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Health Technology Assessment

Volume 25 • Issue 60 • November 2021

ISSN 1366-5278

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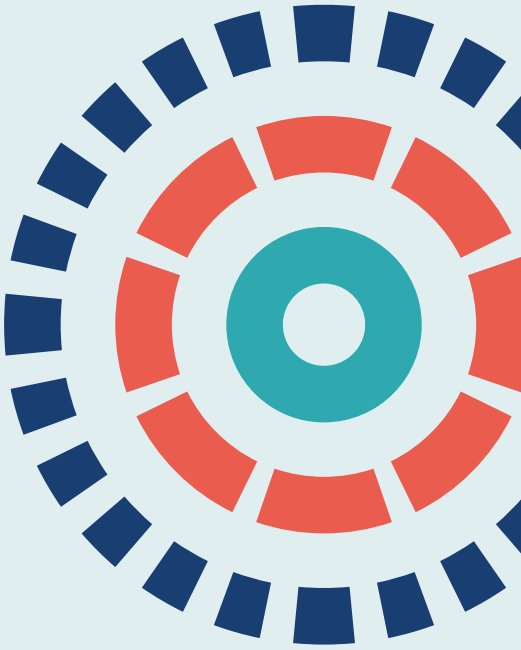

DOI 10.3310/hta25600

Amoxicillin duration and dose for community-acquired pneumonia in children: the CAP-IT factorial non-inferiority RCT

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Declared competing interests of authors: David Dunn reports grants from the National Institute for Health Research during the conduct of the study (RP-PG-1212-20006). Saul N Faust reports personal fees or grants from AstraZeneca plc (Cambridge, UK)/Medimmune (Gaithersburg, MA, USA), Sanofi SA (Paris, France), Pfizer Inc. (New York, NY, USA), Seqirus UK Ltd (Maidenhead, UK), Sandoz (Holzkirchen, Germany), Merck KGAA (Darmstadt, Germany), GlaxoSmithKline plc (Brentford, UK) and Johnson & Johnson

(Brunswick, NJ, USA) outside the submitted work. In addition, Saul N Faust received grants for contract commercial clinical trials, which were paid to Saul N Faust's institution (with no personal payment of any kind). Last, Saul N Faust is a member of the Health Technology Assessment Commissioning Committee (2017–22). Adam Finn reports grants from GlaxoSmithKline plc, Pfizer Inc., Novavax (Gaithersburg, MA, USA), Sanofi Pasteur (Lyon, France), VBI Vaccines Inc. (Cambridge, MA, USA), Janssen Pharmaceuticals (Beerse, Belgium), Valneva SE (Saint-Herblain, France) and JITSUVAX outside the submitted work.

Published November 2021
DOI: 10.3310/hta25600

This report should be referenced as follows:

Barratt S, Bielicki JA, Dunn D, Faust SN, Finn A, Harper L, *et al*. Amoxicillin duration and dose for community-acquired pneumonia in children: the CAP-IT factorial non-inferiority RCT. *Health Technol Assess* 2021;**25**(60).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/88/11. The contractual start date was in March 2016. The draft report began editorial review in October 2020 and was accepted for publication in June 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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Abstract

Amoxicillin duration and dose for community-acquired pneumonia in children: the CAP-IT factorial non-inferiority RCT

Sam Barratt[1], Julia A Bielicki[2], David Dunn[1], Saul N Faust[3], Adam Finn[4], Lynda Harper[1†], Pauline Jackson[5], Mark D Lyttle[5,6], Colin VE Powell[7,8], Louise Rogers[9], Damian Roland[10,11], Wolfgang Stöhr[1], Kate Sturgeon[1], Elia Vitale[2], Mandy Wan[12], Diana M Gibb[1] and Mike Sharland[2*] on behalf of the CAP-IT Trial Team and the PERUKI and GAPRUKI Networks

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Background: Data are limited regarding the optimal dose and duration of amoxicillin treatment for community-acquired pneumonia in children.

Objectives: To determine the efficacy, safety and impact on antimicrobial resistance of shorter (3-day) and longer (7-day) treatment with amoxicillin at both a lower and a higher dose at hospital discharge in children with uncomplicated community-acquired pneumonia.

Design: A multicentre randomised double-blind 2 × 2 factorial non-inferiority trial in secondary care in the UK and Ireland.

Setting: Paediatric emergency departments, paediatric assessment/observation units and inpatient wards.

Participants: Children aged > 6 months, weighing 6–24 kg, with a clinical diagnosis of community-acquired pneumonia, in whom treatment with amoxicillin as the sole antibiotic was planned on discharge.

Interventions: Oral amoxicillin syrup at a dose of 35–50 mg/kg/day compared with a dose of 70–90 mg/kg/day, and 3 compared with 7 days' duration. Children were randomised simultaneously to each of the two factorial arms in a 1 : 1 ratio.

Main outcome measures: The primary outcome was clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including community-acquired pneumonia), other than trial medication, up to 28 days after randomisation. Secondary outcomes included severity and duration of parent/guardian-reported community-acquired pneumonia symptoms, drug-related adverse events (including thrush, skin rashes and diarrhoea), antimicrobial resistance and adherence to trial medication.

Results: A total of 824 children were recruited from 29 hospitals. Ten participants received no trial medication and were excluded. Participants [median age 2.5 (interquartile range 1.6–2.7) years; 52% male] were randomised to either 3 ($n = 413$) or 7 days ($n = 401$) of trial medication at either lower ($n = 410$) or higher ($n = 404$) doses. There were 51 (12.5%) and 49 (12.5%) primary end points in the 3- and 7-day arms, respectively (difference 0.1%, 90% confidence interval −3.8% to 3.9%) and 51 (12.6%) and 49 (12.4%) primary end points in the low- and high-dose arms, respectively (difference 0.2%, 90% confidence interval −3.7% to 4.0%), both demonstrating non-inferiority. Resolution of cough was faster in the 7-day arm than in the 3-day arm for cough (10 days vs. 12 days) ($p = 0.040$), with no difference in time to resolution of other symptoms. The type and frequency of adverse events and rate of colonisation by penicillin-non-susceptible pneumococci were comparable between arms.

Limitations: End-of-treatment swabs were not taken, and 28-day swabs were collected in only 53% of children. We focused on phenotypic penicillin resistance testing in pneumococci in the nasopharynx, which does not describe the global impact on the microflora. Although 21% of children did not attend the final 28-day visit, we obtained data from general practitioners for the primary end point on all but 3% of children.

Conclusions: Antibiotic retreatment, adverse events and nasopharyngeal colonisation by penicillin-non-susceptible pneumococci were similar with the higher and lower amoxicillin doses and the 3- and 7-day treatments. Time to resolution of cough and sleep disturbance was slightly longer in children taking 3 days' amoxicillin, but time to resolution of all other symptoms was similar in both arms.

Future work: Antimicrobial resistance genotypic studies are ongoing, including whole-genome sequencing and shotgun metagenomics, to fully characterise the effect of amoxicillin dose and duration on antimicrobial resistance. The analysis of a randomised substudy comparing parental electronic and paper diary entry is also ongoing.

Trial registration: Current Controlled Trials ISRCTN76888927, EudraCT 2016-000809-36 and CTA 00316/0246/001-0006.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 60. See the NIHR Journals Library website for further project information.

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List of abbreviations

AE	adverse event
BNFc	*British National Formulary for Children*
BTS	British Thoracic Society
CAP	community-acquired pneumonia
CAP-IT	Community-Acquired Pneumonia: a protocol for a randomIsed controlled Trial
CI	confidence interval
ED	emergency department
ERC	End-Point Review Committee
GP	general practitioner
ID	identification
IDMC	Independent Data Monitoring Committee
IMP	investigational medicinal product
IQR	interquartile range
ITT	intention to treat
MIC	minimal inhibitory concentration
PCV	pneumococcal conjugate vaccine
PED	paediatric emergency department
PPI	patient and public involvement
RCT	randomised controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
T > MIC	time spent above the minimum inhibitory concentration
TSC	Trial Steering Committee
WHO	World Health Organization

Plain English summary

Pneumonia (an acute lung infection) is a common diagnosis in young children worldwide. To cure this, some children are given antibiotics, but we do not currently know the best amount (dose) to give and the ideal number of days (duration) of treatment.

Taking antibiotics causes changes in bacteria, making them more resistant to treatment. This may be affected by the dose and duration, and is important because resistant bacteria are harder to treat and could spread to other people.

Amoxicillin is the most common antibiotic treatment for children with pneumonia. CAP-IT (Community-Acquired Pneumonia: a protocol for a randomIsed controlled Trial) tested if lower doses and shorter durations of amoxicillin are as good as higher doses and longer durations, and whether or not these affect the presence of resistant bacteria.

In total, 824 children in the UK and Ireland with pneumonia participated. They received either high- or low-dose amoxicillin for 3 or 7 days following discharge from hospital. To ensure that neither doctors nor parents were influenced by knowing which group a child was in, we included dummy drugs (placebo).

We measured how often children were given more antibiotics for respiratory infections in the 4 weeks after starting the trial medicine. To check for resistant bacteria, a nose swab was collected before starting treatment and again after 4 weeks.

One in every eight participating children was given additional antibiotics. We found no important difference in this proportion between 3 days and 7 days of amoxicillin treatment, or between lower or higher doses. Although children's coughs took slightly longer to go away when they received only 3 days of antibiotics, rash was reported slightly more often in children taking 7 days of antibiotics. There was no effect of dose of amoxicillin on any of the symptom measurements. No effect of duration of treatment or dose was observed for antibiotic resistance in bacteria living in the nose and throat.

Scientific summary

Background

Antibiotics are among the most frequently prescribed medicines for children worldwide, and the most common indication is acute respiratory tract infection. Community-acquired pneumonia (CAP) accounts for a substantial proportion. Although the majority of pneumonia deaths occur in low- and middle-income countries, CAP is a major cause of morbidity in Europe and North America.

According to current guidance, including guidance from the *British National Formulary for Children* (BNFc) and the British Thoracic Society (BTS) in the UK, amoxicillin is the recommended treatment for childhood CAP. Twice-daily dosing is widely recommended internationally, but the BNFc currently recommends amoxicillin (250 mg) three times daily for children aged 1–5 years, with a total daily dose similar to countries using twice-daily dosing. Owing to this age-banded dose selection, there is considerable variability in the effective total daily dose for treated children in the UK. In terms of duration, the 2019 National Institute for Health and Care Excellence treatment guidelines for childhood pneumonia recommend a 5-day course be prescribed, European and World Health Organization guidance has suggested that a 3- to 5-day course be prescribed and the BTS recognises that there are no robust data to inform duration. Overall, there is insufficient evidence to inform optimal amoxicillin dose or duration for childhood CAP.

Streptococcus pneumoniae is the bacterial pathogen most commonly associated with childhood CAP. The pneumococcal conjugate vaccination (PCV13) covers 13 serotypes of *S. pneumoniae* and was introduced in the UK in 2010, with an uptake of nearly 95%. Despite this, there has not been a significant reduction in CAP-related hospital admissions in young children. *S. pneumoniae* resistance to penicillin in the UK is relatively rare and generally low level, reported to be identified in approximately 15% of respiratory isolates and 4–6% of blood culture isolates. To the best of our knowledge, there are virtually no data on the impact of duration and dose of antibiotic treatment on colonisation with resistant bacteria in children, but the relationship is likely to be dynamic and highly complex.

Although there is clear agreement that amoxicillin should be used as the first-line agent in children requiring antibiotic treatment, there are insufficient data on the impact of amoxicillin dose and duration on clinical cure, drug toxicity and resistance to key bacteria, including *S. pneumoniae*.

Objectives

The main objective CAP-IT (Community-Acquired Pneumonia: a protocol for a randomIsed controlled Trial) was to determine the following for young children with uncomplicated CAP treated after discharge from hospital if:

- a 3-day course of amoxicillin is non-inferior to a 7-day course, determined by receipt of a clinically indicated systemic antibiotic other than trial medication for respiratory tract infection (including CAP) in the 4 weeks after randomisation up to day 28
- lower-dose amoxicillin is non-inferior to higher-dose amoxicillin under the same conditions.

Secondary objectives were to evaluate the impact of lower-dose and shorter-duration amoxicillin on antimicrobial resistance, severity and duration of parent/guardian-reported CAP symptoms and specified clinical adverse events (AEs) (i.e. rash and diarrhoea).

Methods

Trial design

CAP-IT was a multicentre clinical trial with a target sample size of 800 participants conducted in hospitals in the UK and Ireland. It was a randomised, double-blind, placebo-controlled, 2 × 2 factorial, non-inferiority trial that evaluated amoxicillin dose and duration in young children with CAP.

Eligibility and recruitment

Patients presenting to 28 UK NHS hospitals and one children's hospital in Ireland were recruited in emergency departments (EDs), assessment/observation units and inpatient wards.

Participants

Children were eligible if they had a diagnosis of uncomplicated CAP, were aged > 6 months, weighed 6–24 kg and treatment with amoxicillin as the sole antibiotic was planned on discharge. CAP diagnosis was defined as cough within the previous 96 hours, fever (≥ 38 °C) in the previous 48 hours and respiratory distress and/or focal chest signs. Children could have received either no antibiotics or < 48 hours of beta-lactam antibiotics prior to randomisation.

Children were excluded for any severe underlying chronic disease with an increased risk of complicated CAP (including sickle cell anaemia, immunodeficiency, chronic lung disease and cystic fibrosis), documented penicillin allergy or other contraindication to amoxicillin, diagnosis of complicated pneumonia (i.e. shock, hypotension, altered mental state, ventilatory support, empyema, pneumothorax or pulmonary abscess) or bilateral wheezing without focal chest signs.

Interventions

Amoxicillin suspension was orally administered by parents/guardians twice daily. All children were weighed during eligibility screening to determine dose volume according to seven weight bands. Children were randomised to receive either a lower (35–50 mg/kg/day) or a higher (70–90 mg/kg/day) dose, and to receive either 3 or 7 days of amoxicillin at the point of discharge from hospital.

Randomisation and blinding

Patients underwent two simultaneous factorial 1 : 1 randomisations (dose and duration), resulting in their allocation to one of the four amoxicillin regimens (low dose, short duration; low dose, long duration; high dose, short duration; or high dose, long duration) using computer-generated random permuted blocks of size eight, stratified according to whether or not they had received non-trial antibiotics in hospital before being enrolled. Initially, stratification was by paediatric ED or ward group, reflecting whether participants were admitted to inpatient wards or observation units or discharged directly from the ED. Following an amendment for the joint analysis of these groups, stratification was effectively based on whether or not participants had received in-hospital antibiotics prior to randomisation. Blinded investigational medicinal product (IMP) labels were applied to each treatment pack and participants were randomised by dispensing the next sequentially numbered pack in the active block.

All treating clinicians, parents/guardians and outcome assessors were blinded to the allocated treatment. Dose blinding was achieved by using otherwise identical amoxicillin products of two different strengths (125 mg/5 ml and 250 mg/5 ml). A placebo manufactured to match oral amoxicillin suspension was used to blind the duration. One brand of amoxicillin was used for the first 3 days, followed by either a second brand of amoxicillin or placebo for days 4–7. Parents were informed to expect a taste change between bottles, but they did not know whether this was because of placebo or alternative amoxicillin.

Outcomes

The primary outcome for CAP-IT was defined as any clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including CAP) other than trial medication within 4 weeks of randomisation (including if prescribed at the final follow-up visit at day 28). An expert clinician End-Point Review Committee (ERC) adjudicated the main clinical indication for all reported primary outcomes.

Secondary outcomes included phenotypic resistance to penicillin at day 28 measured in nasopharyngeal *S. pneumoniae* isolates, severity and duration of parent/guardian-reported CAP symptoms (including fever, cough, phlegm, fast breathing, wheeze, disturbed sleep, eating/drinking less, interference with normal activity and vomiting), adherence to trial medication, the occurrence of specified clinical AEs (including skin rash, thrush and diarrhoea) and serious adverse events (SAEs).

Data collection

Data on primary and secondary end points were collected on paper case report forms by site staff at trial entry, via telephone contact at days 3, 7, 14 and 21 and at a final face-to-face visit on day 28. In the case of children who did not attend the final face-to-face visit, consent was obtained for the trial team to contact their general practitioner (GP) to ascertain whether or not they had received a further course of antibiotics for any respiratory illness. In addition, parents/guardians completed a daily diary from day 1 to day 14.

Sample size

The sample size was calculated assuming a 15% event rate, an 8% non-inferiority margin (on a risk difference scale) assessed against a two-sided 90% confidence interval (CI), 90% power and 15% loss to follow-up, resulting in a sample size of 800 children.

Statistical methods

Statistical analyses were performed according to a modified intention-to-treat (ITT) principle, including all patients enrolled and analysed according to the group to which they were randomised. The one modification to the strict ITT principle was the exclusion of randomised patients who did not take any IMP from all statistical analyses.

The primary outcome was compared between the randomised groups using time-to-event methods, analysing time from enrolment to the first occurrence of the primary end point. Participants with incomplete primary outcome data were censored at the time of their last contact (including contact with their GP). Kaplan–Meier estimates were used to derive the risk difference between the randomised groups for the primary end point at day 28.

Four predefined sensitivity analyses for the primary outcome were performed: (1) including all systemic antibacterial treatments regardless of reason or indication; (2) limiting to end points where either CAP or chest infection (rather than respiratory tract infection generally) was adjudicated as the reason for treatment; (3) as the second analysis, but also including end points where the clinical indication was judged as 'unlikely' by the ERC; and (4) for the duration comparison only, disregarding prescriptions occurring within 3 days of randomisation because these cannot, by definition, be related to this randomisation.

Two predefined subgroup/stratified analyses were performed: (1) including participants at the higher end of the severity spectrum only, defined as two or more abnormalities at presentation [i.e. a raised respiratory rate (> 37 breaths/minute for children aged 1–2 years; > 28 breaths/minute for children aged 3–5 years), oxygen saturation < 92% in room air, presence of chest retractions]; and (2) a stratification by calendar time, based on Public Health England reports of circulating viruses/bacteria in the winter seasons spanned by CAP-IT.

Results

Primary end point

Of 814 participants in the analysis population, 100 (12.5%, 90% CI 10.7% to 14.6%) met the primary end point [51 (12.6%) participants in the lower-dose arm and 49 (12.4%) participants in the higher-dose arm (difference 0.2%, 90% CI −3.7% to 4.0%); 51 (12.5%) participants in the shorter-duration arm and 49 (12.5%) participants in the longer-duration arm (difference 0.1%, 90% CI −3.8% to 3.9%)].

For both comparisons, the upper 90% confidence limit was less than the non-inferiority margin of 8%, indicating non-inferiority of lower to higher dose and shorter to longer duration. There was no evidence of an interaction between the two randomisation arms or between the individual randomisation arms and pre-treatment with antibiotics.

All four of the sensitivity analyses supported the primary analysis, demonstrating non-inferiority for the dose and duration comparisons.

Community-acquired pneumonia symptoms

There was no evidence for a difference between the lower- and higher-dose groups in time to resolution of any of the nine parent/guardian-reported symptoms ($p > 0.05$).

There was evidence of a faster time to resolution of cough in the longer-duration group (median 10 days) than in the shorter-duration group (median 12 days) ($p = 0.040$). A similar difference was also observed for sleep disturbed by cough ($p = 0.026$). There was no significant difference between the duration groups in time to resolution of the other seven symptoms ($p > 0.05$).

Adverse events

A SAE was experienced by 43 of 814 (5.3%) participants. One participant (0.1%) experienced a serious adverse reaction and no participants experienced a suspected unexpected adverse reaction. The proportion of participants who experienced a SAE was similar in the different dose and duration groups.

There was no difference in the time to onset or severity of diarrhoea or thrush for either the dose or duration randomisation. The proportion of participants who reported skin rash after baseline was slightly higher in the longer-duration arm (106/387, 27.4%) than in the shorter-duration arm (87/404, 21.5%; $p = 0.055$).

Limitations

Limitations of the trial were that end-of-treatment swabs were not taken and 28-day swabs were collected in only 53% of children. In addition, we focused on phenotypic penicillin resistance testing in pneumococci in the nasopharynx, which does not describe the global affect on the microflora. Although 21% of children did not attend the final 28-day visit, we obtained data from general practitioners for the primary end point on all but 3% of children.

Conclusions

In summary, we found a 3-day treatment course of amoxicillin to be non-inferior to a 7-day course of amoxicillin, and a lower daily dose of amoxicillin to be non-inferior to a higher daily dose of amoxicillin, in terms of antibiotic retreatment for respiratory tract infection within 28 days. Time to resolution of parent/guardian-reported symptoms was similar in randomisation arms, except that mild cough lasted, on average, 2 days longer in participants in the shorter-duration arm than in participants in the longer-duration arm. AE rates and health-care services use within the 28-day follow-up period and penicillin non-susceptible pneumococcal colonisation rates at 28 days were similar in all dose and duration randomisation groups. No penicillin-resistant pneumococci were identified in samples from CAP-IT participants. Based on these findings, 3 days could be considered for the duration of amoxicillin treatment for children with uncomplicated pneumonia treated in the ambulatory setting. Current BNFc age-banded dosing in the UK results in a wide range of total daily doses, spanning both the lower and higher doses investigated in CAP-IT.

Future work

Antimicrobial resistance genotypic studies are ongoing, including whole-genome sequencing and shotgun metagenomics, to fully characterise the effect of amoxicillin dose and duration on antimicrobial resistance. The analysis of a randomised substudy comparing parental electronic and paper diary entry is also ongoing.

Trial registration

This trial is registered as ISRCTN76888927, EudraCT 2016-000809-36 and CTA 00316/0246/001-0006.

Funding

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Chapter 1 Introduction

This chapter includes material that has been adapted from the trial protocol, which has been published in *BMJ Open*.[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

Background

Antibiotics are among the most frequently prescribed medicines for children worldwide.[2,3] In the UK, Italy and the Netherlands, almost 50% of children have received antibiotics by their second birthday. Annually, it is estimated that 30% of children aged 2–11 years receive antibiotics.[3]

Of the possible indications in children aged < 5 years, the most common are acute respiratory tract infections, including community-acquired pneumonia (CAP).[4–6] CAP is one of the most common serious bacterial childhood infections. Although the majority of pneumonia deaths occur in low- and middle-income countries, CAP is a major cause of morbidity in Europe and North America.[5,7] In the UK, 62% of all antibiotics prescribed for community-acquired infections are for CAP.[8] In the USA, respiratory symptoms, fever or cough are responsible for one-third of all childhood medical visits, and 7–15% of these children will be diagnosed with CAP.[9,10]

Emergency department (ED) attendances and hospital admissions of children with respiratory complaints have increased in recent decades, mostly in preschool children.[9,11,12] According to Hospital Episode Statistics,[13] children aged 0–4 years accounted for around 2.11 million ED attendances in 2017–18. More than 11,000 children aged < 15 years were admitted to hospitals in England with a diagnosis of bacterial pneumonia in 2008, and 9000 1- to 4-year-old inpatients with non-influenza pneumonia were recorded in 2012/13.[13,14]

The bacterial pathogen most commonly associated with childhood CAP is *Streptococcus pneumoniae*, including in countries where pneumococcal conjugate vaccine (PCV) is routinely administered.[7,15–17] In 2010, PCV13 (which covers 13 *S. pneumoniae* serotypes) was introduced in the UK, with almost 95% uptake in young children.[18,19] However, despite an observed impact on invasive pneumococcal disease, a decrease in CAP-related hospital admissions in young children has not been observed.[11,14,20,21]

What are the current challenges in the management of childhood community-acquired pneumonia?

