similarly to the I^2 .

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24 199 ***Duration-effect meta-analysis***

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27 200 In the duration-effect meta-analysis, we assumed that the relative efficacy of a certain
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30 201 treatment duration ($duration_i$) against another ($duration_j$) can be expressed in the log-
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32
33 202 odds ratio ($\log OR_{ij}$) and that it is a function of both durations ($\log OR_{ij} = f(duration_i;$
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36 203 $duration_j)$). We fitted restricted cubic splines with three knots to the dataset obtained by
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39 204 the systematic review because this model has shown sufficient flexibility to capture
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42 205 different shapes.[37] Given the clinical and methodological heterogeneity likely present in
43
44
45 206 the included studies, we used the random effects model. We used three knots, equally
46
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48 207 spaced across the duration range (25%, 50%, 75%). Typically, in dose-effect meta-
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51 208 analyses, the reference dose is assigned to the zero or the minimal dose to make
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54 209 interpretation easier.[37] As this duration-effect meta-analysis aimed to test the non-

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6 210 inferiority of the shorter treatment duration, we decided to use the maximum duration as the
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9 211 reference to make interpretation easier. Also, the reference we set (10-day treatment) can be
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12 212 regarded as the current practice.[7,8,27] We tested the non-inferiority with the non-
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15 213 inferiority margin of 10%, as previously proposed,[28] and the superiority of the shorter
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18 214 duration examined against 10-day treatment using the ITT dataset.

215

216 *Sensitivity analyses*

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

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6 **227 Amendments**

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9 **228** We report amendments with the date and the rationale in the appendix (eAppendix3).
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15 **230 RESULTS**

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18 **231** We identified 1,994 records via database and one record via searching websites, which

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21 **232** revealed that some different records refer to the same clinical trial. We assessed 38 full-text

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24 **233** records for eligibility and included 11 eligible studies. (Fig1) Of these, eight were

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27 **234** published,[13–15,27,38–41] one was unpublished[42] and two studies were still

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30 **235** ongoing,[43,44] resulting in nine trials for the primary outcome analysis. The lists of

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33 **236** included and excluded studies are provided in the appendix (eAppendix4 and 5). The nine

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36 **237** studies with 2,399 participants in total included 18 eligible arms. Treatment duration ranged

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39 **238** from three to ten days. The study year ranged between 1999 and 2021. Table 1 presents the

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41
42 **239** characteristics of the included studies.

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45 **240** The included studies were all parallel-group and individually randomised. Seven out of

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48 **241** nine were reported as non-inferiority trials. In total, 1,199 participants were randomly

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51 **242** assigned to the shorter duration arm and 1,200 to the longer duration arm. The mean age

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54 **243** was 61.2 years (standard deviation 22.1); 831 (39%) of 2,140 reported were women. Six
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6 244 were conducted in a single European country, one in the US, and the two were cross-
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9 245 continental. CAP was defined as newly confirmed clinical symptoms (eg, dyspnoea, cough,
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12 246 purulent sputum, or crackles), and radiological findings. Antibiotic treatment was
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15 247 discontinued when the patient was clinically stable and the pre-determined treatment period
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18 248 was completed. Clinical stability was often defined as apyrexia (temperature ≤ 37.8 C) for
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21 249 48 hours, heart rate below 100 beats per min, a respiratory rate below 24 breaths per min,
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24 250 arterial oxygen saturation of 90% or higher, systolic blood pressure of 90 mmHg or higher,
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27 251 and normal mental status.[45] Clinical improvement was often described as “clinical cure”
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29
30 252 or “clinical success” and was often defined as the resolution of fever and improvement of
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33 253 symptoms related to pneumonia without further antibiotics. More detailed definitions of
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35
36 254 clinical improvement in each included study are listed in the appendix. (eAppendix6) The
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39 255 percentage of pneumonia severity index class IV or V was on average 19% (362 of 1,896
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42 256 reported; ranging from 2 to 41%). Seven studies focused on inpatients, whereas one study
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45 257 focused on outpatients and one included both. Antibiotics used included β -lactams
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48 258 (amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, ceftazidime, ceftriaxone,
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51 259 cefuroxime, piperacillin/tazobactam), macrolides (azithromycin, clarithromycin),
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54 260 quinolones (ciprofloxacin, gemifloxacin, levofloxacin, telithromycin), amikacin,
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7 261 doxycycline, and meropenem. Pharmaceutical companies funded four studies.[13–15,38]
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10 262 Four studies had a high overall risk of bias, four some concerns, and only one had a low
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12 263 overall risk of bias. (Table 1)
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264 **Table 1 Characteristics of included studies**

| Study | Age, | | Female, % | PSI IV+V, % | Setting | Duration, day, median | Antibiotics | No. of partici pants | No. of clinical improvement on day 15 | Risk of bias | | | | | Ove rall | Spon sored |
|--------------------------|-------------|---------------|--------------|-------------------|------------|-----------------------------|--------------------------------------|----------------------------|---|--------------|----|----|----|----|-------------|---------------|
| | mean , y | Age, SD, y | | | | | | | | D1 | D2 | D3 | D4 | D5 | | |
| 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 |
| Strálin 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

For peer review only

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7 **274 Assessment of heterogeneity and publication bias**

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9 **275** We assessed the heterogeneity in the efficacy outcome across the duration range (9 studies).

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12 **276** VPC values were constantly below 10% which suggests low levels of heterogeneity. Visual

13
14
15 **277** inspection of the funnel plot suggested no significant publication bias. However, these

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18 **278** assessments need to be carefully interpreted due to the small number of included studies.

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21 **279** (eAppendix8 and 9)

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24 **280**

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27 **281 Duration-effect meta-analysis**

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30 **282** We present the duration-effect curves in Figure 2 and Figure 3, and the tabulation of results

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32
33 **283** in Table 2. The x-axis of the figures represents the treatment duration in days. The y-axis

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35
36 **284** represents the odds ratio of the outcome on a logarithmic scale, just as in the forest plot of

37
38
39 **285** conventional pairwise meta-analysis using binary outcomes. The thin dotted horizontal line

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41
42 **286** in the clinical improvement figures and the all-cause mortality figure corresponds to the

43
44
45 **287** non-inferiority margin translated into OR. (The weighted average percentage of clinical

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47
48 **288** improvement rate on day 15 in the 10-day treatment arms was 68%. The non-inferiority

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50
51 **289** margin was therefore 58% and the corresponding OR was 0.65. For all-cause mortality, the

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54 **290** numbers were 3%, 13% and OR 4.8, respectively. For clinical improvement on day 30, the

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6 291 numbers were 77%, 67% and OR 0.61, respectively. We did not show the non-inferiority
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8
9 292 margin in the figures for severe adverse events, because the position paper did not provide
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11
12 293 any margin for this outcome.[28]) The thick solid line represents the dose duration-effect
13
14
15 294 curve and the thick dotted lines represent its 95% CI. The 95% CI band becomes narrower
16
17
18 295 when the duration range was examined by many trials or when it gets closer to the
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21 296 reference point. For the beneficial outcomes (clinical improvement), OR > 1 means more
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23
24 297 effective. For the harmful outcomes (all-cause mortality and serious adverse events), OR <
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27 298 1 means safer.

29
30 299 The duration-effect curve is monotonic with a longer duration leading to a lower
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33 300 probability of improvement. The lower 95%CI curve was constantly above the prespecified
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36 301 non-inferiority margin, meaning that a shorter treatment duration (3-9 days) was likely to
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38
39 302 be non-inferior to the standard treatment duration (10 days). It was slightly above the OR =
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42 303 1 around 3-day treatment, suggesting 3-day treatment may be superior to 10-day treatment.
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44
45 304 Harmful outcome curves (all-cause mortality and severe adverse events) were almost flat
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48 305 and 95%CI curves did not cross the OR = 1, indicating no association. Although the
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51 306 confidence interval curves were wide for all-cause mortality, shorter treatment duration (3-
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54 307 9 days) was likely to be non-inferior to 10-day treatment. Clinical improvement on day 30
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6 308 showed a similar trend with the primary outcome with the lower 95%CI curve constantly
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9 309 above the prespecified non-inferiority margin. We made a league table (eAppendix10),
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12 310 which showed that shorter treatment duration was likely to be non-inferior to longer
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15 311 treatment duration, regardless of the reference duration.
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18 312 Odds ratios need to be translated into absolute event rates so that the results can be
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21 313 interpreted from the clinical point of view. The weighted average percentage of clinical
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24 314 improvement rate on day 15 in the 10-day treatment arms was 68%, based on a single
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27 315 proportion meta-analysis of the included studies. Using this average, we computed the
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30 316 absolute clinical improvement rates at the following durations as follows: 3-day treatment
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33 317 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day treatment 69% (61
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36 318 to 76%). (Table 2)
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320 **Table 2 Primary and secondary outcomes for 3, 5, 7 and 10-day treatment**

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| 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% | - |

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6 **323 Sensitivity analyses**
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9 **324** Sensitivity analyses were in line with the primary analyses. Sensitivity analyses using
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11 **325** different locations of knots confirmed the stability of the shape of the spline curves.
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15 **326** (eAppendix 11, Figures S1) Sensitivity analyses excluding trials with an overall high risk of
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18 **327** bias were also in agreement with the primary analyses. (eAppendix 11, Figure S2.1)
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21 **328** Sensitivity analyses excluding trials with outpatients also confirmed the main findings,
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24 **329** suggesting the results are generalisable to inpatients, except for those admitted to the
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27 **330** intensive care unit. (eAppendix 11, Figure S2.2) Sensitivity analyses using the per protocol
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30 **331** dataset and those including only trials that used antibiotics recommended for empirical
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33 **332** treatment of CAP by clinical guidelines also confirmed the results. (eAppendix 11, Figure
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36 **333** S3 and S4) Exploratory sensitivity analyses showed that non-inferiority of the shorter
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39 **334** duration was more likely to be the case in studies that randomised patients who had reached
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42 **335** clinical stability early (eAppendix 11, Figure S5)
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48 **337 DISCUSSION**
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51 **338** To our knowledge, this is the first systematic review and duration-effect meta-analysis of
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54 **339** antibiotics treatment for CAP in adults. The results showed that shorter treatment duration
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6 340 (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for
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9 341 CAP in adults if they achieved clinical stability. There may be no significant difference in
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12 342 all-cause mortality or serious adverse events. Shorter treatment duration (3-5 days)
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15 343 probably achieves the optimal balance between efficacy and treatment burden. Multiple
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18 344 sensitivity analyses confirmed the primary findings.
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21 345 This is in line with the previous pairwise meta-analyses that showed shorter
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24 346 duration was non-inferior to longer duration.[10–12] We updated the systematic review and
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27 347 found four trials that were not included in the previous studies. This allowed us to focus on
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30 348 trials that used the same antibiotics with the same daily dosage. The previous studies
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33 349 included trials using different antibiotics or different daily dosages, so the results may not
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36 350 have reflected the differences in treatment durations alone. Moreover, they subcategorised
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39 351 the treatment durations and may have thus lost some statistical power to detect meaningful
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42 352 differences among durations. We overcame this limitation by examining the duration of
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45 353 antibiotic treatment range in days as a continuous variable and found that three to nine-day
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48 354 treatment is likely to be non-inferior to 10-day treatment. Our results are in line with the
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51 355 guidelines for CAP recommending antibiotics to be prescribed for a duration shorter (5-8
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54 356 days) than current clinical standard practice (10 days).[4–6] Our results suggest that an
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6 357 even shorter duration (3-5 days) may be considered, which is in line with the trials that
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9 358 found 3-day treatment was non-inferior to 8-day treatment.[39,41] Possibility of 3-day
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12 359 treatment being superior to 10-day treatment should be carefully interpreted, as none of the
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15 360 included trials, previous meta-analyses[11,12] or the pairwise meta-analysis of the included
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18 361 trials (eAppendix7, post hoc analysis) showed the superiority of shorter treatment duration.
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21 362 This could be explained by the fact that most of the combinations of treatment durations
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24 363 examined (7 days vs 10 days, 5 days vs 10 days, 5 days vs 7 days, 3 days vs 8 days)
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27 364 suggested better efficacy of shorter durations, if not statistically significant alone.
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30 365 (eAppendix7, post hoc analysis) The duration-effect meta-analysis combined these
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33 366 findings, leading to the possible superiority of the shortest duration examined (3 days) over
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36 367 the longest duration examined (10 days). Further research focusing on the shorter duration
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39 368 range is warranted to confirm this finding.
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48 371 Limitations

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51 372 Our study has several limitations. First, most of the included studies presented a moderate
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54 373 to high overall risk of bias, which compromises the validity of this meta-analysis. Second,
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6 374 the number of studies was small, leaving confidence intervals for secondary outcomes
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9 375 wide. Third, original studies excluded patients with complications of CAP and therefore the
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12 376 results of this study may not be generalisable to those patients. Forth, baseline severity of
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15 377 the included studies varied. We included both the outpatients and inpatients, which may
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18 378 have concealed important heterogeneity in the study results. However, sensitivity analyses
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21 379 excluding trials with outpatients generally confirmed the primary analyses (eAppendix 11)
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24 380 and the overall statistical heterogeneity was low. Fifth, we did not include patients admitted
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27 381 to the intensive care units and the results of this study may not be generalisable to those
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30 382 patients.

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34 35 36 384 **Strengths**

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39 385 First, we did a comprehensive systematic review and found four studies that were not
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42 386 included in the previous systematic reviews. Second, we treated duration as a continuous
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45 387 variable, which allowed us to estimate the duration-effect relationship with greater
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48 388 resolution of change points. Third, we examined the impacts of treatment duration not only
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51 389 for clinical improvement but also for all-cause mortality and severe adverse events and
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54 390 made sure that a shorter treatment duration would not translate into more harmful events.
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6 391 Finally, the very nature of shortened duration treatment offers a unique opportunity for
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9 392 interpretation. Shorter treatment duration has been examined by non-inferiority trials. The
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12 393 underlying assumption has been that there was a trade-off between a loss in the efficacy of
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15 394 standard treatment duration and other benefits of shortened treatment duration, [46,47] such
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18 395 as less time, less cost and probably a diminished rate of antimicrobial resistance. This study
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21 396 suggests that there may be even no trade-off for antibiotic treatments of three to five days.
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24 397 The shorter treatment duration reduces the burden on patients, the healthcare system and
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27 398 the risk of antimicrobial resistance and might even offer better clinical outcomes at the
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30 399 same time.

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34 35 36 401 **CONCLUSIONS**

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39 402 Short treatment duration (3-9 days) was likely to be non-inferior to the standard treatment
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42 403 duration (10 days) for adults with CAP if they achieved clinical stability. Shorter range (3-5
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45 404 days) probably results in an optimal balance between efficacy and treatment burden.
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48 405 However, the small number of included studies and the overall moderate to high risk of bias
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51 406 may compromise the certainty of the results. Further research focusing on the shorter
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54 407 duration range is required.

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9 **410 Abbreviations**

10 411 CAP: community-acquired pneumonia

11 412 CI: confidence interval

12 413 ITT: intention-to-treat

13 414 OR: odds ratio

14 415 PP: per protocol

15 416 PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

16 417 SD: standard deviation

17 418 VPC: variance partition coefficient

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23 **420 DECLARATIONS**

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25 **421 Ethics approval and consent to participate**

26 422 This study uses published aggregate data and did not require ethical approval.

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28 **423 Consent for publication**

29 424 Not applicable.

30
31 **425 Availability of data and materials**

32 426 Data and code used for analyses are available from the corresponding author upon

33 427 reasonable request.

34
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17
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19
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21
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454 Author Contributions

455 All authors had full access to all of the data (including statistical reports and tables) in this
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457 analysis. Conception and design: YF, YL, SF, AO, EGO, TAF, YK. Analysis and
458 interpretation of the data: YF, YL, SF, AO, EGO, TH, TAF, YK. Drafting of the article:
459 YF. Critical revision of the article for important intellectual content: YL, SF, AO, EGO,
460 TH, TAF, YK. Final approval of the article: YF, YL, SF, AO, EGO, TH, TAF, YK.
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462 Collection and assembly of data: YF, YL, SF, AO, EGO. Guarantor: YF. Transparency
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472 REFERENCE

- 473 1. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional,
474 and national morbidity, mortality, and aetiologies of lower respiratory infections in 195
475 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.
476 *Lancet Infect Dis.* 2018;18(11):1191-1210. doi:10.1016/s1473-3099(18)30310-4
- 477 2. Most Frequent Conditions in U.S. Hospitals, 2011. Accessed December 8, 2021.
478 <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf>
- 479 3. Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final Data for 2013. *Natl Vital*
480 *Stat Rep.* 2016;64(2):1-119.
- 481 4. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with
482 Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American

