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REVIEW

Shorter versus longer duration of Amoxicillin-based treatment for pediatric patients with community-acquired pneumonia: a systematic review and meta-analysis

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Abstract

Streptococcus pneumoniae is the most common typical bacterial cause of pneumonia among children. The World Health Organization (WHO) recommends a 5-day Amoxicillin-based empiric treatment. However, longer treatments are frequently used. This study aimed to compare shorter and longer Amoxicillin regimens for children with uncomplicated community-acquired pneumonia (CAP). A search of PubMed, EMBASE, and Cochrane Central was conducted to identify randomized controlled trials (RCTs) comparing 5-day and 10-day courses of Amoxicillin for the treatment of CAP in children older than 6 months in an outpatient setting. Studies involving overlapping populations, lower-than-standard antibiotic doses, and hospitalized patients were excluded. The outcome of interest was clinical cure. Statistical analysis was performed using RevMan 5.4. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. Two independent authors conducted the critical appraisal of the included studies according to the RoB-2 tool for assessing the risk of bias in randomized trials, and disagreements were resolved by consensus. We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) tool to evaluate the certainty of evidence of our results. Three RCTs and 789 children aged from 6 months to 10 years were included, of whom 385 (48.8%) underwent a 5-day regimen. Amoxicillin-based therapy was used in 774 (98%) patients. No differences were found between 5-day and 10-day therapy regarding clinical cure (RR 1.01; 95% *CI* 0.98–1.05; $p = 0.49$; $I^2 = 0\%$). Subgroup analysis of children aged 6–71 months showed no difference in the rates of the same outcome (RR 1.01; 95% *CI* 0.98–1.05; $p = 0.38$; $I^2 = 0\%$). The GRADE tool suggested moderate certainty of evidence.

Conclusion: These findings suggest that a short course of Amoxicillin (5 days) is just as effective as a longer course (10 days) for uncomplicated CAP in children under 10 years old. Nevertheless, generalizations should be made with caution considering the socioeconomic settings of the studies included.
PROSPERO Identifier: CRD42022328519.

What is Known:
- *In the outpatient setting, a few international guidelines recommend a 10-day Amoxicillin course as first-line treatment for community-acquired pneumonia (CAP).*
- *Recent trials have shown that shorter courses of Amoxicillin may be as effective as 10-day regimens in uncomplicated pneumonia.*

What is New:
- *When comparing 5-day to 10-day Amoxicillin regimens, evidence suggests no significant difference in clinical cure rates for uncomplicated CAP in outpatient settings.*
- *Generalizations should be made with caution considering the socioeconomic context of the population within the included studies.*

Keywords Community-acquired pneumonia · Children · Duration of therapy · Antibiotics · Short-course treatment

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Abbreviations

CAP	Community-acquired pneumonia
CI	Confidence interval
DOOR	Desirability of Outcome Ranking

GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IDSA	Infectious Diseases Society of America
PIDS	Pediatric Infectious Diseases Society
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RR	Relative risk
RSV	Respiratory Syncytial Virus
WHO	World Health Organization

Introduction

The World Health Organization (WHO) reports that pneumonia is responsible for 14% of all deaths in children under 5 years of age, and *Streptococcus pneumoniae* is the most common pathogen responsible for the disease [1]. The 2011 guidelines from the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) recommend a 10-day Amoxicillin course as first-line treatment for community-acquired pneumonia (CAP) in the outpatient setting, while recognizing that shorter courses for uncomplicated pneumonia might also be effective [2, 3].

Traditionally, pneumonia has been treated with antibiotics for at least 7 days since the 1940s [4]. However, in the last 2 decades, many trials have demonstrated that shorter therapies are just as effective for different infections that were customarily treated for longer periods, including CAP [4, 5]. Evidence reveals that prolonged antibiotic exposure can also be harmful. Children who have recently received antibiotics are significantly more likely to carry drug-resistant strains of *S. pneumoniae* than those who have not, suggesting that the use of antimicrobials is strongly associated with the pattern of antibiotic resistance [6–8]. Through sustained selective pressure, excessive lengths of therapy contribute to the perpetuation of these resistant bacteria by preventing a spontaneous resolution of the carrier state [7, 8]. Within this framework, and given the increasing antimicrobial resistance worldwide, there is a crucial need to limit antibiotic use to the shortest effective regimen possible [6–8].