There is no test capable of accurately distinguishing between bacterial and viral CAP.[22] Interobserver agreement for chest radigoraphic findings is poor, casting doubt on the usefulness of chest radiographs for identifying bacterial CAP, and culturing of microbiological samples, such as sputum, has low diagnostic value and samples are often difficult to take from young children.[23–25] Diagnosis of bacterial CAP presents a challenge for treating clinicians, who rely largely on clinical criteria.[22] Children presenting with fever, raised respiratory rate, focal chest signs and other respiratory signs and symptoms (such as cough) are commonly ascribed a diagnosis of bacterial CAP,[10,26–28] whereas wheezing is associated with the absence of radiographic pneumonia and failure to detect bacteria in clinical samples.[26,29] If bacterial CAP is considered the likely diagnosis, treatment with antibiotics is instituted.[10,30] This diagnostic challenge is particularly problematic in secondary care, where the proportion of children presenting with serious bacterial infections is higher than in primary practice.[31,32]

A further challenge for clinicians is severity assessment. Available validated predictive scoring systems for CAP severity include the Pneumonia Severity Index and the CURB-65 (confusion, urea, respiratory rate, blood pressure, and 65 years of age or older) score, but these are not applicable to children.[33,34] Pneumonia mortality risk scores for children have been developed in low-resource settings, but do not differentiate between viral and bacterial pneumonia.[35,36] Low oxygen saturation in room air is included as one component in these risk scores, and is an important factor for differentiating between non-severe and severe pneumonia.[37–39]

Finally, assessing the efficacy of childhood CAP treatment is complex. Key measures in studies assessing efficacy early in the treatment course include lack of improvement or worsening of clinical symptoms and signs, such as respiratory rate and oxygen saturation.[40] According to British Thoracic Society (BTS) guidance, such criteria should trigger clinical review of children treated with oral antibiotics for CAP,[22] including where the following features are present at 48 hours: (1) persistent high fever, (2) increasing or persistently increased effort of breathing and (3) persistent or increasing oxygen requirement to maintain saturations $\geq$ 92%.[22] Approximately 15% of children with CAP receive further antibiotics within 28 days of starting treatment because of symptoms that concern parents.[41–44] However, only half of children show recovery from symptoms of acute respiratory illness by day 9 or 10, and 90% of children recover by 3.5 weeks after symptom onset.[45–47]

What are the current management recommendations for childhood community-acquired pneumonia?

Amoxicillin is the drug of choice for the treatment of childhood CAP according to the *British National Formulary for Children* (BNFc) and BTS and National Institute for Health and Care Excellence guidelines, as well as several international guidelines,[22,48–51] as it can effectively target and treat *S. pneumoniae* in the absence of high-level penicillin resistance. As a result, amoxicillin accounts for a very high proportion of overall oral antibiotic use among young children in many settings. Despite this, there is insufficient evidence to inform optimal treatment dose or duration.

What are the current dose recommendations?

Antibiotic dose selection should be driven by pharmacokinetic/pharmacodynamic considerations. The key pharmacokinetic/pharmacodynamic parameter for beta-lactams (including amoxicillin) is time spent above the minimum inhibitory concentration (T > MIC) (mainly focused here on pneumococcus). The recommended T > MIC is 40–50% of the dosing interval; however, the exact relationship between blood pharmacokinetics and concentrations of amoxicillin in the lungs is unclear.[48,52] The half-life of oral amoxicillin is about 1.0–1.5 hours and, on this basis, a three times daily regimen has been widely recommended.[53] However, there are few data to inform whether or not three times daily dosing is likely to achieve pharmacokinetic/pharmacodynamic parameters better than twice-daily dosing. The available data suggest that, in the case of total amoxicillin doses of 25–50 mg/kg/day, twice-daily dosing should be sufficient to achieve adequate T > MIC[53] and a Brazilian group recently demonstrated non-inferiority of twice-daily dosing compared with thrice-daily dosing in childhood CAP.[54] Together with a likely improvement in adherence to less frequent administration, twice-daily dosing is, therefore, widely recommended.[48–50,52] Currently, the BNFc recommends amoxicillin (250 mg) thrice daily for children aged 1–5 years with CAP, resulting in highly variable dosing, between approximately 40 mg/kg/day and 80 mg/kg/day, depending on the weight of the child.[55] Therefore, alternative strategies, such as weight-banded dosing, may be more appropriate.[56] Furthermore, much higher daily doses of amoxicillin, up to 200 mg/kg/day, are recommended for the treatment of severe infections.[55]

What are the current duration recommendations?

Several large randomised controlled trials (RCTs) have found shorter treatment courses in childhood CAP to be effective in low- and middle-income settings in terms of clinical cure, treatment failure and relapse rate.[57,58] However, these trials enrolled children with symptoms indicative of a viral infection not requiring antibiotics, and generalisability to the UK has, therefore, been questioned.[22]

The BTS recognises that there are no robust data to inform guidance on duration of antibiotic treatment in childhood CAP.[22] The BNFc guidance relevant at the start of this trial recommended a 7-day course, whereas European and World Health Organization (WHO) guidance suggests a 3- to 5-day course.[48,55] In 2019, the National Institute for Health and Care Excellence published guidance recommending stopping amoxicillin treatment after 5 days (250 mg thrice daily) for children aged 1–4 years, unless microbiological results suggest that a longer course length is needed or the patient is not clinically stable.[51]

What is the impact of antimicrobial resistance in childhood community-acquired pneumonia?

In the UK, the rates of penicillin non-susceptibility of *S. pneumoniae* are relatively low, at approximately 15% for respiratory samples (mainly from adults) and 4–6% for blood culture isolates.[59] Penicillin resistance [i.e. minimal inhibitory concentration (MIC) > 2 μg/ml] has not been observed in blood culture isolates and has been found in < 1% of respiratory *S. pneumoniae* isolates in the UK since 2010.[59] However, some worrying trends are observed in resistance of gut bacteria, and this situation will be exacerbated in a setting where antibiotics are used injudiciously.[60]

The relationship between MIC (an in vitro phenomenon) and clinical outcome in CAP is complex, and data on the level of *S. pneumoniae* antimicrobial resistance that reduces amoxicillin effectiveness are limited. Harmonisation of European breakpoints (i.e. the MIC at which an isolate is considered susceptible, intermediate or resistant) attempts to provide a link between clinical impact and in vitro observation of resistance.[61] Clinical breakpoints are determined based on a variety of data, in addition to efficacy studies. This includes pharmacokinetic/pharmacodynamic data, which for penicillin usually take T > MIC of 40% as the key exposure measure.

Children have high rates of bacterial colonisation, which often represents an increased level of carriage of resistant organisms[62,63] These may be passed on to others in the community, especially within child-care settings.[64,65] Interventions to maintain a low level of antimicrobial resistance among colonising bacteria may, therefore, have population implications.

The limited existing data on the specific impact of duration and dose of antibiotic treatment on subsequent colonisation with resistant bacteria in vivo suggest a complex and dynamic relationship.[62–73] Experimental models suggest that insufficiently high dosing could promote selection of resistant pathogens. In addition, although most of the effect on bacterial load is achieved early during antibiotic exposure, resistant isolates emerge after 4 or 5 days.[74–78] RCTs assessing the effect of antibiotic duration and dose have been called for, as they will probably provide the strongest evidence for the relationship between antibiotic exposure and colonisation with resistant bacteria.[79] One such RCT found that higher-dose shorter-duration amoxicillin therapy for childhood CAP led to less colonisation with resistant bacteria after 4 weeks, and was associated with better treatment adherence.[72] However, mathematical modelling indicates that this may come at the price of selecting isolates with higher levels of resistance, and clinical efficacy was not addressed in the trial.[72,78]

Trial rationale

Despite the reduction in incidence of invasive pneumococcal disease since the introduction of the conjugate vaccine,[20] CAP remains one of the most commonly identified and treated childhood infections in the UK. Although there is clear agreement that amoxicillin should be the first-line treatment, there are insufficient data to inform selection of dose and duration, and the impact that different regimens have on antimicrobial resistance is unknown.

Effectiveness and resistance-outcome data pertaining to dose and duration of amoxicillin could inform antimicrobial stewardship strategies in the large group of children with a high likelihood of bacterial CAP targeted by CAP-IT (Community-Acquired Pneumonia: a protocol for a randomIsed controlled Trial). A better understanding of the relationship between dose and duration of antibiotic treatment, and the impact on clinical outcomes and antimicrobial resistance, would make it possible to formulate improved evidence-based treatment recommendations for childhood CAP.

Objectives

The main objective of CAP-IT was to determine the following for young children with uncomplicated CAP treated after discharge from hospital if:

- a 3-day course of amoxicillin is non-inferior to a 7-day course, determined by receipt of a clinically indicated systemic antibiotic other than trial medication for respiratory tract infection (including CAP) in the 4 weeks after randomisation up to day 28
- lower-dose amoxicillin is non-inferior to higher-dose amoxicillin under the same conditions.

Secondary objectives were to evaluate the impact of lower-dose and shorter-duration amoxicillin on antimicrobial resistance, severity and duration of parent/guardian-reported CAP symptoms and specified clinical adverse events (AEs).

Chapter 2 Methods

Trial design

The CAP-IT study was a multicentre clinical trial with a target sample size of 800 participants in the UK and Ireland. In design, it was a randomised double-blind placebo-controlled 2 × 2 factorial non-inferiority trial of amoxicillin dose and duration in young children with CAP (*Figure 1*).

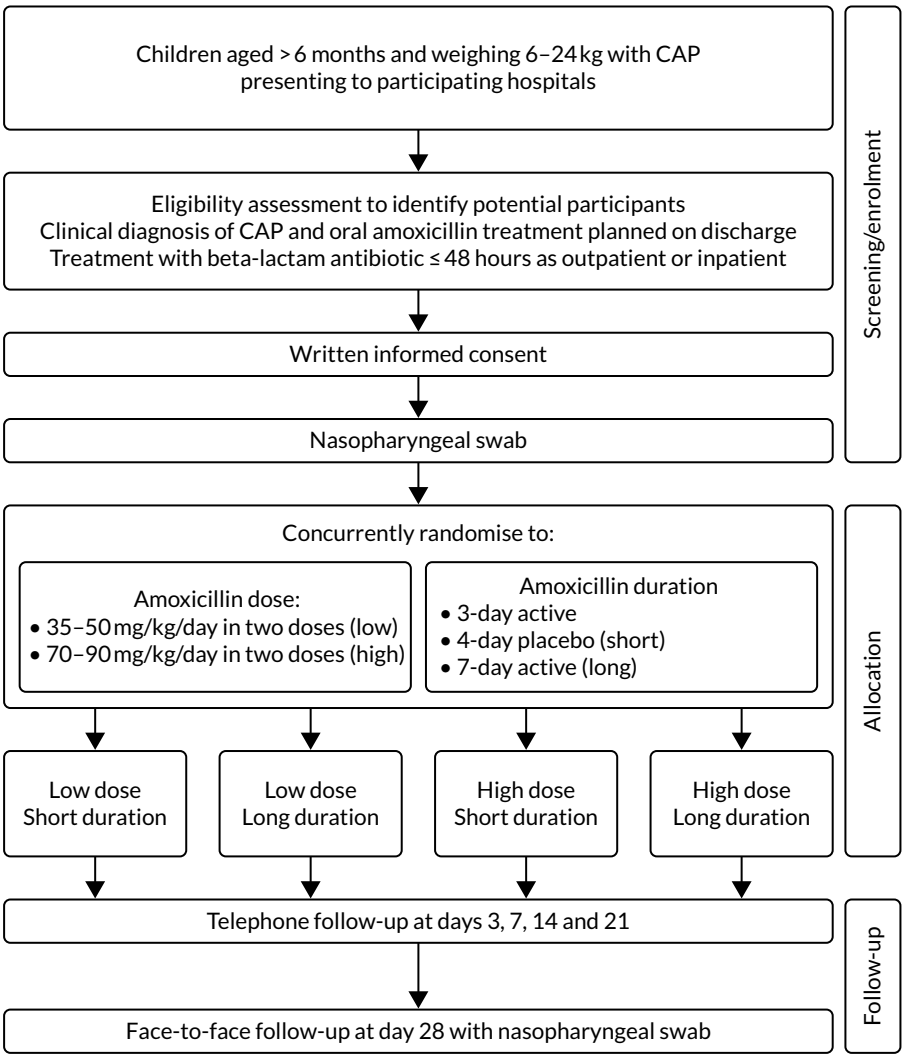


FIGURE 1 The CAP-IT schema.

Trial setting

Participants were recruited from 28 UK NHS hospitals and one children's hospital in Ireland:

1. Alder Hey Children's Hospital NHS Foundation Trust (Liverpool, UK)
2. Barts Health NHS Trust (London, UK)
3. Birmingham Women's and Children's NHS Foundation Trust (Birmingham, UK)
4. Brighton and Sussex University Hospitals NHS Trust (Brighton, UK)
5. Chelsea and Westminster Hospital NHS Foundation Trust (London, UK)
6. Children's Health Ireland (Dublin, Ireland)
7. City Hospitals Sunderland NHS Foundation Trust (Sunderland, UK)
8. Countess of Chester Hospital NHS Foundation Trust (Chester, UK)
9. County Durham and Darlington NHS Foundation Trust (Darlington, UK)
10. Guy's and St Thomas' NHS Foundation Trust (London, UK)
11. Hull and East Yorkshire Teaching Hospitals NHS Trust (Hull, UK)
12. Imperial College Healthcare NHS Trust (London, UK)
13. King's College Hospital NHS Foundation Trust (London, UK)
14. The Leeds Teaching Hospitals NHS Trust (Leeds, UK)
15. Manchester University NHS Foundation Trust (Manchester, UK)
16. Nottingham University Hospitals NHS Trust (Nottingham, UK)
17. Oxford University Hospitals NHS Foundation Trust (Oxford, UK)
18. Southport and Ormskirk Hospital NHS Trust (Southport, UK)
19. Royal Hospital for Children (Glasgow, UK)
20. Sheffield Children's NHS Foundation Trust (Sheffield, UK)
21. South Tees Hospitals NHS Foundation Trust (Middlesbrough, UK)
22. St George's University Hospitals NHS Foundation Trust (London, UK)
23. University Hospitals Bristol and Weston NHS Foundation Trust (Bristol, UK)
24. University Hospitals of Derby and Burton NHS Foundation Trust (Derby, UK)
25. University Hospitals of Leicester NHS Trust (Leicester, UK)
26. University Hospitals Lewisham (London, UK)
27. University Hospital Southampton NHS Foundation Trust (Southampton, UK)
28. University Hospital of Wales (Cardiff, UK).

Participating sites were tertiary or secondary hospitals with paediatric emergency departments (PEDs) and inpatient facilities, and were selected in collaboration with Paediatric Emergency Research in the UK & Ireland[80] on the basis of clinical and research infrastructure, experience in clinical research and likely eligible population size.

Participants

Patients presenting to participating hospitals were identified in PEDs, assessment/observation units or inpatient wards. Potential participants were screened as early as possible during the initial clinical assessment. Informed consent was sought from a parent/guardian once eligibility had been confirmed, but only after full explanation of the trial aims, methods and potential risks and benefits. Discussions regarding the trial took place between families and clinical teams when the child's clinical condition was stable, to minimise distress. Extensive information and recruitment materials were available for recruiting sites, including printed and video materials [accessible at URL: www.capitstudy.org.uk (accessed 29 July 2021)]. CAP-IT information film was designed to assist research teams in the recruitment process and provided information to parents/guardians about the purpose of the trial, the use of placebo and trial procedures. Parents/guardians could watch the film in their own time while in hospital, and research teams reported that the film was a useful tool during the recruitment process.

The film was made with input from the trial patient and public involvement (PPI) representative and featured a site principal investigator and research nurse, as well as graphics to aid explanation of trial procedures. [It can be viewed at https://vimeo.com/217849985 (accessed 29 July 2021).] Families were able to decline participation in the trial at any time without providing a reason and without incurring any penalty or affecting clinical management.

Recruitment pathways

Children were recruited through two different pathways based on whether they received any inpatient antibiotic treatment (ward group) or not (PED group). Children in either group may have had up to 48 hours of oral or parenteral beta-lactam treatment before enrolment. The PED group contained children who had not received any in-hospital antibiotic treatment (but may have had up to 48 hours of beta-lactam antibiotics in the community), whereas the ward group contained children who received any in-hospital oral or intravenous beta-lactam therapy prior to randomisation. Children in the latter group may have received beta-lactam treatment in the community first and subsequently in hospital, without interruption, for a total of < 48 hours.

Inclusion criteria

Children were eligible if they had a clinical diagnosis of uncomplicated CAP, were aged > 6 months and weighed 6–24 kg, and treatment with amoxicillin as the sole antibiotic was planned on discharge. *Box 1* shows the clinical criteria required for a diagnosis of CAP in CAP-IT.

Exclusion criteria

Children were excluded if they had received ≥ 48 hours of beta-lactam antibiotics or any non-beta-lactam agents, or if they had severe underlying chronic disease with increased risk of complicated CAP (including sickle cell anaemia, immunodeficiency, chronic lung disease and cystic fibrosis), documented penicillin allergy or other contraindication to amoxicillin, complicated pneumonia (including shock, hypotension, altered mental state, ventilatory support, empyema, pneumothorax and pulmonary abscess) or bilateral wheezing without focal chest signs.

Changes to selection criteria

During the trial enrolment period, eligibility criteria were modified based on emerging data to better reflect clinical management and facilitate inclusion of all children to whom the results of the trial may be of relevance.

Age and weight criteria were amended from 'age from 1 to 5 years (up to their 6th birthday)' in protocol v2.0 to 'greater than 6 months and weighing 6–24 kg' in protocol v3.0. Children recruited to protocol v2.0 were excluded if they were receiving systemic antibiotic treatment at presentation. This was modified in protocol v3.0 for the PED group and in protocol v4.0 for the ward group, such that children were eligible if they had received ≤ 48 hours' systemic antibiotic treatment at trial entry, as per section 2.3 of the protocol.

BOX 1 Definition of clinical diagnosis of CAP

Clinical diagnosis of CAP is defined as:

- cough (reported by parents/guardians within 96 hours before presentation)
- temperature ≥ 38 °C measured by any method or likely fever within 48 hours before presentation
- signs of laboured/difficult breathing or focal chest signs (i.e. one or more of nasal flaring, chest retractions, abdominal breathing, focal dullness to percussion, focal reduced breath sounds, crackles with asymmetry or lobar pneumonia on chest radiograph).

Children in the ward group were excluded in protocol v2.0 if they had 'current oxygen requirement' or 'current age-specific tachypnoea'; however, these criteria were removed in protocol v3.0 and replaced with the inclusion criterion 'child is considered fit for discharge at randomisation'.

The CAP diagnostic criterion relating to fever changed from 'temperature ≥ 38 °C measured by any method OR history of fever in last 24 hours reported by parents/guardians' in protocol v2.0 to 'temperature ≥ 38 °C measured by any method OR likely fever in last 48 hours' in protocol v3.0 to account for the accompanying parent/guardian not measuring temperature in the preceding 24 hours.

Interventions

The investigational medicinal product (IMP) for treatment at home was provided as a powder to be suspended on the day of randomisation. Children received oral amoxicillin suspension twice daily, commencing on the day of randomisation. All children were weighed during eligibility screening and was used to determine dose volume according to seven weight bands (*Table 1*).

Participants were randomised to receive either a lower (35–50 mg/kg/day) or a higher (70–90 mg/kg/day) dose, concealment of which was achieved by using amoxicillin products of two different strengths (125 mg/5 ml and 250 mg/5 ml). Therefore, children in each dose arm in the same weight band were administered the same volume of suspension .

Participants were simultaneously randomised to receive either 3 or 7 days of amoxicillin treatment at home. A placebo manufactured to match the characteristics of oral amoxicillin suspension was used to blind parents/guardians and clinical staff to the duration allocation. Both active drug and placebo formed a yellow-coloured similar-tasting suspension. However, because of difficulties in exactly taste-matching the placebo suspension to amoxicillin, one brand of amoxicillin was used for the first 3 days of treatment followed by a second brand for days 4–7 when duration of treatment was 7 days. Parents were instructed to expect a taste change between bottles, but they did not know whether this was due to moving to placebo or to a new brand of amoxicillin. Allocated treatment duration to be given after discharge from hospital was fixed at 3 or 7 days independently of any antibiotics received before randomisation, with up to 48 hours of oral or parenteral beta-lactam treatment permitted before enrolment.

This resulted in four treatment arms, as shown in *Figure 2*.

The hypothesis is that higher doses of amoxicillin given for a longer duration are non-inferior to lower doses of amoxicillin given for a shorter duration for the treatment of children attending hospital with CAP in terms of antibiotic retreatment.

TABLE 1 Weight bands used for dosing of CAP-IT IMP

Weight range (kg)	Dosing intructions
≤ 6.4	4.5 ml twice a day
6.5–8.4	6 ml twice a day
8.5–10.4	7.5 ml twice a day
10.5–13.4	9.5 ml twice a day
13.5–16.9	12 ml twice a day
17.0–20.9	15 ml twice a day
21.0–24.0	16.5 ml twice a day

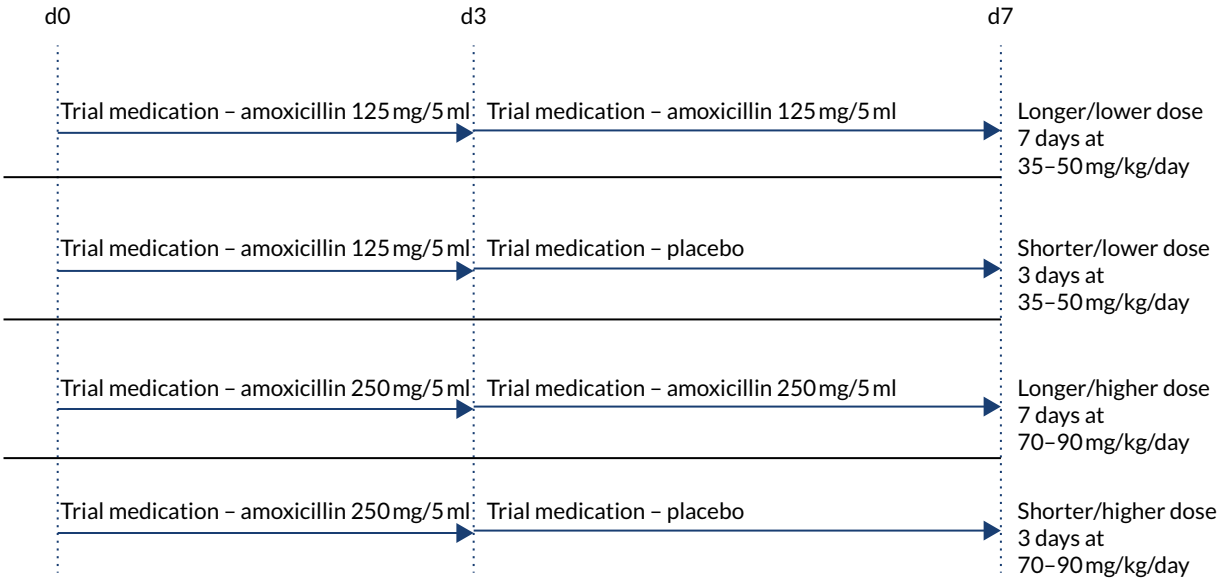


FIGURE 2 Treatment arms.