- 1
2
3
4
5
6 483 Thoracic Society and Infectious Diseases Society of America. *Am J Resp Crit Care*.
7 484 2019;200(7):e45-e67. doi:10.1164/rccm.201908-1581st
8
9
10 485 5. National Institute of Health and Care Excellence (NICE). Pneumonia (community-
11 486 acquired): antimicrobial prescribing. Accessed December 8, 2021.
12 487 <https://www.nice.org.uk/guidance/NG138>
13
14
15 488 6. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower
16 489 respiratory tract infections - Full version. *Clin Microbiol Infect*. 2011;17(s6):E1-E59.
17 490 doi:10.1111/j.1469-0691.2011.03672.x
18
19
20
21 491 7. Aliberti S, Blasi F, Zanaboni AM, et al. Duration of antibiotic therapy in hospitalised
22 492 patients with community-acquired pneumonia. *Eur Respir J*. 2009;36(1):128-134.
23 493 doi:10.1183/09031936.00130909
24
25
26
27 494 8. Yi SH, Hatfield KM, Baggs J, et al. Duration of Antibiotic Use Among Adults With
28 495 Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United
29 496 States. *Clin Infect Dis*. 2017;66(9):1333-1341. doi:10.1093/cid/cix986
30
31
32
33 497 9. Guillemot D, Carbon C, Balkau B, et al. Low Dosage and Long Treatment Duration of β -
34 498 Lactam: Risk Factors for Carriage of Penicillin-Resistant *Streptococcus pneumoniae*.
35 499 *JAMA*. 1998;279(5):365-370. doi:10.1001/jama.279.5.365
36
37
38 500 10. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, Grammatikos AP, Athanassa Z,
39 501 Falagas ME. Short- versus Long-Course Antibacterial Therapy for Community-Acquired
40 502 Pneumonia. *Drugs*. 2008;68(13):1841-1854. doi:10.2165/00003495-200868130-00004
41
42
43
44 503 11. Tansarli GS, Mylonakis E. Systematic Review and Meta-analysis of the Efficacy of
45 504 Short-Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults.
46 505 *Antimicrob Agents Ch*. 2018;62. doi:10.1128/aac.00635-18
47
48
49
50 506 12. Furlan L, Erba L, Trombetta L, et al. Short- vs long-course antibiotic therapy for
51 507 pneumonia: a comparison of systematic reviews and guidelines for the SIMI Choosing
52 508 Wisely Campaign. *Intern Emerg Med*. 2019;14:377-94. doi:10.1007/s11739-018-1955-2
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 509 13. Siegel RE, Alicea M, Lee A, Blaiklock R. Comparison of 7 Versus 10 Days of
7 510 Antibiotic Therapy for Hospitalized Patients with Uncomplicated Community-Acquired
8 511 Pneumonia. *Am J Ther.* 1999;6(4):217-222. doi:10.1097/00045391-199907000-00007
9
10
11 512 14. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological
12 513 efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10
13 514 day regimen of clarithromycin twice daily in patients with mild to moderate community-
14 515 acquired pneumonia. *J Antimicrob Chemoth.* 2004;54(2):515-523. doi:10.1093/jac/dkh356
15
16
17
18 516 15. File TM, Mandell LA, Tillotson G, Kostov K, Georgiev O. Gemifloxacin once daily for
19 517 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized,
20 518 multicentre, double-blind study. *J Antimicrob Chemoth.* 2007;60(1):112-120.
21 519 doi:10.1093/jac/dkm119
22
23
24
25 520 16. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response
26 521 meta-analysis for aggregated data. *Stat Methods Med Res.* 2019;28(5):1579-1596.
27 522 doi:10.1177/0962280218773122
28
29
30
31 523 17. Filippini T, Naska A, Kasdagli M, et al. Potassium Intake and Blood Pressure: A
32 524 Dose-Response Meta-Analysis of Randomized Controlled Trials. *J Am Hear Assoc*
33 525 2020;9(12):e015719. doi:10.1161/jaha.119.015719
34
35
36
37 526 18. Filippini T, Malavolti M, Whelton PK, Naska A, Orsini N, Vinceti M. Blood Pressure
38 527 Effects of Sodium Reduction. *Circulation.* 2021;143(16):1542-1567.
39 528 doi:10.1161/circulationaha.120.050371
40
41
42
43 529 19. Højlund M, Kemp AF, Haddad PM, Neill JC, Correll CU. Standard versus reduced
44 530 dose of antipsychotics for relapse prevention in multi-episode schizophrenia: a systematic
45 531 review and meta-analysis of randomised controlled trials. *Lancet Psychiatry.*
46 532 2021;8(6):471-486. doi:10.1016/s2215-0366(21)00078-x
47
48
49
50 533 20. Leucht S, Bauer S, Sifakis S, et al. Examination of Dosing of Antipsychotic Drugs for
51 534 Relapse Prevention in Patients With Stable Schizophrenia. *JAMA Psychiat.* 2021;78(11).
52 535 doi:10.1001/jamapsychiatry.2021.2130
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 536 21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated
7 537 guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
8
9
10 538 22. Montes-Andujar L, Tinoco E, Baez-Pravia O, et al. Empiric antibiotics for community-
11 539 acquired pneumonia in adult patients: a systematic review and a network meta-analysis.
12 540 *Thorax*. Published online 2021:thoraxjnl-2019-214054. doi:10.1136/thoraxjnl-2019-214054
13
14
15 541 23. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for
16 542 community-acquired pneumonia in adult outpatients. *Cochrane Db Syst Rev*.
17 543 2014;10(10):CD002109. doi:10.1002/14651858.cd002109.pub4
18
19
20
21 544 24. Keren R, Shah SS, Srivastava R, et al. Comparative Effectiveness of Intravenous vs
22 545 Oral Antibiotics for Postdischarge Treatment of Acute Osteomyelitis in Children. *JAMA*
23 546 *Pediatr*. 2014;169(2):120. doi:10.1001/jamapediatrics.2014.2822
24
25
26
27 547 25. Li HK, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone
28 548 and Joint Infection. *New Engl J Med*. 2019;380(5):425-436. doi:10.1056/nejmoa1710926
29
30
31 549 26. Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic
32 550 Treatment of Endocarditis. *New Engl J Med*. 2019;380(5):415-424.
33 551 doi:10.1056/nejmoa1808312
34
35
36
37 552 27. Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-
38 553 Acquired Pneumonia: A Multicenter Randomized Clinical Trial. *JAMA Intern Med*.
39 554 2016;176(9):1257. doi:10.1001/jamainternmed.2016.3633
40
41
42 555 28. Spellberg B, Talbot GH, Brass EP, et al. Position paper: recommended design features
43 556 of future clinical trials of antibacterial agents for community-acquired pneumonia. *Clin*
44 557 *Infect Dis*. 2008;47 Suppl 3:S249-65.
45
46
47
48 558 29. Bai AD, Komorowski AS, Lo CKL, et al. Intention-to-treat analysis may be more
49 559 conservative than per protocol analysis in antibiotic non-inferiority trials: a systematic
50 560 review. *BMC Med Res Methodol*. 2021;21(1):75. doi:10.1186/s12874-021-01260-7
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 561 30. Aberegg SK, Hersh AM, Samore MH. Empirical Consequences of Current
7 562 Recommendations for the Design and Interpretation of Noninferiority Trials. *J Gen Intern*
8 563 *Med.* 2018;33(1):88-96. doi:10.1007/s11606-017-4161-4
9
10
11 564 31. Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in
12 565 meta-analysis. *Res Synth Methods.* 2019;10(3):398-419. doi:10.1002/jrsm.1347
13
14
15 566 32. Doi SA, Furuya-Kanamori L, Xu C, Lin L, Chivese T, Thalib L. Questionable utility of
16 567 the relative risk in clinical research: A call for change to practice. *J Clin Epidemiol.*
17 568 Published online 2020. doi:10.1016/j.jclinepi.2020.08.019
18
19
20
21 569 33. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in
22 570 randomised trials. *BMJ.* 2019;366:14898. doi:10.1136/bmj.14898
23
24
25 571 34. Team RC. R: A Language and Environment for Statistical Computing. R Foundation
26 572 for Statistical Computing.; 2020. <https://www.R-project.org/>
27
28
29 573 35. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a
30 574 practical tutorial. *Évid Based Ment Heal.* 2019;22(4):153. doi:10.1136/ebmental-2019-
31 575 300117
32
33
34
35 576 36. Crippa A, Orsini N. Multivariate Dose-Response Meta-Analysis: The dosresmeta R
36 577 Package. Published online 2016. doi:doi.org/10.18637/jss.v072.c01
37
38
39 578 37. Hamza T, Furukawa TA, Orsini N, et al. Dose–effect meta-analysis for
40 579 psychopharmacological interventions using randomised data. *Évid Based Ment Heal.*
41 580 2022;25:1–6. doi:10.1136/ebmental-2021-300278
42
43
44
45 581 38. Léophonte P, Choutet P, Gaillat J, et al. Efficacité comparée de la ceftriaxone dans un
46 582 traitement de dix jours versus un traitement raccourci de cinq jours des pneumonies aiguës
47 583 communautaires de l'adulte hospitalisé avec facteur de risque. *Médecine Et Maladies*
48 584 *Infect.* 2002;32(7):369-381. doi:10.1016/s0399-077x(02)00384-0
49
50
51
52 585 39. El Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing
53 586 antibiotic treatment after three days versus eight days in mild to moderate-severe
54
55
56
57
58
59
60

- 1
2
3
4
5
6 587 community acquired pneumonia: randomised, double blind study. *BMJ*.
7 588 2006;332(7554):1355. doi:10.1136/bmj.332.7554.1355
8
9
10 589 40. Aliberti S, Ramirez J, Giuliani F, et al. Individualizing duration of antibiotic therapy in
11 590 community-acquired pneumonia. *Pulm Pharmacol Ther*. 2017;45:191-201.
12
13 591 doi:10.1016/j.pupt.2017.06.008
14
15 592 41. Dinh A, Ropers J, Duran C, et al. Discontinuing β -lactam treatment after 3 days for
16 593 patients with community-acquired pneumonia in non-critical care wards (PTC): a double-
17
18 594 blind, randomised, placebo-controlled, non-inferiority trial. *Lancet*. 2021;397(10280):1195-
19
20 595 1203. doi:10.1016/s0140-6736(21)00313-5
21
22 596 42. Strålin K, Rubenson A, Lindroth H, et al. Betalactam treatment until no fever for 48
23 597 hours (at least 5 days) versus 10 days in community-acquired pneumonia: randomised, non-
24
25 598 inferiority, open study. *Pneumonia*. 2014;3:246-281. doi:10.1007/bf03399446
26
27
28 599 43. NCT03609099. Adequate Duration of Antibiotic Treatment in Community-acquired
29
30 600 Pneumonia With High Risk Class and Adequate Initial Clinical Response (2017-001406-
31
32 601 15). <https://clinicaltrials.gov/ct2/show/NCT03609099>
33
34 602 44. NCT04089787. Shortened Antibiotic Treatment of 5 Days in Community-Acquired
35
36 603 Pneumonia (CAP5). <https://clinicaltrials.gov/ct2/show/NCT04089787>
37
38 604 45. Halm EA, Fine MJ, Marrie TJ, et al. Time to Clinical Stability in Patients Hospitalized
39
40 605 With Community-Acquired Pneumonia: Implications for Practice Guidelines. *JAMA*.
41
42 606 1998;279(18):1452-1457. doi:10.1001/jama.279.18.1452
43
44 607 46. Mulla SM, Scott IA, Jackevicius CA, You JJ, Guyatt GH. How to Use a Noninferiority
45
46 608 Trial: Users' Guides to the Medical Literature. *JAMA*. 2012;308(24):2605-2611.
47
48 609 doi:10.1001/2012.jama.11235
49
50 610 47. Acuna SA, Chesney TR, Baxter NN. Incorporating Patient Preferences in
51
52 611 Noninferiority Trials. *JAMA*. 2019;322(4):305-306. doi:10.1001/jama.2019.7059
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FIGURE LEGENDS

Figure 1 PRISMA flow diagram

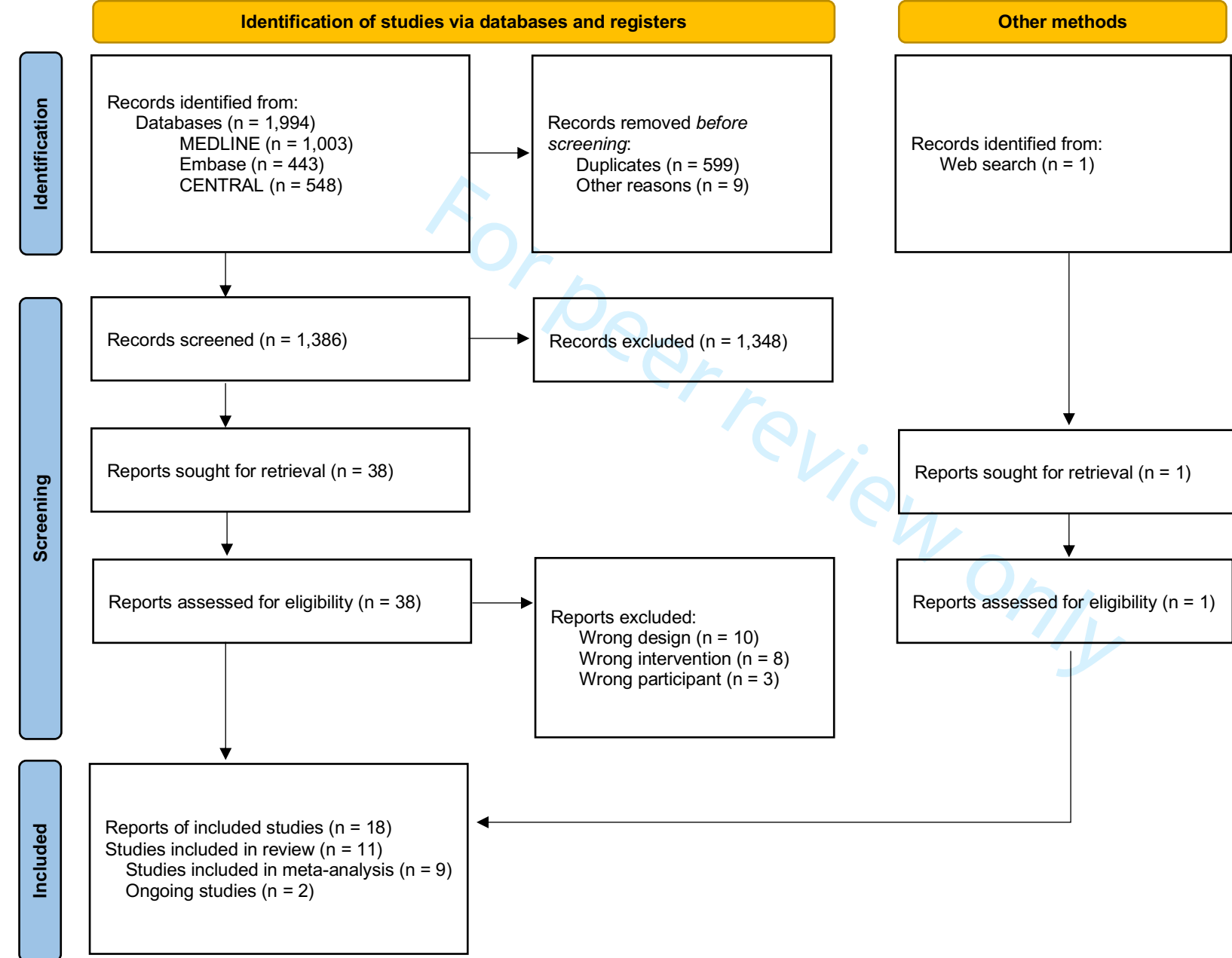
Figure 2 Duration–effect relationship of antibiotics for CAP in adults. Clinical improvement on day 15.

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

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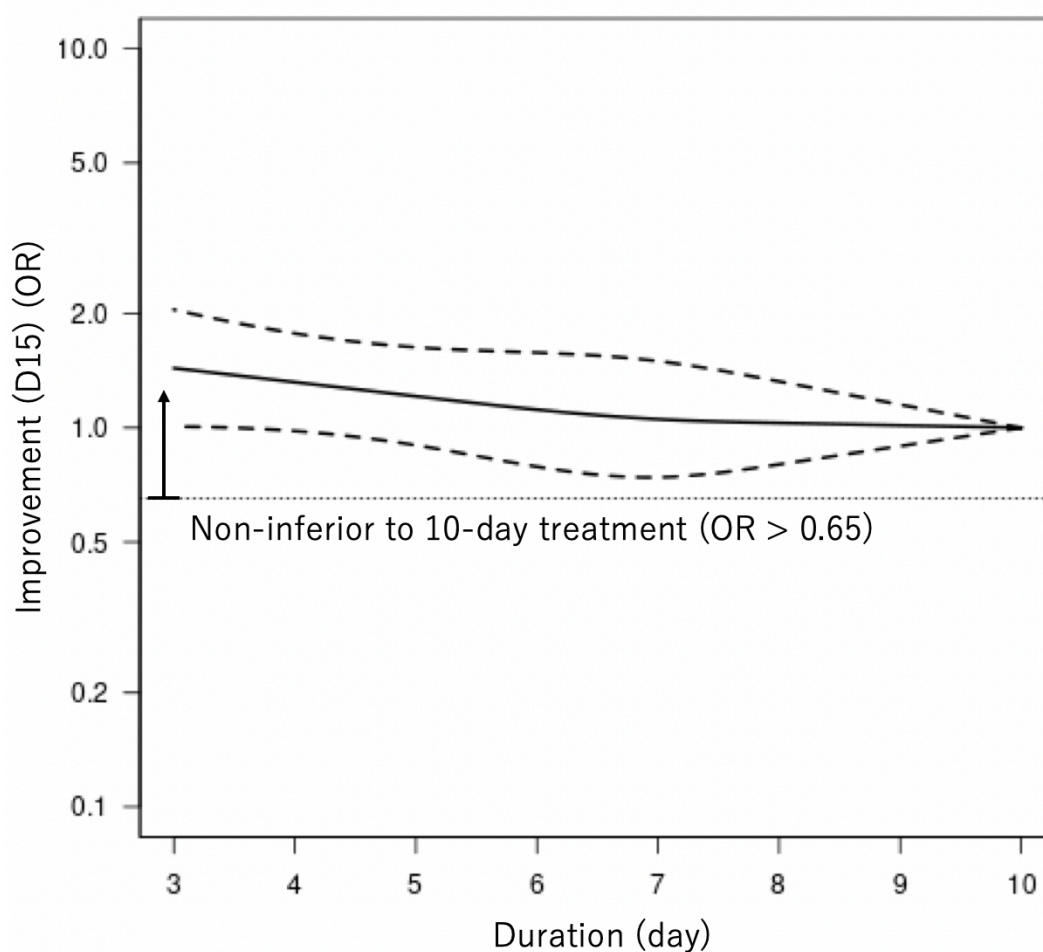
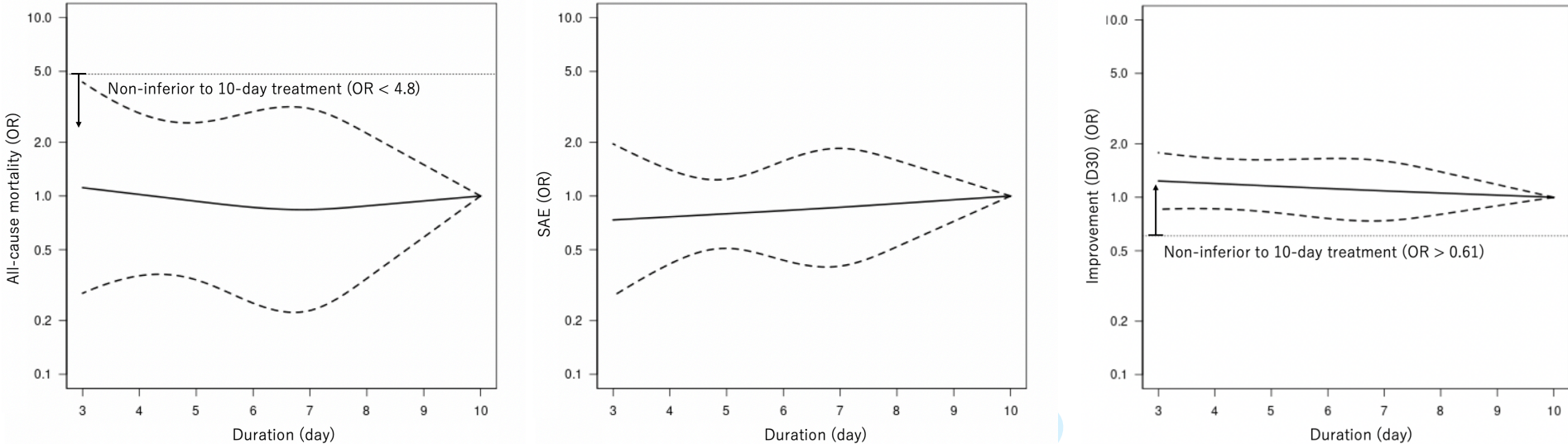


Figure 3 Duration–effect relationships of antibiotics for CAP in adults. (a) All-cause mortality. (b) Severe adverse events. (c) Clinical improvement on day 30.

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).



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3 **Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a**
4 **systematic review and duration-effect meta-analysis (eAppendix)**
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8 Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A
9 Furukawa, Yuki Kataoka
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- 11
12 1. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: protocol for a
13 systematic review and duration-effect meta-analysis (protocol as of 15th August, 2021)
14
15 2. Search strings used for Ovid MEDLINE, Embase, and CENTRAL.
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17 3. Amendments from the protocol
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19 4. List of all included papers
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21 5. List of excluded studies
22
23 6. Definitions of clinical improvement in each included study
24
25 7. Pairwise meta-analysis of the included trials
26
27 8. Funnel plot
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29 9. Heterogeneity: Variance partition coefficient for the primary outcome
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31 10. League table
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33 11. Sensitivity analyses
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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

1
2
3 Cluster-randomized trials will be included as long as proper adjustment for the intra-cluster correlation is conducted in
4 accordance with the Cochrane Handbook for Systematic Reviews of Interventions.

