Antibiotic Treatment Duration for Community-Acquired Pneumonia in Outpatient Children in High-Income Countries—A Systematic Review and Meta-Analysis

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Background. The optimal treatment duration of community-acquired pneumonia (CAP) in children has been controversial in high-income countries. We conducted a meta-analysis to compare short antibiotic treatment (3–5 days) with longer treatment (7–10 days) among children aged ≥6 months.

Methods. On 31 January 2022, we searched PubMed, Scopus, and Web of Science databases for studies published in English from 2003 to 2022. We included randomized controlled trials focusing on antibiotic treatment duration in children with CAP treated as outpatients. We calculated risk differences (RDs) with 95% confidence intervals and used the fixed-effect model (low heterogeneity). Our main outcome was treatment failure, defined as need for retreatment or hospitalization within 1 month. Our secondary outcome was presence of antibiotic-related harms.

Results. A total of 541 studies were screened, and 4 studies with 1541 children were included in the review. Three studies had low risk of bias, and one had some concerns. All 4 studies assessed treatment failures, and the RD was 0.1% (95% confidence interval, −3.0% to 2.0%) with high quality of evidence. Two studies (1194 children) assessed adverse events related to antibiotic treatment, and the RD was 0.0% (−5.0% to 5.0%) with moderate quality of evidence. The diagnostic criteria varied between the included studies.

Conclusions. A short antibiotic treatment duration of 3–5 days was equally effective and safe compared with the longer (current) recommendation of 7–10 days in children aged ≥6 months with CAP. We suggest that short antibiotic courses can be implemented in treatment of pediatric CAP.

Keywords. pneumonia; antibiotic; meta-analysis; children.

Community-acquired pneumonia (CAP) affects 0.3%–1.5% of children yearly in Western countries [1, 2]. The current standard treatment strategy in international guidelines for CAP is 7–10 days of oral amoxicillin, regardless of etiology [2, 3]. In children <5 years of age, viruses alone or in mixed infections with bacteria are the most common cause of CAP. Evidence shows that *Mycoplasma pneumoniae* is involved in more than half of the cases after 10 years of age, but the usefulness of antibiotics remains obscure [4]. At all ages the most important bacterial pathogen is *Streptococcus pneumoniae* [3, 5]. Complications are rare, but when they are present, they usually follow pneumococcal CAP [6].

The optimal treatment duration for CAP in high-income countries has been controversial. A systematic review published in 2014, including randomized controlled trials (RCTs), addressed the efficacy of the shorter treatment duration for CAP. Only 1 of the 8 RCTs was from a high-income country and most of the RCTs did not compare shorter antibiotic treatment with the current treatment recommendation [7]. The most recent systematic review without meta-analysis included 11 trials (of which 8 were from developing countries) and concluded that more studies from high-income countries were needed to determine the safety and effectiveness of shorter antibiotic treatment in children [8].

Shorter antibiotic treatments for pediatric CAP cases have, at least in theory, several potential benefits over current treatment strategies. Shorter courses may prevent development of antibiotic resistance by minimizing exposure of both pathogenic and nonpathogenic microbes of normal flora to antibiotics, which diminishes the selection pressure for emergence of resistant strains [1]. In addition, unnecessary long courses increase the risk of adverse events, such as diarrhea, which is common in young children treated with antibiotics [9].

This meta-analysis comprising RCTs focused on antibiotic treatment duration of CAP in children treated as outpatients in high-income countries. Our primary aim was to determine whether a short antibiotic treatment duration of 3–5 days was as effective and safe as the longer treatment duration of 7–10 days. In addition, we evaluated antibiotic-related adverse events as a secondary objective of the study.

METHODS

Search Strategy

We searched PubMed (MEDLINE), Scopus, and Web of Science databases on 31 January 2022. The full search strategy is shown in Supplement 1. We used language restriction criteria and only included studies published in English. We also used a time restriction filter and restricted the search only to studies published within the last 20 years (2003–2022). The results were then uploaded to Covidence software (Covidence).