The objective is to conduct a RCT in children attending hospital with CAP comparing higher and lower doses of amoxicillin given for 3 or 7 days.

Drug substitutions and discontinuations of trial treatment

Substitution of an alternative amoxicillin formulation or another antibiotic was permitted where tolerability issues could not be overcome by improving acceptability (e.g. by mixing the suspension with formula milk, other liquids or foods) or where a clinical need for continued treatment persisted. In situations of toxicity, for example if an allergic reaction to penicillin was suspected, substitution with an alternative class of antibiotic was permitted.

Discontinuation of trial treatment was permitted if, on clinical review, a change in the child's condition justified discontinuation or modification of trial treatment, if use of a medication with a known major or moderate drug interaction with amoxicillin was essential for the child's management or if the parent/guardian withdrew consent for treatment.

In situations where retreatment was deemed necessary, the choice of antibiotic was left to the treating clinician.

Trial assessments and follow-up

Participants were screened as described in *Participants*, and, following receipt of informed consent, randomisation was performed at the point of discharge from hospital. Following randomisation, all participants were followed up for 29 days for evaluation of the primary and secondary end points described in *Outcomes*. The timing and frequency of assessments are summarised in the trial schedule (*Table 2*) and described below.

Enrolment and randomisation

Following identification, screening and informed consent of eligible patients, baseline information was obtained through interview with the parent/guardian. This included demographic information, such as sex and ethnicity, medical history, including review and duration of symptoms (e.g. cough, temperature and respiratory symptoms), underlying diseases and antibiotic exposure in the preceding 3 months. Details of the physical examination, including weight and vital parameters (e.g. temperature, respiratory rate, heart rate and oxygen saturation in room air), were recorded and a baseline nasopharyngeal swab was obtained.

TABLE 2 The CAP-IT assessment schedule

Assessment	Pre randomisation:[a] ≤ 48 hours before randomisation	Days in trial: Day 0 (randomisation)	Day 3	Days 7–9 (week 1)	Days 14–16 (week 2)	Days 21–23 (week 3)	Days 28–30 (week 4)	Any acute event
Trial participation								
Parent/guardian information sheet[b]	✗	✗						
Informed consent		✗						
Drug supply dispensing		✗						
Adherence questionnaire			✗	✗				(✗)
Adherence review (returned medication)							✗	
Clinical assessment								
Medical history[b]	(✗)	✗						
Physical examination[b]	(✗)	✗					✗	✗
Symptom review[b]	(✗)	✗	✗	✗	✗	✗	✗	✗
EQ-5D		✗	✗	✗			✗	✗
Use of health services		✗		✗	✗	✗	✗	✗
Laboratory assessment								
Nasopharyngeal swab[c]	(✗)	✗					✗	(✗)
Haematology	(✗)	(✗)					(✗)	(✗)
Biochemistry	(✗)	(✗)					(✗)	(✗)
Virology	(✗)	(✗)					(✗)	(✗)
Radiological assessment								
Chest radiography	(✗)	(✗)						(✗)
Parent-completed diary								
Symptom diary			✗	✗	✗			
Ancillary subgroup studies								
Stool sample[c]	✗	✗		✗			✗	

EQ-5D, EuroQol-5 Dimensions.
a Assessments in this column were undertaken only for potential participants receiving inpatient antibiotic treatment.
b May be carried out any time before enrolment discussion.
c Taken before starting antibiotics, where possible.

Notes
Dark-purple shading indicates face-to-face assessment, light-purple shading indicates telephone assessment and aqua shading indicates telephone or face-to-face assessment.
(✗) indicates tests that may be carried out if the child's condition requires it or allows it, but are not mandatory.

No additional tests were mandated, but results were collected if tests were performed as part of clinical care, including haematology tests (e.g. haemoglobin, platelet count, leucocyte count, neutrophil count and lymphocyte count), biochemistry tests (e.g. C-reactive protein, procalcitonin and electrolytes), virology [rapid testing for respiratory syncytial virus and influenza A/B (any method)] and chest radiography.

Parents/guardians were provided with trial materials, including a symptom diary, participant information sheet, IMP administration instructions and contact details for the trial team. The symptom diary collected data pertinent to the primary and secondary outcomes and was completed by parents for 14 days following randomisation.

Follow-up

Telephone contact was made with participants on days 3, 7–9, 14–16 and 21–23, with a face-to face visit within 2 days of day 28. At these contacts, primary and secondary end points were reviewed, including additional antibiotic treatment, clinical signs and symptoms, adverse treatment effects and IMP adherence. During face-to-face visits (final or unscheduled) a nasopharyngeal swab was collected, and, if CAP symptoms were ongoing, physical examination findings and physiological parameters were collected. If a hospitable face-to-face visit was not possible for final follow-up, it was attempted by telephone or as a home visit. If this failed, despite reasonable efforts, primary end-point data were sought through contact with the general practitioner (GP) where consent had been given to do so.

If participants required acute clinical assessment for ongoing/re-emerging symptoms during the follow-up period, the treating clinician's judgement determined if investigations, treatment or hospitalisation was required. On premature discontinuation of IMP, irrespective of reason, parents/guardians were encouraged to remain in follow-up. However, parent/guardian decisions were respected, and if follow-up was stopped prematurely, then data and samples already collected were included in the analysis unless parents/guardians requested otherwise.

Data collection and handling

Data were recorded on paper case report forms and entered onto the CAP-IT database by clinical or research staff at each site. Staff with data entry responsibilities completed standardised database training before being granted access to the database. Data were exported into Stata® (v15.1) (StataCorp LP, College Station, TX, USA) for analysis.

Randomisation

Eligibility was confirmed by CAP-IT site investigators through completion of an eligibility checklist. Patients were randomised simultaneously to each of the two factorial randomisations in a 1 : 1 ratio. Randomisation was stratified by group (PED and ward) according to whether or not they had received any non-trial antibiotics in hospital before being enrolled.

A computer-generated randomisation list was produced by the trial statistician based on random permuted blocks of eight. Each block contained an equal number of the four possible combinations of dose and duration in random order. The IMP supplier packaged the trial medication into kits that were grouped into blocks of eight, in accordance with to the randomisation list specification. Blinded IMP labels were applied to each kit, which contained the kit identifications (IDs). Kit IDs were made up of four numerical digits, the first three of which represented the block ID and fourth specified the kit ID within the block. Blinded randomised blocks of IMP were delivered to trial sites and participants were randomised by dispensing the next sequentially numbered kit within the active block.

Blinding

All treating clinicians, parents/guardians and outcome assessors [including End-Point Review Committee (ERC) members] were blinded to the allocated treatment. The use of placebo, as well as the permuted block randomisation strategy and blinded drug kits, ensured that parents and clinic staff remained blinded to amoxicillin duration and dose.

Access to the randomisation list was restricted to trial statisticians and IMP repackagers, and unblinded data were reviewed confidentially only by the Independent Data Monitoring Committee (IDMC) (annually) and trial statisticians. The Trial Management Team remained blinded until after the trial end and completion of the statistical analysis in accordance with the prespecified statistical analysis plan (SAP).

Unblinding was possible in situations where a treating clinician deemed it necessary, for example in the case of a significant overdose. This could be performed using an emergency unblinding system accessible through the CAP-IT website. Only the treating clinician would then be informed of the child's allocation, maintaining the blinding of the trial team.

Outcomes

Primary outcome

The primary outcome for CAP-IT was defined as any clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including CAP) other than trial medication up to and at week 4 final follow-up (i.e. day 28). Prescription of non-trial medication when the primary reason was (1) illness other than respiratory tract infection, (2) intolerance of or adverse reaction to IMP, (3) parental preference or (4) administrative error did not constitute a primary end point.

An ERC, comprising doctors independent of the Trial Management Group and blinded to randomised allocations, reviewed all cases of a participant being prescribed non-trial systemic antibacterial treatment. The main role of the ERC was to adjudicate, based on all available data, whether or not the primary outcome was met. The ERC classified non-trial systemic antibacterial treatment as being for respiratory tract infection with likelihoods of 'definitely/probably', 'possibly', 'unlikely' or 'too little information'. Those infections categorised as 'CAP', 'chest infection' or 'other respiratory tract infection' with a treatment likelihood assessment of 'definitely/probably' or 'possibly' were regarded as fulfilling the primary end point.

Information on additional antibacterial treatments was collected from parents through follow-up telephone contact with parents on days 3, 7, 14 and 21, at the final visit contact and finally through a daily diary completed by parents on days 1–14.

During enrolment, parents were asked to provide consent for the research teams to contact their child's general practice to collect information regarding antibacterial treatment given during the follow-up period. This additional information supported the ERC in accurately adjudicating events. In addition, this allowed the collection of primary outcome data where contact with participants had been lost prior to completion of the follow-up period.

Changes to primary end point

The primary end-point definition was clarified in protocol v3.0 to specify that 'systemic antibacterial' treatments should avoid inclusion of topical antibiotics, which were not of interest. In protocol v4.0, the primary end point was refined further, resulting in the definition in *Primary outcome*. This definition specified that the systemic antibacterial must be clinically indicated and prescribed for a respiratory tract infection (including CAP), as adjudicated by the ERC.

Secondary outcomes

Secondary outcomes included measures of morbidity, antimicrobial resistance and trial medication adherence.

Morbidity

Morbidity secondary outcomes included severity and duration of parent/guardian-reported CAP symptoms and specified clinical AEs.

The following CAP symptoms were elicited at baseline, in follow-up telephone calls at days 4, 8, 15 and 22 and at the final visit, as well as at unscheduled visits: cough, wet cough (i.e. phlegm), breathing faster (i.e. shortness of breath), wheeze, sleep disturbed by cough, vomiting (including after cough), eating/drinking less and interference with normal activity. Parents/guardians were asked to grade each symptom using the following five categories: (1) not present, (2) slight/little, (3) moderate, (4) bad and (5) severe/very bad. Date of start and resolution were also elicited. Symptoms and their severity (using the same categories) were obtained daily on the symptom diary for 14 days from randomisation.

Information about diarrhoea, skin rash and thrush was collected and graded in the same way as CAP symptoms. In addition, AEs related to the stopping of trial medication or the start of non-trial antibiotics were recorded.

Other AEs meeting the criteria for seriousness [i.e. serious adverse events (SAEs)] were reported within 24 hours of research sites becoming aware of the event. SAEs were classified by system organ class and lower-level term in accordance with the Medical Dictionary for Regulatory Activities (MedDRA®; version 21.1) and were graded using the *Division of Aids (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events*.[81]

Antimicrobial resistance

The antimicrobial resistance secondary end point was defined as phenotypic resistance to penicillin at week 4 measured in *S. pneumoniae* isolates colonising the nasopharynx. Carriage and resistance of *S. pneumoniae* isolates were assessed by analysis of nasopharyngeal samples, collected from participants at baseline, at the final visit (i.e. day 29) and at any unscheduled visits during the follow-up period.

Phenotypic penicillin susceptibility was determined for *S. pneumoniae* isolates by microbroth dilution across a dilution range for penicillin of 0.016–16 mg/l and interpreted in accordance with EUCAST (European Committee on Antimicrobial Susceptibility Testing) clinical break-point tables v10.0 for benzylpenicillin and *S. pneumoniae* (infections other than meningitis) [i.e. sensitive (MIC $\leq$ 0.064 mg/l), non-susceptible (MIC 0.125–2 mg/l) or resistant (MIC $>$ 2 mg/l)].[82] The same approach was taken for amoxicillin susceptibility testing [isolates with MIC $\leq$ 0.5 mg/l were sensitive and isolates with MIC $>$ 1 mg/l were resistant). *S. pneumoniae* ATCC® 49619™ (ATCC, Manassas, VA, USA) was used for quality control.[82]

Adherence

Data on IMP adherence were elicited during follow-up telephone calls, at the final visit (where follow-up telephone calls were not performed) and at unscheduled visits. At each time point, parents/guardians were asked if IMP had been stopped early, and, if so, the date of the last dose taken and for which of the following reasons: CAP improved/cured, CAP worsened/not improving or gagging/spitting out/refusing. In addition, parents/guardians were asked how many doses of each bottle were either missed or were less than the full prescribed volume.

Sample size

The sample size was based on demonstrating non-inferiority for the primary efficacy end point for each of the duration and dose randomisations. Although inflation factors have been advocated for factorial trials to account for interaction between the interventions, or a reduction in the number of events, this is not necessary if either randomised intervention (dose or duration) has a null effect (i.e. the underlying hypothesis with a non-inferiority design), as marginal analyses can then be conducted.

The expected antibiotic retreatment rate was originally assumed to be 5%. However, data emerging during the enrolment phase suggested that the primary outcome event rate was considerably higher, at approximately 15%. This necessitated a change in the non-inferiority margin, which was increased from 4% to 8%. This is still lower than the European Medicines Agency's recommendation of a 10% non-inferiority margin for adult CAP trials.[83] Assuming a 15% event rate, 8% non-inferiority margin (on a risk difference scale) assessed against a two-sided 90% confidence interval (CI) and 15% loss to follow-up, the sample size was calculated as 800 children to achieve 90% power.

Statistical methods

Analysis principles

The primary analysis adopted a modified intention-to-treat (ITT) principle, that is it included all patients enrolled and analysed in accordance with the group to which they were randomised, regardless of treatment actually received. One modification to the strict ITT principle prespecified in the trial SAP was the exclusion of randomised patients who did not take any IMP. Owing to the blinded nature of the trial, the risk of introducing bias by exclusion of these patients was considered minimal. A secondary on-treatment analysis was performed that excluded 'non-adherent' participants, defined as having taken < 80% of scheduled trial medication, based on (1) all trial medication including placebo and (2) active drug only.

In the primary and secondary analyses, the main effect for each randomisation was estimated by collapsing across levels of the other randomisation factor, supplemented by tests for interaction between the two randomisations and with previous systemic antibacterial exposure. Interaction was assessed on an additive scale.

For continuous variables, the mean (with standard deviation) or median [with interquartile range (IQR)] of absolute values and of changes in absolute values from baseline were reported by scheduled telephone calls/visits and by randomised group.

For binary and categorical variables, differences between groups at particular time points were tested using chi-squared tests (or exact tests, if appropriate). For ordered variables, differences between groups at particular time points were tested using rank tests.

For time-to-event outcomes, the time from baseline to the event date was used, applying Kaplan–Meier estimation. Where participants did not experience an event, data were censored at the date of last review of that event. Differences between groups were tested using a log-rank test.

Formal statistical adjustment for multiple comparisons (particularly pertinent for some of the secondary end points) were not applied, and significance tests should be interpreted in the context of the total number of related comparisons performed.

The primary end point was analysed within a non-inferiority framework, where significance testing has no clear role (with emphasis instead on CIs). Secondary outcomes were analysed within a superiority framework (i.e. assessing the null hypothesis of no difference). All estimates, including differences between randomised groups, are presented with two-sided 90% CIs (rather than the more conventional 95%) to achieve consistency with the reporting of the primary end point.

Primary outcome

The proportion of children meeting the primary end point was obtained from the cumulative incidence at day 28, as estimated by Kaplan–Meier methods (i.e. accounting for the differential follow-up times). Participants with incomplete primary outcome data (e.g. as a result of a missed final visit) were censored at the time of their last contact. In the case of participants who missed the final visit but whose GP confirmed that no additional antibacterials were prescribed during the follow-up period, day 28 was used as the censoring date.

Kaplan–Meier estimates were used to derive the risk difference between the randomised groups for the primary end point, and standard errors and CIs for the risk difference were derived from the estimated standard errors of the individual survival functions.

Lower-dose treatment and shorter-duration treatment were considered 'non-inferior' to higher-dose treatment and longer-duration treatment, respectively, if the upper limit of the two-sided 90% CI for the difference in the proportion of children with the primary end point at day 28 was less than the non-inferiority margin of 8%. Although the non-inferiority margin was important to the design of the trial, it is less relevant to its interpretation, which should be based on observed estimates and CIs.

Sensitivity analyses

As described in *Primary outcome*, the primary analysis included only end points confirmed by the ERC as clinically indicated antibacterial treatment for respiratory tract infection (including CAP). To improve confidence in the primary analysis, the following sensitivity analyses were performed for the primary end point:

- including all systemic antibacterial treatments other than trial medication regardless of reason and indication
- including only ERC-adjudicated clinically indicated systemic antibacterial treatment where either CAP or 'chest infection' was specified as the reason for this treatment (rather than any respiratory tract infection)
- as above, but also including, as an end point, all systemic antibacterial treatments for CAP or 'chest infection' where the clinical indication was 'unlikely', as adjudicated by the ERC
- disregarding systemic antibacterial prescriptions occurring within the first 3 days from randomisation, as these events cannot be related to the treatment duration randomisation, to allow comparison of shorter and longer treatment.

Subgroup analyses

Two subgroup analyses were performed. The first considered severity of CAP at enrolment to provide reassurance that a potential null effect was not due to dilution arising from inclusion of children with mild disease. The main efficacy analysis was repeated, but included only participants with severe CAP, defined as two or more of the following abnormal signs/symptoms at enrolment: raised respiratory rate (> 37 breaths/minute for children aged 1–2 years; > 28 breaths/minute for children aged 3–5 years), oxygen saturation < 92% in room air and presence of chest retractions.

The second subgroup analysis considered the potential for seasonal changes in infections, by including only primary end points occurring in the two winter seasons spanned by CAP-IT. This was based on Public Health England reports of circulating viruses/bacteria in the winter seasons spanned by CAP-IT.

Community-acquired pneumonia symptoms

The severity of the symptoms (detailed in *Morbidity*) were reviewed by the number (%) of symptoms in each severity category at each scheduled contact visit and analysed as described for ordered outcomes in *Analysis principles*.

Duration of a symptom was measured as time from baseline to resolution, defined as the first day the symptom was reported as not present. This was analysed as a time-to-event outcome, as specified in *Analysis principles*. Where a symptom was not present at enrolment, participants were excluded from the analysis of that symptom.

Clinical adverse events

Solicited clinical AEs, specified in *Morbidity*, were analysed overall and by randomised arm. Analysis considered total number of events, number of participants with at least one event, the number of participants with at least one new event and event severity. These variables were analysed as described for binary outcomes in *Analysis principles*.

In addition, the number of participants experiencing at least one SAE were compared as a binary outcome (see *Analysis principles*).

Antimicrobial resistance

Descriptive analyses of baseline samples were analysed as follows: proportion of samples with positive *S. pneumoniae* culture, frequency distribution of broth microdilution MIC values and proportion of samples classified as S – susceptible, standard dosing regimen; I – intermediate, increased exposure; and R – resistant (see *Secondary outcomes*).

S. pneumoniae carriage, determined by tabulation of the proportion of samples with positive *S. pneumoniae* culture at the final visit by randomisation group, was compared using tests for binary variables, as described in *Secondary outcomes*. *S. pneumoniae* culture results at the final visit were cross-tabulated with baseline culture results (including missing values).

For the antimicrobial resistance analysis, a descriptive analysis of the proportion of samples with resistance to penicillin (S – susceptible/I – intermediate/R – resistant categorisation) at the final visit was performed using both cut-off points (penicillin and amoxicillin) described in *Secondary outcomes*. This analysis was repeated, first, including only samples with a positive *S. pneumoniae* culture result and, second, including all samples. Randomised groups were compared by tests for binary variables, and cross-tabulation of penicillin resistance at the final visit compared with penicillin resistance at baseline was performed as a descriptive analysis.

Finally, the change in broth microdilution MIC (in patients for whom this was measured at both the baseline and the final visit) was analysed with randomisation group as factors and after adjusting for baseline MIC.

Interim analyses

The trial was reviewed by the CAP-IT IDMC. They met three times over the course of the trial: once at a joint meeting with the Trial Steering Committee (TSC) in June 2017 and twice in strict confidence in January 2018 and January 2019. The IDMC reviewed unblinded safety and efficacy data and made recommendations through correspondence to the TSC following each meeting.

Patient and public involvement

Parents of young children were involved during the development and delivery of CAP-IT. A PPI representative was a member of the TSC, contributing at meetings and in an ad hoc fashion when required. When considering the research question, the trial team were advised by parents that shorter antibiotic courses would be welcomed if equally effective, because of difficulties in giving medicine (due to palatability or challenges with day care and daytime doses). For the same reasons, parents

supported the twice-daily dosing of the CAP-IT. Multiple PPI representatives reviewed and provided input on the patient information materials, including the CAP-IT information film, to ensure that they were clear, easy to understand and not off-putting to parents, while still providing sufficient detail to allow informed consent. Valuable input was provided from the PPI representative on the CAP-IT TSC on the plan for dissemination of the CAP-IT results.

Protocol amendments

The CAP-IT protocol v.2.0 was active when recruitment to CAP-IT commenced in January 2017. Two protocol amendments were completed subsequently, with version 3 implemented in September 2017 and version 4 in December 2018. Amendments were largely in relation to selection criteria (see *Exclusion criteria*) and the SAP (to which three significant updates were made on the basis of accumulating trial data). First, a stratified analysis was originally planned based on the PED and ward groups. This was changed to a joint analysis in protocol version 3 because of significant clinical overlap (see *Appendix 1* for more details) Second, the primary end-point definition was made more specific in protocol version 3 and further refined in version 4 (see *Changes to primary end point*). Finally, the non-inferiority margin was adjusted, as the primary end-point event rate had been substantially underestimated. The trial and all substantial amendments were approved by the London – West London & GTAC Research Ethics Committee (reference 16/LO/0831).