5
6 **2. Studies with multiple treatment groups**

7
8 Where multiple trial arms are reported in a single trial, we will include only the relevant arms.

9
10 ***Types of participants***

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

15
16
17
18 ***Types of interventions***

19
20 We will include trials examining any of the antibiotics, administered orally or intravenously. As we can expect a limited
21 number of studies to include, we will not be able to evaluate individual antibiotics. We will evaluate antibiotics as a class
22 because clinical guidelines recommend treatment duration irrespective of the antibiotic used, (4) and because recent meta-
23 analyses of antibiotics for CAP have not shown efficacy difference among antibiotics. (10,11) Oral and intravenous
24 antibiotics will be merged, because they have been shown equally effective in many infectious conditions. (12–15) We will
25 include trials comparing the same agents used in the same daily dosage but for different durations. We will use the predefined
26 duration for fixed-duration arms and median duration for flexible-duration arms. If median duration is not reported, we will
27 use mean duration. We will prioritize median duration because patients requiring longer duration may inflate the mean
28 duration in flexible-duration arms.

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34 **Primary outcome and secondary outcomes**

35
36 The primary outcome of interest in this study is clinical improvement as defined by the original authors at a time point as
37 close to 15 days (range 7-45 days) as possible in each included study. (16) If equidistant, we will use the longer timeframe.

38
39
40
41 1 Clinical improvement at day 15 (range 7-45 days), as defined by the original study

42
43
44 Secondary outcomes of interest are the following outcomes.

- 45
46 2. All-cause mortality at day 15 (range 7-45 days)
47 3. Serious adverse events as defined by the original study at day 15 (range 7-45 days)
48 4. Clinical improvement, as defined by the original study, at day 30 (range 15-60)
49

50
51 We will use the number of randomized patients as the denominator for intention-to-treat (ITT) dataset and we will use per-
52 protocol (PP) dataset as defined by the original study. Those who had been randomized but not accounted for in the original
53 study will be assumed to have dropped out for some reason other than death or serious adverse events and without clinical
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3 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
4 the primary analysis and PP for a sensitivity analysis. (17,18)
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8 **Search methods for identification of studies**

9 *Electronic searches*

10 Searches for published studies will be undertaken in the following electronic bibliographic databases from inception to
11 present (25 August, 2021): Ovid MEDLINE and Cochrane CENTRAL. We will use search terms for community acquired
12 pneumonia in conjunction with the names of individual antibiotics as well as the names of antibiotic classes. We imposed no
13 date, language or publication status restriction.
14
15

16 *Search formula*

17 Search strategy for Ovid MEDLINE is as follows
18
19
20

21 #1 randomized controlled trial.pt.
22

23 #2 controlled clinical trial.pt.
24

25 #3 randomized.ab.
26

27 #4 placebo.ab.
28

29 #5 drug therapy.fs.
30

31 #6 randomly.ab.
32

33 #7 trial.ab.
34

35 #8 groups.ab.
36

37 #9 or/#1-#8
38

39 #10 exp animals/ not humans.sh.
40

41 #11 #9 not #10
42

43 #12 exp Community-Acquired Infections/
44

45 #13 Pneumonia, Bacterial/dt [Drug Therapy]
46

47 #14 community acquired pneumonia.ab,ti.
48

49 #15 (#12 and #13) or #14
50

51 #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
52 disconti*).mp.
53

54 #17 (beta-lactam* or macrolide* or quinolone* or tetracycline* or amikacin or amoxicillin or ampicillin or azithromycin or
55 cefepim or cefotaxim* or ceftarolin or ceftazidim* or ceftibuten or ceftriaxon* or cefuroxim* or cethromycin or
56 ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or co-amoxiclav or co-trimoxacol or doxycyclin* or
57 ertapenem or erythromycin or fluoroquinolon* or fluorquinolon* or gemifloxacin or gentamicin or imipenem or levofloxacin
58 or linezolid or meropenem or moxifloxacin or penicillin* or piperacillin or roxithromycin or sultamicillin or tazobactam or
59 telithromycin or tetracyclin* or ticarcillin or tobramycin).mp.
60

#18 Anti-Bacterial Agents/ad [Administration & Dosage]

1
2
3 #19 #17 or #18

4 #20 #11 and #15 and #16 and #19

5 6 7 8 **Reference lists and others**

9 We will check the reference lists of all the included studies and review articles for additional references. We will also contact
10 experts in the field to identify unpublished and on-going trials.
11

12 13 14 **Data collection and analysis**

15 **Selection of studies**

16 Two review authors will independently screen titles and abstracts of all the potential studies we identify as a result of the
17 search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full text
18 study reports/publication and two review authors will independently screen the full text and identify studies for inclusion and
19 identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if
20 required, through consultation with a third review author. We will identify and exclude duplicates of the same study so that
21 each study rather than each report is the unit of analysis in the review. We will record the selection process in sufficient detail
22 to complete a PRISMA flow diagram and characteristics of excluded studies table.
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28 29 **Data items**

30 We will use a standardized data collection form for study characteristics and outcome data which will have been piloted on at
31 least one study in the review. Two review authors will extract data independently from the included studies. Any
32 disagreement will be resolved through discussion, or discussed with a third person if necessary. We will abstract the
33 following information.
34
35

36 **1. Characteristics of the studies**

37 Name of the study, year of publication, country, study site (single or multi-center), study design, patient characteristics (mean
38 age, percentage of women, diagnostic criteria used), outcome (definition of clinical success), definition of clinical stability,
39 timing of randomization, sponsorship (rated positive if the trial is directly sponsored by drug company or if any authors are
40 employed by the drug company).
41
42
43

44 **2. Risk of bias**

45 We will use Cochrane Risk of Bias 2.0 tool (RoB2) (19). We will assess the effect of assignment to the interventions at
46 baseline because we use the ITT population in our primary analysis.
47

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

49 Patients (number of participants randomized to each arm)

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

51 Outcomes (number of clinical success, mortality, adverse events).
52
53
54
55

56 **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 *MBNMA* package in R.(20,21) One advantage of the dose-effect network meta-analysis by *MBNMA* 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, ceftazidime, ceftiofur), macrolide (azithromycin, clarithromycin), doxycycline, respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin)

Patient and public involvement

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

Ethics and dissemination

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

Amendments

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

Abbreviations

AMR: antimicrobial resistance

CAP: community-acquired pneumonia

DE-NMA: dose-effect network meta-analysis

ITT: intention-to-treat

PP: per protocol

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

Reference

- 1 GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 2018;18:1191–210. doi:10.1016/s1473-3099(18)30310-4
- 2 Most Frequent Conditions in U.S. Hospitals, 2011. <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf> (accessed 15 Jul 2021).
- 3 Xu J, Murphy SL, Kochanek KD, et al. Deaths: Final Data for 2013. National Vital Statistics Reports Centers Dis Control Prev National Cent Heal Statistics National Vital Statistics Syst 2016;64:1–119.
- 4 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Resp Crit Care* 2019;200:e45–67. doi:10.1164/rccm.201908-1581st
- 5 Aliberti S, Blasi F, Zanaboni AM, et al. Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia. *Eur Respir J* 2009;36:128–34. doi:10.1183/09031936.00130909
- 6 Yi SH, Hatfield KM, Baggs J, et al. Duration of Antibiotic Use Among Adults With Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United States. *Clin Infect Dis* 2017;66:1333–41. doi:10.1093/cid/cix986
- 7 Guillemot D, Carbon C, Balkau B, et al. Low Dosage and Long Treatment Duration of β -Lactam: Risk Factors for Carriage of Penicillin-Resistant *Streptococcus pneumoniae*. *JAMA* 1998;279:365–70. doi:10.1001/jama.279.5.365
- 8 Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, et al. Short- versus Long-Course Antibacterial Therapy for Community-Acquired Pneumonia. *Drugs* 2008;68:1841–54. doi:10.2165/00003495-200868130-00004

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2
3 9 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic
4 reviews. *Br Med J* 2021;372:n71. doi:10.1136/bmj.n71
- 5
6 10 Montes-Andujar L, Tinoco E, Baez-Pravia O, et al. Empiric antibiotics for community-acquired pneumonia in adult
7 patients: a systematic review and a network meta-analysis. *Thorax* 2021;:thoraxjnl-2019-214054. doi:10.1136/thoraxjnl-
8 2019-214054
- 9
10
11 11 Pakhale S, Mulpuru S, Verheij TJ, et al. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane*
12 *Db Syst Rev* 2014;10:CD002109. doi:10.1002/14651858.cd002109.pub4
- 13
14 12 Li HK, Agweyu A, English M, et al. An Unsupported Preference for Intravenous Antibiotics. *Plos Med*
15 2015;12:e1001825. doi:10.1371/journal.pmed.1001825
- 16
17 13 Keren R, Shah SS, Srivastava R, et al. Comparative Effectiveness of Intravenous vs Oral Antibiotics for Postdischarge
18 Treatment of Acute Osteomyelitis in Children. *JAMA Pediatr* 2014;169:120. doi:10.1001/jamapediatrics.2014.2822
- 19
20 14 Li H-K, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. *New Engl J Med*
21 2019;380:425–36. doi:10.1056/nejmoa1710926
- 22
23 15 Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. *New Engl J*
24 *Med* 2019;380:415–24. doi:10.1056/nejmoa1808312
- 25
26 16 Spellberg B, Talbot GH, Brass EP, et al. Position paper: recommended design features of future clinical trials of
27 antibacterial agents for community-acquired pneumonia. *Clin Infect Dis* 2008;47 Suppl 3:S249-65.
- 28
29 17 Bai AD, Komorowski AS, Lo CKL, et al. Intention-to-treat analysis may be more conservative than per protocol analysis
30 in antibiotic non-inferiority trials: a systematic review. *BMC Med Res Methodol* 2021;21:75. doi:10.1186/s12874-021-01260-
31 7
- 32
33 18 Aberegg SK, Hersh AM, Samore MH. Empirical Consequences of Current Recommendations for the Design and
34 Interpretation of Noninferiority Trials. *J Gen Intern Med* 2018;33:88–96. doi:10.1007/s11606-017-4161-4
- 35
36 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*
37 2019;366:14898. doi:10.1136/bmj.14898
- 38
39 20 Mawdsley D, Bennetts M, Dias S, Boucher M, Welton N. Model-Based Network Meta-Analysis: A Framework for
40 Evidence Synthesis of Clinical Trial Data. *Cpt Pharmacometrics Syst Pharmacol*. 2016;5(8):393–401.
- 41
42 21 Team R. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2020.
43 <https://www.R-project.org/>
- 44
45 22 Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth Methods*
46 2019;10:398–419. doi:10.1002/jrsm.1347
- 47
48 23 Doi SA, Furuya-Kanamori L, Xu C, et al. Questionable utility of the relative risk in clinical research: A call for change to
49 practice. *J Clin Epidemiol* Published Online First: 2020. doi:10.1016/j.jclinepi.2020.08.019
- 50
51 24 Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A
52 Multicenter Randomized Clinical Trial. *JAMA Intern Med* 2016;176:1257. doi:10.1001/jamainternmed.2016.3633
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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 fluorquinolon* or gemifloxacin or gentamicin or imipenem or levofloxacin or linezolid 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(communitiy acquired pneumonia) OR ti(communitiy acquired pneumonia)

1
2
3 S3 S2 OR S1

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

7
8
9 S5 ab(beta-lactam* OR macrolide* OR quinolone* OR tetracycline* OR amikacin OR amoxicillin OR ampicillin OR
10 azithromycin OR cefepim OR cefotaxim* OR ceftazolin OR ceftazidim* OR ceftibuten OR ceftriaxon* OR cefuroxim* OR
11 cethromycin OR ciprofloxacin OR clarithromycin OR clavulanic acid OR clindamycin OR co-amoxiclav OR co-trimoxacol
12 OR doxycyclin* OR ertapenem OR erythromycin OR fluoroquinolon* OR fluorochinolon* OR gemifloxacin OR gentamicin
13 OR imipenem OR levofloxacin OR linezolid OR meropenem OR moxifloxacin OR penicillin* OR piperacillin OR
14 roxithromycin OR sultamicillin OR tazobactam OR telithromycin OR tetracyclin* OR ticarcillin OR tobramycin) OR ti(beta-
15 lactam* OR macrolide* OR quinolone* OR tetracycline* OR amikacin OR amoxicillin OR ampicillin OR azithromycin OR
16 cefepim OR cefotaxim* OR ceftazolin OR ceftazidim* OR ceftibuten OR ceftriaxon* OR cefuroxim* OR cethromycin OR
17 ciprofloxacin OR clarithromycin OR clavulanic acid OR clindamycin OR co-amoxiclav OR co-trimoxacol OR doxycyclin*
18 OR ertapenem OR erythromycin OR fluoroquinolon* OR fluorochinolon* OR gemifloxacin OR gentamicin OR imipenem OR
19 levofloxacin OR linezolid OR meropenem OR moxifloxacin OR penicillin* OR piperacillin OR roxithromycin OR
20 sultamicillin OR tazobactam OR telithromycin OR tetracyclin* OR ticarcillin OR tobramycin)

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

22 S7 S6 OR S5

23 S8 S7 AND S4 AND S3

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

26 S10 S9 AND S8

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38 2-3. Search strategy for CENTRAL

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40
41 #1 [mh "Community-Acquired Infections"]

42 #2 [mh "Pneumonia, Bacterial"]

43 #3 "community acquired pneumonia":ti,ab

44 #4 (#1 and #2) or #3

45 #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
46 (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
47 duration:ti,ab,kw OR disconti*:ti,ab,kw

48 #6 beta-lactam*:ti,ab,kw OR macrolide*:ti,ab,kw OR quinolone*:ti,ab,kw OR tetracycline*:ti,ab,kw OR
49 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
50 cefotaxim*:ti,ab,kw OR ceftazolin:ti,ab,kw OR ceftazidim*:ti,ab,kw OR ceftibuten:ti,ab,kw OR ceftriaxon*:ti,ab,kw OR
51 cefuroxim*:ti,ab,kw OR cethromycin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR clarithromycin:ti,ab,kw OR "clavulanic
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3 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
4 ertapenem:ti,ab,kw OR erythromycin:ti,ab,kw OR fluoroquinolon*:ti,ab,kw OR fluorquinolon*:ti,ab,kw OR
5 gemifloxacin:ti,ab,kw OR gentamicin:ti,ab,kw OR imipenem:ti,ab,kw OR levofloxacin:ti,ab,kw OR linezolid:ti,ab,kw OR
6 meropenem:ti,ab,kw OR moxifloxacin:ti,ab,kw OR penicillin*:ti,ab,kw OR piperacillin:ti,ab,kw OR roxithromycin:ti,ab,kw
7 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
8 OR tobramycin:ti,ab,kw

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12 #7 [mh "Anti-Bacterial Agents"]

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14 #8 #6 OR #7

15 #9 #4 AND #5 AND #8
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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

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3
4 - Léophonte P, Choutet P, Gaillat J, et al. Efficacité comparée de la ceftriaxone dans un traitement de dix jours versus un
5 traitement raccourci de cinq jours des pneumonies aiguës communautaires de l'adulte hospitalisé avec facteur de risque.
6 *Médecine Et Maladies Infect* 2002; 32: 369–81.
7

8
9 Siegel1999

- 10
11 - Siegel RE, Alicea M, Lee A, Blaiklock R. Comparison of 7 Versus 10 Days of Antibiotic Therapy for Hospitalized
12 Patients with Uncomplicated Community-Acquired Pneumonia. *Am J Ther* 1999; 6: 217–22.
13

14
15 Stralin2014

- 16
17 - Strålin K, Rubenson A, Lindroth H, et al. Betalactam treatment until no fever for 48 hours (at least 5 days) versus 10
18 days in community-acquired pneumonia: randomized, non-inferiority, open study. *Pneumonia* 2014; 3: 246–81.
19
20 - ISRCTN14523624
21

22
23 Tellier2004

- 24
25 - Tellier G, Niederman MS, Nusrat R, et al. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of
26 telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate
27 community-acquired pneumonia. *J Antimicrob Chemoth* 2004; 54: 515–23.
28
29 - Tellier G, Chang JR, Asche CV, Lavin B, Stewart J, Sullivan SD. Comparison of hospitalization rates in patients with
30 community-acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. *Curr Med Res*
31 *Opin.* 2004;20(5):739-747.
32
33

34
35 4.2. List of ongoing trials
36

37
38 NCT03609099

- 39
40 - NCT03609099. Adequate Duration of Antibiotic Treatment in Community-acquired Pneumonia With High Risk Class
41 and Adequate Initial Clinical Response (2017-001406-15).
42

43
44 NCT04089787

- 45
46 - NCT04089787. Shortened Antibiotic Treatment of 5 Days in Community-Acquired Pneumonia (CAP5).
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58 * found during web search using the sponsor's protocol code number.
59
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5. List of excluded studies

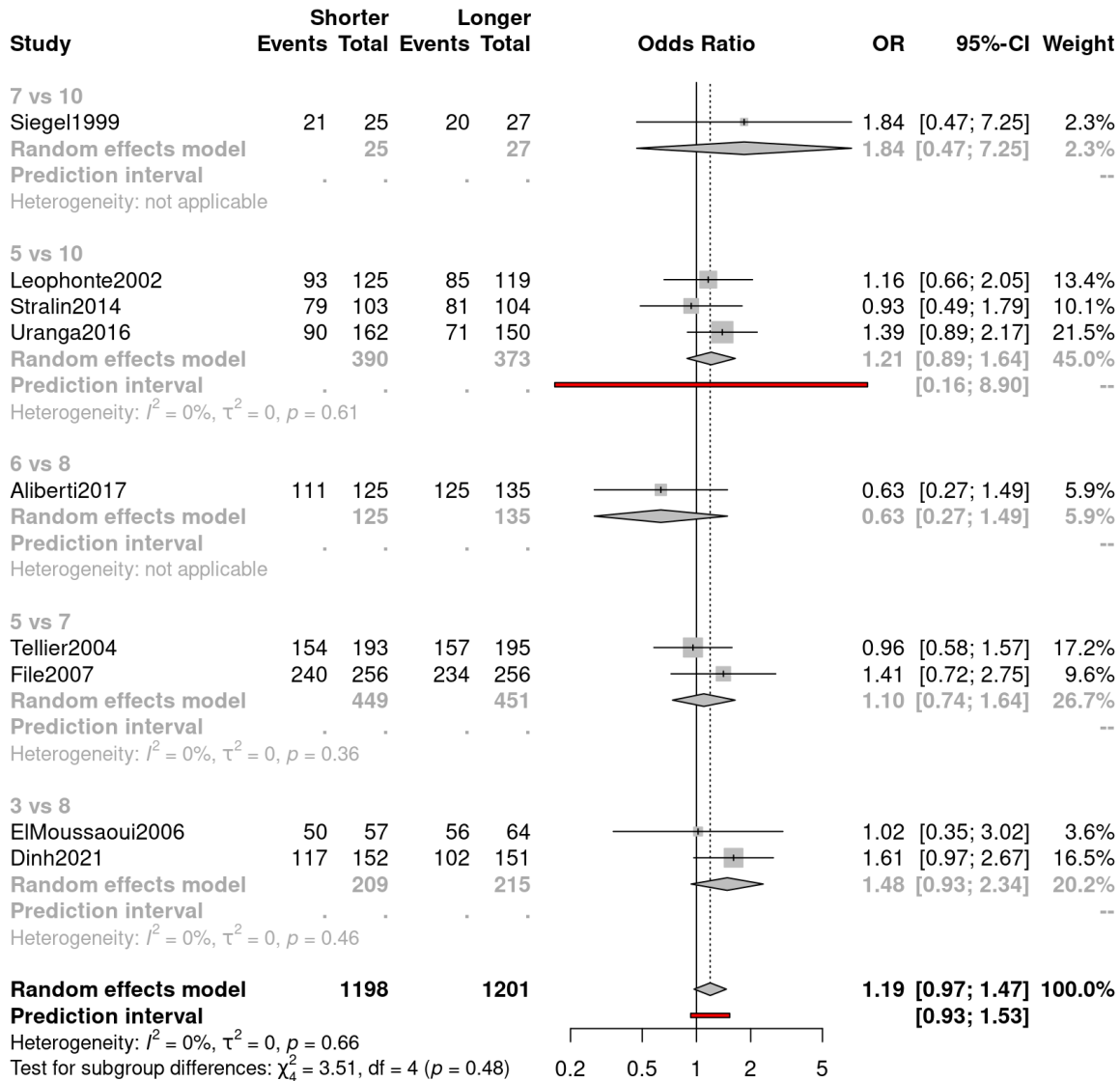
| Name | Title | Comment |
|----------------------|--|--------------------------------------|
| EUCTR2005-000105-65 | Comparative study of the efficacy and tolerance of intravenously administered azithromycin (1.5 g) given either as a single dose or over a 3 day period in patients with community-acquired pneumonia | wrong intervention (different drugs) |
| EUCTR2014-003137-25 | Optimal duration of antibiotic treatment in patients with complicated parapneumonic pleural effusions or empyema | wrong intervention (different drugs) |
| EUCTR2020-004452-15 | ADMINISTRATION OF CLARITHROMYCIN IN COMMUNITY-ACQUIRED PNEUMONIA | wrong intervention (different 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 (different drugs) |
| JPRN-JapicCTI-163439 | A Phase III study of Solithromycin in patients with community-acquired pneumonia | wrong intervention (different 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 (different 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 (different drugs) |
| Weber1987 | Ampicillin versus cefamandole as initial therapy for community-acquired pneumonia | wrong intervention (different drugs) |
| YangJ2020 | The combined treatment of imipenem cilastatin and azithromycin for elderly patients with community-acquired pneumonia | wrong intervention (different drugs) |

