International Journal of Community Medicine and Public Health
Khowaja R et al. Int J Community Med Public Health. 2023 Oct;10(10):3832-3838
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20233123

Meta-Analysis

Comparison of short-course versus long-course antibiotic treatment for community-acquired pneumonia: a meta-analysis of randomized-control trials

Rahil Khowaja[1]*, Fazila Karimi[2]

[1]School of Medicine, Swansea University, Swansea, United Kingdom
[2]Public Health, SZABIST, Karachi, Pakistan

Received: 27 July 2023
Accepted: 12 September 2023

***Correspondence:**
Dr. Rahil Khowaja,
E-mail: khowajarahil16@gmail.com

ABSTRACT

The duration of antibiotic treatment of community acquired pneumonia (CAP) has been a topic of discussion in scientific communities because of the lack of evidence about the current regimen, i.e., 7 to 10 days of treatment. The present meta-analysis aims to compare the effectiveness of shorter-duration antibiotic treatment with longer-duration antibiotic treatment in patients with CAP. This meta-analysis was conducted and reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. Two authors carried out a scientific literature search on online databases, including EMBASE, PubMed and Cochrane Library. The following keywords or corresponding medical subject headings (MeSH) were used for the search of relevant articles: “community-acquired pneumonia”, “antibiotics”, “drug therapy”, “short course”, “long course”, and "duration". The primary outcomes assessed in this meta-analysis were clinical efficacy, microbiological efficacy and radiological resolution, other outcomes included mortality and drug related adverse events. Total 6 RCTs were included in the current meta-analysis. No significant differences were found between shorter-course and longer-course antibiotic treatment in terms of clinical efficacy, microbiological efficiency, radiological resolution, mortality and drug-related adverse events. The findings of the present meta-analysis showed that the treatment of CAP with a shorter course of antibiotic is as effective as a longer course of therapy.

Keywords: CAP, PRISMA, Pneumonia

INTRODUCTION

Community-acquired pneumonia (CAP) is defined as pneumonia acquired outside the hospital setting, or that occurs within 48 hours of hospital admission.[1] CAP is one of the leading causes of mortality and morbidity all over the world.[2] The annual incidence of CAP ranges from 5 to 11 per 1000 adults and is associated with significant healthcare costs.[3,4] Several studies have projected a global rise in antibiotic resistance among CAP-related infections, with substantial clinical and financial ramifications.[4,5] Failure of antibiotic treatment because of inappropriate treatment choice and the resistance may enhance treatment costs if a longer stay in the hospital or a more expensive antibiotic class is needed.[1]

Individuals diagnosed with CAP need efficient antibiotic therapy. The most commonly used antibiotics are fluoroquinolones, macrolides, cephalosporins, and beta-lactams.[6] The selection of an antibiotic is frequently empirical, and individual research findings have not revealed significant differences in the efficiency of different antibiotics.[7] Certain factors can impact decisions regarding treatment choices, including potential pathogens, their regional resistance profiles, and the

safety and efficacy of individual antibiotics.[8] Currently, several recommendations are there related to the treatment duration. However, treatment courses are mostly for 5 to 14 days.[6,8]

Antibiotic therapy duration is vital in the management of patients with CAP. If the duration of antibiotic therapy is short, it will cause treatment failure. On the other hand, longer duration of antibiotic therapy is associated with substantial costs and contributes to increasing rates of antibiotic resistance.[9] Increased prescribers' adherence to guidelines can cause a significant decrease in mortality and morbidity.[4] Several studies have been conducted to determine the impact of the duration of antibiotic therapy on individuals with CAP. It has been found that shorter regimens are as effective as longer courses and are safe in reducing the spread of drug-resistant bacteria, improving compliance, limiting treatment-related costs and decreasing adverse events.[10-12] The duration of antibiotic treatment of CAP has been a topic of discussion in scientific communities because of the lack of evidence about the current regimen, i.e., 7 to 10 days of treatment. Besides this, several studies have been carried out to assess the impact of a shorter duration of antibiotic treatment in CAP patients. The present meta-analysis aims to compare the effectiveness of shorter-duration antibiotic treatment with longer-duration antibiotic treatment in patients with CAP.