Inclusion and Exclusion Criteria

We included RCTs focusing on antibiotic treatment duration in CAP among children at age ≥6 months treated as outpatients, regardless of blinding. We excluded nonrandomized trials and observational studies. We excluded studies conducted in middle- and low-income countries owing to the different definitions of pneumonia and different healthcare facilities and organizations in these countries. Income rankings were based on the list of Organization for Economic Co-operation and Development for the year 2020. Furthermore, we excluded studies focusing on atypical pathogens, such as *M. pneumoniae* and *Chlamydia pneumoniae*. Finally, we excluded studies focusing on pneumonia treatment duration in children aged ≥6 months.

Review Process

Two authors (I. K. and J. J.) individually screened the abstracts, and conflicts were resolved by a third author (M. R.). Full texts were then assessed by 2 authors (I. K. and J.J.), and data were extracted into an Excel spreadsheet. We used the Cochrane risk of bias 2.0 tool to assess risk of bias in the included studies [10]. The risk of bias plot was generated with the robvis package in R software, version 4.0.3 [11]. We assessed reporting quality using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods [12].

Outcome Measures

Our main outcomes were the need for antibiotic retreatment, hospitalization, or treatment failure (including either need for retreatment or hospitalization) within 1 month after the randomization. Our secondary outcomes were antibiotic-related adverse effects.

Statistical Analysis

Review Manager software, version 5.4, was used for the meta-analysis. Data analyses were performed according to the *Cochrane Handbook of Systematic Review Guidelines*. We calculated risk differences (RDs) with 95% confidence intervals (CI) for dichotomous outcomes. Forest plots were presented for all outcomes. We analyzed inconsistency index (I^2) statistics for heterogeneity, and because the heterogeneity was low (<40%) in all analyses, we used the fixed-effect model.

Because one of the studies (Greenberg et al [13]) ended one of its study arms prematurely (3-day treatment duration), we decided to exclude this arm from our analysis. We reported our systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] (Supplement 2).

Protocol Registration

We registered our protocol in Prospero (registration no. 308618).

RESULTS

The initial search retrieved 779 records, and after the removal of duplicates (238 records) we assessed 541 abstracts. We excluded 530 studies based on the abstracts, and 11 full texts were evaluated; finally, 4 studies [13, 15–17] were included in the analysis (Supplementary Figure 1).

All of the included studies were double blinded. Three studies were designed as noninferiority trials [13, 15, 16] and one as a superiority trial [17]. In 3 of 4 studies, the only antibiotic used was amoxicillin, and the fourth study treated patients with amoxicillin, amoxicillin and clavulanate (5.3%), or cefdinir (3.9%) (Supplementary Table 1).

Patients included in the studies were treated as outpatients. In every study, patients with suspected complicated pneumonia were excluded. The definition of pneumonia varied between the studies. Two studies [13, 15] required chest radiographs consistent with CAP to be included, while one [16] made the diagnosis based on symptoms and signs. One study [17] used a different approach: the patients were diagnosed with pneumonia before their inclusion in the study. They were then randomized to further antibiotics or placebo on day 5. The initial diagnoses did not have any specific diagnostic criteria for CAP and the randomization on the fifth day was done for those with early clinical improvement; therefore, it may have included milder pneumonia cases than the other included studies (Supplementary Table 2).