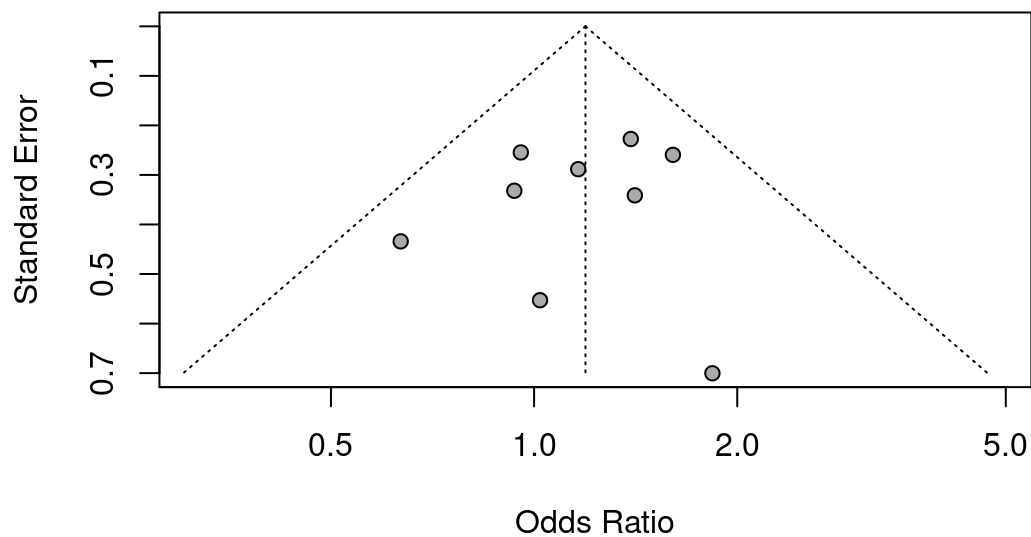
6. Definitions of clinical improvement in each included study

| Study | Definition |
|--------------------------|---|
| Siegel et al, 1999 | <p>“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”</p> |
| Léophonte et al, 2002 | <p>“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.”</p> |
| Tellier et al, 2004 | <p>“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.”</p> |
| El Moussaoui et al, 2006 | <p>“Cure—resolution or improvement of symptoms and clinical signs related to pneumonia without the need for additional or alternative antibiotic therapy”</p> |
| File et al, 2007 | <p>“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)”</p> |
| Strålin et al, 2014 | <p>“Clinical cure”</p> |
| Uraga et al, 2014 | <p>“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).”</p> |
| Aliberti et al, 2017 | <p>“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.”</p> |
| Dinh et al, 2021 | <p>“Cure was defined by the following criteria: apyrexia (temperature $\leq 37.8^{\circ}\text{C}$); 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.”</p> |