Chapter 3 Results

Participant flow

Between 1 February 2017 and 23 April 2019, a total of 2642 children were assessed for eligibility and 824 were randomised. Ten patients were randomised but received no trial medication (owing to, for example, a change of mind by parent/guardian or administrative error) and were, therefore, excluded from the analysis, resulting in an analysis population of 814 patients.

A total of 591 participants had no pre-treatment antibiotic at trial entry. A total of 223 (mainly following admission to assessment units of wards) had received beta-lactam antibiotic pre-treatment for no more than 48 hours. The final follow-up visit occurred on 21 May 2019, which was considered the trial end date.

Six participants were randomised in error but were included in the analysis in accordance with the ITT principle. Of these participants, five did not have all the required symptoms to fulfil the criteria for CAP diagnosis (see *Box 1*). One patient did not have a cough reported in the previous 96 hours at presentation, two patients did not have a reported fever in the previous 48 hours at presentation and two patients lacked documentation of signs of laboured/difficult breathing and/or focal chest signs at presentation. In one of the final two patients, chest radiography was suggestive of lobar pneumonia, prior to this being added to the inclusion criteria as part of protocol version 4.0, and in the other participant pneumonia was diagnosed on chest radiography, but was documented as patchy infiltrate, which did not fulfil the inclusion criteria. The final patient randomised in error received an antibiotic other than a beta-lactam (clarithromycin) before discharge (*Table 3*).

Participants were well distributed between arms, with 208 (25.6%) participants receiving 3 days of lower-dose treatment, 202 (24.8%) participants receiving 7 days of lower-dose treatment, 205 (25.2%) participants receiving 3 days of higher-dose treatment and 199 (24.4%) participants receiving 7 days of higher-dose treatment (*Figure 3* and *Table 4*).

TABLE 3 Ineligible patients

Reason for ineligibility	Treatment arm, *n* (%)				Total (*N* = 814), *n* (%)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Known violation of any inclusion/exclusion criterion	1 (0.2)	5 (1.2)	4 (1.0)	2 (0.5)	6 (0.7)
No presence of cough	0	1	0	1	1
No presence of fever	0	2	2	0	2
No presence of CAP signs	0	2	2	0	2
Pre-treatment with non-beta-lactams	1	0	0	1	1
Excluded from analysis	0	0	0	0	0

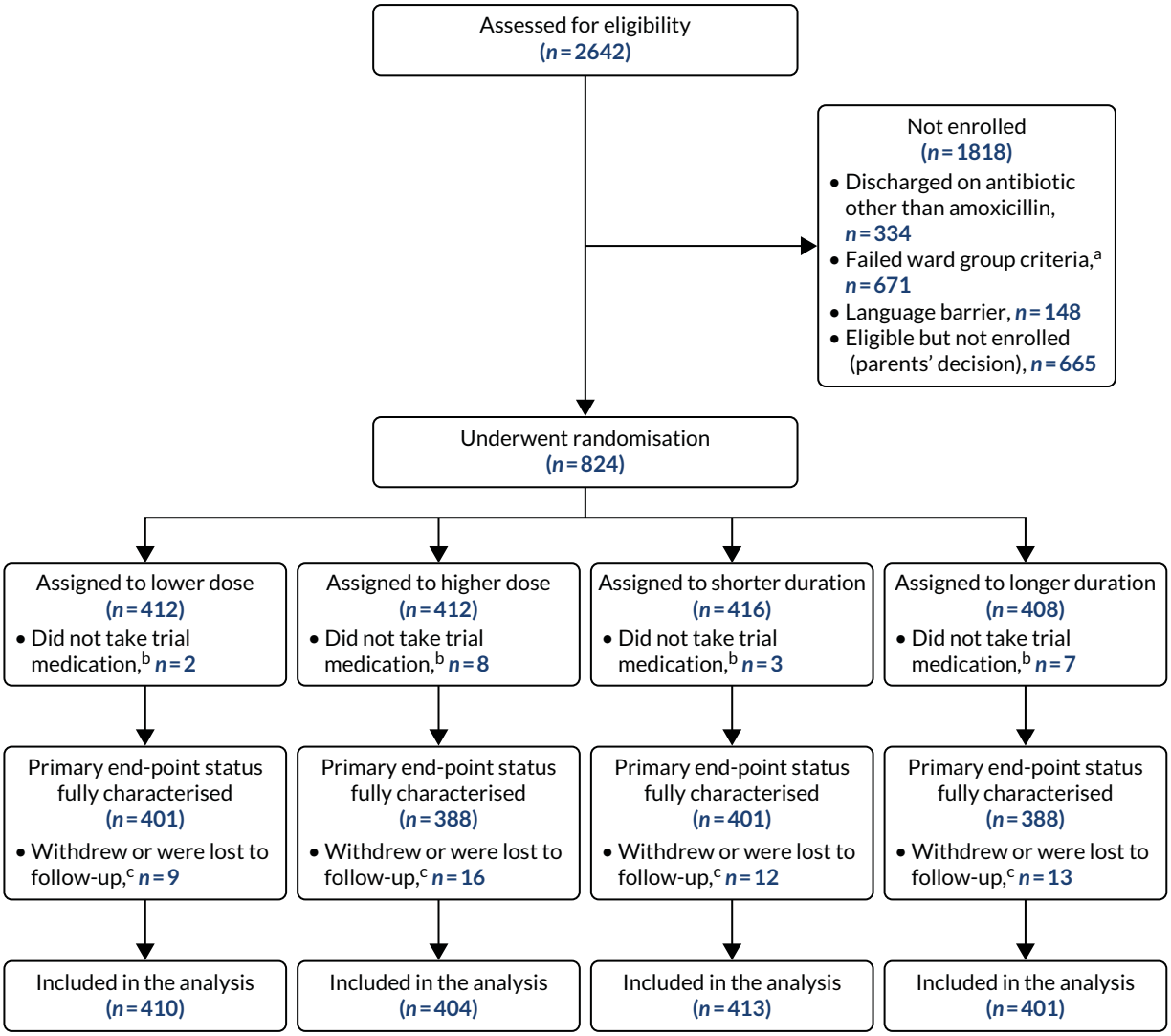


FIGURE 3 A CONSORT (Consolidated Standards of Reporting Trials) flow diagram. a, Inpatient stay > 48 hours and treated with non-beta-lactam antibiotics as inpatients; b, these children have been excluded from all analyses; and c, follow-up included up to time of withdrawal or no further contact.

TABLE 4 Randomisation outcomes: analysis population

Outcome	Treatment arm, *n* (%)		
	PED (*N* = 591)	Ward (*N* = 223)	Total (*N* = 814), *n* (%)
Randomisation arm			
Lower dose plus shorter duration	153 (25.9)	55 (24.7)	208 (25.6)
Lower dose plus longer duration	150 (25.4)	52 (23.3)	202 (24.8)
Higher dose plus shorter duration	146 (24.7)	59 (26.5)	205 (25.2)
Higher dose plus longer duration	142 (24.0)	57 (25.6)	199 (24.4)
Dose randomisation			
Lower	303 (51.3)	107 (48.0)	410 (50.4)
Higher	288 (48.7)	116 (52.0)	404 (49.6)
Duration randomisation			
Shorter	299 (50.6)	114 (51.1)	413 (50.7)
Longer	292 (49.4)	109 (48.9)	401 (49.3)

Baseline

Patient characteristics

Baseline patient characteristics were well balanced between the randomisation groups (see *Table 4*). The median age of participants was 2.5 (IQR 1.6–3.7) years, with a minimum and maximum age of 0.5 and 8.8 years, respectively, and 52% were male (*Table 5*).

Medical history

One-third of participants (30.7%) reported an underlying diagnosis of asthma or use of an asthma inhaler within the past month. The second most common comorbidity (affecting 20% of participants) was eczema, followed by food or drug allergies (9.6%) and hay fever (9.1%). Routine vaccinations had been received by 95% of participants; the remaining 5% either had not had routine vaccinations (3.2%), or were of unknown vaccination status or had been vaccinated outside the UK (1.8%).

Vital parameters and clinical signs

Participant vital parameters were measured at presentation and were similar between randomisation groups (*Table 6*). The median temperature was 38.1 °C (IQR 37.2–38.8 °C) and median oxygen saturation was 96% (IQR 95–98%). The median number of days for which a child had a cough at presentation was 4 (IQR 2–7) days, and the median number of days for which a child had a temperature was 3 (IQR 1–4) days. The median weight was 13.5 (IQR 11.2–16.4) kg.

The most common baseline clinical signs were coryza [affecting 599/814 (73.6%) participants] and chest retractions [affecting 483/814 (59.3%) participants] (*Table 7*). Other baseline clinical signs were less common (enlarged tonsils or pharyngitis, 22.5%; pallor, 20.9%; nasal flaring, 9.3%, inflamed/bulging tympanic membrane or middle ear effusion, 9%; and stridor, 1.2%).

Multiple vital parameters and clinical signs differed at presentation between the children previously exposed and unexposed to antibiotics (see *Table 7*).

TABLE 5 Patient characteristics

Characteristic	Treatment arm				Total (*N* = 814)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Age (years)					
Median (IQR)	2.5 (1.6–3.7)	2.4 (1.6–3.7)	2.5 (1.7–3.7)	2.5 (1.5–3.7)	2.5 (1.6–3.7)
Minimum, maximum	0.5, 8.8	0.5, 8.5	0.5, 8.5	0.5, 8.8	0.5, 8.8
Sex, *n* (%)					
Male	210 (51)	211 (52)	217 (53)	204 (51)	421 (52)
Female	200 (49)	193 (48)	196 (47)	197 (49)	393 (48)
Ethnicity, *n* (%)					
White	275 (67)	279 (69)	283 (69)	271 (68)	554 (68)
Asian or British Asian	55 (13)	51 (13)	53 (13)	53 (13)	106 (13)
Black or black British	40 (10)	36 (9)	40 (10)	36 (9)	76 (9)
Other	40 (10)	38 (9)	37 (9)	41 (10)	78 (10)
Number (%) of households with smokers	69 (17)	62 (16)	61 (15)	70 (18)	131 (16)

TABLE 6 Medical history

Medical history	Treatment arm, *n* (%)				Total (*N* = 814), *n* (%)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Asthma or inhaler use within past month	119 (29)	136 (34)	125 (30)	130 (32)	255 (31)
Hay fever	34 (8)	40 (10)	37 (9)	37 (9)	74 (9)
Food or drug allergy	38 (9)	40 (10)	37 (9)	41 (10)	78 (10)
Eczema	84 (20)	79 (20)	78 (19)	85 (21)	163 (20)
Prematurity	43 (10)	43 (11)	51 (12)	35 (9)	86 (11)
Routine vaccinations?					
Yes	388 (95)	385 (95)	394 (95)	379 (95)	773 (95)
No	14 (3)	12 (3)	15 (4)	11 (3)	26 (3)
Not sure (or vaccinated outside UK)	8 (2)	7 (2)	4 (1)	11 (3)	15 (2)
Other underlying disease	37 (9)	19 (5)	21 (5)	35 (9)	56 (7)

TABLE 7 Vital parameters and clinical signs at presentation by randomisation status

Parameter/clinical sign	Treatment arm				Total (*N* = 814)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Weight (kg), median (IQR)	13.6 (11.2–16.8)	13.3 (11.1–16.2)	13.8 (11.5–16.4)	13.2 (10.9–16.4)	13.5 (11.2–16.4)
Temperature (°C), median (IQR)	38.1 (37.3–38.9)	38.0 (37.2–38.6)	38.0 (37.1–38.7)	38.1 (37.3–38.8)	38.1 (37.2–38.8)
Temperature ≥ 38 °C, *n* (%)	227 (55)	214 (53)	221 (54)	220 (55)	441 (54)
Heart rate (b.p.m.), median (IQR)	146 (131–160)	143 (130–158)	144 (131–158)	146 (130–162)	145 (130–160)
Abnormal heart rate,[a] *n* (%)	307 (75)	271 (67)	282 (68)	296 (74)	578 (71)
Respiratory rate (breaths/minute), median (IQR)	37 (30–44)	38 (32–44)	36 (30–43)	38 (32–45)	37 (30–44)
Abnormal respiratory rate,[b] *n* (%)	270 (66)	258 (64)	262 (64)	266 (67)	528 (65)
Oxygen saturation (%), median (IQR)	96 (95–98)	96 (95–98)	96 (95–98)	96 (95–98)	96 (95–98)
Abnormal oxygen saturation,[c] *n* (%)	18 (4)	25 (6)	18 (4)	25 (6)	43 (5)
Nasal flaring, *n* (%)	33 (8)	42 (10)	35 (9)	40 (10)	75 (9)
Chest retractions, *n* (%)	239 (58)	244 (60)	239 (58)	244 (61)	483 (59)
Pallor, *n* (%)	82 (20)	87 (22)	93 (23)	76 (19)	169 (21)

TABLE 7 Vital parameters and clinical signs at presentation by randomisation status (*continued*)

Parameter/clinical sign	Treatment arm				Total (*N* = 814)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Stridor, *n* (%)	4 (1)	6 (1)	5 (1)	5 (1)	10 (1)
Inflamed/bulging tympanic membrane or middle ear effusion, *n* (%)	37 (9)	35 (9)	39 (10)	33 (8)	72 (9)
Coryza, *n* (%)	291 (71)	308 (76)	304 (74)	295 (74)	599 (74)
Enlarged tonsils or pharyngitis, *n* (%)	95 (24)	86 (22)	92 (22)	89 (23)	181 (23)

b.p.m., beats per minute.
a Abnormal respiratory rate: > 37 breaths/minute for children aged 1–2 years and > 28 breaths/minute for children aged ≥ 3 years.
b Abnormal heart rate: > 140 b.p.m. for children aged 1–2 years and > 120 b.p.m. for children aged ≥ 3 years.
c Abnormal oxygen saturation: < 92%.

Chest examination

Chest examination findings at presentation were reported as absent, bilateral or unilateral. Unilateral findings were present in 691 (85%) participants overall, featuring as crackles/crepitations in 562 (71%) participants, reduced breath sounds in 336 (44%) participants, bronchial breathing in 103 (15%) participants and dullness to percussion in 59 (13%) participants. The proportions of the four chest examination variables were very similar among the randomisation arms (*Table 8*).

TABLE 8 Chest examination at presentation by randomisation status

Chest examination finding	Treatment arm, *n* (%)				Total (*N* = 814), *n* (%)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Dullness to percussion					
Absent	194 (86)	186 (86)	198 (86)	182 (86)	380 (86)
Unilateral	32 (14)	27 (13)	31 (13)	28 (13)	59 (13)
Bilateral	0 (0)	3 (1)	1 (< 1)	2 (1)	3 (1)
Bronchial breathing					
Absent	283 (82)	263 (82)	276 (83)	270 (81)	546 (82)
Unilateral	53 (15)	50 (16)	49 (15)	54 (16)	103 (15)
Bilateral	10 (3)	7 (2)	8 (2)	9 (3)	17 (3)
Reduced breath sounds					
Absent	202 (52)	187 (49)	202 (51)	187 (50)	389 (50)
Unilateral	168 (43)	168 (44)	174 (44)	162 (43)	336 (44)
Bilateral	20 (5)	26 (7)	20 (5)	26 (7)	46 (6)
Crackles/crepitations					
Absent	69 (17)	65 (17)	71 (18)	63 (16)	134 (17)
Unilateral	287 (71)	275 (70)	290 (72)	272 (69)	562 (71)
Bilateral	48 (12)	52 (13)	42 (10)	58 (15)	100 (13)

Parent/guardian-reported community-acquired pneumonia symptoms

Parent/guardian-reported symptom severity at trial entry is shown in *Figure 4*. The most common clinical symptom was cough, reported by 96.5% of participants. Fever and fast breathing were reported for 79.6% and 83.5% of participants, respectively, and the least common symptoms at baseline were vomiting and wheeze, reported in 41.1% and 51.8% of participants, respectively. Sleep disturbance, eating less and interference with normal activity were reported in between 80% and 90% of participants.

Clinical symptoms in patients who received in-hospital antibiotics prior to trial entry (i.e. the ward group) were reported by parents/guardians at presentation (pre trial) and at baseline (trial entry). *Figures 5* and *6* show parent/guardian-reported clinical symptom severity both pre trial and at trial entry for the ward group and at trial entry only for the PED group. For the ward group, the proportion of participants with presence of symptoms at any level of severity decreased between pre trial and trial entry for all symptoms except wet cough (phlegm). The greatest proportional decrease was for fever, for which the proportion of participants with a severity of slight/little or greater decreased from 87.9% to 50.2%.

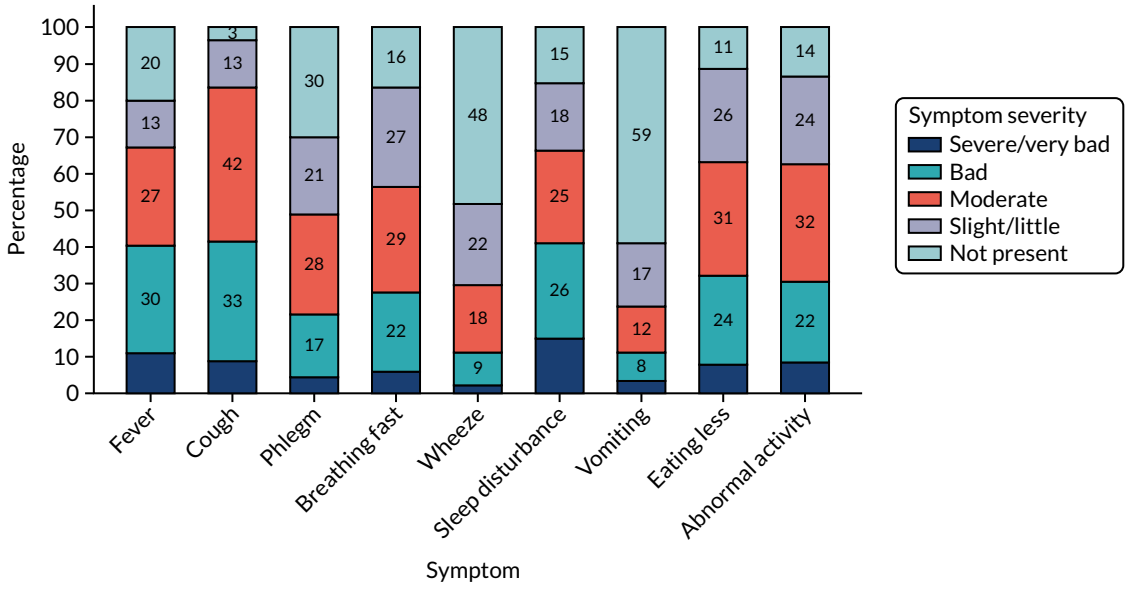


FIGURE 4 Symptoms at trial entry.

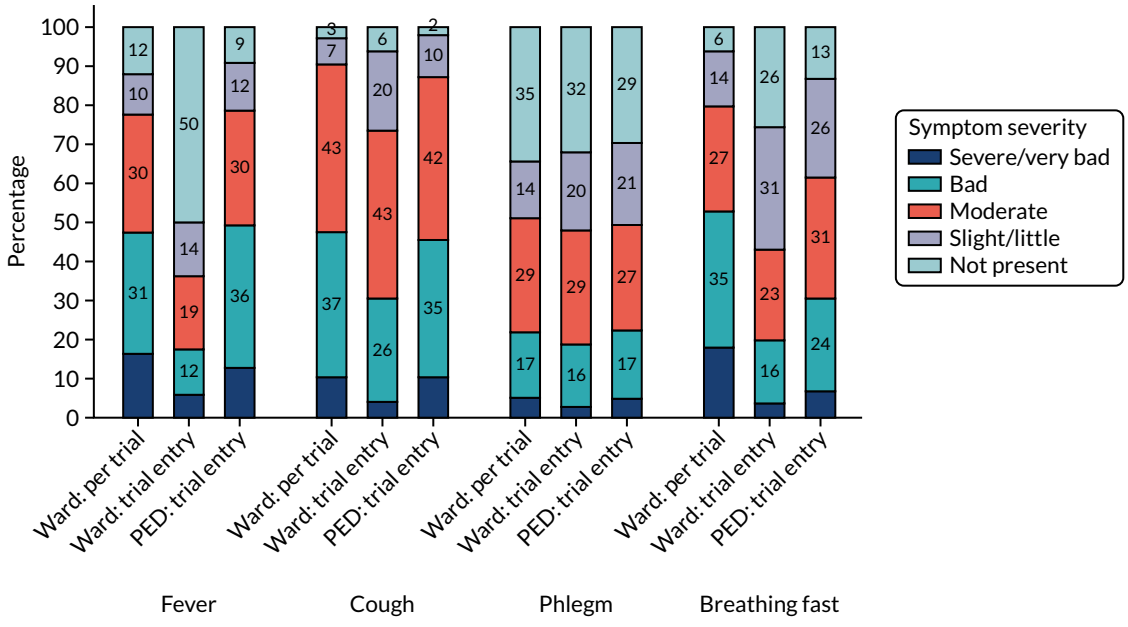


FIGURE 5 Clinical symptoms (i.e. fever, cough, phlegm and breathing fast) at trial entry, by group.

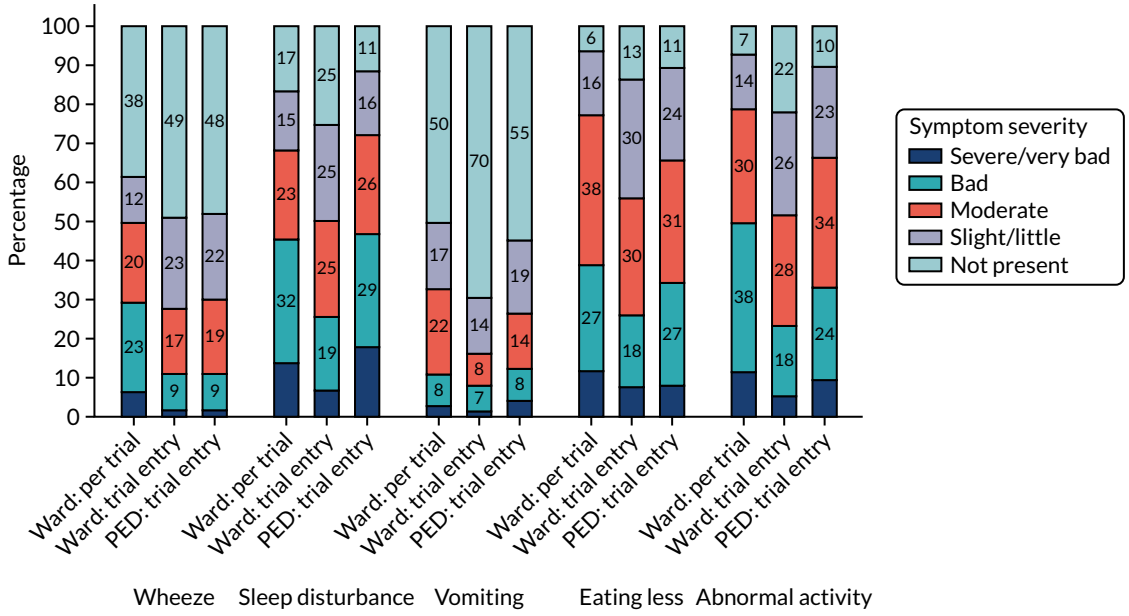


FIGURE 6 Clinical symptoms (i.e. wheeze, sleep disturbance, vomiting, eating less and abnormal activity) at trial entry, by group.