A total of 1573 children were included in the studies, of whom 784 belonged to the short-course and 789 to the long-course arms. The mean ages of children were between 28 and 36.8 months. Only a single study tested patients for respiratory viruses, and 104 children (83.9%) in the short-course group and
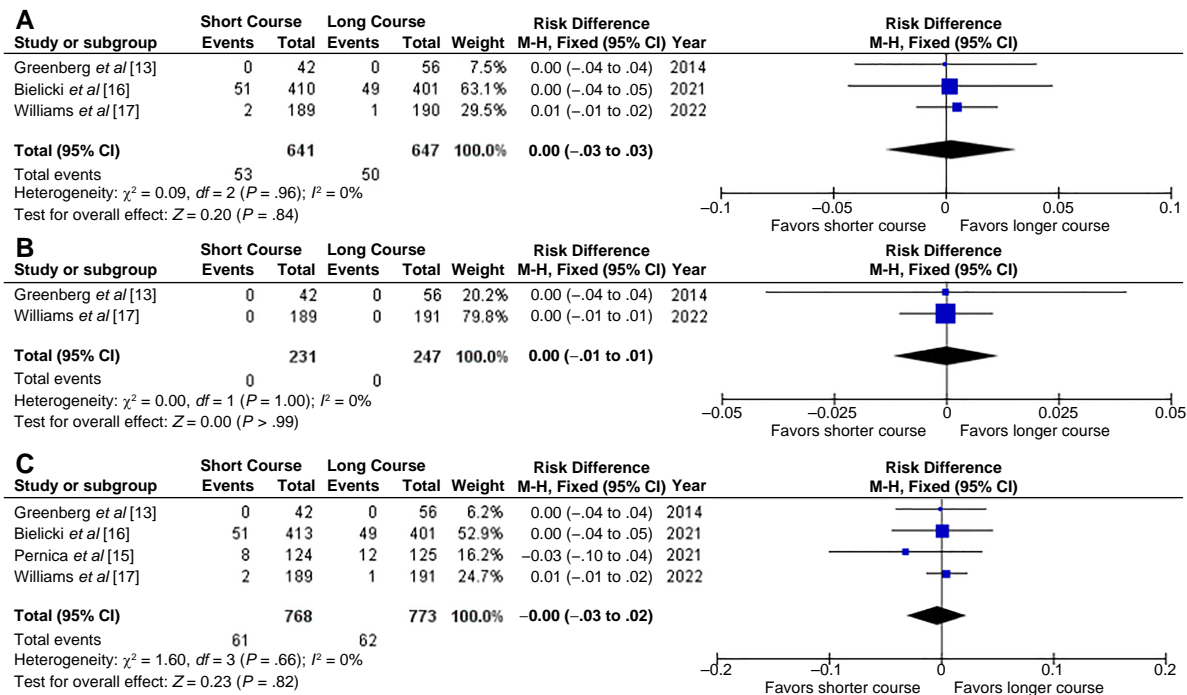
Figure 1. Need for antibiotic retreatment (*A*), need for hospitalization (*B*), and treatment failure (*C*) (includes need for antibiotic retreatment of need for hospitalization) within 1 month after randomization [13, 15–17]. Abbreviations: CI, confidence interval; *df*, degrees of freedom; I^2, inconsistency index; M-H, Mantel–Haenszel test.

101 children (80.1%) in the long-course group tested positive for viruses (Supplementary Table 3).

The risk of bias was considered low in 3 of 4 studies (Supplementary Figure 2). One study [13] had some concerns about deviations from an intended intervention, as it replaced the initial 3-day intervention with a 5-day intervention in the early phase.

Need for Antibiotic Re-treatment

Three studies [13, 16, 17] with 1288 children assessed the need for antibiotic retreatment within 1 month of starting the initial treatment. The need for retreatment was 8.3% in the short-course and 7.7% in the long-course group (RD, 0.00 [95% CI −.03 to .03]; $I^2 = 0\%$) (Figure 1*A*). We ranked the quality of evidence as high and the risk of bias as low (Table 1).

Need for Hospitalization

Two studies [13, 17] with 478 children assessed the need for hospitalization. No hospitalizations occurred in either of the studies (RD, 0.00 [95% CI −.01 to .01]; $I^2 = 0\%$) (Figure 1*B*). We ranked the quality of evidence as high and the risk of bias as low (Table 1).

Treatment Failure

All 4 studies [13, 15–17] assessed the composite outcome of treatment failure (including need for antibiotic retreatment or hospitalization), and 1541 children were included. The treatment failure rates were 7.9% in the short-course and 8.0% in the long-course group (RD, −0.00 [95% CI, −.03 to .02]; $I^2 = 0\%$) (Figure 1*C*). We ranked the quality of the evidence as high and the risk of bias as low (Table 1).

Adverse Events Related to Antibiotic Treatment

Two studies [16, 17] with 1194 children assessed all antibiotic-related adverse events. There were no differences between the groups (RD, −0.00 [CI −.05 to .05]; $I^2 = 0\%$) (Figure 2*A*). Two studies [15, 17] with 661 children assessed only severe antibiotic-related adverse events, there were 1 event in the short-course and 2 in the long-course group (RD, −0.00 [95% CI, −.01 to .01]; $I^2 = 0\%$) (Figure 2*B*). Because one of the studies [13] did not report any information related to adverse events, we downgraded the quality of the evidence to moderate, and the risk of bias was assessed as being of some concern (Table 1).