7. Pairwise meta-analysis of the included trials



8. Funnel plot



review only

9. Heterogeneity: Variance partition coefficient for the primary outcome

VPC is computed for each non-referent arm of each study (those that have $OR \neq 1$). 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
```

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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 |

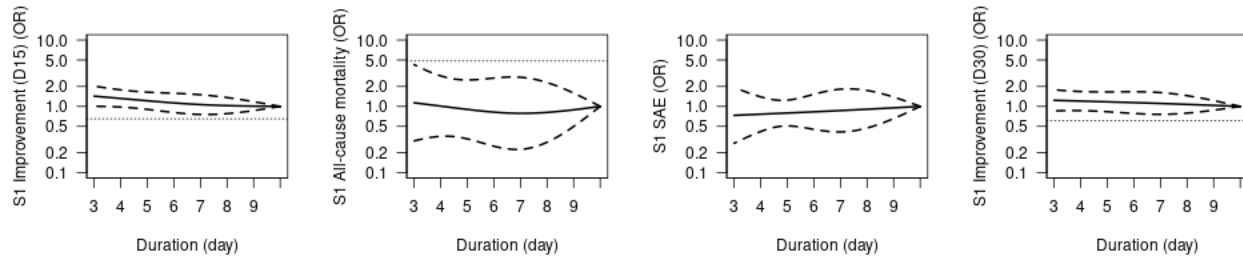
Results of the duration-effect meta-analysis are shown in the bottom-left area. Results of the pairwise meta-analyses of direct comparisons are shown in the upper-right area. Data are odds ratios (95% confidence interval) of the upper-left treatment duration compared with the bottom-right treatment duration.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

11. Sensitivity analyses

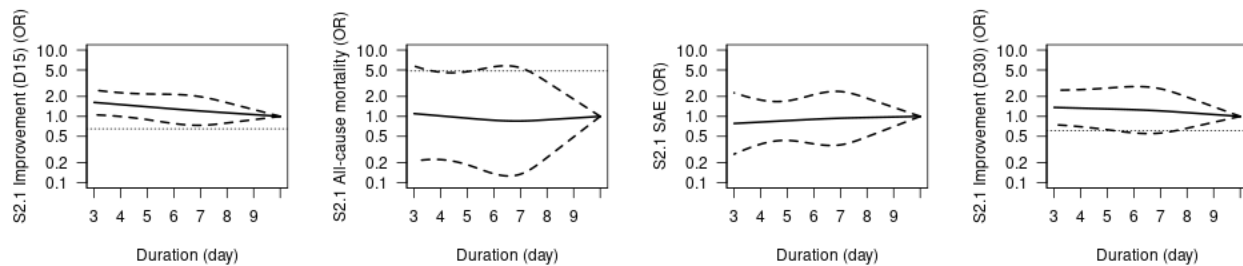
Duration-effect relationship of secondary outcomes could not be computed due to missing data in some cases.

A priori sensitivity analyses

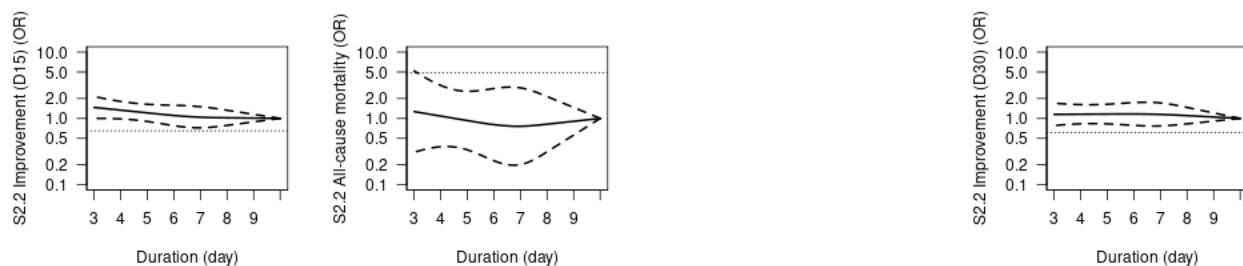
##S1 To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%).



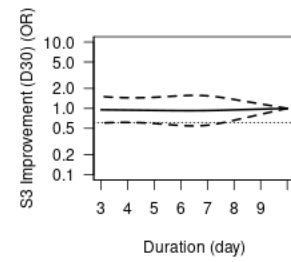
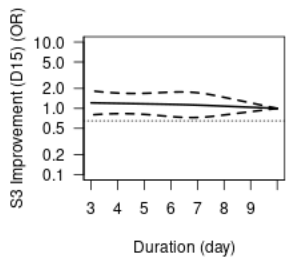
##S2.1 To test the influence of trials included, we conducted sensitivity analyses excluding trials with overall high risk of bias (excluding Siegel1999, Leophonte2002, Stralin2014, Aliberti2017)



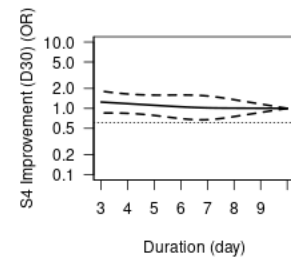
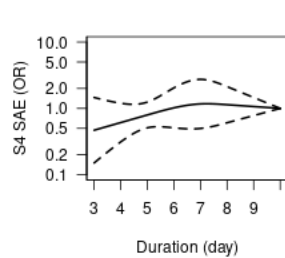
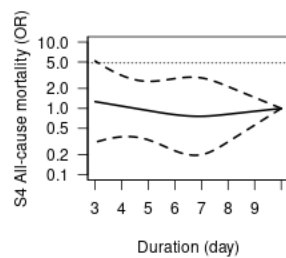
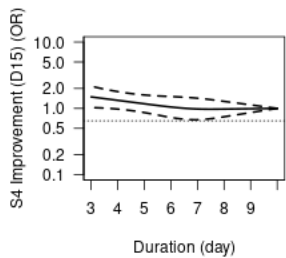
##S2.2 To test the influence of trials included, we conducted sensitivity analyses excluding trials with outpatients (excluding Tellier2004, File2007. SAE not computable)



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

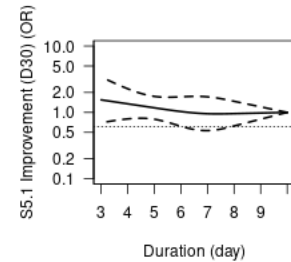
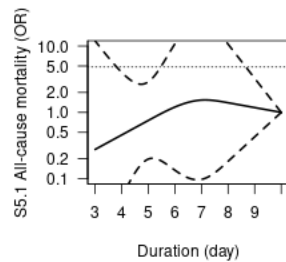
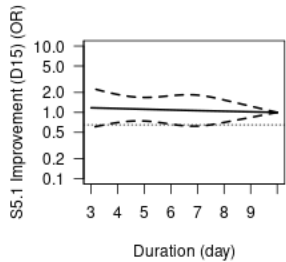


##S4 To test the influence of antibiotics examined, we conducted sensitivity analyses including only antibiotics recommended for empirical treatment of CAP by clinical guidelines. (excluding Siegel1999, Tellier2004. We included trials that used various antibiotics)

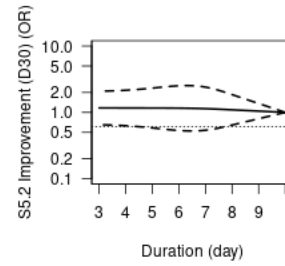
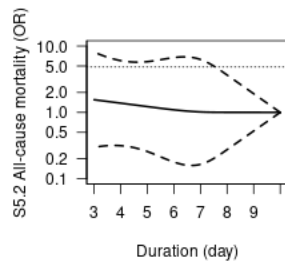
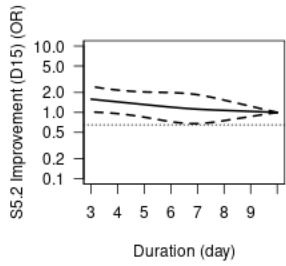


Post-hoc, exploratory sensitivity analyses

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



1
2
3 ##S5.2 Randomization after several days or clinical stability achieved (including ElMoussaoui2006, Uranga2016,
4 Aliberti2017, Dinh2021. SAE not computable)
5
6
7



For peer review only

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 |

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| 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 |

For peer review only

BMJ Open

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

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-061023.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 17-Jan-2023 |
| Complete List of Authors: | FURUKAWA, YUKI; Tokyo Musashino Hospital, Department of Psychiatry; University of Tokyo Hospital, Department of Neuropsychiatry Luo, Yan; Kyoto University Graduate School of Medicine, Department of Health Promotion and Human Behavior Funada, Satoshi; Kyoto University, Urology; Kyoto University, Health Promotion and Human Behavior Onishi, Akira; Graduate School of Medicine, Kyoto University, Department of Advanced Medicine for Rheumatic diseases Ostinelli, Edoardo; University of Oxford, Department of Psychiatry Hamza, Tasnim; University of Bern, Institute of Social and Preventive Medicine Furukawa, Toshi; Kyoto University, Graduate School of Medicine and School of Public Health Kataoka, Yuki; Kyoto Min-Iren Asukai Hospital, Department of Internal Medicine; Kyoto University Graduate School of Medicine Faculty of Medicine, Department of Community Medicine |
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| Secondary Subject Heading: | Evidence based practice, Infectious diseases, Respiratory medicine |
| Keywords: | BACTERIOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory infections < THORACIC MEDICINE |
| | |

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6 **1 TITLE PAGE**

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8
9 **3 Title: Optimal duration of antibiotic treatment for community-acquired pneumonia in**
10 **4 adults: a systematic review and duration-effect meta-analysis**

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16 43 Kyoto, Japan

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22 46 **Word count**

23 47 **3367 words**

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6 49 **ABSTRACT** (300 words)

7 50 **Objectives:** To find the optimal treatment duration with antibiotics for community-
8
9 51 acquired pneumonia (CAP) in adults.

10 52 **Design:** Systematic review and duration-effect meta-analysis.

11 53 **Data sources:** MEDLINE, Embase and CENTRAL through 25 August 2021.

12 54 **Eligibility criteria:** All randomised controlled trials comparing the same antibiotics used at
13
14 55 the same daily dosage but for different durations for CAP in adults. Both outpatients and
15
16 56 inpatients were included but not those admitted to intensive care units. We imposed no
17
18 57 date, language or publication status restriction.

19 58 **Data extraction and synthesis:** Data extraction by two independent reviewers. We
20
21 59 conducted a random-effects, one-stage duration-effect meta-analysis with restricted cubic
22
23 60 splines. We tested the non-inferiority with the pre-specified non-inferiority margin of 10%
24
25 61 examined against 10 days using. The primary outcome was clinical improvement on day 15
26
27 62 (range 7-45 days). Secondary outcomes: all-cause mortality, serious adverse events, and
28
29 63 clinical improvement on day 30 (15-60 days).

30 64 **Results:** We included 9 trials (2,399 patients with a mean [SD] age of 61.2 [22.1]; 39%
31
32 65 women). The duration-effect curve was monotonic with longer duration leading to a lower
33
34 66 probability of improvement, and shorter treatment duration (3-9 days) was likely to be non-
35
36 67 inferior to 10-day treatment. Harmful outcome curves indicated no association. The
37
38 68 weighted average percentage of the primary outcome in the 10-day treatment arms was
39
40 69 68%. Using that average, the absolute clinical improvement rates of the following durations
41
42 70 were: 3-day treatment 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-
43
44 71 day treatment 69% (61 to 76%).

45 72 **Conclusions:** Shorter treatment duration (3-5 days) probably offers the optimal balance
46
47 73 between efficacy and treatment burden for treating CAP in adults if they achieved clinical
48
49 74 stability. However, the small number of included studies and the overall moderate to high
50
51 75 risk of bias may compromise the certainty of the results. Further research on the shorter
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53 76 duration range is required.

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55 77 **Registration:** PROSPERO (CRD 42021273357).
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6 **79 Strengths and limitations of this study**

- 7 80 - We conducted a comprehensive and up-to-date systematic literature review.
8
9 81 - The duration-effect meta-analysis treated duration as a continuous variable, which
10 82 allowed us to estimate the duration-effect relationship with greater resolution than the
11 83 conventional pairwise meta-analysis that dichotomised duration arbitrarily.
12
13 84 - The small number of trials included limited the precision of some study results.
14
15 85 - Most of the trials had a moderate to high overall risk of bias.
16 86 - About 80% of the patients had pneumonia severity index class III or less and thus the
17 87 results may not be generalisable to severely ill patients.
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19 88

20
21 **89 Keywords**

22 90 Community-acquired pneumonia; antibiotic; treatment duration; dose-response meta-
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24 91 analysis
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6 93 **MAIN TEXT (3367 words)**

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8
9 95 **BACKGROUND**

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12 96 Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality

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15 97 globally, especially among the elderly.[1] In the United States, it is the second most

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18 98 common cause of hospitalisation and the top infectious cause of death.[2,3] The initial

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21 99 treatment for CAP is empirical, with guidelines recommending starting several antibiotics

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24 100 depending on patients' severity and risk factors for certain pathogens.[4–6]

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27 101 The optimal duration of antimicrobial therapy remains unclear and

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30 102 controversial. The American and British guidelines recommend a minimum of five days of

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32
33 103 treatment before therapy discontinuation for patients achieving clinical stability.[4,5] The

34
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36 104 European guideline states that the duration of treatment should not exceed eight days in

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39 105 responding patients.[6] In clinical practice, however, antibiotics for pneumonia are often

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42 106 prescribed for 10 up to 14 days.[7,8] This may mean that many patients are receiving more

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45 107 antibiotics than necessary, with a consequent increase in costs and a higher probability of

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48 108 antimicrobial resistance.[9] Finding the optimal duration of antibiotics can facilitate

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51 109 reducing antimicrobial use efficiently. Several meta-analyses have been reported on this

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54 110 topic.[10–12] A major limitation of the method used in the previous pairwise meta-analyses

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6 111 is the arbitrary categorisation of duration when the original studies compared different
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9 112 duration, ranging from three to ten days. A pairwise meta-analysis published in 2008, [10]
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11
12 113 for example, categorised a seven-day treatment arm in one trial as short-course and the
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15 114 same in other two trials as long-course. [13–15] Another pairwise meta-analysis in 2018
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18 115 excluded a trial comparing seven-day against ten-day treatment because they defined long-
19
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21 116 course as seven days or longer.[11] The duration range of short course therapy defined by a
22
23
24 117 systematic review of systematic reviews and guidelines with pairwise meta-analyses in
25
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27 118 2019 was wide (three to seven days) and the duration-effect relationship within that range
28
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30 119 remains unclear.[12] We overcame the limitation of arbitrary dichotomisation of duration
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33 120 by using a novel method called dose-effect meta-analysis.[16] It has been used, for
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36 121 example, to examine the effects of potassium intake or sodium reduction on blood
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39 122 pressure[17,18]. Unlike conventional categorisation-based meta-analyses[19], dose-effect
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42 123 meta-analysis can reveal more fine-grained optimal dose[20]. By treating duration as dose,
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45 124 we aimed to apply this method to obtain a more specific optimal treatment duration.
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126 **METHODS**

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7 127 We summarised the currently available evidence to find the optimal treatment duration of
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9 128 antibiotics for CAP in adults. We followed the Preferred Reporting Items for Systematic
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12 129 reviews and Meta-Analyses (PRISMA 2020) [21]. The protocol has been prospectively
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14
15 130 registered in PROSPERO (CRD 42021273357) and can be found in the appendix
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17
18 131 (eAppendix1).

132 *Patient and Public Involvement*

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

135

136 **Data sources**

137 **Criteria for considering studies for this review**

138 *Types of studies*

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

141 *Types of participants*

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

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6 144 excluded patients who were admitted to the intensive care unit. To focus on individuals at
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9 145 low to medium risk, we excluded trials with 20% or more patients meeting one or more of
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12 146 the following criteria: having immunodeficiency; having been treated with another
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15 147 antibiotic within a month.

18 148 *Types of interventions*

21 149 We included trials examining any antibiotics, administered orally or intravenously. We
22
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24 150 evaluated antibiotics as a class because clinical guidelines recommend treatment duration
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27 151 irrespective of the antibiotic used,[4–6] and because recent meta-analyses of antibiotics for
28
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30 152 CAP have not shown efficacy differences among antibiotics.[22,23] Oral and intravenous
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33 153 antibiotics were merged because they have been shown equally effective in many infectious
34
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36 154 conditions within the same time frame.[24–26] We included trials comparing the same
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39 155 agents used at the same daily dosage but for different durations. We used the predefined
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42 156 duration for fixed-duration arms. If some studies did not prespecified the duration (eg. left
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45 157 it to clinicians' judgment[27]), we used the median duration.

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51 159 **Primary outcome and secondary outcomes**

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7 160 The primary outcome of interest in this study was the clinical improvement as defined by
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10 161 the original authors at a time point as close to 15 days (range 7-45 days) as possible in each
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12 162 included study.[28] Secondary outcomes of interest were: all-cause mortality on day 15
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15 163 (range 7-45 days), serious adverse events as defined by the original study on day 15 (range
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18 164 7-45 days), and clinical improvement as defined by the original study on day 30 (range 15-
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20
21 165 60). We used the number of randomised patients as the denominator for the intention-to-
22
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24 166 treat (ITT) dataset. When only clinical failure was reported, clinical improvement was
25
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27 167 calculated by subtracting clinical failure from the total number randomised. We used ITT
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30 168 for the primary analysis and the per-protocol (PP) dataset for a sensitivity analysis.[29,30]
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33 169 We used the odds ratio (OR) of each outcome to synthesise data. [31,32]
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39 171 **Search methods for identification of studies**

42 172 *Electronic searches*

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45 173 We systematically searched the following electronic bibliographic databases from inception
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48 174 through 25 August 2021: MEDLINE, Embase and CENTRAL. We used search terms for
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51 175 community-acquired pneumonia in conjunction with the names of individual antibiotics as
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6 176 well as the names of antibiotic classes. Detailed search formulas are presented in the
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9 177 appendix (eAppendix2). We imposed no date, language or publication status restriction.

12 178 ***Reference lists***

15 179 We checked the reference lists of all the included studies and review articles for additional
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18 180 references.

21 181

24 182 **Data collection and analysis**

27 183 **Selection of studies**

30 184 Two review authors independently screened and selected the included studies (YF and one
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32
33 185 of AO, EO, SF or YL). Two review authors extracted data independently from the included
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36 186 studies (YF and one of AO, EO, SF or YL). We used the Cochrane risk of bias tool Version
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39 187 2 [33] to assess and summarise the risk of bias. Disagreements were resolved through
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42 188 discussion.

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48 190 **Statistical analysis**

51 191 To perform our analyses, we used the *dosresmeta* package (Version 2.0.1) and *meta*
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54 192 package (Version 5.0-1) for *R* (Version 4.1.0. R foundation, Wien, Austria).[34–36]
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9 194 *Assessment of heterogeneity*

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12 195 We investigated the heterogeneity between studies by the variance partition coefficient
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15 196 (VPC). [16] VPC represents the percentage of variation attributed to heterogeneity rather
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18 197 than sampling error and can be interpreted similarly to the I^2 .

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24 199 *Duration-effect meta-analysis*

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27 200 In the duration-effect meta-analysis, we assumed that the relative efficacy of a certain
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30 201 treatment duration ($duration_i$) against another ($duration_j$) can be expressed in the log-
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33 202 odds ratio ($\log OR_{ij}$) and that it is a function of both durations ($\log OR_{ij} = f(duration_i;$
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36 203 $duration_j)$). We fitted restricted cubic splines with three knots to the dataset obtained by
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39 204 the systematic review because this model has shown sufficient flexibility to capture
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42 205 different shapes.[37] Given the clinical and methodological heterogeneity likely present in
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45 206 the included studies, we used the random effects model. We used three knots, equally
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48 207 spaced across the duration range (25%, 50%, 75%). Typically, in dose-effect meta-
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51 208 analyses, the reference dose is assigned to the zero or the minimal dose to make
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54 209 interpretation easier.[37] As this duration-effect meta-analysis aimed to test the non-

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6 210 inferiority of the shorter treatment duration, we decided to use the maximum duration as the
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9 211 reference to make interpretation easier. Also, the reference we set (10-day treatment) can be
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12 212 regarded as the current practice.[7,8,27] We tested the non-inferiority with the non-
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15 213 inferiority margin of 10%, as previously proposed,[28] and the superiority of the shorter
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18 214 duration examined against 10-day treatment using the ITT dataset.
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24 216 ***Sensitivity analyses***

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27 217 To ascertain the robustness of the primary analyses, we conducted the following sensitivity
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30 218 analyses. To test the stability of the shape of the spline curves, we used different locations
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33 219 of knots (10%, 50%, 90%). To test the influence of trials included, we conducted sensitivity
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36 220 analyses excluding trials with an overall high risk of bias and excluding trials with
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39 221 outpatients. To test the robustness of the analytical method, we used the PP dataset. To test
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42 222 the influence of antibiotics examined, we conducted sensitivity analyses restricting eligible
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45 223 antibiotics only to those recommended by clinical guidelines for empirical treatment of
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48 224 CAP.[4,5] In addition to the pre-defined sensitivity analyses, we conducted exploratory
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51 225 sensitivity analyses including only trials that randomised before the initial antibiotic
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54 226 treatment to test the influence of randomisation timing. We further conducted sensitivity
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6 227 analyses excluding trials with substantial deviation from the day 15 measurement time and
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9 228 analyses imputing missing data as improved outcomes.
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11 229 **Amendments**

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15 230 We report amendments with the date and the rationale in the appendix (eAppendix3).
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19 20 21 232 **RESULTS**

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24 233 We identified 1,994 records via database and one record via searching websites, which
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27 234 revealed that some different records refer to the same clinical trial. We assessed 38 full-text
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30 235 records for eligibility and included 11 eligible studies. (Fig1) Of these, eight were
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33 236 published,[13–15,27,38–41] one was unpublished[42] and two studies were still
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36 237 ongoing,[43,44] resulting in nine trials for the primary outcome analysis. The lists of
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39 238 included and excluded studies are provided in the appendix (eAppendix4 and 5). The nine
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42 239 studies with 2,399 participants in total included 18 eligible arms. Treatment duration ranged
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45 240 from three to ten days. The study year ranged between 1999 and 2021. Table 1 presents the
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48 241 characteristics of the included studies. (more details can be found in eAppendix4)
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51 242 The included studies were all parallel-group and individually randomised. Seven out of
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54 243 nine were reported as non-inferiority trials. In total, 1,199 participants were randomly
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6 244 assigned to the shorter duration arm and 1,200 to the longer duration arm. The mean age
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9 245 was 61.2 years (standard deviation 22.1); 831 (39%) of 2,140 reported were women. Six
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12 246 were conducted in a single European country, one in the US, and the two were cross-
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15 247 continental. CAP was defined as newly confirmed clinical symptoms (eg, dyspnoea, cough,
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18 248 purulent sputum, or crackles), and radiological findings. Antibiotic treatment was
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21 249 discontinued when the patient was clinically stable, and the pre-determined treatment
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24 250 period was completed. Clinical stability was often defined as apyrexia (temperature
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27 251 ≤ 37.8 C) for 48 hours, heart rate below 100 beats per min, a respiratory rate below 24
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30 252 breaths per min, arterial oxygen saturation of 90% or higher, systolic blood pressure of 90
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33 253 mmHg or higher, and normal mental status.[45] Clinical improvement was often described
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36 254 as “clinical cure” or “clinical success” and was often defined as the resolution of fever and
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39 255 improvement of symptoms related to pneumonia without further antibiotics. More detailed
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42 256 definitions of clinical improvement in each included study are listed in the appendix.
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45 257 (eAppendix6) The percentage of pneumonia severity index class IV or V was on average
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48 258 19% (362 of 1,896 reported; ranging from 2 to 41%). Seven studies focused on inpatients,
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51 259 whereas one study focused on outpatients and one included both. Antibiotics used included