The WHO currently recommends a 5-day therapy with a high dose of Amoxicillin for uncomplicated CAP in children [9]. Until recently, there was a paucity of randomized data assessing the effectiveness of a short duration compared to a longer 10-day course in children from high-income countries [10–12]. The recent Short-Course Outpatient Therapy of Community-Acquired Pneumonia (SCOUT-CAP) Clinical Trial significantly expanded the evidence-based knowledge in this field, with 380 patients randomized to receive either a 5-day or a 10-day regimen of antibiotics, 96% of which consisted of Amoxicillin [13].

Considering the results from the SCOUT-CAP trial, we performed a systematic review of the literature and meta-analysis of studies that conducted a direct comparison between 5-day and 10-day course durations of Amoxicillin therapy for uncomplicated CAP in children from 6 months to 10 years of age in an outpatient setting.

Materials and methods

Eligibility criteria

Studies meeting the following criteria were included: (1) randomized controlled trials (RCT), (2) comparison of 5-day versus 10-day courses of oral Amoxicillin therapy, (3) pediatric patients from 6 months to 18 years of age with uncomplicated CAP, (4) outpatient setting, (5) reporting the clinical outcome of interest, clinical cure. We excluded studies with the following: (1) overlapping populations, understood as derived from overlapping institutions and recruitment periods, (2) without a control group, (3) lower-than-standard Amoxicillin doses, standard considered to be 80–100 mg/kg/day, (4) hospitalized patients. There were no restrictions with regard to superiority or noninferiority study designs.

Search strategy and data extraction

The search was conducted via PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for studies that met the eligibility criteria published from inception to April 2022. The search strategy was based on keywords such as the following: "community-acquired pneumonia," "child," "pediatric," "antibiotic," and "short-course," and was conducted by three different authors (IM, IC, and SC). The complete search strategy is available in Online Resource 1. The last search of all databases was conducted in April of 2022. In addition to searching databases, references from the included studies were manually searched. There were no restrictions regarding the language of the articles. Three authors (IM, IC, and SC) independently extracted baseline characteristics and outcome data following predefined search criteria. Disagreements were resolved by consensus among the authors. The prospective meta-analysis protocol was registered on PROSPERO on May 10, 2022. PROSPERO ID: CRD42022328519.

Endpoints and subgroup analyses

The outcome of interest was clinical cure. Considering that definitions could vary slightly between studies, it was established that eligible studies should include both of the following criteria for clinical cure: (1) lack of need for additional

non-Amoxicillin-based therapy and (2) absent hospitalization throughout 1 month of follow-up in the description of this outcome. A predetermined analysis of clinical cure was done using a subgroup of children aged 6 to 71 months.

Quality assessment

The risk-of-bias 2 tool (RoB-2) was used to assess the risk of bias in the included randomized trials [14]. The risk of bias assessment was conducted by two independent authors (IM and IC); disagreements were resolved by consensus after discussing the reasons for the divergence.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used to assess the certainty of the evidence in this review as high, moderate, low, or very low [15]. The grading of the strength of recommendations was carried out by two independent authors (IM and IC) using the GRADEpro Guideline Development Tool [16]; disagreements were settled by a third author (SC).

Statistical analyses

This systematic review and meta-analysis were performed according to the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [17]. Risk ratios (RR) with 95% confidence intervals (*CI*) were used to compare treatment effects for binary endpoints. Heterogeneity was examined with Cochran Q test, I^2 statistics, and visual inspection of forest plots; if *p*-value was inferior to 0.10, I^2 statistics exceeded 25%, or visual inspection of the forest plot was indicative of heterogeneity in effect size, then heterogeneity would have been considered significant. Nevertheless, the endpoint from this review evidenced visual homogeneity, I^2 statistics < 25%, and *p*-value > 0.10, suggesting no heterogeneity, thus, the use of a fixed-effect model. The statistical analysis was conducted using Review Manager 5.4 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Study selection and characteristics

As detailed in Fig. 1, our complete search yielded 1316 results, of which 176 were duplicated records. A total of 1130 articles were considered unrelated based on title or abstract review and were excluded. The remaining 10 articles were fully screened and, after the assessment for the inclusion and exclusion criteria, 3 RCTs were included in this systematic review and meta-analysis. The reasons for