DISCUSSION

The main result of this meta-analysis on the duration of antibiotic courses in children treated for CAP as outpatients was that a short antibiotic course of 3–5 days was not inferior to a long course of 7–10 days (the recommendation in the currently available guidelines) [1, 2]. The analysis included 4 RCTs from high-income countries with a total of 1451 children

Table 1. Body of Evidence for Outcomes Assessed Using Grading of Recommendations Assessment, Development and Evaluation (GRADE) Methods

Outcome	Studies, No.	Design	Quality Assessment					Summary of Findings				Quality of Evidence
			Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Patients, No. With Outcome/Total		Effect (95% CI)		
								Intervention Group	Control Group	Relative Risk	Absolute RD, %	
Need for antibiotic retreatment	3	RCT	Low	No serious limitations	Not present	Serious limitations: CI includes 0	Not present	53/641	50/647	1.07 (.74–1.55)	0.5 (−2.4 to 3.5)	High
Need for hospitalization	2	RCT	Low	No serious limitations	Not present	Serious limitations: CI includes 0	Not present	0/231	0/247	NA	0.0 (−.8 to .8)	High
Treatment failure	4	RCT	Low	No serious limitations	Not present	Serious limitations: CI includes 0	Not present	61/768	62/773	0.99 (.71–1.39)	−0.1 (−2.8 to 2.6)	High
Any antibiotic-related adverse event	2	RCT	Some concerns (1 study did not report any adverse effects and 1 reported only severe effects)	No serious limitations	Not present	Serious limitations: CI includes 0	Not present	374/602	366/592	1.00 (.92–1.09)	0.3 (−5.2 to 5.8)	Moderate
Severe antibiotic-related adverse event	2	RCT	Some concerns (1 study did not report any adverse effects and 1 did not report severity)	No serious limitations	Not present	Serious limitations: CI includes 0	Not present	1/329	2/332	0.50 (.05–5.52)	−0.3 (−1.3 to .7)	Moderate

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RD, risk difference.
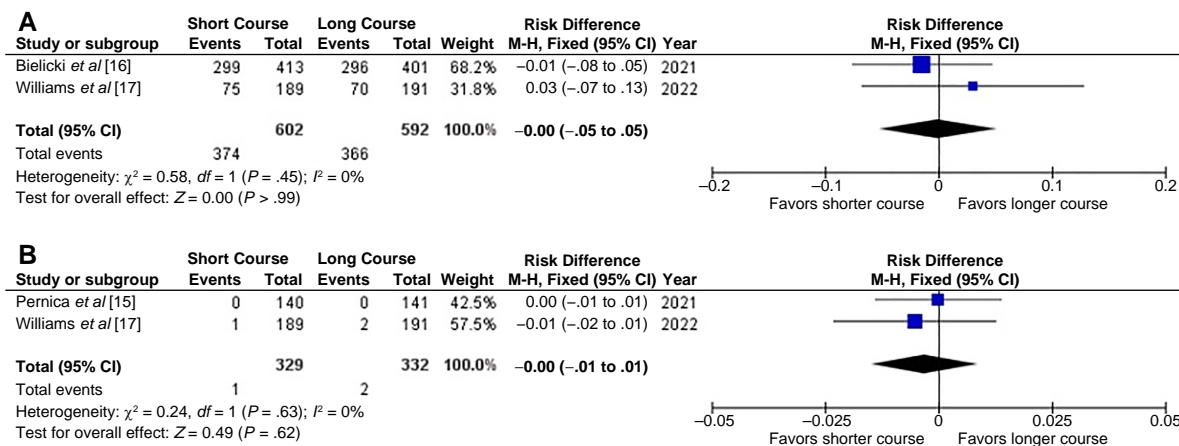
Figure 2. Any antibiotic-related adverse event (*A*) and severe antibiotic-related adverse events (*B*) within 1 month after randomization [13, 15–17]. Abbreviations: CI, confidence interval; *df*, degrees of freedom; I^2, inconsistency index; M-H, Mantel–Haenszel test.

aged ≥6 months [13, 15–17]. Treatment failure was defined as the need for retreatment or hospitalization within 1 month, and the rates were surprisingly similar: 7.9% and 8.0%, respectively. The RD between the arms was 0.1%, and the 95% CI was very narrow, confirming that the result for the primary outcome was reliable. In addition, there was no substantial heterogeneity between the 4 studies for reporting retreatments and hospitalizations within 1 month after starting of primary antibiotics [13, 15–17].