Community-acquired pneumonia symptoms at trial entry, by stratum, are shown in *Appendix 2*, *Table 27*.

Clinical investigations

Clinical investigations, including chest radiography, haematology assessment, biochemistry assessment, blood culture and respiratory samples, were not mandatory in CAP-IT. However, if any of these investigations were undertaken, results were reported.

Chest radiography was the most common investigation and was undertaken in 391 (48%) participants (*Table 9*). Haematological and biochemical assessments were undertaken in 81 (10%) and 82 (10.1%) participants, respectively, while blood cultures and respiratory specimens were obtained in 41 (5%) and 46 (5.7%) participants, respectively.

TABLE 9 Baseline radiographic findings in participants who had chest radiography performed

Result of chest radiography	Treatment arm, *n* (%)				Total (*N* = 391), *n* (%)
	Lower dose (*N* = 192)	Higher dose (*N* = 199)	Shorter duration (*N* = 196)	Longer duration (*N* = 195)	
Suggestive of pneumonia: lobar infiltrate	65 (33.9)	69 (34.7)	64 (32.7)	70 (35.9)	134 (34.3)
Suggestive of pneumonia: patchy infiltrate	72 (37.5)	82 (41.2)	84 (42.9)	70 (35.9)	154 (39.4)
Unsure if suggestive of pneumonia	21 (10.9)	16 (8.0)	15 (7.7)	22 (11.3)	37 (9.5)
Other diagnosis	7 (3.6)	5 (2.5)	6 (3.1)	6 (3.1)	12 (3.1)
No finding/not suggestive of pneumonia	27 (14.1)	27 (13.6)	27 (13.8)	27 (13.8)	54 (13.8)

Of the 46 respiratory samples taken, 44 samples underwent virology assessment and 11 samples underwent bacteriology assessment (*Table 10*). All 11 of the respiratory samples subjected to bacteriological assessment showed no significant growth.

Finally, of the 40 blood samples taken for culture, 37 (93%) returned a negative result. The three positive results were considered probably due to contamination, with two identifying as coagulase-negative staphylococci and one identifying as Gram-positive cocci (not further differentiated).

Prior antibiotic exposure

A total of 242 (29.7%) children received antibiotics for up to 48 hours prior to enrolment, of whom 241 received beta-lactam antibiotics and one received a macrolide. Amoxicillin was the most common antibiotic taken prior to trial entry (209/242, 86.4%), followed by co-amoxiclav (20/242, 8.3%). In children receiving antibiotics prior to enrolment, the median number of doses was 2 (IQR 1–3). More than half of children (55%) were enrolled within 12 hours of commencing antibiotic treatment, with 24.8% enrolled within 12–24 hours, 12.4% within 24–36 hours and 7.9% within 36–48 hours (*Table 11*).

Other medical interventions in exposed group

In addition, 54.3% of children in the ward group received supportive measures, including oxygen (49.3%), nasogastric feeds or fluids (2.7%), parenteral fluids (8.5%) and chest physiotherapy (2.7%). Finally, 82.1% of children in the ward group received pharmacological treatment other than antibiotics in hospital, including salbutamol inhalers (58.3%), paracetamol (52.1%), steroids (22.9%), ibuprofen (15.7%) and ipratropium bromide (8.3%).

TABLE 10 Baseline respiratory sample virology assessment results

Assessment result	Treatment arm, *n* (%)				Total (*N* = 44), *n* (%)
	Lower dose (*N* = 19)	Higher dose (*N* = 25)	Shorter duration (*N* = 24)	Longer duration (*N* = 20)	
Type of respiratory sample for virology					
Nasopharyngeal	13 (68)	21 (84)	20 (83)	14 (70)	34 (77)
Oropharyngeal	6 (32)	4 (16)	4 (17)	6 (30)	10 (23)
Respiratory sample for virology: result					
Rhinovirus	5 (26)	7 (28)	6 (25)	6 (30)	12 (27)
Influenza A/B	1 (5)	1 (4)	0 (0)	2 (10)	2 (5)
Adenovirus	0 (0)	1 (4)	1 (4)	0 (0)	1 (2)
Rhinovirus plus adenovirus	2 (11)	1 (4)	2 (8)	1 (5)	3 (7)
Rhinovirus plus enterovirus	4 (21)	5 (20)	5 (21)	4 (20)	9 (20)
Rhinovirus plus enterovirus plus adenovirus	0 (0)	1 (4)	0 (0)	1 (5)	1 (2)
Rhinovirus plus enterovirus plus coronavirus	1 (5)	0 (0)	1 (4)	0 (0)	1 (2)
Human metapneumovirus	1 (5)	2 (8)	2 (8)	1 (5)	3 (7)
No viral isolate present	5 (26)	7 (28)	7 (29)	5 (25)	12 (27)

TABLE 11 Prior exposure with antibiotics

Prior exposure	Treatment arm				Total (*N* = 814)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Any systemic antibiotic in last 3 months, *n* (%)					
Yes	64 (16)	65 (16)	66 (16)	63 (16)	129 (16)
No	346 (84)	339 (84)	347 (84)	338 (84)	685 (84)
Antibiotics received in last 48 hours?, *n* (%)					
Yes	119 (29)	123 (30)	123 (30)	119 (30)	242 (30)
No	291 (71)	281 (70)	290 (70)	282 (70)	572 (70)
Class of prior antibiotic, *n* (%)					
Beta-lactam	118 (99)	123 (100)	123 (100)	118 (99)	241 (100)
Macrolide	1 (1)	0 (0)	0 (0)	1 (1)	1 (< 1)
Prior antibiotic, *n* (%)					
Amoxicillin	103 (87)	106 (86)	104 (85)	105 (88)	209 (86)
Benzylpenicillin	1 (1)	2 (2)	1 (1)	2 (2)	3 (1)
Ceftriaxone	2 (2)	4 (3)	3 (2)	3 (3)	6 (2)
Cefuroxime	2 (2)	0 (0)	2 (2)	0 (0)	2 (1)
Clarithromycin	1 (1)	0 (0)	0 (0)	1 (1)	1 (< 1)
Co-amoxiclav	9 (8)	11 (9)	13 (11)	7 (6)	20 (8)
Phenoxymethylpenicillin	1 (1)	0 (0)	0 (0)	1 (1)	1 (< 1)
Number of prior antibiotic doses, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Prior antibiotic: route, *n* (%)					
Intravenous	15 (13)	10 (8)	17 (14)	8 (7)	100 (41)
Oral	103 (87)	110 (89)	106 (86)	107 (90)	85 (35)
Intravenous plus oral	1 (1)	3 (2)	0 (0)	4 (3)	28 (12)
Duration (hours) of prior antibiotic treatment, *n* (%)					
< 12	67 (56)	66 (54)	68 (55)	65 (55)	133 (55)
12–24	27 (23)	33 (27)	33 (27)	27 (23)	60 (25)
24–36	13 (11)	17 (14)	13 (11)	17 (14)	30 (12)
36–48	12 (10)	7 (6)	9 (7)	10 (8)	19 (8)

Follow-up

Of the 814 patients included in the analysis, 642 (79%) completed the final assessment. Where possible, this final assessment was carried out face to face at hospital or at home, but if this proved impossible (e.g. if parents/guardians were unable to attend an appointment), then the assessment was completed by telephone. Overall, 25% of final assessments were performed by telephone, 74% were performed in hospital and 1% were performed at home. In 172 (21%) participants, the final assessment was not conducted with the family. Of these 172 participants, 11 had withdrawn consent and a further 161 could not be contacted. However, 150 of these participants (87%) had provided consent for collection of the primary outcome via hospital and GP records, and primary outcome data were successfully collected in 144 of these participants. This ensured that primary outcome data were available for 786 (97%) participants, and only 28 participants (3%) were considered withdrawn or lost to follow-up (*Table 12*).

TABLE 12 Final visit and follow-up data completeness

Final visit and follow-up data	Treatment arm, *n* (%)				Total (*N* = 814), *n* (%)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Attendance					
Final visit completed	329 (80)	313 (77)	315 (76)	327 (82)	642 (79)
Previously withdrawn	8 (2)	3 (1)	6 (1)	5 (1)	11 (1)
Not withdrawn but not completed	73 (18)	88 (22)	92 (22)	69 (17)	161 (20)
Where/how did final visit take place?					
Hospital	242 (74)	236 (75)	231 (73)	247 (76)	478 (74)
Home	3 (1)	3 (1)	3 (1)	3 (1)	6 (1)
Telephone call	84 (26)	74 (24)	81 (26)	77 (24)	158 (25)
Consent for further data collection?					
Yes	71 (88)	79 (87)	87 (89)	63 (85)	150 (87)
No	10 (12)	12 (13)	11 (11)	11 (15)	22 (13)
Day 28 data received from GP?					
Yes	70 (99)	74 (94)	84 (97)	60 (95)	144 (96)
No	1 (1)	5 (6)	3 (3)	3 (5)	6 (4)
Final visit status					
Completed	329 (80)	313 (77)	315 (76)	327 (82)	642 (79)
Not completed, but GP data received	70 (17)	74 (18)	84 (20)	60 (15)	144 (18)
Withdrawn/lost	11 (3)	17 (4)	14 (3)	14 (3)	28 (3)

Follow-up data were also collected by telephone at days 3, 7, 14 and 21 (*Table 13*). Follow-up rates were 88% at day 3, 75% at day 14 and 76% at day 21. A total of 443 (54%) parents/guardians of participants completed all telephone calls and the final visit, with 153 (19%) parents/guardians of participants missing one follow-up visit, 95 (12%) parents/guardians of participants missing two follow-up visits, 51 (6%) parents/guardians of participants missing three follow-up visits and 48 (6%) parents/guardians of participants missing four follow-up visits. Twenty-four (3%) parents/guardians of participants missed all telephone calls and visits.

TABLE 13 Participant follow-up rate

Follow-up	Treatment arm, *n* (%)				Total (*N* = 814), *n* (%)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Trial entry	410 (100)	404 (100)	413 (100)	401 (100)	814 (100)
Day 3	355 (87)	360 (89)	365 (88)	350 (87)	715 (88)
Day 7	332 (81)	343 (85)	342 (83)	333 (83)	675 (83)
Day 14	314 (77)	299 (74)	307 (74)	306 (76)	613 (75)
Day 21	315 (77)	302 (75)	303 (73)	314 (78)	617 (76)
Final visit (day 28)	329 (80)	313 (77)	315 (76)	327 (82)	642 (79)

A symptom diary was to be completed daily by parents/guardians for the first 14 days after trial entry. Completed diary data were available for 406 (49.9%) participants and no diary data were available for 227 (27.9%) participants. Parents/guardians were assigned to complete symptom diaries either electronically (42.5%) or on paper (57.5%) using pseudorandomisation. Summary data on diary completion are presented in *Table 14*.

Adherence

A total of 240 (29.5%) participants deviated from the prescribed IMP regimen for reasons including taking fewer doses or a lower volume, taking too many doses or a greater volume, or deviation in timing (*Table 15*).

For dose randomisation, there was no evidence of an overall difference in adherence deviation between the two arms ($p = 0.21$). However, a greater proportion of participants in the lower-dose arm (7.3%) than in the higher-dose arm (4%) did not take bottle B/C as prescribed ($p = 0.038$).

For duration randomisation, 134 (32.4%) participants in the shorter-duration arm deviated, compared with 106 (26.4%) participants in the longer-duration arm ($p = 0.06$). A greater proportion of participants in the shorter-duration arm (13.3%) than in the longer-duration arm (9.4%) did not complete trial treatment ($p = 0.015$) (see *Table 15*).

TABLE 14 Parent/guardian diary completion rate

Diary completion	Treatment arm, *n* (%)				Total (*N* = 814), *n* (%)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
Diary status					
Completed: all days	201 (49.0)	205 (50.7)	212 (51.3)	194 (48.4)	406 (49.9)
Completed: partly	97 (23.7)	84 (20.8)	79 (19.1)	102 (25.4)	181 (22.2)
No diary data available	112 (27.3)	115 (28.5)	122 (29.5)	105 (26.2)	227 (27.9)
Number of days completed					
None	112 (27.3)	115 (28.5)	122 (29.5)	105 (26.2)	227 (27.9)
1–4	26 (6.3)	11 (2.7)	14 (3.4)	23 (5.7)	37 (4.5)
5–8	27 (6.6)	32 (7.9)	33 (8.0)	26 (6.5)	59 (7.2)
9–12	44 (10.7)	41 (10.1)	32 (7.7)	53 (13.2)	85 (10.4)
13	201 (49.0)	205 (50.7)	212 (51.3)	194 (48.4)	406 (49.9)
No diary data: reason					
Withdrawal	7 (6.3)	2 (1.7)	5 (4.1)	4 (3.8)	9 (4.0)
Paper: no final visit	40 (35.7)	48 (41.7)	49 (40.2)	39 (37.1)	88 (38.8)
Paper: final visit as telephone call	23 (20.5)	18 (15.7)	17 (13.9)	24 (22.9)	41 (18.1)
Lost/forgot	21 (18.8)	19 (16.5)	24 (19.7)	16 (15.2)	40 (17.6)
Technical/password issue	8 (7.1)	13 (11.3)	11 (9.0)	10 (9.5)	21 (9.3)
No time	4 (3.6)	6 (5.2)	6 (4.9)	4 (3.8)	10 (4.4)
Site error	0 (0.0)	1 (0.9)	1 (0.8)	0 (0.0)	1 (0.4)
Unknown	9 (8.0)	8 (7.0)	9 (7.4)	8 (7.6)	17 (7.5)

TABLE 15 Adherence to trial medication by randomisation arm

Adherence to trial medication	Treatment arm, *n* (%)			Treatment arm, *n* (%)			
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	*p*-value	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	*p*-value	Total (*N* = 814), *n* (%)
Early cessation of trial treatment							
Trial treatment completed	355 (86.6)	366 (90.6)	0.10	358 (86.7)	363 (90.5)	0.015	721 (88.6)
Early cessation for clinical improvement	7 (1.7)	1 (0.2)		5 (1.2)	3 (0.7)		8 (1.0)
Early cessation for clinical deterioration	16 (3.9)	11 (2.7)		10 (2.4)	17 (4.2)		27 (3.3)
Early cessation for other reason	32 (7.8)	26 (6.4)		40 (9.7)	18 (4.5)		58 (7.1)
Day of last dose of trial medication							
Day 0 or 1	11 (20)	4 (11)	0.62	9 (16)	6 (16)	0.61	15 (16)
Day 2 or 3	17 (31)	15 (39)		16 (29)	16 (42)		32 (34)
Day 4 or 5	22 (40)	15 (39)		24 (44)	13 (34)		37 (40)
Day 6 or after	5 (9)	4 (11)		6 (11)	3 (8)		9 (10)
Bottles received							
Taken bottle A but not bottles B/C	30 (7.3)	16 (4.0)	0.038	21 (5.1)	25 (6.2)	0.48	46 (5.7)
Taken bottle A and bottles B/C	380 (92.7)	388 (96.0)		392 (94.9)	376 (93.8)		768 (94.3)
Overall: fewer doses taken than scheduled							
Yes	86 (21.0)	77 (19.1)	0.49	85 (20.6)	78 (19.5)	0.69	163 (20.0)
No	324 (79.0)	327 (80.9)		328 (79.4)	323 (80.5)		651 (80.0)
Overall: fewer doses or less volume taken than scheduled							
Yes	104 (25.4)	95 (23.5)	0.54	113 (27.4)	86 (21.4)	0.050	199 (24.4)
No	306 (74.6)	309 (76.5)		300 (72.6)	315 (78.6)		615 (75.6)
Overall: any deviation (including too many doses/volume or timing deviations)							
Yes	128 (31.2)	107 (26.5)	0.14	133 (32.2)	102 (25.4)	0.033	235 (28.9)
No	282 (68.8)	297 (73.5)		280 (67.8)	299 (74.6)		579 (71.1)

Primary outcome

End-Point Review Committee results

There were 143 events of non-trial systemic antibacterial treatment in 139 participants (four participants had two events). All events were adjudicated by the ERC (see *Chapter 2*, *Primary outcome*) and reasons for starting new non-trial antibacterials are given in *Table 16*. Of 139 participants, 100 (71.9%) met the criteria for a primary end point (see *Table 16*). Among the 100 participants who had an event that met the criteria for a primary end point, 'CAP/chest infection' was the most common reason for treatment, accounting for 76 (76%) events (see *Table 16*). The ERC adjudicated 38% of the events as definitely/probably clinically indicated and 62% of the events as possibly indicated (*Table 17*).

TABLE 16 Reasons for starting non-trial systemic antibacterials, as adjudicated by the ERC

Reason	Treatment arm (*n*)				
	Lower dose (*N* = 74)	Higher dose (*N* = 65)	Shorter duration (*N* = 73)	Longer duration (*N* = 66)	Total (*N*) (*N* = 139)
CAP/chest infection	38	40	40	38	78
Other respiratory tract infection	19	12	18	13	31
Otitis media	7	3	6	4	10
URTI	7	2	4	5	9
Tonsillitis	3	5	5	3	8
Other[a]	2	2	3	1	4
Other bacterial infection	8	7	9	6	15
Skin infection	2	2	3	1	4
Urinary tract infection	2	2	3	1	4
Cellulitis	1	2	2	1	3
Scarlet fever	1	1	0	2	2
Nail infection	1	0	0	1	1
Salmonella gastroenteritis	1	0	1	0	1
Other illness/injury	4	2	3	3	6
Appendicitis	1	0	1	0	1
Asthma	0	1	0	1	1
Bronchospasm/asthma	1	0	1	0	1
Dental abscess	0	1	1	0	1
Lymphadenitis	1	0	0	1	1
Prophylaxis	1	0	0	1	1
Intolerance to IMP/AE	3	5	5	3	8
Vomiting	1	4	4	1	5
Diarrhoea	1	0	0	1	1
Rash	0	1	0	1	1
Refusing IMP	1	0	1	0	1
Parental preference	3	0	0	3	3
Pharmacy/administration error	1	1	2	0	2

URTI, upper respiratory tract infection.
a Bronchiolitis, *n* = 1; cough, *n* = 2; scarlet fever and tonsillitis, *n* = 1.

Note
Four patients had two events.

TABLE 17 End-Point Review Committee primary end-point adjudication results

Primary end-point adjudication result	Treatment arm				Total
	Lower dose	Higher dose	Shorter duration	Longer duration	
Patients who started systemic non-trial antibacterials					
N	74	65	73	66	139
Patients who had a primary end point, *n* (%)					
Yes	51 (69)	49 (75)	51 (70)	49 (74)	100 (712)
No	23 (31)	16 (25)	22 (30)	17 (26)	39 (28)
Events that met the criteria for primary end point					
N	51	49	51	49	100
Primary reason for starting new antibacterials, *n* (%)					
CAP/chest infection	37 (73)	39 (80)	39 (76)	37 (76)	76 (76)
Otitis media	5 (10)	3 (6)	4 (8)	4 (8)	8 (8)
Tonsillitis	3 (6)	5 (10)	5 (10)	3 (6)	8 (8)
URTI	5 (10)	2 (4)	3 (6)	4 (8)	7 (7)
Other respiratory tract infection	1 (2)	0 (0)	0 (0)	1 (2)	1 (1)
Clinical indication, *n* (%)					
Definitely/probably	19 (37)	19 (39)	19 (37)	19 (39)	38 (38)
Possibly	32 (63)	30 (61)	32 (63)	30 (61)	62 (62)
First new antibiotic, *n* (%)					
Amoxicillin	25 (49)	24 (49)	23 (45)	26 (53)	49 (49)
Amoxicillin (i.v.)	0 (0)	1 (2)	1 (2)	0 (0)	1 (1)
Azithromycin	3 (6)	1 (2)	2 (4)	2 (4)	4 (4)
Azithromycin plus amoxicillin (i.v.)	1 (2)	0 (0)	1 (2)	0 (0)	1 (1)
Cefuroxime	0 (0)	1 (2)	0 (0)	1 (2)	1 (1)
Cefuroxime plus clarithromycin	1 (2)	0 (0)	1 (2)	0 (0)	1 (1)
Clarithromycin	8 (16)	9 (18)	13 (25)	4 (8)	17 (17)
Co-amoxiclav	5 (10)	5 (10)	2 (4)	8 (16)	10 (10)
Co-amoxiclav plus azithromycin	2 (4)	0 (0)	0 (0)	2 (4)	2 (2)
Co-amoxiclav (i.v.)	1 (2)	0 (0)	1 (2)	0 (0)	1 (1)
Erythromycin	3 (6)	4 (8)	3 (6)	4 (8)	7 (7)
Phenoxymethylpenicillin	2 (4)	4 (8)	4 (8)	2 (4)	6 (6)
Who prescribed the antibiotic, *n* (%)[a]					
CAP-IT investigator	3 (6)	3 (7)	3 (6)	3 (7)	6 (6)
Other hospital doctor	18 (38)	16 (36)	17 (36)	17 (37)	34 (37)
GP	24 (50)	25 (56)	27 (57)	22 (48)	49 (53)
Other	3 (6)	1 (2)	0 (0)	4 (9)	4 (4)
Time new antibiotic started, *n* (%)					
Days 0–14	29 (57)	25 (51)	28 (55)	26 (53)	54 (54)
Days 15–28	22 (43)	24 (49)	23 (45)	23 (47)	46 (46)

i.v., intravenous; URTI, upper respiratory tract infection.

a Information about the prescriber was missing in seven cases because this was not asked for at the beginning of the trial.

The most commonly prescribed antibacterial was oral amoxicillin, which was prescribed in 49 (49%) participants who met the criteria for a primary end point. Oral clarithromycin and co-amoxiclav accounted for 17% and 10% of prescriptions for participants who met the criteria for a primary end point, respectively, and erythromycin, phenoxymethylpenicillin and azithromycin accounted for 7%, 6% and 4%, respectively.

Analysis of primary end point

Overall

Overall, 100 participants in the analysis population ($n = 814$) met the criteria for a primary end point during the follow-up period (i.e. a cumulative proportion of 12.5%, 90% CI 10.7% to 14.6%, as estimated with Kaplan–Meier methods).

Dose randomisation

The observed number of primary end points was similar in the lower-dose arm ($n = 51$, 12.6%) and in the higher-dose arm ($n = 49$, 12.4%). The estimated risk difference at day 28 was 0.2% (90% CI −3.7% to 4.0%), meeting the criterion for non-inferiority (*Figure 7*).