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54 260 β -lactams (amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, ceftazidime,
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6 261 ceftriaxone, cefuroxime, piperacillin/tazobactam), macrolides (azithromycin,
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9 262 clarithromycin), quinolones (ciprofloxacin, gemifloxacin, levofloxacin, telithromycin),
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12 263 amikacin, doxycycline, and meropenem. Pharmaceutical companies funded four
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14
15 264 studies.[13–15,38] Four studies had a high overall risk of bias, four some concerns, and
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18 265 only one had a low overall risk of bias. (eAppendix 7)
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266 **Table 1 Characteristics of included studies**

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| 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 |

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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

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7 **275 Assessment of heterogeneity and publication bias**

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9 **276** We assessed the heterogeneity in the efficacy outcome across the duration range (9 studies).

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11 **277** VPC values were constantly below 10% which suggests low levels of heterogeneity. Visual

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15 **278** inspection of the funnel plot suggested no significant publication bias. However, these

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18 **279** assessments need to be carefully interpreted due to the small number of included studies.

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21 **280** (eAppendix8 and 9)

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24 **281**

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27 **282 Duration-effect meta-analysis**

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30 **283** We present the duration-effect curves in Figure 2 and Figure 3, and the tabulation of results

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33 **284** in Table 2. The x-axis of the figures represents the treatment duration in days. The y-axis

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36 **285** represents the odds ratio of the outcome on a logarithmic scale, just as in the forest plot of

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39 **286** conventional pairwise meta-analysis using binary outcomes. The thin dotted horizontal line

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42 **287** in the clinical improvement figures and the all-cause mortality figure corresponds to the

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45 **288** non-inferiority margin translated into OR. (The weighted average percentage of clinical

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48 **289** improvement rate on day 15 in the 10-day treatment arms was 68%. The non-inferiority

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51 **290** margin was therefore 58% and the corresponding OR was 0.65. For all-cause mortality, the

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54 **291** numbers were 3%, 13% and OR 4.8, respectively. For clinical improvement on day 30, the

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6 292 numbers were 77%, 67% and OR 0.61, respectively. We did not show the non-inferiority
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9 293 margin in the figures for severe adverse events, because the position paper did not provide
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12 294 any margin for this outcome.[28]) The thick solid line represents the duration-effect curve
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15 295 and the thick dotted lines represent its 95% CI. The 95% CI band becomes narrower when
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18 296 the duration range was examined by many trials or when it gets closer to the reference
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21 297 point. For the beneficial outcomes (clinical improvement), $OR > 1$ means more effective.
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24 298 For the harmful outcomes (all-cause mortality and serious adverse events), $OR < 1$ means
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27 299 safer.

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31 The duration-effect curve is monotonic with a longer duration leading to a lower
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33 301 probability of improvement. The lower 95%CI curve was constantly above the prespecified
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36 302 non-inferiority margin, meaning that a shorter treatment duration (3-9 days) was likely to
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39 303 be non-inferior to the standard treatment duration (10 days). It was slightly above the $OR =$
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42 304 1 around 3-day treatment, suggesting 3-day treatment may be superior to 10-day treatment.
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45 305 Harmful outcome curves (all-cause mortality and severe adverse events) were almost flat
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48 306 and 95%CI curves did not cross the $OR = 1$, indicating no association. Although the
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51 307 confidence interval curves were wide for all-cause mortality, shorter treatment duration (3-
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54 308 9 days) was likely to be non-inferior to 10-day treatment. Clinical improvement on day 30

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6 309 showed a similar trend with the primary outcome with the lower 95%CI curve constantly
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9 310 above the prespecified non-inferiority margin. We made a league table (eAppendix10),
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12 311 which showed that shorter treatment duration was likely to be non-inferior to longer
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15 312 treatment duration, regardless of the reference duration.

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18 313 Odds ratios need to be translated into absolute event rates so that the results can be
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21 314 interpreted from the clinical point of view. The weighted average percentage of clinical
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24 315 improvement rate on day 15 in the 10-day treatment arms was 68%, based on a single
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27 316 proportion meta-analysis of the included studies. Using this average, we computed the
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30 317 absolute clinical improvement rates at the following durations as follows: 3-day treatment
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33 318 75% (95%CI: 68 to 81%), 5-day treatment 72% (66 to 78%), and 7-day treatment 69% (61
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36 319 to 76%). (Table 2)

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

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| 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% |

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6 **324 Sensitivity analyses**
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9 **325** Sensitivity analyses were in line with the primary analyses. Sensitivity analyses using
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11 **326** different locations of knots confirmed the stability of the shape of the spline curves.
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15 **327** (eAppendix 11, Figures S1) Sensitivity analyses excluding trials with an overall high risk of
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18 **328** bias were also in agreement with the primary analyses. (eAppendix 11, Figure S2.1)
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21 **329** Sensitivity analyses excluding trials with outpatients also confirmed the main findings,
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24 **330** suggesting the results are generalisable to inpatients, except for those admitted to the
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27 **331** intensive care unit. (eAppendix 11, Figures S2.2) Sensitivity analyses using the per protocol
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30 **332** dataset and those including only trials that used antibiotics recommended for empirical
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33 **333** treatment of CAP by clinical guidelines also confirmed the results. (eAppendix 11, Figures
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36 **334** S3 and S4) Exploratory sensitivity analyses showed that non-inferiority of the shorter
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39 **335** duration was more likely to be the case in studies that randomised patients who had reached
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42 **336** clinical stability early. (eAppendix 11, Figures S5.1 and S5.2) Furthermore, post-hoc
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45 **337** sensitivity analyses which excluded trials with substantial deviation from the day 15
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48 **338** measurement time (eAppendix 11, Figures S5.3) and those which imputed missing data as
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51 **339** clinically improved (eAppendix 11, and S5.4) also aligned with the primary analyses.
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54 **340 DISCUSSION**
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7 341 To our knowledge, this is the first systematic review and duration-effect meta-analysis of
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9 342 antibiotics treatment for CAP in adults. The results showed that shorter treatment duration
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12 343 (3-9 days) was likely to be non-inferior to the standard treatment duration (10 days) for
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15 344 CAP in adults if they achieved clinical stability. There may be no significant difference in
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18 345 all-cause mortality or serious adverse events. Shorter treatment duration (3-5 days)
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21 346 probably achieves the optimal balance between efficacy and treatment burden. Multiple
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24 347 sensitivity analyses confirmed the primary findings.
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27 348 This is in line with the previous pairwise meta-analyses that showed shorter
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30 349 duration was non-inferior to longer duration.[10–12] We updated the systematic review and
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33 350 found four trials that were not included in the previous studies. This allowed us to focus on
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36 351 trials that used the same antibiotics with the same daily dosage. The previous studies
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39 352 included trials using different antibiotics or different daily dosages, so the results may not
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42 353 have reflected the differences in treatment durations alone. Moreover, they subcategorised
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45 354 the treatment durations and may have thus lost some statistical power to detect meaningful
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48 355 differences among durations. We overcame this limitation by examining the duration of
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51 356 antibiotic treatment range in days as a continuous variable and found that three to nine-day
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54 357 treatment is likely to be non-inferior to 10-day treatment. Our results are in line with the
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6 358 guidelines for CAP recommending antibiotics to be prescribed for a duration shorter (5-8
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9 359 days) than current clinical standard practice (10 days).[4–6] Our results suggest that an
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12 360 even shorter duration (3-5 days) may be considered, which is in line with the trials that
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15 361 found 3-day treatment was non-inferior to 8-day treatment.[39,41] Possibility of 3-day
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18 362 treatment being superior to 10-day treatment should be carefully interpreted, as none of the
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21 363 included trials, previous meta-analyses[11,12] or the pairwise meta-analysis of the included
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24 364 trials (eAppendix12, post hoc analysis) showed the superiority of shorter treatment
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27 365 duration. This could be explained by the fact that most of the combinations of treatment
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30 366 durations examined (7 days vs 10 days, 5 days vs 10 days, 5 days vs 7 days, 3 days vs 8
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33 367 days) suggested better efficacy of shorter durations, if not statistically significant alone.
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36 368 (eAppendix12, post hoc analysis) The duration-effect meta-analysis combined these
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39 369 findings, leading to the possible superiority of the shortest duration examined (3 days) over
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42 370 the longest duration examined (10 days). Further research focusing on the shorter duration
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45 371 range is warranted to confirm this finding.
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54 374 **Limitations**
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6 375 Our study has several limitations. First, most of the included studies presented a moderate
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9 376 to high overall risk of bias, which compromises the validity of this meta-analysis. Second,
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12 377 the number of studies was small, leaving confidence intervals for secondary outcomes
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15 378 wide. Third, original studies excluded patients with complications of CAP and therefore the
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18 379 results of this study may not be generalisable to those patients. Forth, baseline severity of
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21 380 the included studies varied. We included both the outpatients and inpatients, which may
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24 381 have concealed important heterogeneity in the study results. However, sensitivity analyses
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27 382 excluding trials with outpatients generally confirmed the primary analyses (eAppendix 11)
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30 383 and the overall statistical heterogeneity was low. Fifth, we did not include patients admitted
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33 384 to the intensive care units and the results of this study may not be generalisable to those
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36 385 patients. Sixth, the actual measurement day for the primary outcome in each included study
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39 386 varied (7 to 44 days) and this may have introduced between-study heterogeneity. However,
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42 387 post-hoc sensitivity analyses excluding trials with large deviation from the day 15
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45 388 measurement time were in line with the primary analyses.

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54 391 Strengths

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6 392 First, we did a comprehensive systematic review and found four studies that were not
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9 393 included in the previous systematic reviews. Second, we treated duration as a continuous
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12 394 variable, which allowed us to estimate the duration-effect relationship with greater
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15 395 resolution of change points. Third, we examined the impacts of treatment duration not only
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18 396 for clinical improvement but also for all-cause mortality and severe adverse events and
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21 397 made sure that a shorter treatment duration would not translate into more harmful events.
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24 398 Finally, the very nature of shortened duration treatment offers a unique opportunity for
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27 399 interpretation. Shorter treatment duration has been examined by non-inferiority trials. The
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30 400 underlying assumption has been that there was a trade-off between a loss in the efficacy of
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33 401 standard treatment duration and other benefits of shortened treatment duration, [46,47] such
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36 402 as less time, less cost and probably a diminished rate of antimicrobial resistance. This study
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39 403 suggests that there may be even no trade-off for antibiotic treatments of three to five days.
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42 404 The shorter treatment duration reduces the burden on patients, the healthcare system and
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45 405 the risk of antimicrobial resistance and might even offer better clinical outcomes at the
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48 406 same time.
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54 408 **CONCLUSIONS**
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6 409 Short treatment duration (3-9 days) was likely to be non-inferior to the standard treatment
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9 410 duration (10 days) for adults with CAP if they achieved clinical stability. Shorter range (3-5
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12 411 days) probably results in an optimal balance between efficacy and treatment burden.
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15 412 However, the small number of included studies and the overall moderate to high risk of bias
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18 413 may compromise the certainty of the results. Further research focusing on the shorter
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21 414 duration range is required.
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25 417 **Abbreviations**

26 418 CAP: community-acquired pneumonia

27 419 CI: confidence interval

28 420 ITT: intention-to-treat

29 421 OR: odds ratio

30 422 PP: per protocol

31 423 PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

32 424 SAE: serious adverse events

33 425 SD: standard deviation

34 426 VPC: variance partition coefficient

35 427

36 428 **DECLARATIONS**

37 429 **Ethics approval and consent to participate**

38 430 This study uses published aggregate data and did not require ethical approval.

39 431 **Consent for publication**

40 432 Not applicable.

41 433 **Availability of data and materials**

42 434 Data and code used for analyses are available from the corresponding author upon

43 435 reasonable request.

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6 **436 Competing interests**

7 **437** YL is receiving a Grant-in-Aid for JSPS Fellow (KAKENHI Grant Number 21J15050).

8 **438** SF has a research grant from JSPS KAKENHI Grant Number JP 20K18964 and the KDDI
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10 **440** AO obtained speakers fees from Chugai Pharmaceutical Co. Ltd, Asahi Kasei Corporation,
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13 **443** submitted work.

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17 **447** Research (NIHR) Applied Research Collaboration (ARC) Oxford and Thames Valley, by
18 **448** the National Institute for Health Research (NIHR) Oxford cognitive health Clinical
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21 **451** TAF reports grants and personal fees from Mitsubishi-Tanabe, personal fees from MSD,
22 **452** personal fees from Shionogi, personal fees from Sony, outside the submitted work; In
23 **453** addition, TAF has a patent 2018-177688 concerning smartphone CBT apps pending, and
24 **454** intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe.

25 **455** YK received a research grant from the Systematic Review Workshop Peer Support Group,
26 **456** the Japan Osteoporosis Foundation, and Yasuda Memorial Medical Foundation for other
27 **457** research purposes.

28 **458** YF, TH declare no conflicts of interest.

29 **459 Acknowledgements**

30 **460** Not applicable.
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6 **462 Author Contributions**

7 **463** All authors had full access to all of the data (including statistical reports and tables) in this
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9 **464** study and take full responsibility for the integrity of the data and the accuracy of the data
10 **465** analysis. Conception and design: YF, YL, SF, AO, EGO, TAF, YK. Analysis and
11 **466** interpretation of the data: YF, YL, SF, AO, EGO, TH, TAF, YK. Drafting of the article:
12 **467** YF. Critical revision of the article for important intellectual content: YL, SF, AO, EGO,
13 **468** TH, TAF, YK. Final approval of the article: YF, YL, SF, AO, EGO, TH, TAF, YK.
14
15 **469** Obtaining of funding: none. Administrative, technical or logistic support: YF, TH.
16
17 **470** Collection and assembly of data: YF, YL, SF, AO, EGO. Guarantor: YF. Transparency
18 **471** declaration: As guarantor, YF affirms that the manuscript is an honest, accurate and
19 **472** transparent account of the study being reported; that no important aspects of the study have
20 **473** been omitted; and that any discrepancies from the study as planned have been explained.
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27 **477** or not-for-profit sectors.
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31 **479**
32 **480 REFERENCE**

- 33
34
35 **481** 1. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional,
36 **482** and national morbidity, mortality, and aetiologies of lower respiratory infections in 195
37 **483** countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.
38 **484** *Lancet Infect Dis.* 2018;18(11):1191-1210. doi:10.1016/s1473-3099(18)30310-4
39
40
41
42 **485** 2. Most Frequent Conditions in U.S. Hospitals, 2011. Accessed December 8, 2021.
43 **486** <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf>
44
45
46 **487** 3. Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final Data for 2013. *Natl Vital*
47 **488** *Stat Rep.* 2016;64(2):1-119.
48
49
50
51 **489** 4. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with
52 **490** Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 491 Thoracic Society and Infectious Diseases Society of America. *Am J Resp Crit Care*.
7 492 2019;200(7):e45-e67. doi:10.1164/rccm.201908-1581st
8
9
10 493 5. National Institute of Health and Care Excellence (NICE). Pneumonia (community-
11 494 acquired): antimicrobial prescribing. Accessed December 8, 2021.
12 495 <https://www.nice.org.uk/guidance/NG138>
13
14
15 496 6. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower
16 497 respiratory tract infections - Full version. *Clin Microbiol Infect*. 2011;17(s6):E1-E59.
17 498 doi:10.1111/j.1469-0691.2011.03672.x
18
19
20
21 499 7. Aliberti S, Blasi F, Zanaboni AM, et al. Duration of antibiotic therapy in hospitalised
22 500 patients with community-acquired pneumonia. *Eur Respir J*. 2009;36(1):128-134.
23 501 doi:10.1183/09031936.00130909
24
25
26
27 502 8. Yi SH, Hatfield KM, Baggs J, et al. Duration of Antibiotic Use Among Adults With
28 503 Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United
29 504 States. *Clin Infect Dis*. 2017;66(9):1333-1341. doi:10.1093/cid/cix986
30
31
32
33 505 9. Guillemot D, Carbon C, Balkau B, et al. Low Dosage and Long Treatment Duration of β -
34 506 Lactam: Risk Factors for Carriage of Penicillin-Resistant *Streptococcus pneumoniae*.
35 507 *JAMA*. 1998;279(5):365-370. doi:10.1001/jama.279.5.365
36
37
38 508 10. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, Grammatikos AP, Athanassa Z,
39 509 Falagas ME. Short- versus Long-Course Antibacterial Therapy for Community-Acquired
40 510 Pneumonia. *Drugs*. 2008;68(13):1841-1854. doi:10.2165/00003495-200868130-00004
41
42
43
44 511 11. Tansarli GS, Mylonakis E. Systematic Review and Meta-analysis of the Efficacy of
45 512 Short-Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults.
46 513 *Antimicrob Agents Ch*. 2018;62. doi:10.1128/aac.00635-18
47
48
49
50 514 12. Furlan L, Erba L, Trombetta L, et al. Short- vs long-course antibiotic therapy for
51 515 pneumonia: a comparison of systematic reviews and guidelines for the SIMI Choosing
52 516 Wisely Campaign. *Intern Emerg Med*. 2019;14:377-94. doi:10.1007/s11739-018-1955-2
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 517 13. Siegel RE, Alicea M, Lee A, Blaiklock R. Comparison of 7 Versus 10 Days of
7 518 Antibiotic Therapy for Hospitalized Patients with Uncomplicated Community-Acquired
8 519 Pneumonia. *Am J Ther.* 1999;6(4):217-222. doi:10.1097/00045391-199907000-00007
10
11 520 14. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological
12 521 efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10
13 522 day regimen of clarithromycin twice daily in patients with mild to moderate community-
14 523 acquired pneumonia. *J Antimicrob Chemoth.* 2004;54(2):515-523. doi:10.1093/jac/dkh356
17
18 524 15. File TM, Mandell LA, Tillotson G, Kostov K, Georgiev O. Gemifloxacin once daily for
19 525 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized,
20 526 multicentre, double-blind study. *J Antimicrob Chemoth.* 2007;60(1):112-120.
21 527 doi:10.1093/jac/dkm119
24
25 528 16. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response
26 529 meta-analysis for aggregated data. *Stat Methods Med Res.* 2019;28(5):1579-1596.
27 530 doi:10.1177/0962280218773122
30
31 531 17. Filippini T, Naska A, Kasdagli M, et al. Potassium Intake and Blood Pressure: A
32 532 Dose-Response Meta-Analysis of Randomized Controlled Trials. *J Am Hear Assoc*
33 533 2020;9(12):e015719. doi:10.1161/jaha.119.015719
35
36 534 18. Filippini T, Malavolti M, Whelton PK, Naska A, Orsini N, Vinceti M. Blood Pressure
37 535 Effects of Sodium Reduction. *Circulation.* 2021;143(16):1542-1567.