Adverse events, which was the secondary outcome of the analyses, were reported in 2 studies [16, 17] and they did not differ between the short-course and long-course treatment arms. Adverse events rates were 62.1% and 61.8%, respectively. These adverse events, such as diarrhea and rash, were mild and were often seen in children during antibiotic treatment. Two studies [15, 17] reported severe adverse events, and such events were seen in 0.3% of the cases, which means that the short-course antibiotic therapy was safe. A previous meta-analysis stated that each additional day of antibiotic treatment increases the rates of antibiotic-related adverse effects [9]. Two of the included studies [16, 17] also analyzed the effects of treatment duration on antibiotic resistance and found the shorter course to be more beneficial, but we did not include this as an outcome in the meta-analysis.

High-dose amoxicillin (80–100 mg/kg/d) was the prescribed antibiotic in 3 of the 4 studies [13, 15, 16], and in the fourth study 5% received amoxicillin-clavulanic acid [17]. A study from England compared short and long amoxicillin courses with low (35–50 mg/kg/d) and high amoxicillin doses separately. It found that short courses were not inferior to long courses with either dose, and low doses were not inferior to high doses [16].

High doses of amoxicillin have been needed in areas where penicillin or multiple antibiotic resistance is common in pneumococcal strains, but a double amoxicillin dose equates to double antibiotic exposure. Therefore, countries with low resistance rates have used low-dose amoxicillin as the first choice for children's CAP [18, 19], and the efficacy of low-dose in shorter duration should be confirmed in further studies.

The original purpose of the study was to compare clinical cures between short-course and long-course arms, but the clinical parameters expressing cure were heterogenous between the included studies and could not be pooled to produce any summary estimates. Instead, the retreatments and hospitalizations within 1 month were constantly reported in all studies, and these failures were combined and used as the primary outcome in the analyses. Furthermore, owing to the low failure rates in the included studies, we decided to use RDs in the analyses instead of risk ratios. Three of the included studies were noninferiority-designed RCTs, but the pooling of these with a cenventional parallel superiority-designed RCT is feasible, and we aimed to seek differences between groups in our conventional meta-analysis instead of using a prespecified noninferiority margin in the analyses [20, 21].

Until now, most data on the length of antibiotic courses have come from low-income or middle-income countries. The main differences in relation to the high-income countries concern the definition of CAP by the World Health Organization criteria for developing countries [22], which highlight increased respiratory rate and rates of severe treatment failure >5% [8, 23], which are not acceptable in Western countries.

The main strength of our review is the high quality and low risk of bias of the included studies, which increases the validity of our results. Furthermore, we did not have any major protocol deviations. Moreover, the numbers of cases—1451 for the primary outcome and 1194 for the secondary outcome of antibiotic-related adverse events—allow reliable meta-analysis. The exclusion of studies focusing on treatment of atypical

pneumonias increased the consistency of data, since the necessity to treat them remains open [4].

A minor limitation to our results is the fact that more than half of the patients were from a single study [16], but this should not cause bias in the estimates, given that the results were similar in all studies. The main limitation of our study is the differing definition of CAP in the included studies, because 2 of them required chest radiographs and 2 did not. The currently available guidelines recommend that the diagnosis of CAP treated at home is clinical, and imaging is needed only in complicated cases [1, 2]. Viral determinations were performed in only one study, but virus identification does not necessarily influence decision making in CAP, since mixed viral-bacterial infections are common and it is recommended that all pediatric CAP cases in children ≥6 months of age are treated with antibiotics. Therefore, future studies should focus more on optimal differential recognition of bacterial and viral pneumonia, and a double-blinded placebo design should be used to determine whether antibiotics are needed at all in mild pneumonia. As seen in a previous study from England, antibiotics did not improve outcomes in nonsevere lower respiratory tract infections [24].

In conclusion, our meta-analysis, including 4 high-level RCTs, showed that short treatment was equally safe and effective as longer treatment of 7–10 days for CAP in outpatient children aged ≥6 months in high-income countries. We suggest that this shorter treatment for 3–5 days can now be implemented into clinical practice.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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