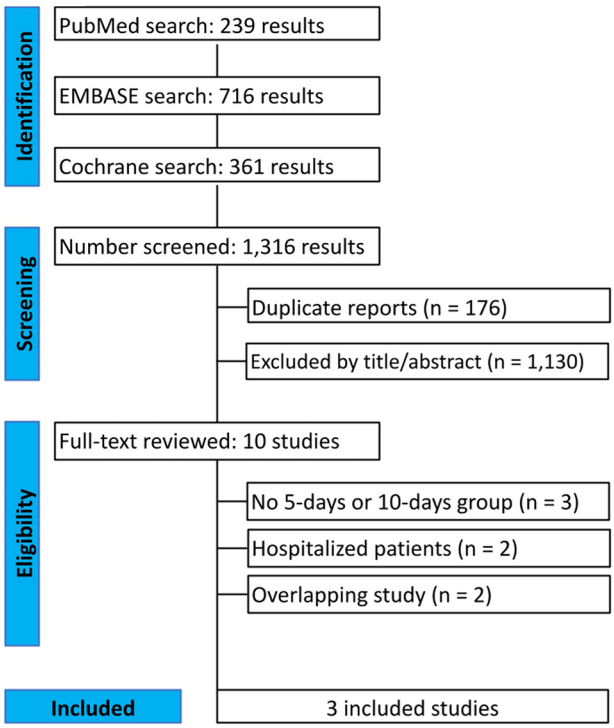

Fig. 1 PRISMA flow diagram of study screening and selection

study exclusion were different intervention or control groups ($n=3$), inclusion of hospitalized patients ($n=2$), and overlapping studies ($n=2$). References for the fully screened but excluded articles are available in Online Resource 2. The main characteristics of individual included studies are presented in Table 1.

A total of 789 children aged from 6 months to 10 years were included, of whom 428 (54.2%) were males. Of those, 385 (48.8%) patients were randomized to receive a 5-day course therapy, while the remaining patients underwent a 10-day course therapy (51.2%). Amoxicillin-based therapy was used in 774 (98%) patients. Standard doses for Amoxicillin ranged from 80 to 100 mg/kg/day divided twice or three times daily. For those prescribed Cefdinir, the standard dose ranged from 12 to 16 mg/kg/day. Two trials conducted a noninferiority model, while the most recent one consists of a superiority study.

The definition of clinical cure used in each trial is also shown in Table 1. As previously mentioned, definitions varied slightly. Therefore, it is important to elucidate the exact data extracted from each study that was used in this meta-analysis. In Greenberg et al. the extracted data corresponds to the absolute numbers expressed for the primary outcome [18]. In the SAFER trial, the selected outcome was the post hoc analysis of "clinical cure not requiring additional intervention" discounting the missing data, and the subgroup analysis was possible given the additional information

Table 1 Baseline characteristics of included studies [13, 18, 19]

	Country	Design	Follow-up, days	Definition of clinical cure	Primary outcome	Inclusion criteria	Exclusion criteria	5-day group			
								No. of patients	Male, *n* (%)	Age[a], months	Amoxi, *n* (%)
Greenberg 2015 [15]	Israel	Noninferiority RCT	35	Absence of need to replace the study drug + absence of hospitalization due to deterioration/no response to the study treatment + absence of clinical relapse	Absence of treatment failure within 30 days	(1) Age 6–59 months; (2) alveolar pneumonia in chest radiography; (3) temperature ≥ 38.5 °C; (4) WBC ≥ 15,000/mm3; (5) community-acquired disease; (6) patient judged to be manageable as outpatient and (7) an informed consent was obtained from parents or legal guardian	(1) Antimicrobial drug received within ≤ 14 days; (2) need of parenteral treatment; (3) oxygen saturation < 94%; (4) known impaired immunity; (5) ≥ 2 pneumonia episodes in last year; (6) chronic illness potentially influencing current illness; (7) presence of an additional infection necessitating a longer or different antibiotic treatment; (8) unavailability for follow-up; (9) known β-lactam hypersensitivity; (10) known allergy to soy milk	56	32 (57.1)	27.5 ± 14.4 [b]	56 (100)
Pernica 2021 SAFER [17]	Canada	Noninferiority RCT	30	- Clinical cure: lack of a requirement for additional antibacterials or admission to hospital because of persistent or progressive lower respiratory illness + initial improvement during the first 4 days after enrollment + significant improvement in dyspnea and increased work of breathing and no recorded tachypnea + no more than 1 fever spike as a result of possible bacterial respiratory illness from day 4 up - Clinical cure not requiring additional intervention (post hoc): lack of a requirement for additional antibacterials or admission to hospital because of persistent/progressive lower respiratory illness + initial improvement during the first 4 days after enrollment	Overall clinical cure at 14 to 21 days after enrollment	(1) Children aged 6 months to 10 years; (2) with CAP; (3) well enough to be treated as outpatients	(1) Children with conditions predisposing to severe disease and/or pneumonia with atypical microbiology; (2) those who received more than 24 h of β-lactam antibiotic therapy at presentation, at least a 5-day course of β-lactam therapy less than 72 h before presentation, or intravenous cephalosporin or azithromycin in the ED; (3) children receiving either warfarin or tetracyclines; (4) children with suspected infectious mononucleosis; (5) children with a prolonged admission to the hospital in the prior 2 months, CAP diagnosed in the previous month, or lung abscess in the previous 6 months; (6) children with penicillin allergy	140	70 (50.7)	30.6 (18.6–53.9)	140 (100)
Williams 2022 SCOUT-CAP [11]	USA	Superiority RCT	25	Absence of receipt of non-study antibiotics for persistent/worsening pneumonia + absence of a medically attended visit (ED, outpatient clinic, or hospitalization) + absence of a surgical procedure	Response adjusted for duration of antibiotic risk (RADAR) at 6–10 days	(1) Healthy children aged 6–71 months; (2) diagnosed with uncomplicated CAP; (3) in an outpatient clinic, urgent care, or ED; (4) prescribed either Amoxicillin, Amoxicillin and Clavulanate, or Cefdinir	(1) Subjective fever or documented temperature 38.3 °C or higher in the preceding 24 h; (2) tachypnea; (3) and severe cough	189	94 (50)	34.6 ± 16.6	183 (96.8)