This meta-analysis was conducted as well as the reported in accordance with the guidelines of the PRISMA statement.

LITERATURE SEARCH

Two authors carried out a scientific literature search on online databases, including EMBASE, PubMed and Cochrane library. The following keywords or corresponding MeSH were used for the search of relevant articles: “community-acquired pneumonia”, “antibiotics”, “drug therapy”, “short course”, “long course”, and "duration". We also manually searched the reference lists of the included studies and reviews. The search time limit was from the inception to 31st December 2022, and the search languages were limited to English only.

Literature screening and data extraction

Two researchers independently screened the literature and extracted data. Firstly, title and abstract screening were done after removing duplicates. Full texts of all eligible studies were retrieved and screened for eligibility criteria using pre-specified inclusion and exclusion criteria. Disagreements between the two researchers were resolved via discussion. Data were extracted using pre-designed data extraction forms designed using Microsoft Excel. Data extracted included the author's name, year of publication, groups, sample size and dose of the antibiotic.

Eligibility criteria

We included only randomized-controlled trials comparing short-course antibiotic treatment with a more prolonged course in patients diagnosed with CAP. A short course of antibiotic treatment was defined as the treatment of 5 days or less, while seven or more days were defined as long-course antibiotic treatment. We excluded studies conducted on patients with comorbidities like lung cancer and chronic lung diseases. We excluded studies that compared two different antibiotics. We excluded studies that were conducted in children (under 18 years).

Outcome measures

The primary outcomes assessed in this meta-analysis were clinical efficacy (defined as pneumonia associated clinical signs and symptoms were resolved), microbiological efficacy (defined as eradication of bacterial cultures or reduction in the amount of bacterial colonies from baseline) and radiological resolution (areas of consolidation completely resolved), Other outcomes included mortality and drug related adverse events.

Risk of bias assessment

Risk of bias assessment of each included study was assessed by 2 authors independently using Cochrane Risk of bias Assessment tool. Any disagreements between 2 authors resolved by consensus and discussion. Seven domains were assessed and each domain rated as high risk, low risk/unclear risk of bias as per judgment criteria.

Statistical analysis

We used the review manager 5.4.1 software for data analysis. The heterogeneity among the study results was assessed by the I-square statistics. I-square is less than or equal to 50%, indicating low heterogeneity among the study results, and a fixed-effect model was used for data analysis. In case of heterogeneity of more than 50%, a random effect model was used. Outcomes were expressed as risk ratio (RR) and 95% confidence interval (CI). In the present meta-analysis, a p=0.05 was kept as a cut-off. Subgroup analysis was performed.

RESULTS

The process of studies selection is presented in Figure 1. We identified 324 articles through database searching. We excluded 180 articles based on titles and abstract screening. After reviewing 28 full-texts, we further excluded 22 RCTs based on the pre-specified inclusion and exclusion criteria. Eventually, 6 RCTs were included in the current meta-analysis. Table 1 shows the characteristics of included studies. Out of 6 studies, three compared levofloxacin, while gemifloxacin, amixicilin and Quinolones were assessed by one study each. Majority of patients in all studies were males. Figure 2 shows the risk of bias graph.

Table 1: Characteristics of included studies.

Authors	Year	Country	Groups	Duration	Dose (mg)	Sample size	Mean age (In years)	Males (%)
Dunbar et al[13]	2003	United States	Short duration	5 days	Levofloxacin 750	198	54.1	58.2
			Long duration	10 days	Levofloxacin 500	192		
File et al[14]	2007	9 countries	Short duration	5 days	Gemifloxacin 320	256	45.4	57.6
			Long duration	7 days	Gemifloxacin 320	254		
Moussaoui[15]	2006	Netherland	Short duration	3 days	Amoxicillin 750	56	57	51.3
			Long duration	8 days	Amoxicillin 750	63		
Uranga et al[16]	2016	Spain	Short duration	5 days	Quinolones	162	65.5	62.8
			Long duration	10 days	Quinolones	150		
Zhao et al[17]	2016	China	Short duration	5 days	Levofloxacin 750	208	41.2	49.2
			Long duration	7-14 days	Levofloxacin 500	219		
Zhao et al[18]	2014	China	Short duration	5 days	Levofloxacin 750	121	40.9	55.6
			Long duration	7-14 days	Levofloxacin 500	120		