38 536 doi:10.1161/circulationaha.120.050371
41
42 537 19. Højlund M, Kemp AF, Haddad PM, Neill JC, Correll CU. Standard versus reduced
43 538 dose of antipsychotics for relapse prevention in multi-episode schizophrenia: a systematic
44 539 review and meta-analysis of randomised controlled trials. *Lancet Psychiatry.*
45 540 2021;8(6):471-486. doi:10.1016/s2215-0366(21)00078-x
47
48 541 20. Leucht S, Bauer S, Sifakis S, et al. Examination of Dosing of Antipsychotic Drugs for
49 542 Relapse Prevention in Patients With Stable Schizophrenia. *JAMA Psychiat.* 2021;78(11).
50 543 doi:10.1001/jamapsychiatry.2021.2130
51
52
53
54
55
56
57
58
59
60

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2
3
4
5
6 544 21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated
7 545 guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
8
9
10 546 22. Montes-Andujar L, Tinoco E, Baez-Pravia O, et al. Empiric antibiotics for community-
11 547 acquired pneumonia in adult patients: a systematic review and a network meta-analysis.
12 548 *Thorax*. Published online 2021:thoraxjnl-2019-214054. doi:10.1136/thoraxjnl-2019-214054
13
14
15 549 23. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for
16 550 community-acquired pneumonia in adult outpatients. *Cochrane Db Syst Rev*.
17 551 2014;10(10):CD002109. doi:10.1002/14651858.cd002109.pub4
18
19
20
21 552 24. Keren R, Shah SS, Srivastava R, et al. Comparative Effectiveness of Intravenous vs
22 553 Oral Antibiotics for Postdischarge Treatment of Acute Osteomyelitis in Children. *JAMA*
23 554 *Pediatr*. 2014;169(2):120. doi:10.1001/jamapediatrics.2014.2822
24
25
26
27 555 25. Li HK, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone
28 556 and Joint Infection. *New Engl J Med*. 2019;380(5):425-436. doi:10.1056/nejmoa1710926
29
30
31 557 26. Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic
32 558 Treatment of Endocarditis. *New Engl J Med*. 2019;380(5):415-424.
33 559 doi:10.1056/nejmoa1808312
34
35
36
37 560 27. Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-
38 561 Acquired Pneumonia: A Multicenter Randomized Clinical Trial. *JAMA Intern Med*.
39 562 2016;176(9):1257. doi:10.1001/jamainternmed.2016.3633
40
41
42 563 28. Spellberg B, Talbot GH, Brass EP, et al. Position paper: recommended design features
43 564 of future clinical trials of antibacterial agents for community-acquired pneumonia. *Clin*
44 565 *Infect Dis*. 2008;47 Suppl 3:S249-65.
45
46
47
48 566 29. Bai AD, Komorowski AS, Lo CKL, et al. Intention-to-treat analysis may be more
49 567 conservative than per protocol analysis in antibiotic non-inferiority trials: a systematic
50 568 review. *BMC Med Res Methodol*. 2021;21(1):75. doi:10.1186/s12874-021-01260-7
51
52
53
54
55
56
57
58
59
60

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2
3
4
5
6 569 30. Aberegg SK, Hersh AM, Samore MH. Empirical Consequences of Current
7 570 Recommendations for the Design and Interpretation of Noninferiority Trials. *J Gen Intern*
8 571 *Med.* 2018;33(1):88-96. doi:10.1007/s11606-017-4161-4
- 10
11 572 31. Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in
12 573 meta-analysis. *Res Synth Methods.* 2019;10(3):398-419. doi:10.1002/jrsm.1347
- 14
15 574 32. Doi SA, Furuya-Kanamori L, Xu C, Lin L, Chivese T, Thalib L. Questionable utility of
16 575 the relative risk in clinical research: A call for change to practice. *J Clin Epidemiol.*
17 576 Published online 2020. doi:10.1016/j.jclinepi.2020.08.019
- 20
21 577 33. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in
22 578 randomised trials. *BMJ.* 2019;366:l4898. doi:10.1136/bmj.l4898
- 24
25 579 34. Team RC. R: A Language and Environment for Statistical Computing. R Foundation
26 580 for Statistical Computing.; 2020. <https://www.R-project.org/>
- 28
29 581 35. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a
30 582 practical tutorial. *Évid Based Ment Heal.* 2019;22(4):153. doi:10.1136/ebmental-2019-
31 583 300117
- 34
35 584 36. Crippa A, Orsini N. Multivariate Dose-Response Meta-Analysis: The dosresmeta R
36 585 Package. Published online 2016. doi:doi.org/10.18637/jss.v072.c01
- 38
39 586 37. Hamza T, Furukawa TA, Orsini N, et al. Dose–effect meta-analysis for
40 587 psychopharmacological interventions using randomised data. *Évid Based Ment Heal.*
41 588 2022;25:1–6. doi:10.1136/ebmental-2021-300278
- 43
44
45 589 38. Léophonte P, Choutet P, Gaillat J, et al. Efficacité comparée de la ceftriaxone dans un
46 590 traitement de dix jours versus un traitement raccourci de cinq jours des pneumonies aiguës
47 591 communautaires de l'adulte hospitalisé avec facteur de risque. *Médecine Et Maladies*
48 592 *Infect.* 2002;32(7):369-381. doi:10.1016/s0399-077x(02)00384-0
- 50
51
52 593 39. El Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing
53 594 antibiotic treatment after three days versus eight days in mild to moderate-severe

- 1
2
3
4
5
6 595 community acquired pneumonia: randomised, double blind study. *BMJ*.
7 596 2006;332(7554):1355. doi:10.1136/bmj.332.7554.1355
8
9
10 597 40. Aliberti S, Ramirez J, Giuliani F, et al. Individualizing duration of antibiotic therapy in
11 598 community-acquired pneumonia. *Pulm Pharmacol Ther*. 2017;45:191-201.
12 599 doi:10.1016/j.pupt.2017.06.008
13
14
15 600 41. Dinh A, Ropers J, Duran C, et al. Discontinuing β -lactam treatment after 3 days for
16 601 patients with community-acquired pneumonia in non-critical care wards (PTC): a double-
17 602 blind, randomised, placebo-controlled, non-inferiority trial. *Lancet*. 2021;397(10280):1195-
18 603 1203. doi:10.1016/s0140-6736(21)00313-5
19
20
21
22 604 42. Strålin K, Rubenson A, Lindroth H, et al. Betalactam treatment until no feve for 48
23 605 hours (at least 5 days) versus 10 days in community-acquired pneumonia: randomised, non-
24 606 inferiority, open study. *Pneumonia*. 2014;3:246-281. doi:10.1007/bf03399446
25
26
27
28 607 43. NCT03609099. Adequate Duration of Antibiotic Treatment in Community-acquired
29 608 Pneumonia With High Risk Class and Adequate Initial Clinical Response (2017-001406-
30 609 15). <https://clinicaltrials.gov/ct2/show/NCT03609099>
31
32
33
34 610 44. NCT04089787. Shortened Antibiotic Treatment of 5 Days in Community-Acquired
35 611 Pneumonia (CAP5). <https://clinicaltrials.gov/ct2/show/NCT04089787>
36
37
38 612 45. Halm EA, Fine MJ, Marrie TJ, et al. Time to Clinical Stability in Patients Hospitalized
39 613 With Community-Acquired Pneumonia: Implications for Practice Guidelines. *JAMA*.
40 614 1998;279(18):1452-1457. doi:10.1001/jama.279.18.1452
41
42
43
44 615 46. Mulla SM, Scott IA, Jackevicius CA, You JJ, Guyatt GH. How to Use a Noninferiority
45 616 Trial: Users' Guides to the Medical Literature. *JAMA*. 2012;308(24):2605-2611.
46 617 doi:10.1001/2012.jama.11235
47
48
49 618 47. Acuna SA, Chesney TR, Baxter NN. Incorporating Patient Preferences in
50 619 Noninferiority Trials. *JAMA*. 2019;322(4):305-306. doi:10.1001/jama.2019.7059
51
52
53
54
55
56
57
58
59
60

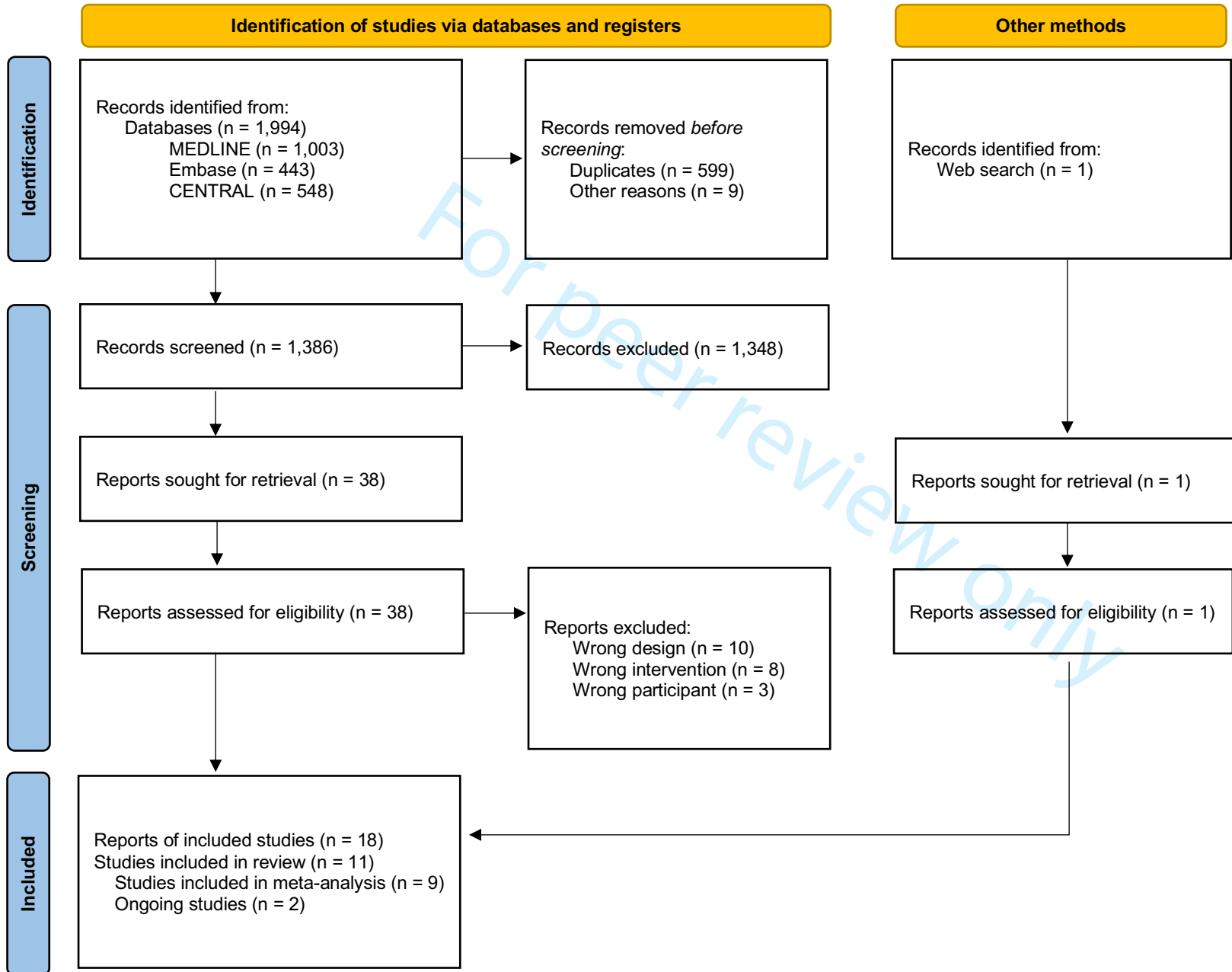
FIGURE LEGENDS**Figure 1 PRISMA flow diagram****Figure 2 Duration–effect relationship of antibiotics for CAP in adults. Clinical improvement on day 15.**

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

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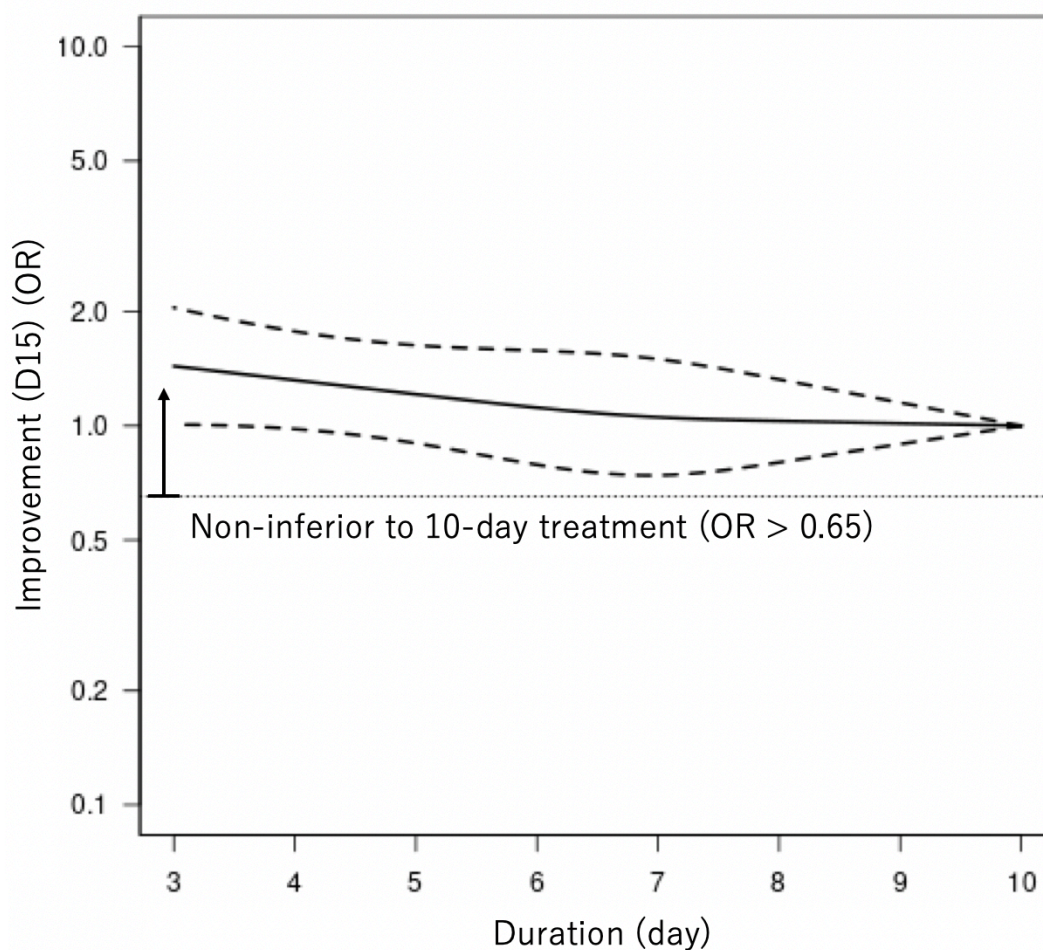
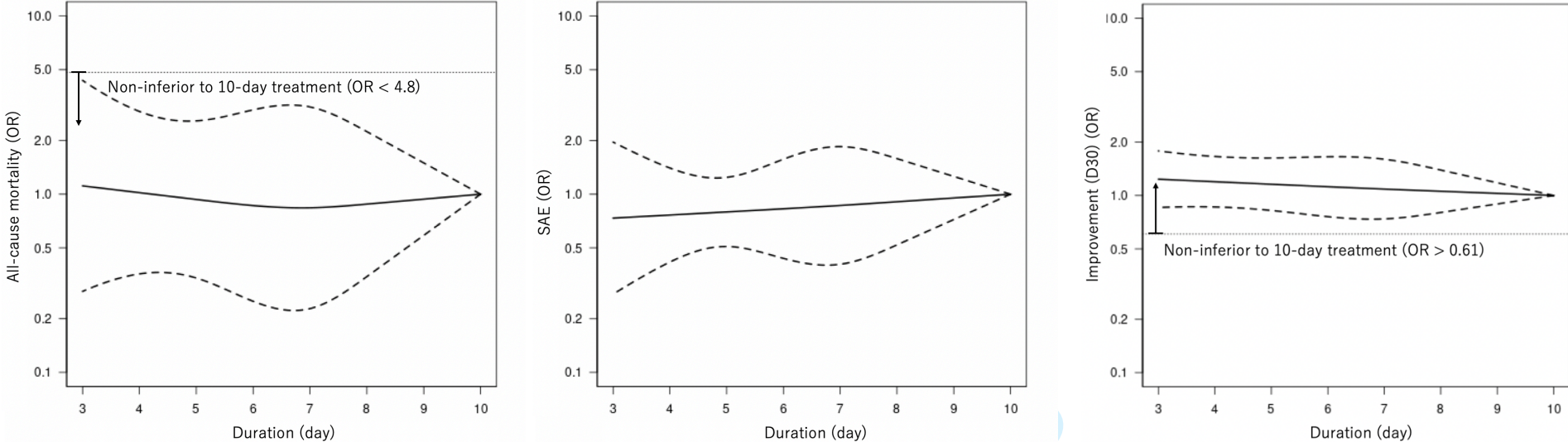


Figure 3 Duration–effect relationships of antibiotics for CAP in adults. (a) All-cause mortality. (b) Severe adverse events. (c) Clinical improvement on day 30.

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).



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3 **Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a**
4 **systematic review and duration-effect meta-analysis (eAppendix)**
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8 Yuki Furukawa, Yan Luo, Satoshi Funada, Akira Onishi, Edoardo G Ostinelli, Tasnim Hamza, Toshi A
9 Furukawa, Yuki Kataoka
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12 eAppendix 1. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults:
13 protocol for a systematic review and duration-effect meta-analysis (protocol as of 15th August, 2021)

14 eAppendix 2. Search strings used for Ovid MEDLINE, Embase, and CENTRAL.
15

16 eAppendix 3. Amendments from the protocol
17

18 eAppendix 4. List of all included papers and table of characteristics of included trials
19

20 eAppendix 5. List of excluded studies
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22 eAppendix 6. Definitions of clinical improvement in each included study
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24 eAppendix 7. Risk of bias
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26 eAppendix 8. Heterogeneity: Variance partition coefficient for the primary outcome
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28 eAppendix 9. Funnel plot
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30 eAppendix 10. League table
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32 eAppendix 11. Sensitivity analyses
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34 eAppendix 12. Pairwise meta-analysis of the included trials
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eAppendix 1. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: protocol for a systematic review and duration-effect network meta-analysis (protocol as of 15th August, 2021)

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

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

5
6 2. Studies with multiple treatment groups

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

9
10 ***Types of participants***

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

15
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17
18 ***Types of interventions***

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

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34 **Primary outcome and secondary outcomes**

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

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41 1 Clinical improvement at day 15 (range 7-45 days), as defined by the original study

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44 Secondary outcomes of interest are the following outcomes.

- 45
46 2. All-cause mortality at day 15 (range 7-45 days)
47 3. Serious adverse events as defined by the original study at day 15 (range 7-45 days)
48 4. Clinical improvement, as defined by the original study, at day 30 (range 15-60)
49

50
51 We will use the number of randomized patients as the denominator for intention-to-treat (ITT) dataset and we will use per-
52 protocol (PP) dataset as defined by the original study. Those who had been randomized but not accounted for in the original
53 study will be assumed to have dropped out for some reason other than death or serious adverse events and without clinical
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3 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
4 the primary analysis and PP for a sensitivity analysis. (17,18)
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8 **Search methods for identification of studies**

9 *Electronic searches*

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

17 Search strategy for Ovid MEDLINE is as follows
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21 #1 randomized controlled trial.pt.
22

23 #2 controlled clinical trial.pt.
24

25 #3 randomized.ab.
26

27 #4 placebo.ab.
28

29 #5 drug therapy.fs.
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31 #6 randomly.ab.
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33 #7 trial.ab.
34

35 #8 groups.ab.
36

37 #9 or/#1-#8
38

39 #10 exp animals/ not humans.sh.
40

41 #11 #9 not #10
42

43 #12 exp Community-Acquired Infections/
44

45 #13 Pneumonia, Bacterial/dt [Drug Therapy]
46

47 #14 community acquired pneumonia.ab,ti.
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49 #15 (#12 and #13) or #14
50

51 #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
52 disconti*).mp.
53

54 #17 (beta-lactam* or macrolide* or quinolone* or tetracycline* or amikacin or amoxicillin or ampicillin or azithromycin or
55 cefepim or cefotaxim* or ceftarolin or ceftazidim* or cefibuten or ceftriaxon* or cefuroxim* or cethromycin or
56 ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or co-amoxiclav or co-trimoxacol or doxycyclin* or
57 ertapenem or erythromycin or fluoroquinolon* or fluorquinolon* or gemifloxacin or gentamicin or imipenem or levofloxacin
58 or linezolid or meropenem or moxifloxacin or penicillin* or piperacillin or roxithromycin or sultamicillin or tazobactam or
59 telithromycin or tetracyclin* or ticarcillin or tobramycin).mp.
60

#18 Anti-Bacterial Agents/ad [Administration & Dosage]

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2
3 #19 #17 or #18

4 #20 #11 and #15 and #16 and #19

8 **Reference lists and others**

9 We will check the reference lists of all the included studies and review articles for additional references. We will also contact
10 experts in the field to identify unpublished and on-going trials.
11

14 **Data collection and analysis**

15 **Selection of studies**

16
17 Two review authors will independently screen titles and abstracts of all the potential studies we identify as a result of the
18 search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full text
19 study reports/publication and two review authors will independently screen the full text and identify studies for inclusion and
20 identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if
21 required, through consultation with a third review author. We will identify and exclude duplicates of the same study so that
22 each study rather than each report is the unit of analysis in the review. We will record the selection process in sufficient detail
23 to complete a PRISMA flow diagram and characteristics of excluded studies table.
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29 **Data items**

30 We will use a standardized data collection form for study characteristics and outcome data which will have been piloted on at
31 least one study in the review. Two review authors will extract data independently from the included studies. Any
32 disagreement will be resolved through discussion, or discussed with a third person if necessary. We will abstract the
33 following information.
34
35

36 **1. Characteristics of the studies**

37 Name of the study, year of publication, country, study site (single or multi-center), study design, patient characteristics (mean
38 age, percentage of women, diagnostic criteria used), outcome (definition of clinical success), definition of clinical stability,
39 timing of randomization, sponsorship (rated positive if the trial is directly sponsored by drug company or if any authors are
40 employed by the drug company).
41
42
43

44 **2. Risk of bias**

45 We will use Cochrane Risk of Bias 2.0 tool (RoB2) (19). We will assess the effect of assignment to the interventions at
46 baseline because we use the ITT population in our primary analysis.
47

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

49 Patients (number of participants randomized to each arm)

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

51 Outcomes (number of clinical success, mortality, adverse events).
52
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56 **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 *MBNMA* package in R.(20,21) One advantage of the dose-effect network meta-analysis by *MBNMA* 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, ceftaroline), macrolide (azithromycin , clarithromycin), doxycycline, respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin)

Patient and public involvement

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

Ethics and dissemination

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

Amendments

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

Abbreviations

AMR: antimicrobial resistance

CAP: community-acquired pneumonia

DE-NMA: dose-effect network meta-analysis

ITT: intention-to-treat

PP: per protocol

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

Reference

- 1 GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 2018;18:1191–210. doi:10.1016/s1473-3099(18)30310-4
- 2 Most Frequent Conditions in U.S. Hospitals, 2011. <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf> (accessed 15 Jul 2021).
- 3 Xu J, Murphy SL, Kochanek KD, et al. Deaths: Final Data for 2013. National Vital Statistics Reports Centers Dis Control Prev National Cent Heal Statistics National Vital Statistics Syst 2016;64:1–119.
- 4 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Resp Crit Care* 2019;200:e45–67. doi:10.1164/rccm.201908-1581st
- 5 Aliberti S, Blasi F, Zanaboni AM, et al. Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia. *Eur Respir J* 2009;36:128–34. doi:10.1183/09031936.00130909
- 6 Yi SH, Hatfield KM, Baggs J, et al. Duration of Antibiotic Use Among Adults With Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United States. *Clin Infect Dis* 2017;66:1333–41. doi:10.1093/cid/cix986
- 7 Guillemot D, Carbon C, Balkau B, et al. Low Dosage and Long Treatment Duration of β -Lactam: Risk Factors for Carriage of Penicillin-Resistant *Streptococcus pneumoniae*. *JAMA* 1998;279:365–70. doi:10.1001/jama.279.5.365
- 8 Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, et al. Short- versus Long-Course Antibacterial Therapy for Community-Acquired Pneumonia. *Drugs* 2008;68:1841–54. doi:10.2165/00003495-200868130-00004

- 1
2
3 9 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic
4 reviews. *Br Med J* 2021;372:n71. doi:10.1136/bmj.n71
5
6 10 Montes-Andujar L, Tinoco E, Baez-Pravia O, et al. Empiric antibiotics for community-acquired pneumonia in adult
7 patients: a systematic review and a network meta-analysis. *Thorax* 2021;:thoraxjnl-2019-214054. doi:10.1136/thoraxjnl-
8 2019-214054
9
10 11 Pakhale S, Mulpuru S, Verheij TJ, et al. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane*
12 *Db Syst Rev* 2014;10:CD002109. doi:10.1002/14651858.cd002109.pub4
13
14 12 Li HK, Agweyu A, English M, et al. An Unsupported Preference for Intravenous Antibiotics. *Plos Med*
15 2015;12:e1001825. doi:10.1371/journal.pmed.1001825
16
17 13 Keren R, Shah SS, Srivastava R, et al. Comparative Effectiveness of Intravenous vs Oral Antibiotics for Postdischarge
18 Treatment of Acute Osteomyelitis in Children. *JAMA Pediatr* 2014;169:120. doi:10.1001/jamapediatrics.2014.2822
19
20 14 Li H-K, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. *New Engl J Med*
21 2019;380:425–36. doi:10.1056/nejmoa1710926
22
23 15 Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. *New Engl J*
24 *Med* 2019;380:415–24. doi:10.1056/nejmoa1808312
25
26 16 Spellberg B, Talbot GH, Brass EP, et al. Position paper: recommended design features of future clinical trials of
27 antibacterial agents for community-acquired pneumonia. *Clin Infect Dis* 2008;47 Suppl 3:S249-65.
28
29 17 Bai AD, Komorowski AS, Lo CKL, et al. Intention-to-treat analysis may be more conservative than per protocol analysis
30 in antibiotic non-inferiority trials: a systematic review. *BMC Med Res Methodol* 2021;21:75. doi:10.1186/s12874-021-01260-
31 7
32
33 18 Aberegg SK, Hersh AM, Samore MH. Empirical Consequences of Current Recommendations for the Design and
34 Interpretation of Noninferiority Trials. *J Gen Intern Med* 2018;33:88–96. doi:10.1007/s11606-017-4161-4
35
36 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*
37 2019;366:14898. doi:10.1136/bmj.14898
38
39 20 Mawdsley D, Bennetts M, Dias S, Boucher M, Welton N. Model-Based Network Meta-Analysis: A Framework for
40 Evidence Synthesis of Clinical Trial Data. *Cpt Pharmacometrics Syst Pharmacol*. 2016;5(8):393–401.
41
42 21 Team R. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2020.
43 <https://www.R-project.org/>
44
45 22 Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth Methods*
46 2019;10:398–419. doi:10.1002/jrsm.1347
47
48 23 Doi SA, Furuya-Kanamori L, Xu C, et al. Questionable utility of the relative risk in clinical research: A call for change to
49 practice. *J Clin Epidemiol* Published Online First: 2020. doi:10.1016/j.jclinepi.2020.08.019
50
51 24 Uranga A, España PP, Bilbao A, et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A
52 Multicenter Randomized Clinical Trial. *JAMA Intern Med* 2016;176:1257. doi:10.1001/jamainternmed.2016.3633
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Appendix 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 fluorochinolon* or gemifloxacin or gentamicin or imipenem or levofloxacin
or linezolid 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(communitary acquired pneumonia) OR ti(communitary acquired pneumonia)

1
2
3 S3 S2 OR S1

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

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8
9 S5 ab(beta-lactam* OR macrolide* OR quinolone* OR tetracycline* OR amikacin OR amoxicillin OR ampicillin OR
10 azithromycin OR cefepim OR cefotaxim* OR ceftazolin OR ceftazidim* OR ceftibuten OR ceftriaxon* OR cefuroxim* OR
11 cethromycin OR ciprofloxacin OR clarithromycin OR clavulanic acid OR clindamycin OR co-amoxiclav OR co-trimoxacol
12 OR doxycyclin* OR ertapenem OR erythromycin OR fluoroquinolon* OR fluorochinolon* OR gemifloxacin OR gentamicin
13 OR imipenem OR levofloxacin OR linezolid OR meropenem OR moxifloxacin OR penicillin* OR piperacillin OR
14 roxithromycin OR sultamicillin OR tazobactam OR telithromycin OR tetracyclin* OR ticarcillin OR tobramycin) OR ti(beta-
15 lactam* OR macrolide* OR quinolone* OR tetracycline* OR amikacin OR amoxicillin OR ampicillin OR azithromycin OR
16 cefepim OR cefotaxim* OR ceftazolin OR ceftazidim* OR ceftibuten OR ceftriaxon* OR cefuroxim* OR cethromycin OR
17 ciprofloxacin OR clarithromycin OR clavulanic acid OR clindamycin OR co-amoxiclav OR co-trimoxacol OR doxycyclin*
18 OR ertapenem OR erythromycin OR fluoroquinolon* OR fluorochinolon* OR gemifloxacin OR gentamicin OR imipenem OR
19 levofloxacin OR linezolid OR meropenem OR moxifloxacin OR penicillin* OR piperacillin OR roxithromycin OR
20 sultamicillin OR tazobactam OR telithromycin OR tetracyclin* OR ticarcillin OR tobramycin)

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

22 S7 S6 OR S5

23 S8 S7 AND S4 AND S3

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

26 S10 S9 AND S8

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38 2-3. Search strategy for CENTRAL

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41 #1 [mh "Community-Acquired Infections"]

42 #2 [mh "Pneumonia, Bacterial"]

43 #3 "community acquired pneumonia":ti,ab

44 #4 (#1 and #2) or #3

45 #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
46 (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
47 duration:ti,ab,kw OR disconti*:ti,ab,kw

48 #6 beta-lactam*:ti,ab,kw OR macrolide*:ti,ab,kw OR quinolone*:ti,ab,kw OR tetracycline*:ti,ab,kw OR
49 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
50 cefotaxim*:ti,ab,kw OR ceftazolin:ti,ab,kw OR ceftazidim*:ti,ab,kw OR ceftibuten:ti,ab,kw OR ceftriaxon*:ti,ab,kw OR
51 cefuroxim*:ti,ab,kw OR cethromycin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR clarithromycin:ti,ab,kw OR "clavulanic
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3 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
4 ertapenem:ti,ab,kw OR erythromycin:ti,ab,kw OR fluoroquinolon*:ti,ab,kw OR fluorquinolon*:ti,ab,kw OR
5 gemifloxacin:ti,ab,kw OR gentamicin:ti,ab,kw OR imipenem:ti,ab,kw OR levofloxacin:ti,ab,kw OR linezolid:ti,ab,kw OR
6 meropenem:ti,ab,kw OR moxifloxacin:ti,ab,kw OR penicillin*:ti,ab,kw OR piperacillin:ti,ab,kw OR roxithromycin:ti,ab,kw
7 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
8 OR tobramycin:ti,ab,kw

9
10
11
12 #7 [mh "Anti-Bacterial Agents"]

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14 #8 #6 OR #7

15 #9 #4 AND #5 AND #8
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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)

Appendix 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

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4 - Léophonte P, Choutet P, Gaillat J, et al. Efficacité comparée de la ceftriaxone dans un traitement de dix jours versus un
5 traitement raccourci de cinq jours des pneumonies aiguës communautaires de l'adulte hospitalisé avec facteur de risque.
6 *Médecine Et Maladies Infect* 2002; 32: 369–81.
7

8
9 Siegel1999

- 10
11 - Siegel RE, Alicea M, Lee A, Blaiklock R. Comparison of 7 Versus 10 Days of Antibiotic Therapy for Hospitalized
12 Patients with Uncomplicated Community-Acquired Pneumonia. *Am J Ther* 1999; 6: 217–22.
13

14
15 Stralin2014

- 16
17 - Strålin K, Rubenson A, Lindroth H, et al. Betalactam treatment until no fever for 48 hours (at least 5 days) versus 10
18 days in community-acquired pneumonia: randomized, non-inferiority, open study. *Pneumonia* 2014; 3: 246–81.
19
20 - ISRCTN14523624
21

22
23 Tellier2004

- 24
25 - Tellier G, Niederman MS, Nusrat R, et al. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of
26 telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate
27 community-acquired pneumonia. *J Antimicrob Chemoth* 2004; 54: 515–23.
28
29 - Tellier G, Chang JR, Asche CV, Lavin B, Stewart J, Sullivan SD. Comparison of hospitalization rates in patients with
30 community-acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. *Curr Med Res*
31 *Opin.* 2004;20(5):739-747.
32
33

34
35 4.2. List of ongoing trials
36

37
38 NCT03609099

- 39
40 - NCT03609099. Adequate Duration of Antibiotic Treatment in Community-acquired Pneumonia With High Risk Class
41 and Adequate Initial Clinical Response (2017-001406-15).
42

43
44 NCT04089787

- 45
46 - NCT04089787. Shortened Antibiotic Treatment of 5 Days in Community-Acquired Pneumonia (CAP5).
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58 * found during web search using the sponsor's protocol code number.
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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 | |

1 **4.3 Characteristics of included studies (continued)**

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

3 AMC = amoxicillin-clavulanic acid; AMX = amoxicillin; CRO = ceftriaxone; CXM = cefuroxime; GMI = gemifloxacin; PSI = pneumonia severity
4 index; SAE = serious adverse events; SD = standard deviation; TEL = telithromycin
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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 (different drugs) |
| EUCTR2014-003137-25 | Optimal duration of antibiotic treatment in patients with complicated parapneumonic pleural effusions or empyema | wrong intervention (different drugs) |
| EUCTR2020-004452-15 | ADMINISTRATION OF CLARITHROMYCIN IN COMMUNITY-ACQUIRED PNEUMONIA | wrong intervention (different 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 (different drugs) |
| JPRN-JapicCTI-163439 | A Phase III study of Solithromycin in patients with community-acquired pneumonia | wrong intervention (different 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 (different 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 (different drugs) |
| Weber1987 | Ampicillin versus cefamandole as initial therapy for community-acquired pneumonia | wrong intervention (different drugs) |
| YangJ2020 | The combined treatment of imipenem cilastatin and azithromycin for elderly patients with community-acquired pneumonia | wrong intervention (different 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 $\leq 37.8^{\circ}\text{C}$); 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

| Study | Risk of bias | | | | | Overall | Sponsored |
|--------------------------|--------------|----|----|----|----|---------|-----------|
| | D1 | D2 | D3 | D4 | D5 | | |
| 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 $OR \neq 1$). 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.

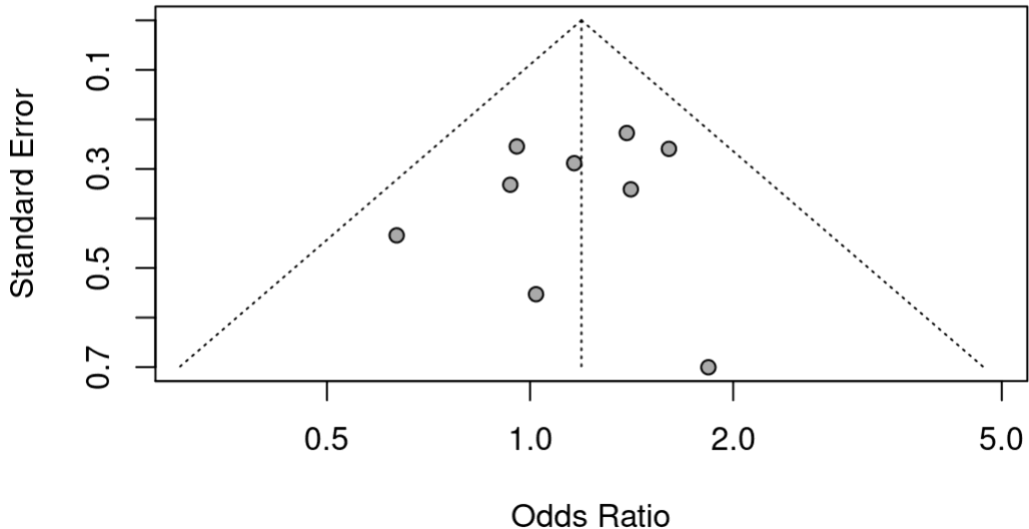
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> vpc(mod1)
```