Table 1 (continued)

10-day group				Total			
No. of patients	**Male, *n* (%)**	**Age[a], months**	**Amoxi, *n* (%)**	**No. of patients**	**Male, *n* (%)**	**Age[a], months**	**Amoxi, *n* (%)**
72	42 (58.3)	27.7 ± 15.0 [b]	72 (100)	128	74 (57.8)	27.6 ± 14.6 [b]	128 (100)
141	90 (63.8)	31.3 (19.4–61.3)	141 (100)	281	160 (57.3)	NA	281 (100)
191	100 (52)	36.8 ± 17.8	182 (95.2)	380	194 (51)	35.7 ± 17.2	365 (96)

Amoxi amoxicillin, *ED* emergency department, *NA* not available, *No* number, *RCT* randomized controlled trial, *WBC* white blood count

[a]Mean ± standard deviation or median (interquartile range)

[b]Data obtained from combining two subgroups using the formulae recommended in the Cochrane Handbook for Systematic Reviews of Interventions [29]

available in the Supplementary Online Content [19]. At last, in the SCOUT-CAP trial, an analysis of the "Desirability of Outcome Ranking (DOOR)" in outcome assessment visit (OAV2), corresponding to study days 19 to 25, was performed pooling DOOR (1) to (4) as equivalent to clinical cure in this review's criteria, information made available in the Supplementary Online Content [13].

Pooled analysis of outcomes and subgroup analyses

In a follow-up that ranged from 25 to 35 days, no significant difference was found between 5-day and 10-day regimens in terms of clinical cure, as shown in Fig. 2a (RR 1.01; 95% *CI* 0.98–1.05; $p = 0.49$; $I^2 = 0\%$). Moreover, the analysis restricted to children aged 6–71 months yielded similar results (RR 1.01; 95% *CI* 0.98–1.05; $p = 0.38$; $I^2 = 0\%$ Fig. 2b).

Quality assessment

Figure 3 summarizes the individual evaluation of each RCT included in the meta-analysis. One study was classified with a low risk of bias, while two others presented some concerns. There was no definitive evidence of publication bias by funnel plots, although these analyses were limited by the small number of studies (Fig. 4a and b).

Considering the potential bias inherent to the post hoc analysis conducted in the SAFER trial, a sensitivity analysis was performed using data from the pre-defined primary outcome. In this analysis, there was also no significant difference between 5-day and 10-day regimens for clinical cure, as shown in Fig. 5a (RR 1.01; 95% *CI* 0.96–1.05; $p = 0.77$; $I^2 = 0\%$). In addition, results were similar for the sensitivity analysis when restricted to children aged 6 to 71 months (RR 1.01; 95% *CI* 0.97–1.04; $p = 0.72$; $I^2 = 26\%$ Fig. 5b).

Based on the GRADE tool, the overall certainty of the evidence for the outcomes assessed was moderate due to serious indirectness. As evidenced in Table 1, patients assessed in the included trials were children younger than 10 years of age, previously healthy, immunocompetent, and most likely acquired infections in the community. Consequently, the generalizability of the results to older children or those with baseline conditions is limited as the predominant etiology of CAP varies with age and comorbidities. Figure 6 summarizes the GRADE assessment and the findings from this review.