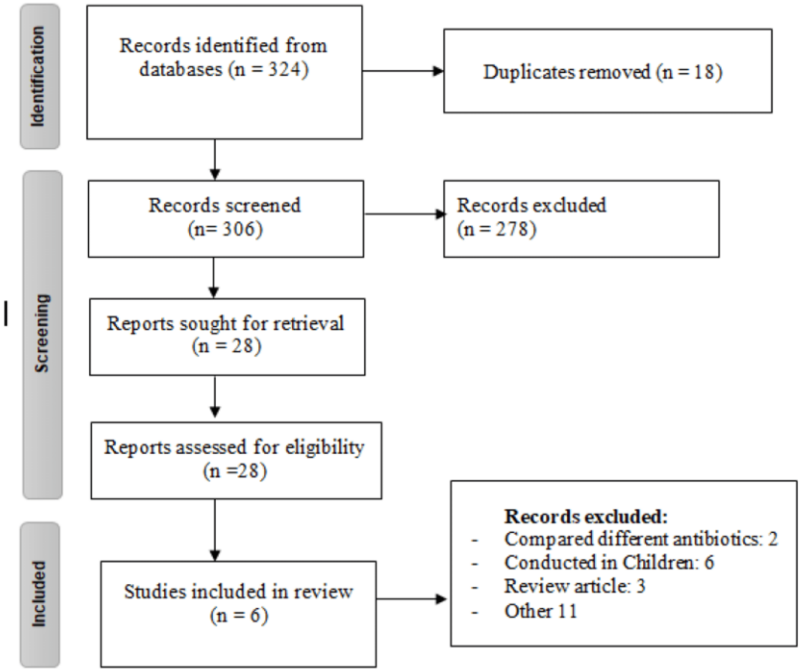


Figure 1: Process of study selection.

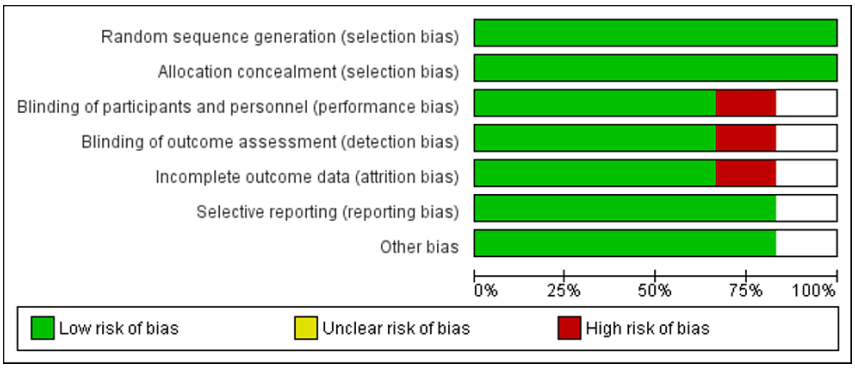


Figure 2: Risk of bias graph.