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      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
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eAppendix 9. Funnel plot



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4 **eAppendix 10. League table**
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|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| 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 |

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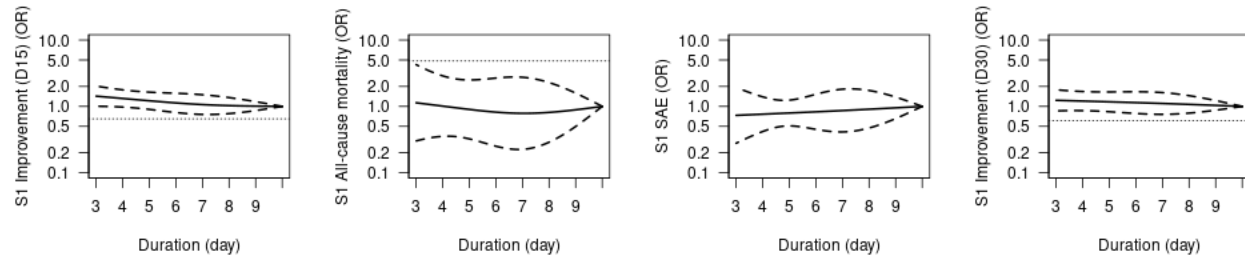
Results of the duration-effect meta-analysis are shown in the bottom-left area. Results of the pairwise meta-analyses of direct comparisons are shown in the upper-right area. Data are odds ratios (95% confidence interval) of the upper-left treatment duration compared with the bottom-right treatment duration.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

eAppendix 11. Sensitivity analyses

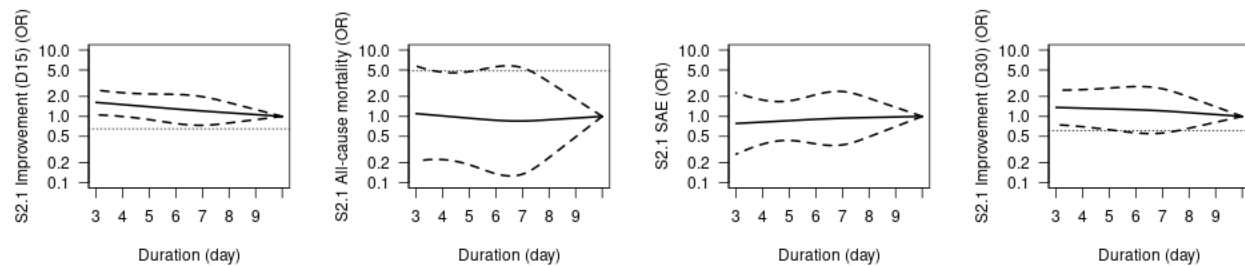
Duration-effect relationship of secondary outcomes could not be computed due to missing data in some cases.

A priori sensitivity analyses

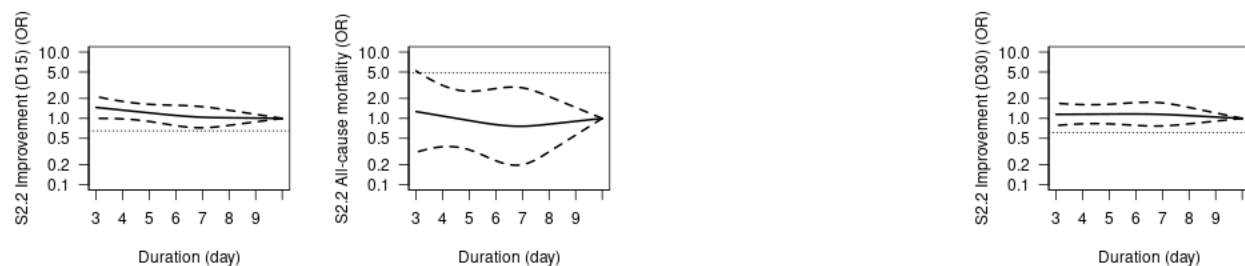
##S1 To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50%, 90%).



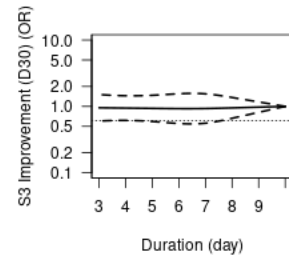
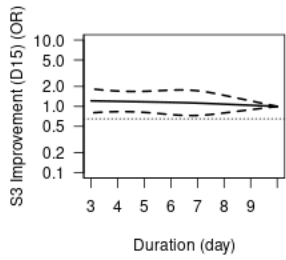
##S2.1 To test the influence of trials included, we conducted sensitivity analyses excluding trials with overall high risk of bias (excluding Siegel1999, Leophonte2002, Stralin2014, Aliberti2017)



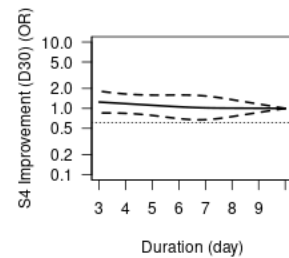
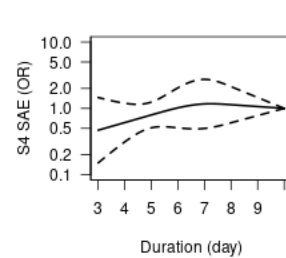
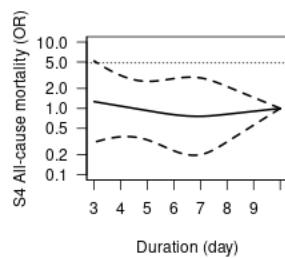
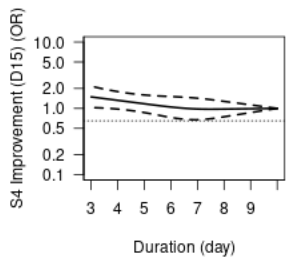
##S2.2 To test the influence of trials included, we conducted sensitivity analyses excluding trials with outpatients (excluding Tellier2004, File2007. SAE not computable)



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

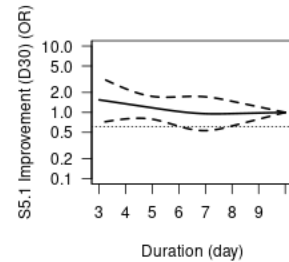
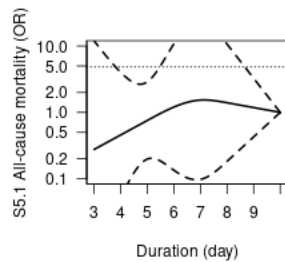
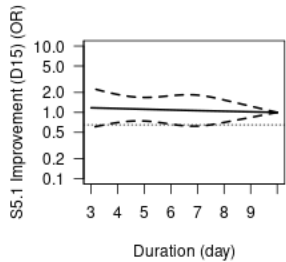


##S4 To test the influence of antibiotics examined, we conducted sensitivity analyses including only antibiotics recommended for empirical treatment of CAP by clinical guidelines. (excluding Siegel1999, Tellier2004. We included trials that used various antibiotics)



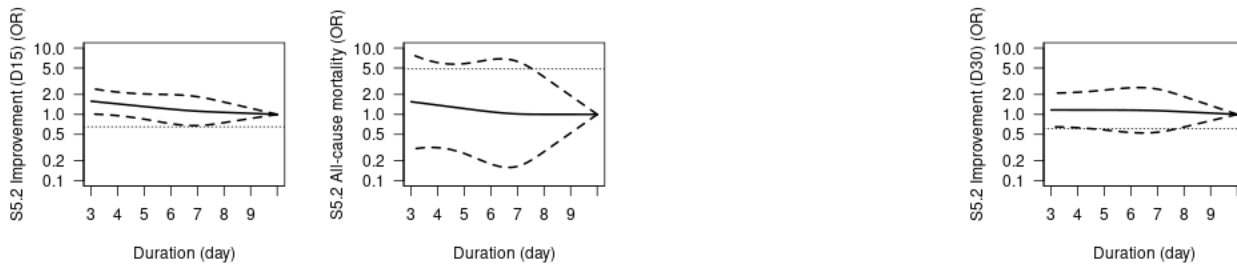
Post-hoc, exploratory sensitivity analyses

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

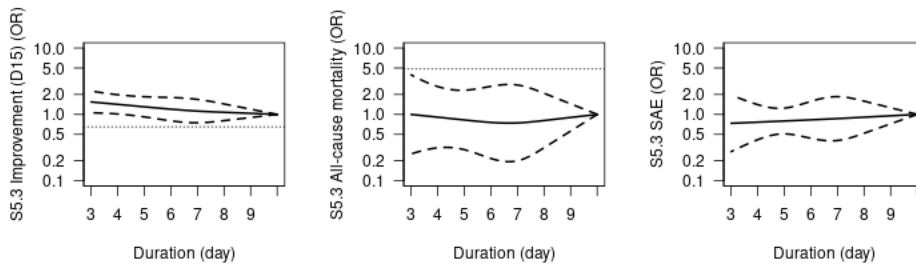


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##S5.2 Randomization after several days or clinical stability achieved (including ElMoussaoui2006, Uranga2016, Aliberti2017, Dinh2021. SAE not computable)



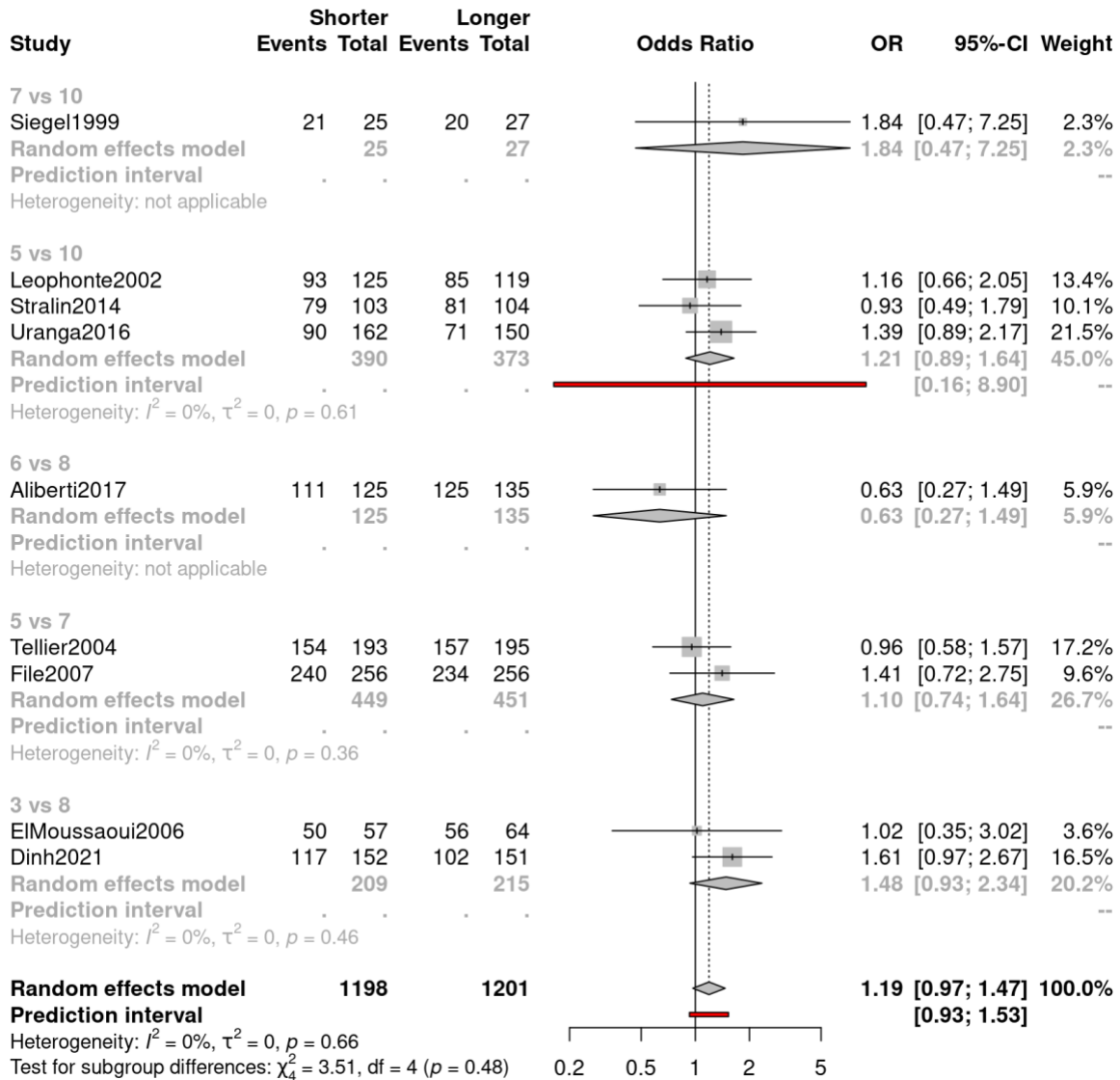
##S5.3 To test the influence of trials with large deviation from the day 15 measurement time (excluding Siegel1999, Stralin2014, Aliberti2017. Clinical improvement on day 30 not applicable.)



##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 |

For peer review only