Discussion

Through a systematic review and meta-analysis of three randomized controlled trials, which included 789 patients, a 5-day course was compared to a 10-day course of Amoxicillin

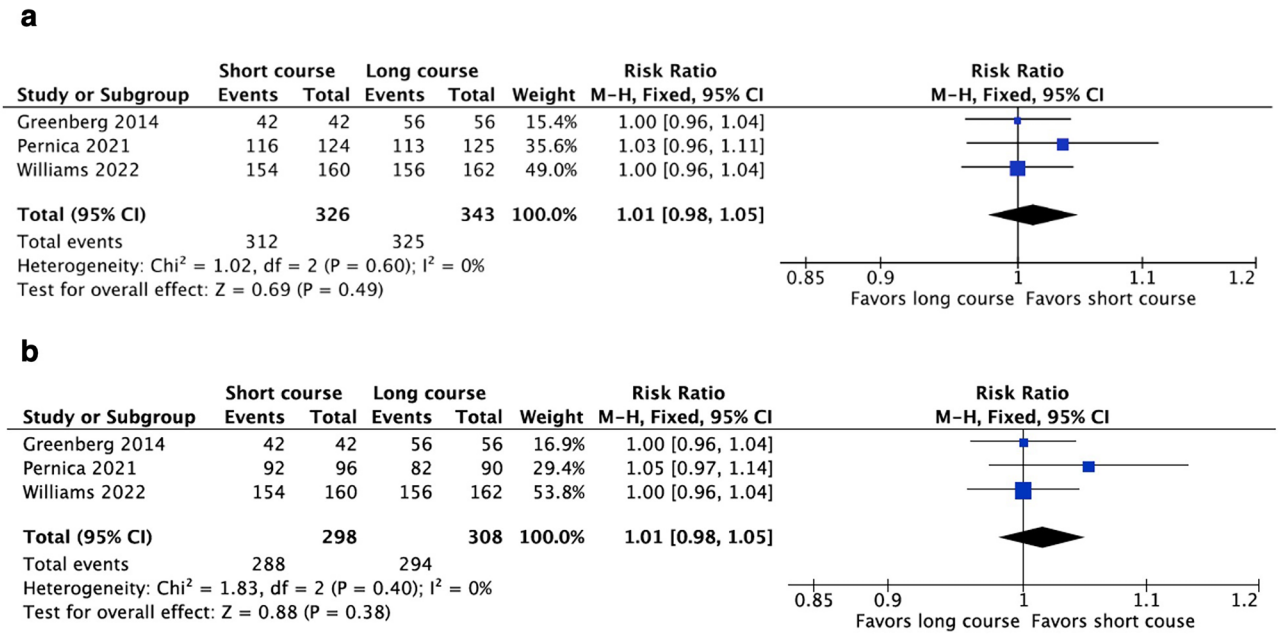

Fig. 2 **a** Clinical cure was not significantly different between the short and long course groups. **b** Clinical cure analysis restricted to children aged 6–71 months was not significantly different between the short and long course groups

for children with uncomplicated CAP who were in an outpatient setting. The main findings were as follows: (1) there was no significant difference between groups with regard to the efficacy outcome of clinical cure and (2) the rates of clinical cure restricted to children aged 6–71 months also revealed that either 5 days or 10 days were equally effective. The GRADE assessment revealed a moderate quality of the evidence.

This study addressed a crucial component of antibiotic therapy for CAP, namely the optimal duration. Evidence supporting the efficacy of short-course therapies for acute lower respiratory tract infections originates primarily from studies conducted in low-income countries and resource-poor environments. However, the recommendation of 10-day courses still prevails in high-income countries, although short courses lead to several benefits. The current meta-analysis is unique in combining data from available studies with the same duration of short and long courses, and in prioritizing the use of the same antibiotic in similar doses. In addition, to the best of our knowledge, this is the first study to report results from high-income countries.