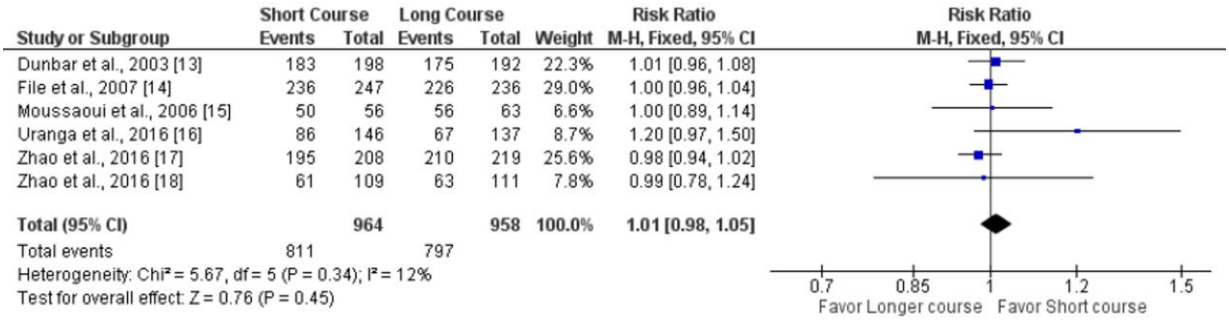


Figure 3: Comparison of short-course and long-course antibiotic therapy on clinical efficacy.

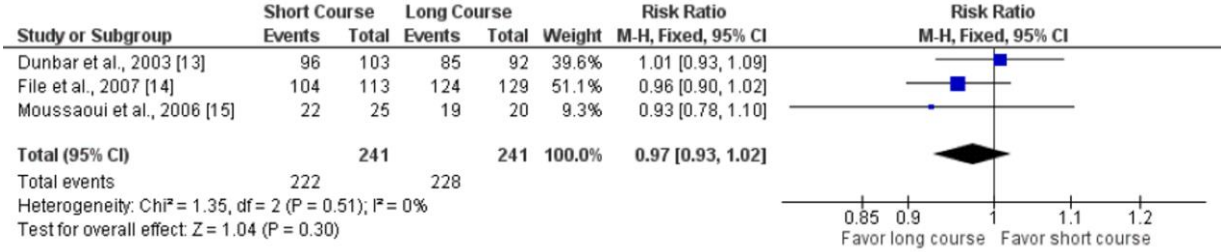


Figure 4: Comparison of short-course and long-course antibiotic therapy on radiographic resolution.

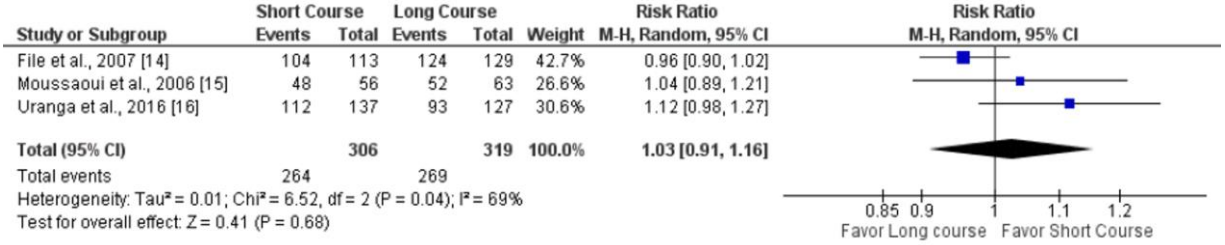
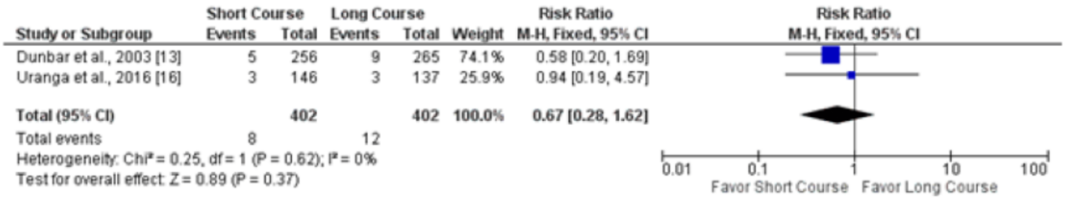


Figure 5: Comparison of short-course and long-course antibiotic therapy on radiographic resolution.