Duration randomisation

A total of 51 (12.5%) participants experienced a primary end point in the shorter-duration arm and 49 (12.5%) participants experienced a primary end point in the longer-duration arm. The estimated risk difference at day 28 was 0.1% (90% CI −3.8% to 3.9%), again satisfying the non-inferiority criterion (*Figure 8*).

Interaction effects

The outcomes for the analyses of interaction effects between the two randomisations (i.e. dose and duration), between pre-exposure to antibiotics and dose randomisation and between pre-exposure to antibiotics and duration randomisation are shown in *Figures 9–11*, respectively.

There was no evidence of an interaction between either of the two randomisation arms ($p = 0.625$), between the dose randomisation arm and pre-exposure to antibiotics ($p = 0.456$) or between the duration randomisation arm and pre-exposure to antibiotics ($p = 0.592$). This justifies analysis of the 'main effects' for the two randomisations (see *Figures 7* and *8*).

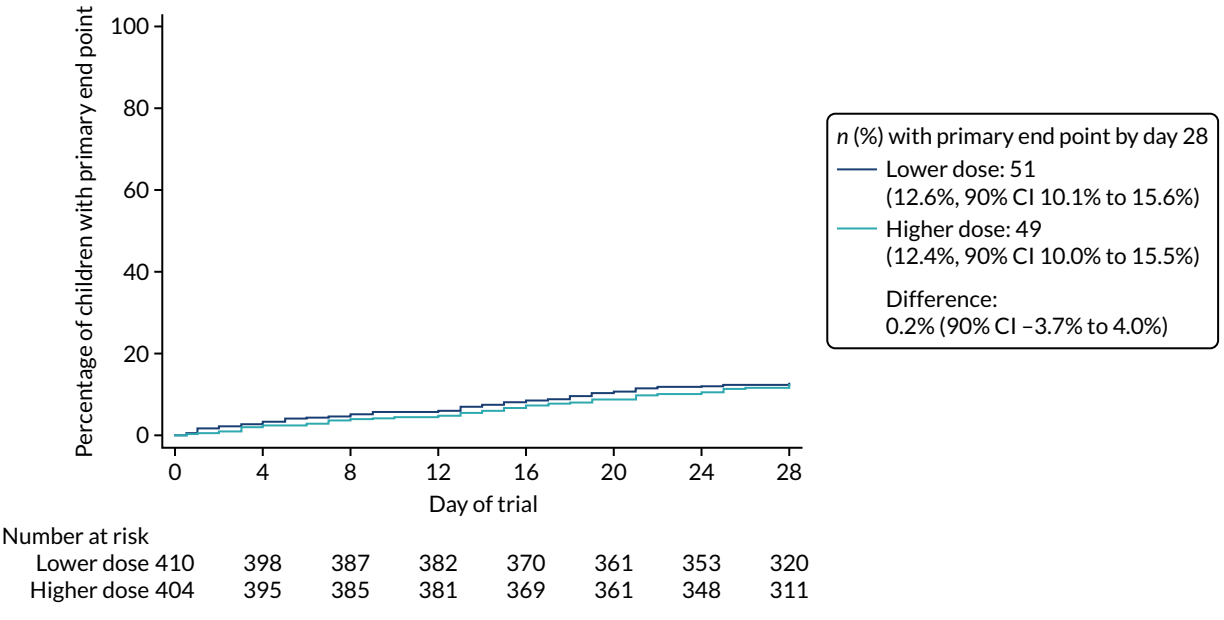
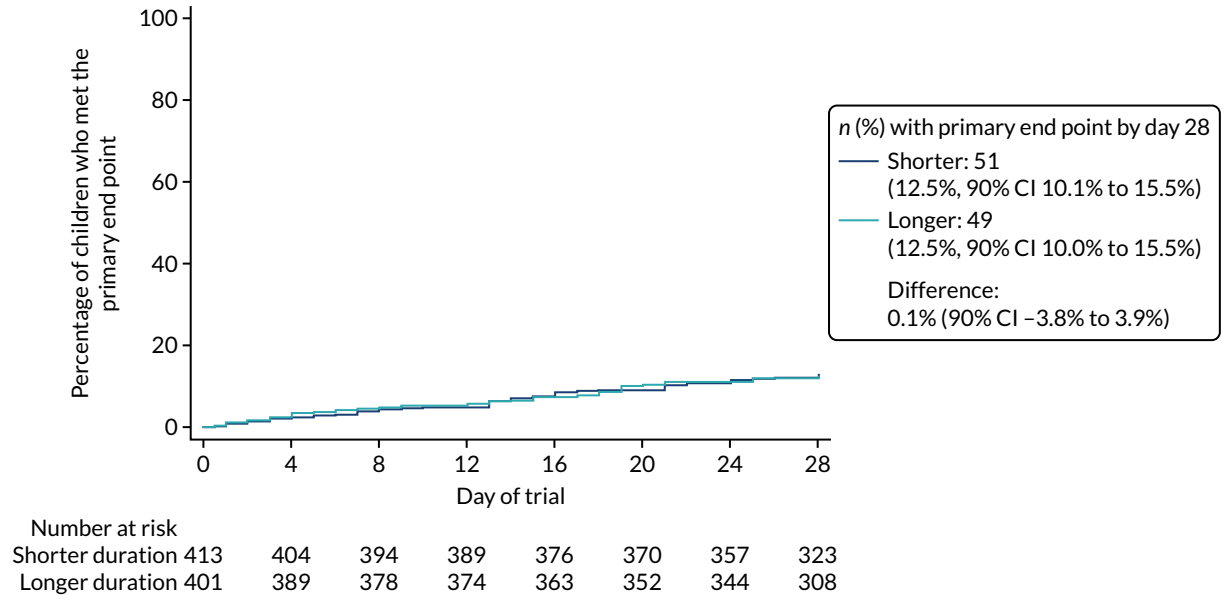
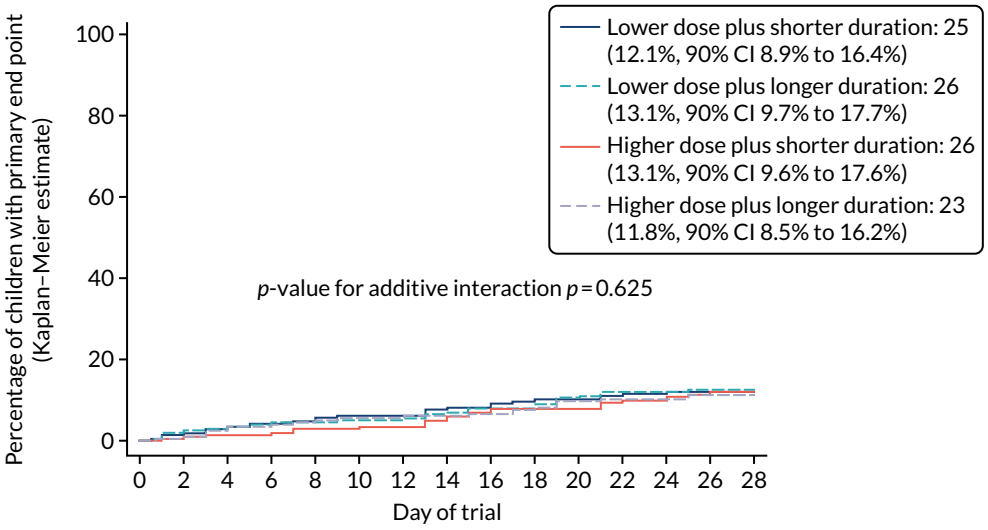


FIGURE 7 Kaplan–Meier curve for primary end point: dose randomisation.



Number at risk							
Shorter duration 413	404	394	389	376	370	357	323
Longer duration 401	389	378	374	363	352	344	308

FIGURE 8 Kaplan–Meier curve for primary end point: duration randomisation.



Number at risk								
Lower dose plus shorter duration	208	202	196	193	189	185	180	166
Lower dose plus longer duration	202	196	191	189	181	176	173	154
Higher dose plus shorter duration	205	202	198	196	187	185	177	157
Higher dose plus longer duration	199	193	187	185	182	176	171	154

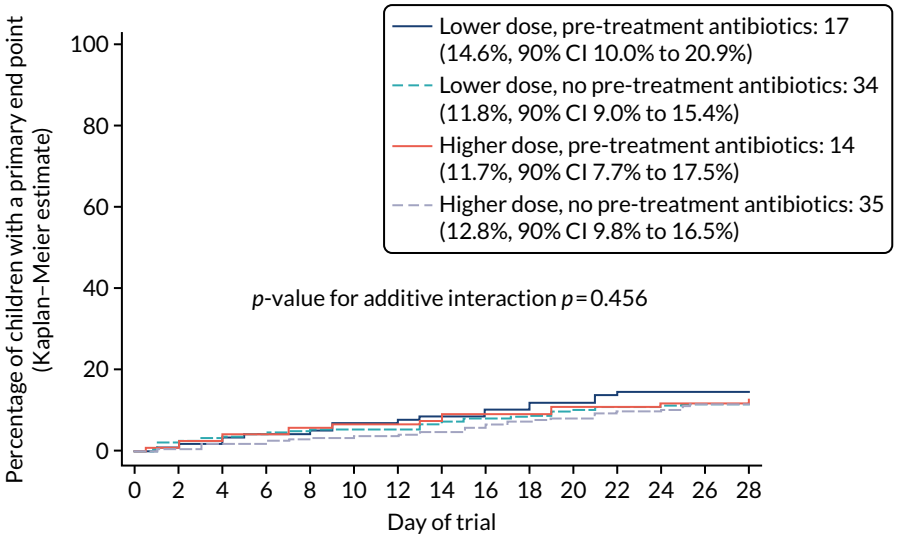
FIGURE 9 Kaplan–Meier curve for analysis of interaction between the two randomisations.

Primary end-point sensitivity analyses

The results of the sensitivity and subgroup analyses are summarised in *Figures 12* and *13*. Non-inferiority was demonstrated for all sensitivity analyses for both dose and duration comparisons.

All systemic antibacterial treatments

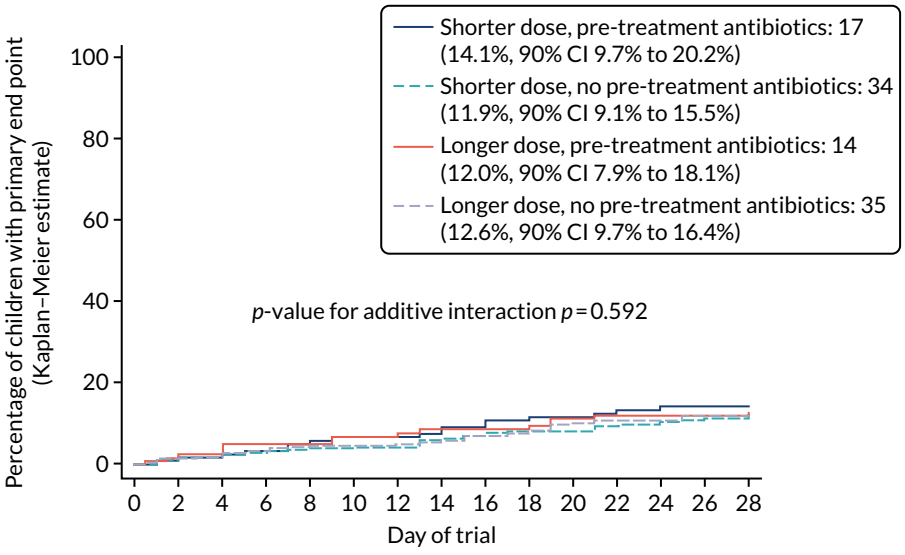
The first sensitivity analysis repeated the primary analysis and considered all systemic antibacterial treatments other than trial medication, regardless of reason and indication. The total number of participants experiencing an end point in this analysis was 139 of 814 participants (17.4%, 90% CI 15.3% to 19.7%).



Number at risk

Lower dose, pre-treatment antibiotics	119	117	113	109	105	101	98	90
Lower dose, no pre-treatment antibiotics	291	281	274	273	265	260	255	230
Higher dose, pre-treatment antibiotics	123	119	113	111	108	106	104	91
Higher dose, no pre-treatment antibiotics	281	276	272	270	261	255	244	220

FIGURE 10 Kaplan–Meier curve for analysis of interaction between pre-exposure with antibiotics and dose randomisation.



Number at risk

Shorter dose, pre-treatment antibiotics	123	121	115	112	109	106	103	92
Shorter dose, no pre-treatment antibiotics	290	283	279	277	267	264	254	231
Longer dose, pre-treatment antibiotics	119	115	111	108	104	101	99	89
Longer dose, no pre-treatment antibiotics	282	274	267	266	259	251	245	219

FIGURE 11 Kaplan–Meier curve for analysis of interaction between pre-exposure with antibiotics and duration randomisation.

For the dose comparison, the estimated risk difference at day 28 was 1.9% (90% CI −2.5% to 6.3%). For the duration comparison, the estimated risk difference at day 28 was 1.0% (90% CI −3.4% to 5.4%). For both comparisons, the upper limit of the 90% CI was less than the non-inferiority margin of 8%, supporting the observations of the primary end-point analysis.

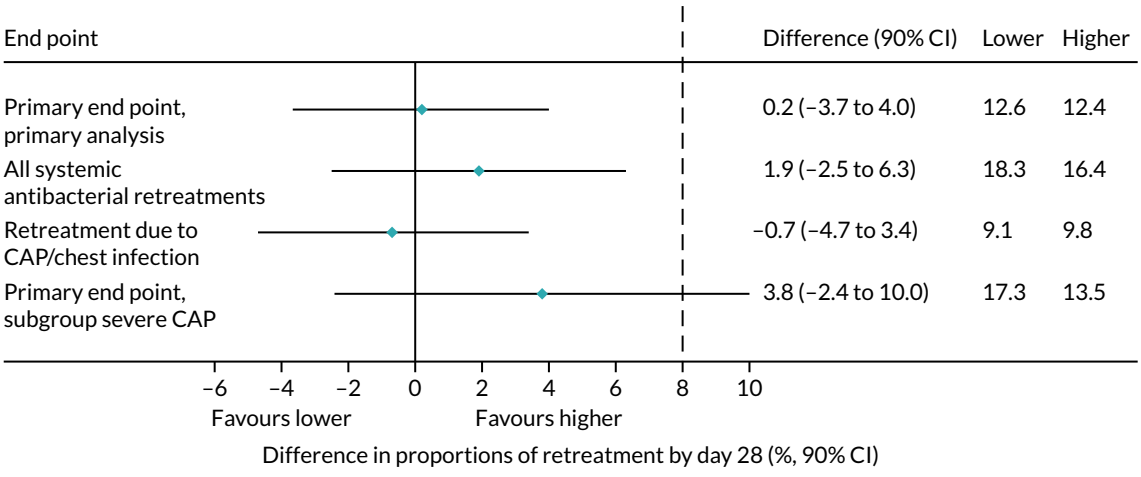


FIGURE 12 Forest plot summarising sensitivity and subgroup analyses outcomes in terms of difference in proportions of retreatment by day 28 for the dose randomisation.

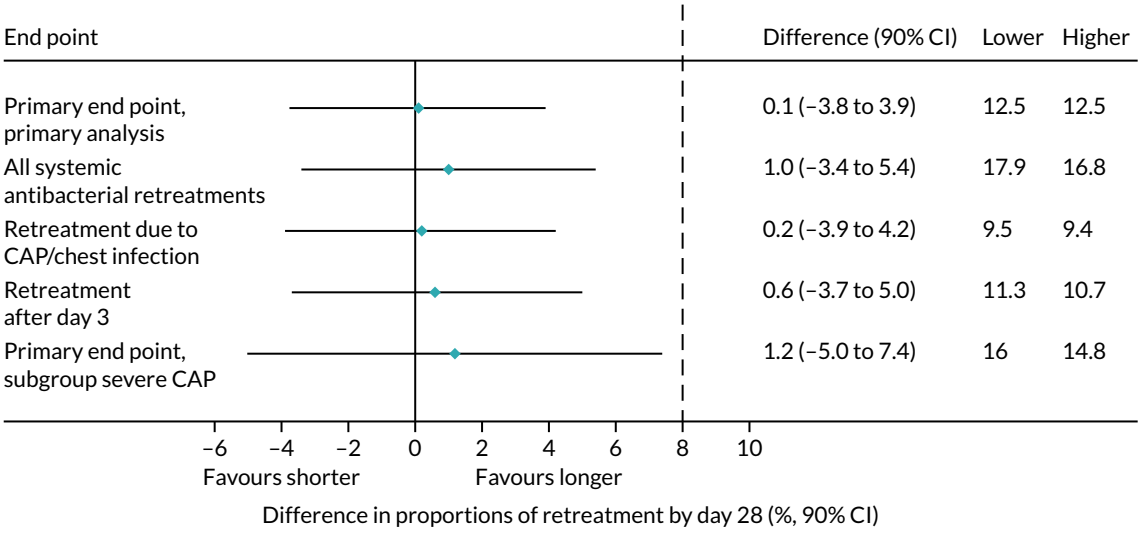


FIGURE 13 Forest plot summarising sensitivity and subgroup analyses outcomes in terms of difference in proportions of retreatment by day 28 for the duration randomisation.

Treatment events for community-acquired pneumonia/chest infection

In a second sensitivity analysis, only those treatment events for which the clinical indication was adjudicated by the ERC to be CAP/chest infection were included. The total number of participants experiencing an end point in this analysis was 76 out of 814 (9.4%, 90% CI 7.9% to 11.3%).

For the dose comparison, the estimated risk difference at day 28 was −0.7% (90% CI −4.7% to 3.4%). For the duration comparison, the estimated risk difference at day 28 was 0.2% (90% CI −3.9% to 4.2%). As for the first sensitivity analysis, for both comparisons the upper limit of the 90% CI was less than the non-inferiority margin, supporting the observations of the primary end-point analysis.

All treatment events for community-acquired pneumonia/chest infection

A third sensitivity analysis considered treatment events for which the clinical indication was adjudicated by the ERC to be CAP/chest infection, including those adjudicated ‘unlikely’ to be clinically indicated. The number of participants experiencing an end point in this analysis was 78 of 814 participants (9.7%, 90% CI 8.1% to 11.6%).

For the dose comparison, the estimated risk difference at day 28 was –0.7% (90% CI –4.8% to 3.4%). For the duration comparison, the estimated risk difference at day 28 was 0.2% (90% CI –3.9% to 4.3%). For both comparisons, the upper limit of the 90% CI was less than the non-inferiority margin, supporting the observations of the primary end-point analysis.

Only treatment events started after the first 3 days (duration randomisation)

A final sensitivity analysis considered only ERC-adjudicated primary end points when non-trial antibacterial treatment was started after the first 3 days. This assessment was relevant for the duration randomisation only, and the estimated risk difference at day 28 was 0.6% (90% CI –3.7% to 5.0%). Non-inferiority was demonstrated, with the upper CI (5.0%) less than the non-inferiority margin of 8%, supporting the observations of the primary end-point analysis.

On-treatment analyses

The on-treatment analyses gave very similar results to the primary analysis. For both the dose and the duration comparison, the upper 90% CI limit of the estimated difference at day 28 was lower than the non-inferiority margin of 8% for both definitions of non-adherence (see *Appendix 3*, *Figures 21–24*).

Subgroup analyses

Participants with severe community-acquired pneumonia

This a priori subgroup analysis repeated the primary analysis, limited to participants defined as having severe CAP. *Table 18* shows the total number (%) of participants with each abnormality by randomisation group. Only 155 (19%) participants had none of these abnormalities at presentation; 291 (35.7%) participants had one, 341 (41.9%) had two and 27 (3.3%) had three. A total of 368 (45.2%) participants were included in the subgroup analysis.

TABLE 18 Abnormalities at presentation considered for subgroup analysis for severe CAP

	Treatment arm, *n* (%)			Treatment arm, *n* (%)			
Abnormality	Lower dose (*N* = 410)	Higher dose (*N* = 404)	*p*-value	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	*p*-value	Total (*N* = 814), *n* (%)
Chest retractions	239 (58.4)	244 (60.4)	0.57	239 (58.0)	244 (60.8)	0.41	483 (59.4)
Oxygen saturation < 92%	18 (4.4)	25 (6.2)	0.25	18 (4.4)	25 (6.3)	0.23	43 (5.3)
High respiratory rate	270 (65.9)	258 (64.3)	0.65	262 (63.7)	266 (66.5)	0.41	528 (65.1)
Number of abnormalities			0.62			0.47	
0	75 (18.3)	80 (19.8)		82 (19.9)	73 (18.2)		155 (19.0)
1	155 (37.8)	136 (33.7)		154 (37.3)	137 (34.2)		291 (35.7)
2	168 (41.0)	173 (42.8)		166 (40.2)	175 (43.6)		341 (41.9)
3	12 (2.9)	15 (3.7)		11 (2.7)	16 (4.0)		27 (3.3)
> 1	180 (43.9)	188 (46.5)	0.45	177 (42.9)	191 (47.6)	0.17	368 (45.2)

In total, 56 (15.4%) participants experienced a primary end point. There was no significant difference between the arms for either the dose comparison ($p = 0.283$) or the duration comparison ($p = 0.821$). For duration randomisation, the estimated risk difference at day 28 was 1.2% (90% CI −5.0% to 7.4%) (*Figure 14*). For dose randomisation, the estimated difference at day 28 was 3.8% (90% CI −2.4% to 10.0%). This is consistent with no effect, although the 90% CI crossed the non-inferiority margin (*Figure 15*).

Seasonal effect

A further a priori planned subgroup analysis repeated the primary analysis, but including only events occurring during the two winter periods spanned by CAP-IT (i.e. 2017/18 and 2018/19), based on Public Health England reports of circulating viruses/bacteria.

The overall event rate in 2017/18 was 14.1% and 12.2% in 2018/19 ($p = 0.515$). There was no evidence of an interaction with either the duration or dose randomisations ($p = 0.848$ and $p = 0.677$, respectively).