Notably, the recently published CAP-IT trial endorses the thesis that a shorter regimen of Amoxicillin is non-inferior to longer ones regarding the need for additional non-Amoxicillin antibiotics within a month after the initial treatment [20]. This non-inferiority study conducted in the UK evaluated not only the duration but also the optimal dose of Amoxicillin for the treatment of childhood CAP in a similar population to the one included in this review [20]. Nevertheless, this trial was not included in the meta-analysis for clinical cure as it met our exclusion criteria due to the mixed data analysis for different doses of Amoxicillin, including 70–90 mg/kg/day and

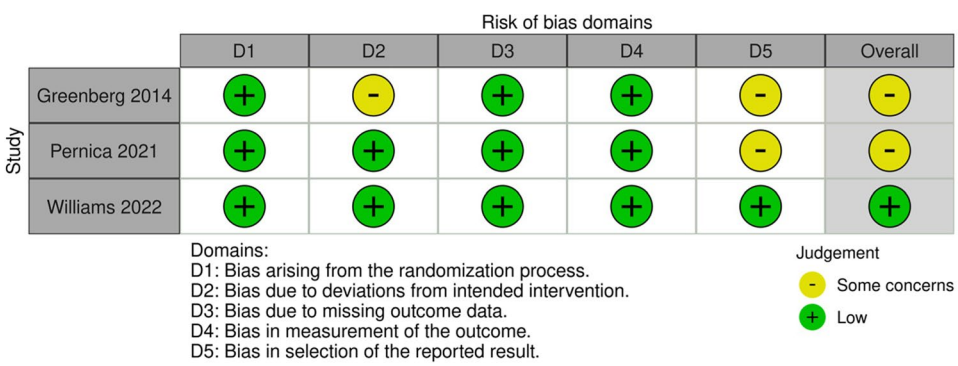

Fig. 3 Critical appraisal according to the RoB-2 tool for assessing risk of bias in randomized trials

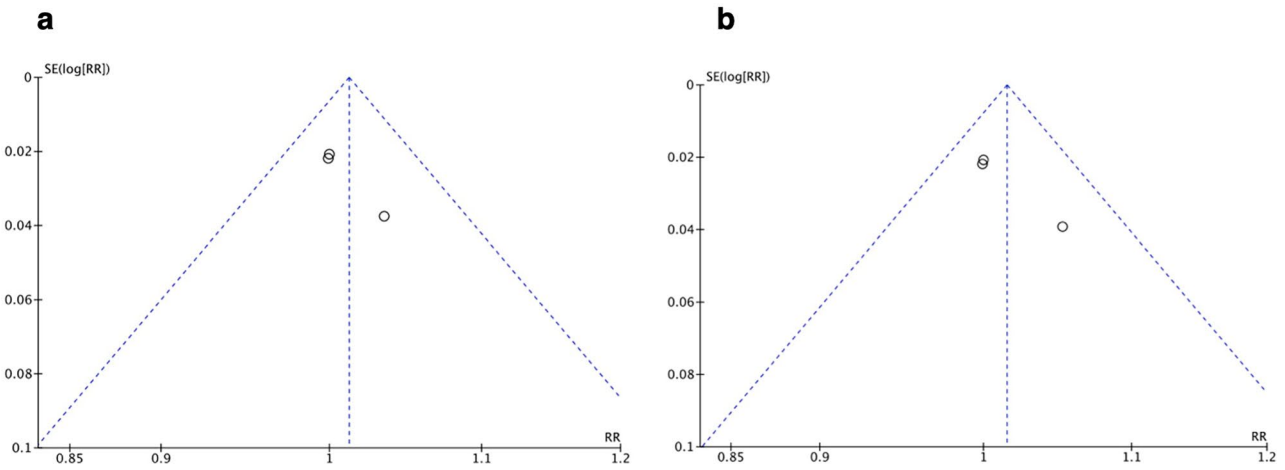

Fig. 4 **a** Funnel plot for clinical cure. **b** Funnel plot for clinical cure restricted to children aged 6–71 months

35–50 mg/kg/day. The results of the CAP-IT trial support our study findings since the authors found that the short antibiotic course of 3 days was non-inferior to the antibiotic course of 7 days regarding the need for antibiotic re-treatment within 28 days (12.5% versus 12.5%, respectively; difference, 0.1% [1-sided 95% *CI*, −∞ to 3.9%]) [20].

To effectively treat CAP, it is important to determine the likely pathogen, which is related to the child's age; thus, we conducted a subgroup analysis of pre-school-aged children (6 months to 5 years). Among this age group, viruses are the predominant etiology, with Respiratory Syncytial Virus (RSV) being the most common pathogen [10]. Other viruses worth mentioning due to their incidence in this group are influenza and parainfluenza viruses, adenovirus, rhinovirus, and human metapneumovirus, most of which cannot be prevented by routine immunization [10, 21]. Part of the clinical burden of primary viral infections is a result of the added risk of secondary bacterial pneumonia, a common condition in young children [10, 21]. Regarding bacteria, the most common pathogen is *S. pneumoniae* [21, 22]. With increasing age, viral etiology becomes less common, and atypical organisms (*Mycoplasma pneumoniae* and *Chlamydia*