a) Mortality



b) Drug-related Adverse Events

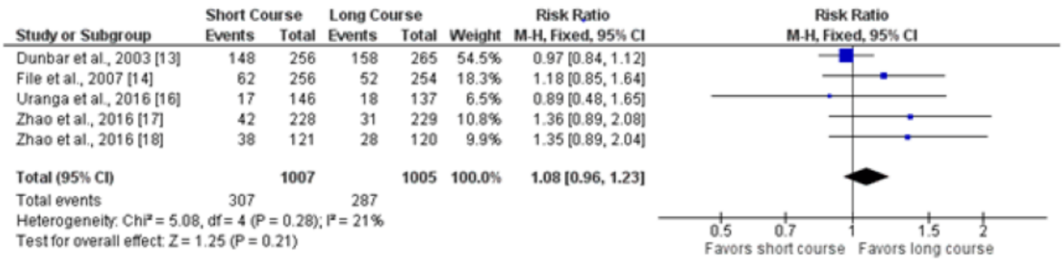


Figure 6: Comparison of short-course and long-course antibiotic therapy on (a) mortality (b) drug-related adverse events.

Table 2: Results of subgroup analysis.

Outcomes	Sub-groups	RR (95% CI)	P value of sub-group differences
Clinical efficacy	Same antibiotic dose	1.00 (0.96-1.04)	0.49
	Different antibiotic dose	1.02 (0.97-1.07)	
Microbiological efficacy	Same antibiotic dose	0.95 (0.90-1.01)	0.26
	Different antibiotic dose	1.01 (0.93-1.09)	
Radiological resolution	Same antibiotic dose	0.97 (0.91-1.04)	0.06
	Different antibiotic dose	1.12 (0.98-1.27)	

Comparison of short-term and long-term on rate of clinical efficacy, microbiological efficacy and radiological resolution

Six studies reported the rate of clinical efficacy between short-term and long-term antibiotic treatment. The clinical efficacy rate at the end of treatment in the CAP population was not significantly different between the shorter and longer antibiotic courses (84.23% versus 83.19%, RR: 1.01, 95% CI: 0.98-1.05, I-square: 12%) as shown in Figure 3. In the pooled analysis of the 3 RCTs that reported the microbiological efficacy, the microbiological efficacy rates were 92.11% and 94.61% in short-course and long-course groups, respectively (RR: 0.97, 95% CI: 0.93-1.02, I-square: 0%) as shown in Figure 4. In the pooled analysis of 3 RCT compared radiological resolution between two study arms, no significant differences were reported in terms of rate of radiological resolution (RR: 1.03, 95% CI: 0.91-1.16, I-square: 69%) (Figure 5).

Mortality and drug related adverse events

Two studies compared risk of mortality between two study groups. Incidence of mortality in patients randomized to short-term antibiotic regimen was 2% compared to 3% in long-term antibiotic regimen group (RR: 0.67, 95% CI: 0.28-1.62, I-square: 0%). Five studies assessed drug-related adverse events between patients randomized to short-term and long term antibiotic treatment. Meta-analysis showed that the risk of drug-related adverse events was not significantly different in two study arms (RR: 1.08, 95% CI: 0.96-1.23, I-square: 21%) as shown in Figure 6.

Subgroup analysis

In the subgroup analysis of the studies that used use dose of antibiotics and different dose across each study group, we found no significant difference between two subgroup in any of the primary outcomes ($p>0.05$). Results were similar to overall pooled meta-analysis as shown in Table 2.

DISCUSSION

The present meta-analysis found that adults with CAP had statistically similar clinical efficacy rates, microbiological efficacy rates, and radiological resolution rates in patients receiving short-course of antibiotics and long-course of antibiotics. In addition, there was no significant difference between the two groups in terms of drug-related adverse events. A meta-analysis conducted by Tansarli et al reported that the clinical efficacy rates were similar in patients receiving antibiotic treatment for a short duration (6 or fewer days) and longer duration (7 or more days).[19]