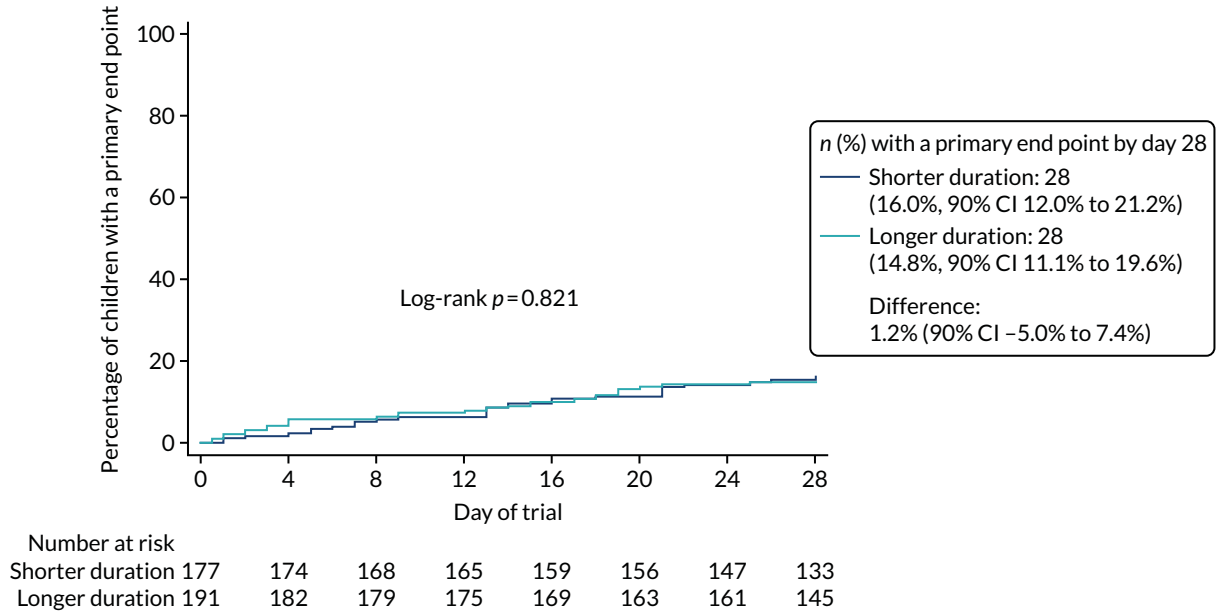


FIGURE 14 Kaplan–Meier curve for severe CAP subgroup primary analysis for duration randomisation.

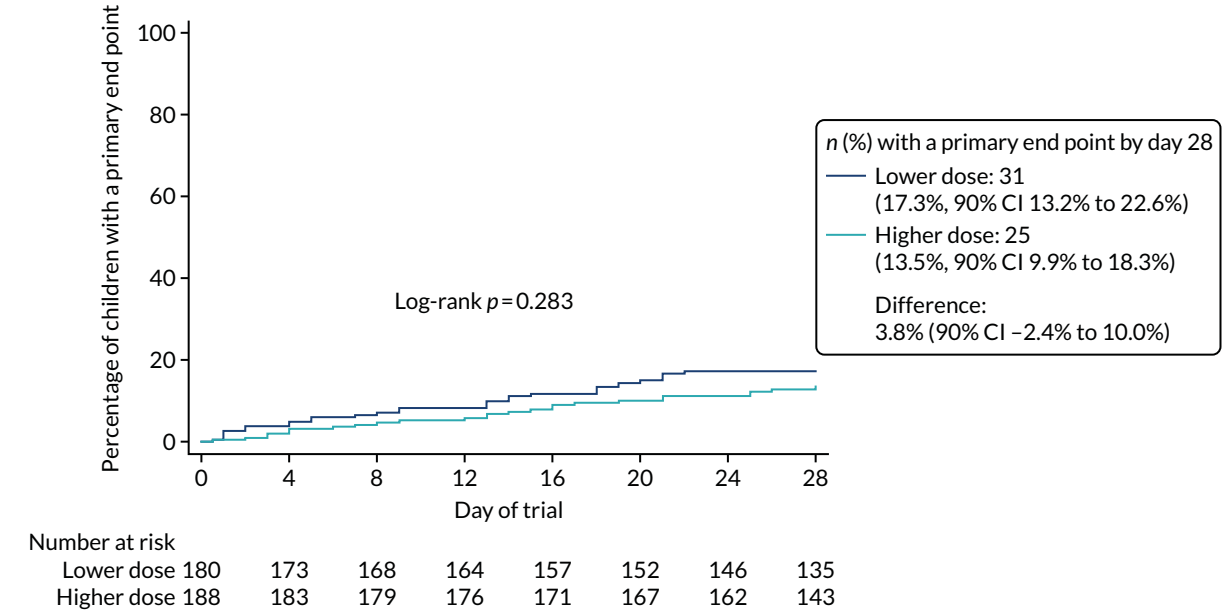


FIGURE 15 Kaplan–Meier curve for severe CAP subgroup primary analysis for dose randomisation.

Streptococcus pneumoniae carriage and resistance

Carriage and resistance to penicillin of *S. pneumoniae* isolates were assessed by analysis of nasopharyngeal samples collected from participants at baseline, at the final visit and at any unscheduled visits during follow-up.

Availability of nasopharyngeal culture results

Of the 814 participants in the analysis population, 647 (79%) had a nasopharyngeal sample taken at baseline and 437 (54%) had a sample taken at the final visit. There were 376 (46%) participants who had both a baseline and final visit sample taken, 271 (33%) who had just a baseline sample taken and 61 (7%) who had just a final visit sample taken. The remaining 106 (13%) participants did not have a sample taken. In addition, 28 (4%) participants had a sample taken at an unscheduled visit and four participants had samples taken at two unscheduled visits (1%) (*Table 19*).

Streptococcus pneumoniae *carriage*

Overall, 272 of 647 (42%) baseline samples and 129 of 437 (30%) final visit samples were culture positive for *S. pneumoniae*. Of the participants with a culture result at both baseline and final visit, 70 of 376 (19%) were positive for *S. pneumoniae* at both visits, 100 of 376 (27%) were positive at baseline only and 41 of 376 (11%) were positive at the final visit only. The remaining 165 (44%) sample cultures were negative at both visits (*Table 20*).

Streptococcus pneumoniae *penicillin non-susceptibility*

No penicillin-resistant pneumococcal isolates were identified in CAP-IT. Penicillin non-susceptibility was detected in 45 of 647 (7%) baseline samples providing a culture result (either positive or negative) (17% of *S. pneumoniae*-positive samples) and in 21 (5%) samples taken at the final visit and providing a culture result (either positive or negative) (16% of *S. pneumoniae*-positive samples). Of participants with positive or negative culture results at both baseline and final visit, 23 (6%) had pneumococcal penicillin non-susceptibility identified in the baseline sample only, 11 (3%) participants had pneumococcal penicillin non-susceptibility identified in in the final visit sample only and seven (2%) participants had pneumococcal penicillin non-susceptibility identified in both baseline and final visit samples. In the remaining 335 (89%) participants, penicillin resistance was not identified in either sample culture.

TABLE 19 Availability of nasopharyngeal culture results

Culture result	Group, *n* (%)		*p*-value	Total (*N* = 814), *n* (%)
	PED (*N* = 591)	Ward (*N* = 223)		
Baseline culture available	474 (80)	173 (78)	0.41	647 (79)
Final visit culture available	316 (53)	121 (54)	0.84	437 (54)
If final visit happened hospital, at home	316 (89)	121 (92)	0.25	437 (90)
Summary availability				
None	75 (13)	31 (14)	0.84	106 (13)
Both baseline and final visit	274 (46)	102 (46)		376 (46)
Baseline only	200 (34)	71 (32)		271 (33)
Final visit only	42 (7)	19 (9)		61 (7)
Unscheduled visit: number of culture samples available				
0	490 (95)	186 (97)	0.37	676 (95)
1	22 (4)	6 (3)		28 (4)
2	4 (1)	0 (1)		4 (1)

TABLE 20 *Streptococcus pneumoniae* carriage

	Treatment arm, *n* (%)			Treatment arm, *n* (%)			
***S. pneumoniae* carriage**	**Lower dose**	**Higher dose**	***p*-value**	**Shorter duration**	**Longer duration**	***p*-value**	**Total, *n* (%)**
Baseline: positive	133 (41)	139 (43)		132 (42)	140 (42)		272 (42)
Final visit: positive	66 (29)	63 (30)	0.98	65 (32)	64 (28)	0.35	129 (30)
Summary: pneumococcal carriage[a]							
Never	93 (48)	72 (40)		76 (44)	89 (43)		165 (44)
Baseline only	46 (24)	54 (30)		39 (23)	61 (30)		100 (27)
Final visit only	21 (11)	20 (11)		20 (12)	21 (10)		41 (11)
Both	34 (18)	36 (20)		36 (21)	34 (17)		70 (19)

a Patients with culture results at both time points.

There was no evidence of a difference between the lower- and higher-dose randomisation groups in the penicillin non-susceptibility of isolates cultured from either baseline or final visit samples, or between the shorter- and longer-duration randomisation groups in the penicillin non-susceptibility of isolates cultured from baseline samples (see *Table 21*). The proportion of pneumococcal isolates cultured from final visit samples that were penicillin non-susceptible was slightly higher in the shorter-duration group ($n = 14$, 7% of all samples, 22% of *S. pneumoniae*-positive samples) than in the longer-duration group [$n = 7$, 3% of all samples ($p = 0.063$), 11% of *S. pneumoniae*-positive samples ($p = 0.10$)]. This pattern was also found when the analysis was limited to participants with a positive culture result for *S. pneumoniae* (excluding all samples with a negative culture result), with penicillin non-susceptibility detected in 22% ($n = 14$) of samples taken from participants in the shorter-duration arm and in 11% ($n = 7$) of samples from participants in the longer-duration arm ($p = 0.10$).

Streptococcus pneumoniae *amoxicillin resistance/non-susceptibility*

Amoxicillin non-susceptibility or resistance was detected in *S. pneumoniae* isolates cultured from seven (2%) baseline samples with a culture result (either positive or negative) and in four final visit (1%) samples with a culture result (either positive or negative). Among participants for whom culture results (positive or negative) were available for both baseline and final visit samples, amoxicillin resistance was detected in isolates cultured from the baseline sample only in the case of one (< 1%) participant, in isolates cultured from the final visit sample only in the case of two (1%) participants and in isolates from both samples in the case of one (< 1%) participant. In the remaining 361 (99%) participants, neither amoxicillin non-susceptibility nor resistance was identified in any samples.

There was no evidence of a difference between the lower- and higher-dose groups in the amoxicillin non-susceptibility of isolates cultured from either baseline or final visit sample cultures, or between the shorter- and longer-duration groups groups in the amoxicillin non-susceptibility of isolates cultured from either baseline or final visit samples (*Table 21*). This was also found when the analysis of amoxicillin non-susceptibility was limited to participants whose samples provided a positive culture result for *S. pneumoniae* (excluding all samples with a negative culture result).

Community-acquired pneumonia symptoms

Parent/guardian-reported symptom data were elicited at follow-up telephone calls and through parental/guardian completion of a daily diary up to day 14. The proportion of participants for whom parent/guardian-reported symptom data from any source were available reduced from days 3 (93%), 7 (88%), 14 (83%) and 21 (76%) to day 28 (75%) (*Figure 16*).

TABLE 21 Penicillin and amoxicillin resistance/non-susceptibility in all participants with a culture result, either negative or positive for *S. pneumoniae*

Penicillin and amoxicillin resistance/non-susceptibility	Treatment arm, *n* (%)			Treatment arm, *n* (%)		
	Lower dose	Higher dose	*p*-value	Shorter duration	Longer duration	*p*-value
Penicillin non-susceptibility at baseline						
No	302 (92)	299 (93)	0.59	293 (92)	308 (93)	0.65
Yes	25 (8)	21 (7)		24 (8)	22 (7)	
Penicillin non-susceptibility at the final visit						
No	212 (95)	204 (96)	0.58	191 (93)	225 (97)	0.063
Yes	12 (5)	9 (4)		14 (7)	7 (3)	
Penicillin non-susceptibility: summary[a]						
Never	175 (90)	166 (91)	0.79	151 (88)	190 (93)	0.29
Baseline only	10 (5)	9 (5)		9 (5)	10 (5)	
Final visit only	6 (3)	3 (2)		6 (4)	3 (1)	
Both baseline and final visit	3 (2)	4 (2)		5 (3)	2 (1)	
Amoxicillin resistance/non-susceptibility at baseline						
No	318 (98)	311 (99)	0.27	309 (99)	320 (98)	0.28
Yes	5 (2)	2 (1)		2 (1)	5 (2)	
Amoxicillin resistance/non-susceptibility at the final visit						
No	218 (99)	210 (99)	0.97	199 (99)	229 (99)	0.89
Yes	2 (1)	2 (1)		2 (1)	2 (1)	
Amoxicillin resistance/non-susceptibility: summary[a]						
Never	185 (99)	176 (99)	0.26	162 (99)	199 (99)	0.56
Baseline only	1 (1)	0 (0)		0 (0)	1 (< 1)	
Final visit only	0 (0)	2 (1)		1 (1)	1 (< 1)	
Both baseline and final visit	1 (1)	0 (0)		1 (1)	0 (0)	

a In patients with culture results at both time points.

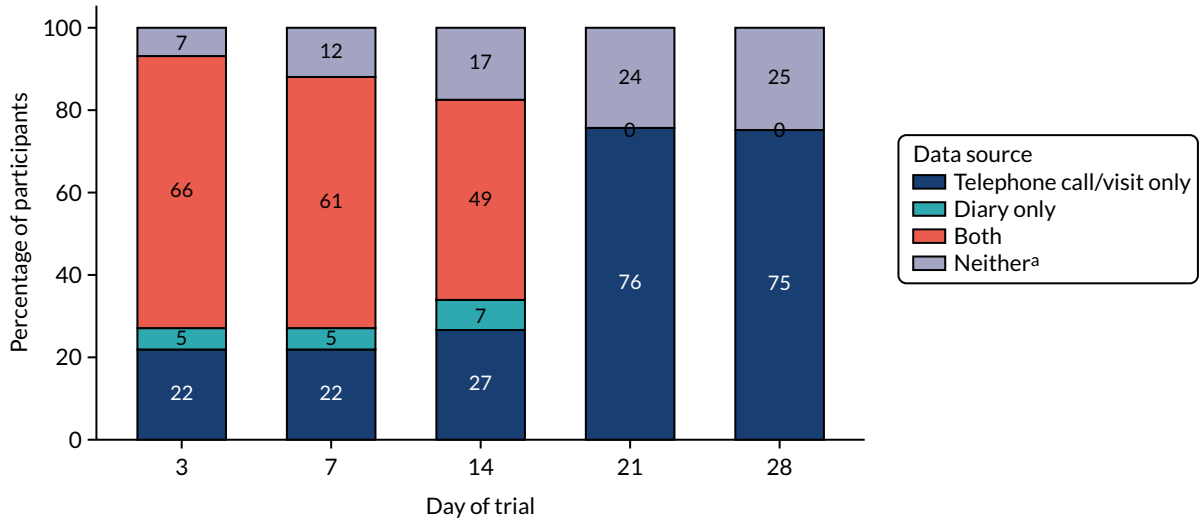


FIGURE 16 Availability of symptom data over time, by data source. a, No data available because telephone call/visit did not happen or no data were reported.

Time to resolution of community-acquired pneumonia symptoms: overall

Severity was elicited for nine CAP symptoms, each of which was analysed separately in terms of time to resolution. As multiple comparisons were performed, the *p*-value from each individual analysis needs to be interpreted cautiously. Participants were included in the analysis only if a symptom was present at trial entry. Cough had the longest median time to resolution (11 days), followed by the related symptom wet cough (phlegm) (6 days). An estimated 20% of participants still had cough symptoms at day 28 (*Figure 17*). Vomiting and fever both resolved rapidly, in a median of 1 day and 2 days, respectively. The remaining symptoms had a median time to resolution of between 3 and 5 days.

Time to resolution of community-acquired pneumonia symptoms: dose randomisation

There was no significant difference between participants receiving lower and higher doses in time to resolution of any of the nine symptoms (log-rank $p > 0.05$).

Time to resolution of community-acquired pneumonia symptoms: duration randomisation

For duration randomisation, there was no significant difference between groups for seven symptoms (log-rank $p > 0.05$). However, there was a difference in time to resolution of cough ($p = 0.040$) and sleep disturbed by cough ($p = 0.026$), with a significantly faster time to resolution in the longer-duration arm in both cases (*Figures 18* and *19*).

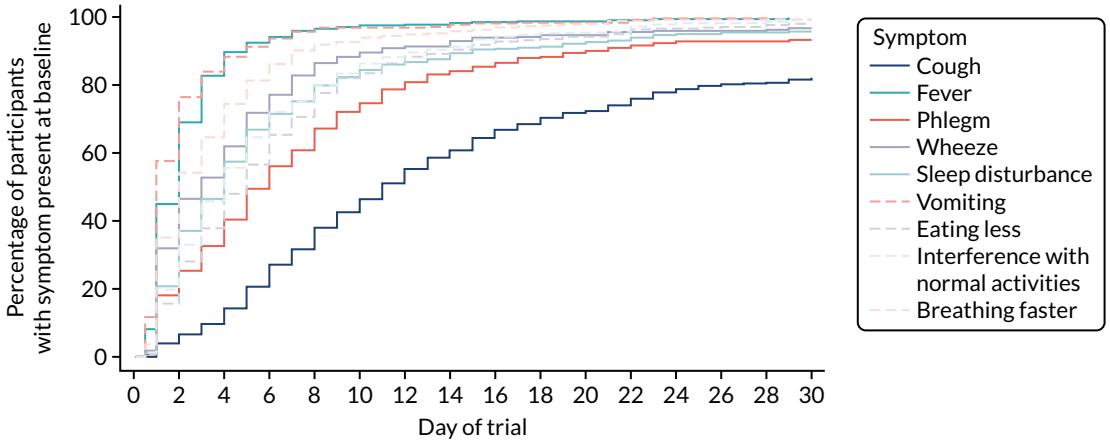


FIGURE 17 Kaplan–Meier curves for time to symptom resolution across all randomisation arms. Participants excluded if symptom not present at enrolment.

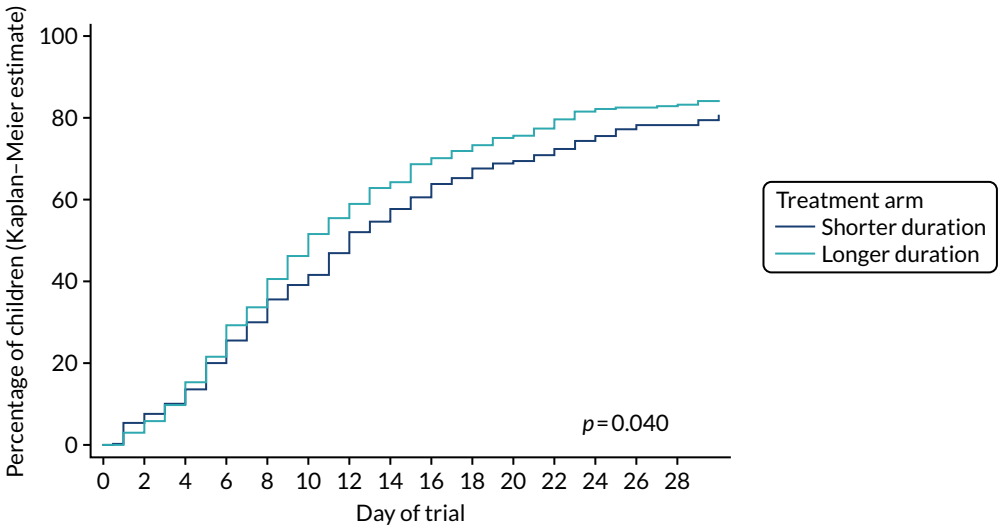


FIGURE 18 Kaplan–Meier curve for time to resolution of cough in the duration treatment arms. Participants excluded if symptom not present at enrolment.

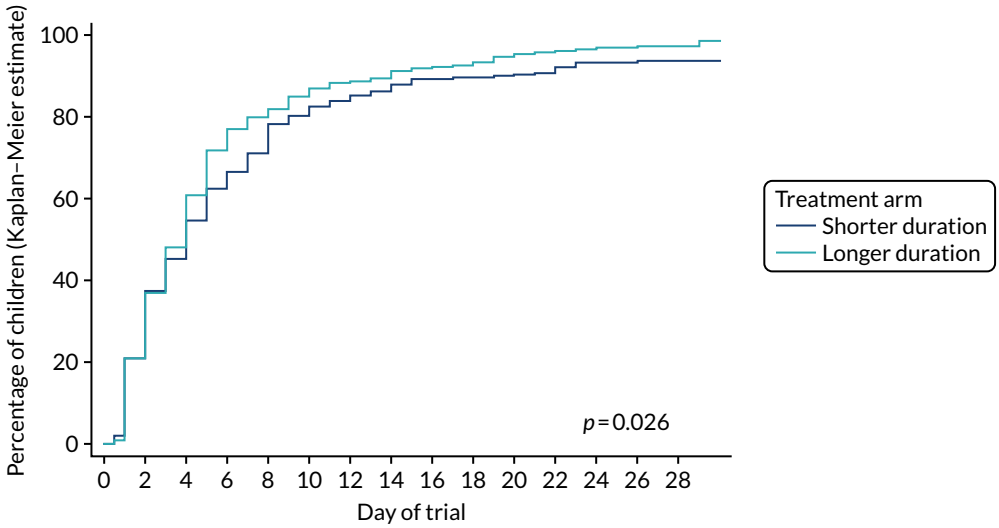


FIGURE 19 Kaplan–Meier curve for time to resolution of sleep disturbed by cough in the duration treatment arms. Participants excluded if symptom not present at enrolment.

Sensitivity analysis for duration randomisation

As symptom resolution within the first 3 days from randomisation cannot, by definition, be related to the treatment duration randomisation, a prespecified sensitivity analysis was performed, changing the time origin to day 4 for the comparison of shorter and longer treatment.

Log-rank tests were repeated and the same pattern was observed as in the main analyses. Participants in the shorter-duration arm had a significantly longer time to resolution of cough ($p = 0.039$) and sleep disturbed by cough ($p = 0.031$) than participants in the longer-duration arm. There was no evidence of a significant difference between the two duration arms in time to resolution of the remaining seven symptoms.

Adverse events

Serious adverse events

In total, 43 (5.3%) participants experienced a SAE, one participant (0.1%) experienced a serious adverse reaction (SAR) and no participants experienced a suspected unexpected SAR. There was no evidence of differences between proportions of participants experiencing a SAE in any of the dose or duration treatment arms (*Table 22*).

TABLE 22 Summary of SAEs

	Treatment arm, *n* (%)			Treatment arm, *n* (%)			
SAE summary	Lower dose (*N* = 410)	Higher dose (*N* = 404)	*p*-value	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	*p*-value	Total (*N* = 814), *n* (%)
Number of SAEs per participant							
0	387 (94.4)	384 (95.0)	0.67	388 (93.9)	383 (95.5)	0.32	771 (94.7)
1	23 (5.6)	20 (5.0)		25 (6.1)	18 (4.5)		43 (5.3)
SAR confirmed	0 (0.0)	1 (0.2)	0.50	1 (0.2)	0 (0.0)	1.00	1 (0.1)
SUSAR confirmed	0	0		0	0		0

SUSAR, suspected unexpected serious adverse reaction.