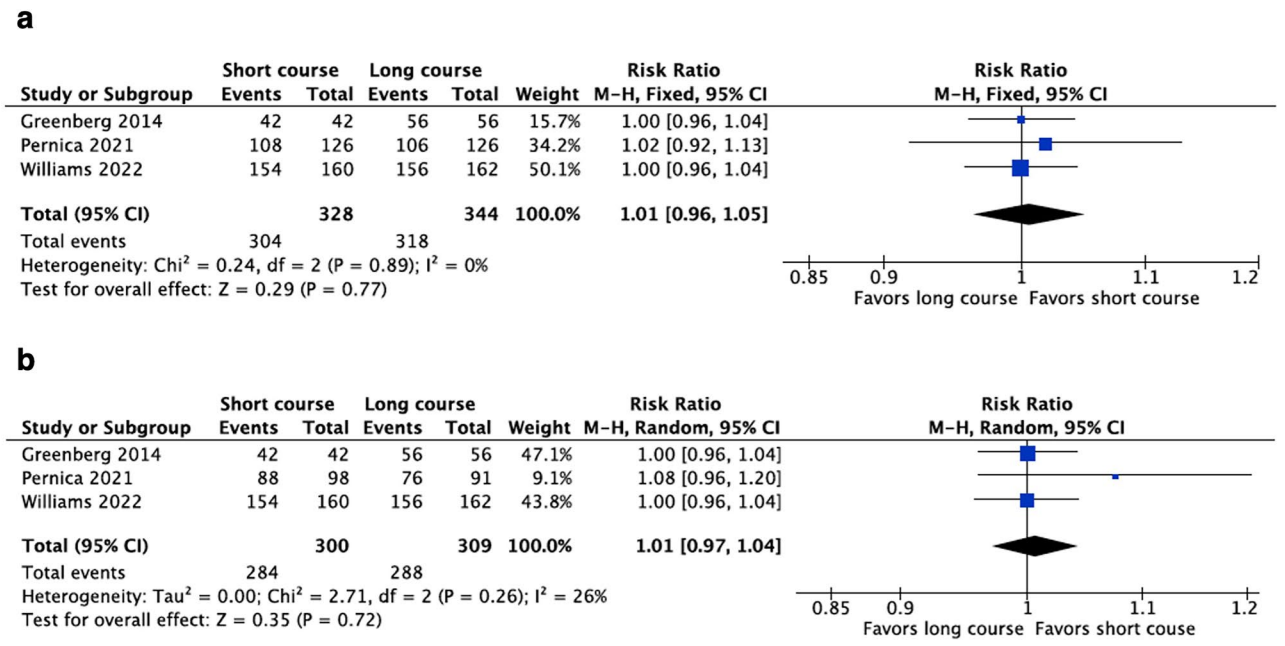

Fig. 5 **a** Sensitivity analysis, clinical cure was not significantly different between the short and long course groups. **b** Sensitivity analysis, clinical cure analysis restricted to children aged 6–71 months was not significantly different between the short and long course groups