The efficiency of short-course antibiotic therapy for CAP reported in this meta-analysis is also supported by additional studies. There is growing evidence that a shorter duration of antibiotic use can be tried in other forms of respiratory tract infections without change in clinical effectiveness.[20,21] An observational study conducted by Montravers et al found that after three days of antibiotic therapy, infection was significantly reduced or cleared in many patients with ventilator-associated pneumonia.[22] Current guidelines by American thoracic society and IDSA recommend that antibiotics can be stopped after minimum use of 5 days, if afebrile for 48-72 hours and no more than 1 sign of clinical instability.[23]

Shortened antibiotic therapy can reduce the risk of antimicrobial resistance, antibiotic-related adverse events, the risk of bacterial superinfection, and individual and healthcare system-related costs.[24] Longer-course antibiotic therapy may reduce patients' adherence to the prescribed regimen after the initial days or resolution of symptoms.[25,26] Reduced adherence can lead to enhanced exposure of pathogens to low drug concentrations, leading to drug resistance emergence.[27]

Regarding the safety of short-course and long-course antibiotic therapy, a more recent systematic review showed no significant differences between the two groups in adverse events.[28] The present meta-analysis showed similar findings. However, a review conducted by Gundersen et al found that a shorter course of antibiotics was associated with reduced rates of adverse events compared to longer courses of antibiotics.[29]

Moreover, some of the included studies used different antibiotic doses in the short-course and long-course antibiotic regimens. It reduces the comparability of RCTs and instead asks whether it is the duration of therapy or the dose of antibiotic that matters to the efficacy rate.

However, we tried to answer this question by performing a subgroup analysis, and the results were consistent with the overall pooled analysis.

The present meta-analysis has certain limitations. Firstly, none of the studies assessed the relationship between antibiotic course and the emergence of resistant microorganisms. Since we were unable to report on this finding, it may be stated that the risk of antimicrobial resistance may be reduced by reducing the duration of antibiotic exposure. Secondly, most studies used different doses in both groups, so it decreases the comparability of included RCTs. Therefore, in the future, more clinical trials need to be conducted that compare short-course and long-course antibiotic therapy with the same antibiotic type and with the same daily dosage.

CONCLUSION

The findings of the present meta-analysis showed that the treatment of CAP with a shorter course of antibiotic is as effective as a longer course of therapy as no significant differences were found between the two groups in radiological resolution, microbiological efficacy and clinical efficacy rate. In terms of safety, we did not find any significant difference in mortality rate and drug-related adverse events. However, only six RCTs were included in the present meta-analysis; therefore, more clinical trials need to be conducted to determine the optimum duration of antibiotic treatment in CAP. These studies need to compare treatment with the same type of antibiotic and the same dose of antibiotic. In addition, studies should focus on adverse events as well, like the development of resistant bacteria to aid in development of recommendations to treat CAP in outpatient clinics.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. López-Alcalde J, Rodriguez-Barrientos R, Redondo-Sánchez J et al. Short-course versus long-course therapy of the same antibiotic for community-acquired pneumonia in adolescent and adult outpatients. Cochrane Database of Systematic Reviews. 2018;9(9):CD009070.pub2.
2. World Health Organization. The top ten causes of death. 2019. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
3. Mandell LA. Epidemiology and etiology of community-acquired pneumonia. Infect Dis Clin. 2004;1:761-76.
4. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;1:71-9.
5. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(2):155-64.
6. Torres A, Barberán J, Falguera M, Menéndez R, Molina J, Olaechea P et al. Grupo de la Guía Multidisciplinar para el Manejo de la Neumonía Adquirida en la Comunidad. Guía multidisciplinar para la valoración pronóstica, diagnóstico y tratamiento de la neumonía adquirida en la comunidad. Med Clín. 2013;140(5):223-1.
7. Kaysin A, Viera AJ. Community-acquired pneumonia in adults: diagnosis and management. Am Family Physician. 2016;94(9):698-706.
8. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell JD, Dean NC et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(2):27-72.
9. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;18:340.
10. Chalmers JD, Akram AR, Singanayagam A, Wilcox MH, Hill AT. Risk factors for Clostridium difficile infection in hospitalized patients with community-acquired pneumonia. J Infect. 2016;1(2):45-53.
11. Longcor J, Hopkins S, Wickler M, Laurence L. A phase 2 study of the safety and efficacy of oral delafloxacin (DLX) in community acquired pneumonia (CAP). ID week. 2012;17(2):17-21.
12. Dinh A, Bouchand F, Salomon J, Bernard L. Short-course antibiotic regimens: up-to-date. La Revue de Med Interne. 2016;8(4):466-72.
13. Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM et al. High-Dose, Short-Course Levofloxacin for Community-Acquired Pneumonia: A New Treatment Paradig. Clin Infect Dis. 2003;37(6):752-60.
14. File Jr TM, Mandell LA, Tillotson G, Kostov K, Georgiev O. 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(1):112-20.
15. El Moussaoui R, De Borgie CA, Van den Broek P, Hustinx WN, Bresser P, Van den Berk GEL 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(7554):1355.
16. Uranga A, España PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. JAMA Internal Med. 2016;176(9):1257-65.
17. Zhao T, Chen LA, Wang P, Tian G, Ye F, Zhu H et al. A randomized, open, multicenter clinical study on

the short course of intravenous infusion of 750 mg of levofloxacin and the sequential standard course of intravenous infusion/oral administration of 500 mg of levofloxacin for treatment of community-acquired pneumonia. J Thoracic Dis. 2016;8(9):2473.
18. Zhao X, Wu JF, Xiu QY, Wang C, De-Ping Z, Jian-An H et al. A randomized controlled clinical trial of levofloxacin 750 mg versus 500 mg intravenous infusion in the treatment of community-acquired pneumonia. Diagnostic Microbiol Infect Dis. 2014;80(2):141-7.
19. Tansarli GS, Mylonakis E. Systematic review and meta-analysis of the efficacy of short-course antibiotic treatments for community-acquired pneumonia in adults. Antimicrob Agents Chemother. 2018;62(9):e00635-18.
20. Casey JR, Pichichero ME. Meta-analysis of short course antibiotic treatment for group a *Streptococcal tonsillopharyngitis*. Pediatr Infect Dis J. 2005;24:909-17.
21. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA. 2003;290:2588-98.
22. Montravers P, Fagon JY, Chastre J, Lecso M, Dombret MC, Trouillet JL et al. Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. Am Rev Respiratory Dis. 1993;147(1):38-44.
23. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K 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 Respiratory Crit Care Med. 2019;200(7):45-67.
24. Spellberg B. The new antibiotic mantra-"shorter is better". JAMA Internal Med. 2016;176:1254-5.
25. Branthwaite AJ, Pechère JC. Pan-European survey of patients' attitudes to antibiotics and antibiotic use. J Int Med Res. 1996;24:229-38.
26. Hoppe JE, Blumenstock G, Grotz W, Med C, Selbmann HK. Compliance of German pediatric patients with oral antibiotic therapy: results of a nationwide survey. The. Pediatr Infect Dis J. 1999;18:1085-91.
27. Guillemot D, Carbon C, Balkau B, Geslin P, Lecoeur H, Vauzelle-Kervroëdan F et al. Low dosage and long treatment duration of β-lactam: risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae*. JAMA. 1998;294(5):365-70.
28. Dawson-Hahn EE, Mickan S, Onakpoya I, Roberts N, Kronman M, Butler CC et al. Short-course versus long-course oral antibiotic treatment for infections treated in outpatient settings: a review of systematic reviews. Family practice. 2017;34(5):511-9.
29. Møller Gundersen K, Nygaard Jensen J, Bjerrum L, Hansen MP. Short-course vs long-course antibiotic treatment for community-acquired pneumonia: A literature review. Basic Clin Pharmacol Toxicol. 2019;124:550-9.

Cite this article as: Khowaja R, Karimi F. Comparison of short-course versus long-course antibiotic treatment for community-acquired pneumonia: a meta-analysis of randomized-control trials. Int J Community Med Public Health 2023;10:3832-8.