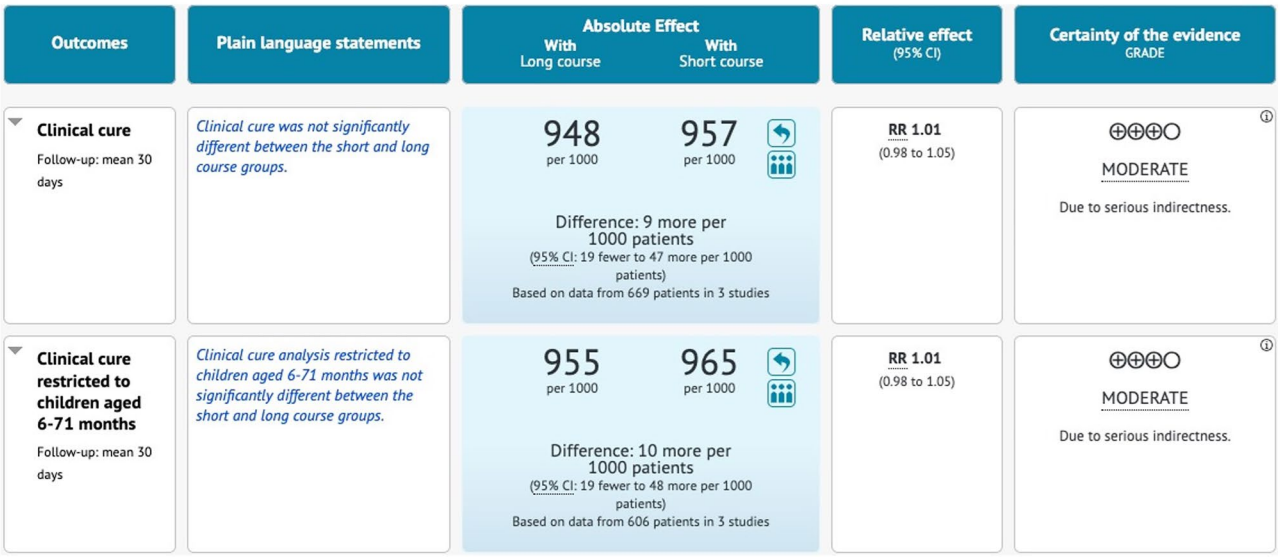

Fig. 6 GRADE assessment and summary of findings for the endpoint: short course compared to long course for pediatric patients with CAP

pneumoniae) more prevalent [21]. However, *S. pneumoniae* tends to be more invasive and causes increasingly severe disease. For these reasons, Amoxicillin is still considered the first-line agent to treat uncomplicated CAP across all age groups [2].

It is challenging to distinguish between bacterial and viral pneumonia in clinical practice. Current diagnostic criteria for non-severe pneumonia may misdiagnose a significant proportion of children with viral pathogens as bacterial infections, who may be unnecessarily prescribed an antibacterial agent [9, 23, 24]. Even though chest radiographs cannot properly determine the etiology, they are often performed in developing countries for assessment of infiltrates where imaging is easily accessible [10–12]. However, it has been demonstrated that reducing diagnostic testing, like performing chest radiographs, does not reduce the prescription of antibiotics in the outpatient setting, supporting the recommendation that imaging is not routinely required for the diagnosis of CAP [2, 25, 26].

Short-course antibiotic therapy can offer a variety of benefits to both the individual and the healthcare system. Despite the absence of cost analysis in this review, these findings could potentially translate into reduced overall costs. Additionally, the extensive use of antibiotics increases the risk of antimicrobial resistance, which is an ongoing concern for *S. pneumoniae* infections [7, 8]. Shorter durations could contribute to diminishing the risk of antimicrobial resistance [27]. Other potential advantages of shorter therapies are better patient adherence to treatment and fewer adverse effects related to antibacterial therapy [27, 28].

A few limitations apply to this meta-analysis. First, the studies included in this review enrolled children from 6 months to 10 years of age. Consequently, the generalizability of our results to older children is limited as the spectrum of causative pathogens varies with age. Furthermore, children assessed in the included trials were previously healthy, immunocompetent, and acquired their infections in the community. Consequently, numerous exceptions such as immunosuppressed children or those with cystic fibrosis are outside the scope of this article. Likewise, it was previously mentioned that among the population sampled for these studies, viruses are the most common cause of pneumonia. As a result, it is possible that findings tend towards neutrality. Additionally, in contrast with the trial led by Greenberg et al. and the SAFER trial, the SCOUT-CAP trial did not routinely perform chest radiography for the diagnosis of CAP [13, 18, 19]. This information may be interpreted as a disadvantage, considering that the clinical-radiologic criteria for deciding whether to implement antibiotic therapy for pneumonia or not are one of the greatest distinctions in the management of CAP in high-income countries. Nevertheless, this divergence might also be a strength as it brings the results from this review closer to the real world, where guidelines differ between countries, regions, and hospitals; one strict criterion does not fit all.

Conclusion

This meta-analysis, including 789 children from 6 months to 10 years, suggests that the clinical cure for uncomplicated CAP in an outpatient setting is not significantly different when comparing 5-day to 10-day Amoxicillin regimens. These findings indicate that the treatment of uncomplicated

CAP in immunocompetent children may be shortened to a 5-day course without compromising clinical effectiveness.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-022-04603-8.

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Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Isabela R. Marques, Izabela P. Calvi, and Sara A. Cruz. The first draft of the manuscript was written by Isabela R. Marques, Izabela P. Calvi, Sara A. Cruz, Luana M. F. Sanchez, and Isis F. Baroni. All authors critically reviewed previous versions of the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work.

Data sharing Because this meta-analysis was based on data extracted from previously published research, all the data and study materials are available in the public domain. The authors of this meta-analysis do not have access to patient-level data of the individual studies. Researchers with an interest in individual-level data from the studies included in this meta-analysis are encouraged to contact the corresponding author from each study for such requests.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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