Of the 43 SAEs, 42 (98%) were hospitalisations and one (2%) (exacerbation of asthma, unrelated to the trial medication) was classified as life-threatening (*Table 23*), necessitating intubation and transfer of the patient to a paediatric intensive care unit. Respiratory events were the most common diagnoses, accounting for 35 of 43 SAEs (81%), of which 16 (37%) were classified as respiratory distress, eight (19%) were lower respiratory tract infection and five (12%) were pneumonia; the remaining six were asthma ($n = 3$, 7%), bronchiolitis ($n = 2$, 5%) and influenza ($n = 1$, 2%). Most SAEs occurred between days 1 and 4 ($n = 29$, 67%).

TABLE 23 Serious adverse event details

SAE details	Treatment arm, *n* (%)				Total (*N* = 43), *n* (%)
	Shorter duration (*N* = 25)	Longer duration (*N* = 18)	Lower dose (*N* = 23)	Higher dose (*N* = 20)	
Type of SAE					
Life-threatening	0	1 (6)	0	1 (5)	1 (2)
Hospitalisation	25 (100)	17 (94)	23 (100)	19 (95)	42 (98)
Body system					
Dermatological	1 (4)	1 (6)	1 (4)	1 (5)	2 (5)
Cyanosis peripheral	0	1 (6)	1 (4)	0	1 (2)
Herpes simplex oral	1 (4)	0	0	1 (5)	1 (2)
Gastrointestinal	4 (16)	0	2 (9)	2 (10)	4 (9)
Coffee ground vomiting	1 (4)	0	0	1 (5)	1 (2)
Epiploic appendagitis	1 (4)	0	1 (4)	0	1 (2)
Salmonella gastroenteritis	1 (4)	0	1 (4)	0	1 (2)
Vomiting	1 (4)	0	0	1 (5)	1 (2)
Neurological	1 (4)	1 (6)	2 (9)	0	2 (5)
Cerebellar tumour	0	1 (6)	1 (4)	0	1 (2)
Febrile seizure	1 (4)	0	1 (4)	0	1 (2)
Respiratory	19 (76)	16 (89)	18 (78)	17 (85)	35 (81)
Asthma	1 (4)	2 (11)	0	3 (15)	3 (7)
Bronchiolitis	2 (8)	0	2 (9)	0	2 (5)
Influenza	1 (4)	0	1 (4)	0	1 (2)
Lower respiratory tract infection viral	1 (4)	7 (39)	3 (13)	5 (25)	8 (19)
Pneumonia	2 (8)	3 (17)	5 (22)	0	5 (12)
Respiratory distress	12 (48)	4 (22)	7 (30)	9 (45)	16 (37)
Trial study day of hospitalisation[a]					
Days 0–3	20 (80)	9 (50)	16 (70)	13 (65)	29 (67)
Days 4–7	0	2 (11)	1 (4)	1 (5)	2 (5)
Days 8–14	2 (8)	1 (6)	1 (4)	2 (10)	3 (7)
Days 15–21	0	2 (11)	0	2 (10)	2 (5)
Days 22–28	3 (12)	4 (22)	5 (22)	2 (10)	7 (16)

TABLE 23 Serious adverse event details (*continued*)

SAE details	Treatment arm, *n* (%)				Total (*N* = 43), *n* (%)
	Shorter duration (*N* = 25)	Longer duration (*N* = 18)	Lower dose (*N* = 23)	Higher dose (*N* = 20)	
Event grade					
1	11 (44)	4 (22)	9 (39)	6 (30)	15 (35)
2	6 (24)	9 (50)	7 (30)	8 (40)	15 (35)
3	8 (32)	3 (17)	6 (26)	5 (25)	11 (26)
4	0	2 (11)	1 (4)	1 (5)	2 (5)
Relationship to trial medication					
Not related	20 (80)	16 (89)	19 (83)	17 (85)	36 (84)
Unlikely	5 (20)	2 (11)	4 (17)	3 (15)	7 (16)
Possibly	0	0	0	0	0
Probably	0	0	0	0	0
Definitely	0	0	0	0	0
Expected of trial medication					
Expected	7 (29)	0	5 (22)	2 (11)	7 (17)
Unexpected	17 (71)	18 (100)	18 (78)	17 (89)	35 (83)
Action on trial medication					
None	16 (64)	8 (44)	10 (43)	14 (70)	24 (56)
Treatment delayed	1 (4)	0	1 (4)	0	1 (2)
Treatment stopped	8 (32)	10 (56)	12 (52)	6 (30)	18 (42)
Started new antibiotic during SAE?	12 (48)	15 (83)	16 (70)	11 (55)	27 (63)
Event status at the end of follow-up					
Resolved	24 (96)	17 (94)	21 (91)	20 (100)	41 (95)
Ongoing at study exit	1 (4)	1 (6)	2 (9)	0	2 (5)

a This includes the life-threatening SAE.

The SAR was a diagnosis of vomiting, originally classified by the site investigator as unlikely to be related to the IMP. However, on clinical review by the Trial Management Team, it was felt that the SAE could be related to the IMP and the event was, therefore, reclassified as a SAR.

Specified clinical adverse events (diarrhoea, thrush and skin rash)

Presence and severity of diarrhoea, thrush and skin rash were elicited from parents at trial entry and throughout follow-up. Diarrhoea was the most common clinical AE and was present in 345 (43.6%) participants after baseline. Skin rash was present in 193 (24.4%) participants and oral thrush in 57 (7.2%) participants after baseline. For both dose and duration randomisations, there was no evidence of a difference between the randomised arms in terms of overall prevalence of diarrhoea and oral thrush after baseline (*Table 24*). For skin rash, there was some evidence of a difference between shorter- and longer-duration arms in terms of prevalence after baseline, with the number of participants ever having skin rash after baseline being 106 (27.4%) in the longer-duration arm and 87 (21.5%) in the shorter-duration arm ($p = 0.055$).

TABLE 24 Prevalence of diarrhoea, oral thrush and skin rash after baseline

Prevalence of diarrhoea, oral thrush and skin rash	Treatment arm, *n* (%)				Total (*N* = 814), *n* (%)
	Lower dose (*N* = 410)	Higher dose (*N* = 404)	Shorter duration (*N* = 413)	Longer duration (*N* = 401)	
First diarrhoea after baseline[a]					
No	276 (78.0)	252 (76.4)	259 (75.1)	269 (79.4)	528 (77.2)
Yes	78 (22.0)	78 (23.6)	86 (24.9)	70 (20.6)	156 (22.8)
p-value	$p = 0.62$		$p = 0.18$		
New diarrhoea after baseline or worse than at baseline					
No	303 (75.6)	288 (73.8)	296 (73.3)	295 (76.2)	591 (74.7)
Yes	98 (24.4)	102 (26.2)	108 (26.7)	92 (23.8)	200 (25.3)
p-value	$p = 0.58$		$p = 0.34$		
Ever diarrhoea after baseline					
No	234 (58.2)	213 (54.6)	217 (53.7)	230 (59.3)	447 (56.4)
Yes	168 (41.8)	177 (45.4)	187 (46.3)	158 (40.7)	345 (43.6)
p-value	$p = 0.31$		$p = 0.11$		
First thrush after baseline[b]					
No	386 (96.3)	381 (96.0)	390 (96.8)	377 (95.4)	767 (96.1)
Yes	15 (3.7)	16 (4.0)	13 (3.2)	18 (4.6)	31 (3.9)
p-value	$p = 0.83$		$p = 0.33$		
New thrush after baseline or worse than at baseline					
No	385 (96.0)	374 (95.9)	390 (96.5)	369 (95.3)	759 (96.0)
Yes	16 (4.0)	16 (4.1)	14 (3.5)	18 (4.7)	32 (4.0)
p-value	$p = 0.94$		$p = 0.40$		
Ever thrush after baseline					
No	374 (93.3)	360 (92.3)	379 (93.8)	355 (91.7)	734 (92.8)
Yes	27 (6.7)	30 (7.7)	25 (6.2)	32 (8.3)	57 (7.2)
p-value	$p = 0.60$		$p = 0.26$		
First rash after baseline[c]					
No	310 (86.6)	317 (86.8)	329 (88.4)	298 (84.9)	627 (86.7)
Yes	48 (13.4)	48 (13.2)	43 (11.6)	53 (15.1)	96 (13.3)
p-value	$p = 0.92$		$p = 0.16$		
New rash after baseline or worse than at baseline					
No	348 (86.8)	331 (84.9)	354 (87.6)	325 (84.0)	679 (85.8)
Yes	53 (13.2)	59 (15.1)	50 (12.4)	62 (16.0)	112 (14.2)
p-value	$p = 0.44$		$p = 0.14$		
Ever rash after baseline					
No	307 (76.6)	291 (74.6)	317 (78.5)	281 (72.6)	598 (75.6)
Yes	94 (23.4)	99 (25.4)	87 (21.5)	106 (27.4)	193 (24.4)
p-value	$p = 0.52$		$p = 0.055$		

a Excludes all participants with diarrhoea at trial entry.
b Excludes all participants with thrush at trial entry.
c Excludes all participants with rash at trial entry.

In addition, when considering skin rash severity during the treatment period only, there was evidence of a difference between the shorter- and longer-duration arms. Participants in the longer-duration arm experienced greater skin rash severity than participants in the shorter-duration arm at days 3 ($p = 0.019$) and 7 ($p = 0.005$) (*Figure 20*). There was no evidence of a difference between dose randomisation arms in terms of skin rash severity during the treatment period, and there was no evidence of a difference between the dose and duration randomisation arms in severity of diarrhoea or oral thrush during the treatment period (see *Table 24*).

Health-care services

Utilisation of health-care services was unrelated to randomisation arm. Hospital admissions and visits to the ED without admission were reported in 46 (5.7%) and 43 (5.3%) participants, respectively, whereas a larger proportion of participants reported using any health-care service ($n = 304$, 37.3%) (*Table 25*).

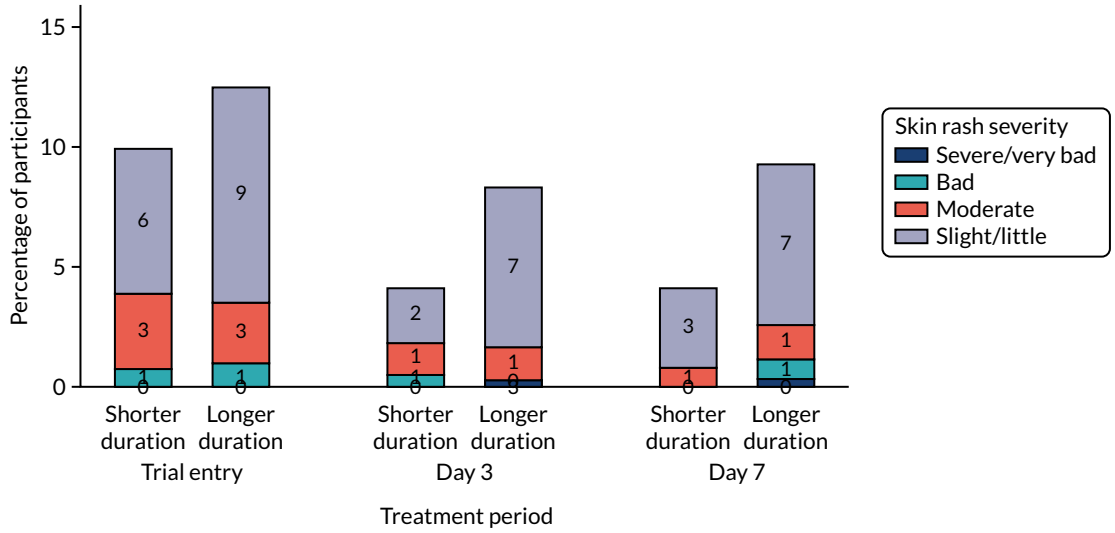


FIGURE 20 Skin rash severity during treatment period: duration randomisation.

TABLE 25 Health-care service utilisation

Health-care service utilisation	Treatment arm, *n* (%)			Treatment arm, *n* (%)			
	Lower dose ($N = 410$)	Higher dose ($N = 404$)	*p*-value	Shorter duration ($N = 413$)	Longer duration ($N = 401$)	*p*-value	Total ($N = 814$), *n* (%)
Ever admitted to hospital?							
Yes	24 (5.9)	22 (5.4)	0.80	27 (6.5)	19 (4.7)	0.27	46 (5.7)
No	386 (94.1)	382 (94.6)		386 (93.5)	382 (95.3)		768 (94.3)
Visited ED (without admission)?							
Yes	21 (5.1)	22 (5.4)	0.84	18 (4.4)	25 (6.2)	0.23	43 (5.3)
No	389 (94.9)	382 (94.6)		395 (95.6)	376 (93.8)		771 (94.7)
Ever used any other health-care service?							
Yes	149 (36.3)	155 (38.4)	0.55	152 (36.8)	152 (37.9)	0.75	304 (37.3)
No	261 (63.7)	249 (61.6)		261 (63.2)	249 (62.1)		510 (62.7)

Daily activities and child care

Data on daily activities and child care were available from parent/guardian-completed diaries for 441 participants (*Table 26*). No differences in reported disruption to daily activities and child care were found between randomisation arms. In total, 73.9% of participants reported that the child had missed school, day care or nursery, and the median number of days missed was 4 (IQR 0–6) days. In addition, 63.8% of parents reported missing work, with a median of 3 (IQR 0–5) days missed, and 34.9% of parents reported requiring additional care for the child.

TABLE 26 Daily activities and child care

	Treatment arm			Treatment arm			
Daily activity/child care	Lower dose (*N* = 298)	Higher dose (*N* = 289)	*p*-value	Shorter duration (*N* = 291)	Longer duration (*N* = 296)	*p*-value	Total (*N* = 441)
Child missed school, day care or nursery: ever, *n* (%)							
Yes	152 (71.0)	174 (76.7)	0.18	159 (72.3)	167 (75.6)	0.43	326 (73.9)
No	62 (29.0)	53 (23.3)		61 (27.7)	54 (24.4)		115 (26.1)
Days child missed school, day care or nursery, median (IQR)	4 (0–5)	4 (2–6)	0.14	4 (0–6)	4 (2–6)	0.62	4 (0–6)
Parent missed work: ever, *n* (%)							
Yes	128 (64.0)	136 (63.6)	0.92	127 (62.9)	137 (64.6)	0.71	264 (63.8)
No	72 (36.0)	78 (36.4)		75 (37.1)	75 (35.4)		150 (36.2)
Days parent missed work, median (IQR)	3 (0–4)	3 (0–5)	0.43	3 (0–4)	3 (0–5)	0.20	3 (0–5)
Parent missed other activities: ever, *n* (%)							
Yes	50 (33.6)	56 (33.7)	0.97	53 (34.2)	53 (33.1)	0.84	106 (33.7)
No	99 (66.4)	110 (66.3)		102 (65.8)	107 (66.9)		209 (66.3)
Days parent missed other activities: cumulative, median (IQR)	0 (0–4)	0 (0–4)	0.88	0 (0–5)	0 (0–4)	0.50	0 (0–4)
Additional care needed for child: ever, *n* (%)							
Yes	73 (36.3)	72 (33.5)	0.54	73 (34.9)	72 (34.8)	0.98	145 (34.9)
No	128 (63.7)	143 (66.5)		136 (65.1)	135 (65.2)		271 (65.1)
Days additional care needed for child: cumulative, median (IQR)	0 (0–3)	0 (0–3)	0.54	0 (0–3)	0 (0–3)	0.83	0 (0–3)

Note
Data are as reported in the symptom diary.

Chapter 4 Discussion

We investigated the impact of dose and duration of amoxicillin treatment for uncomplicated CAP in children discharged from hospital after assessment in a PED, or after a short stay on an assessment unit or inpatient ward. Regarding duration, we focused on oral amoxicillin treatment after discharge rather than total treatment duration, given that discharge home is a key time point for clinical decision-making, as close monitoring of the child will no longer be possible. In this population, we found a 3-day treatment course of amoxicillin to be non-inferior to a 7-day course, and a lower total daily dose to be non-inferior to a higher dose, in terms of antibiotic retreatment for respiratory tract infection within 28 days.

Limitations

In contrast to the majority of trials addressing optimal antibiotic treatment duration and dose of a single drug for childhood pneumonia, CAP-IT was conducted in a high-income setting where the expected mortality, even from moderate to severe CAP, is low. We selected antibiotic retreatment for respiratory tract infection during a follow-up period of 28 days as a clinically relevant and ascertainable event with limited risk of bias in a placebo-controlled trial.[84]

To further guard against bias, an independent ERC, comprising experienced clinicians, adjudicated all antibiotic retreatments during the trial period, regarding the reason (i.e. respiratory tract infection or other) and clinical indication. Of note, the primary end point could be ascertained in 97% of CAP-IT participants either at final follow-up or through contact with the GP. Therefore, we consider the impact of loss to follow-up negligible.

We aimed to exclude children in whom antibiotics would not be expected to have any beneficial effect, primarily those likely to have obstructive airway disease only. However, a mixed picture was common for hospitalised children, with 16% of children receiving either salbutamol or steroids during their hospital stay. Mostly, this affected children with pre-existing hyper-reactive airway disease, and treatment was discontinued in a majority of cases by the time children were discharged home. Compared with the 48% bronchodilator use observed in the most recent UK paediatric pneumonia audit[85] the use of salbutamol or steroids was low in CAP-IT, indicating that there was a strong clinical suspicion of CAP likely to benefit from antibiotics in enrolled children.

We observed no relevant impact of either amoxicillin duration or dose on pneumococcal penicillin non-susceptibility at 28 days, but did not assess pneumococcal resistance at other time points. We did not obtain end-of-treatment samples on all children for resistance analysis for several reasons. First, an additional face-to-face visit would have been a major barrier to participation for many families. Second, penicillin colonisation rates at, or shortly after, the end of antibiotic treatment are expected to be very low, whereas significant recolonisation or regrowth was expected (and observed) by 28 days. Finally, we considered penicillin-resistant pneumococcal colonisation at final follow-up to be the most relevant population- and individual-level resistance marker, as children colonised at this time point could transmit resistant pneumococci to others and would be at higher risk of potentially more difficult to treat respiratory tract infections in the future.[86]

Generalisability

Children were enrolled in the trial based on clinically diagnosed pneumonia requiring antibiotic treatment with amoxicillin, and are typical of children treated for pneumonia with amoxicillin in PEDs. We included children discharged from hospital within 48 hours of admission for observation or initial

clinical management, as hospital stays for acute respiratory tract infections, including pneumonia, are mostly of very short duration.[87,88] Data from the pilot phase confirmed that these children could be considered part of the same spectrum of disease as those discharged directly home from the ED. Only 13% of screened children were not approached because of physician preference for an antibiotic other than amoxicillin at discharge. This is in keeping with guidance suggesting that amoxicillin is used as the first-line antibiotic for oral treatment of uncomplicated childhood pneumonia in the community.

We excluded children with complicated pneumonia requiring prolonged hospitalisation, and those receiving non-beta-lactam treatment. Our findings, therefore, cannot be directly generalised to more severely ill children or those treated for atypical pneumonia. However, it is highly likely that our observations are relevant to children with mild to moderate pneumonia seen in primary care, who would be treated with oral amoxicillin at home. In primary care, the acuity of disease is generally lower and a lower rate of pneumonia likely to benefit from antibiotic treatment is expected.

No nasopharyngeal penicillin-resistant pneumococcal isolates were observed in the trial, either at baseline or at final follow-up, which is consistent with reported low penicillin resistance levels in northern Europe.[89] Therefore, our findings for the effectiveness of lower compared with higher amoxicillin dose, and impact on resistance, may be of limited generalisability to children with pneumonia in other high-income settings with higher pneumococcal penicillin resistance prevalence.

Twice-daily dosing of amoxicillin in line with WHO and other international recommendations was used in CAP-IT, rather than administration in three daily doses, as recommended by the BNFc. This was selected as it is known to maximise adherence, which would be particularly important in children allocated to the lower-dose and shorter-duration arms. In addition, patient representatives involved in the design phase indicated this approach to be particularly family friendly, as an additional mid-day dose is difficult to give to children who attend day care. Consequently, our findings, especially for antimicrobial resistance outcomes, may not be generalisable to children being treated with a thrice-daily amoxicillin regimen. However, participants in CAP-IT had rates of antibiotic retreatment and secondary or rehospitalisation similar to those described in observational studies conducted in settings with standard administration of amoxicillin in three doses.[41,87,90,91]

Interpretation

To the best of our knowledge, few head-to-head comparisons of the same antibiotic in different dosing or duration regimens have been conducted in children being treated for pneumonia. Most of the existing literature reports on trials conducted in low- and middle-income settings prior to the widespread availability of PCVs and in an era with lower pneumococcal penicillin resistance.[92,93] Two recent relevant trials[94,95] conducted in Malawi investigated 3-day compared with 5-day amoxicillin treatment and 3-day amoxicillin treatment compared with placebo in young children with non-severe pneumonia and not infected with human immunodeficiency virus. In summary, 3-day treatment at a dose corresponding to the higher total daily dose in CAP-IT was found to be non-inferior to 5-day treatment for early treatment failure, but this was not the case for placebo compared with 3-day treatment. The same trial identified the number needed to treat for children with non-severe fast-breathing pneumonia to be 33. These trials used high-sensitivity, but low-specificity eligibility criteria appropriate for a high-mortality setting. Evidence specific to high-income settings is lacking and has led some guideline-setting bodies to question the generalisability of findings from large trials in low- or middle-income countries to high-income settings. The persisting evidence gap for children identified as having pneumonia applying higher specificity clinical criteria in high-income settings has now been addressed by CAP-IT.

A relatively high retreatment rate of 12.5% was observed in the CAP-IT cohort. This is consistent with similarly high retreatment rates in primary care reported in large observational studies, but has not

previously been described for children with CAP seen in EDs or discharged from hospital after a short stay. Similarly, the secondary or rehospitalisation rate of around 5% was similar to that described for children with pneumonia in observational studies.

We observed remarkably similar retreatment rates for respiratory tract infections between the 3- and 7-day treatment durations, despite 2-day slower resolution of mild cough, on average, in the shorter-duration arm. We did not identify any differences between the lower- and higher-dose treatment arms. Antibiotic retreatment for respiratory tract infection during the follow-up period could be related to true failure of the initial treatment or could be linked to persistent symptoms unlikely to be responsive to amoxicillin because they were mainly triggered by a viral (co-)infection or new respiratory tract infection episodes.

Children and parents in the 3-day randomisation arm were not reported to have spent a longer time away from day care or school and work, making it unlikely that cough had a major impact on children's usual routines. Slightly longer time to symptom resolution in placebo arms or placebo-controlled shorter-duration arms has been reported for acute otitis media.[96] However, it is unclear how children being mildly symptomatic for longer is weighed against the benefits of shorter treatment by children and their families. When symptoms are minor, shorter treatment is likely to be a key factor in allowing children to return to usual activities and will maximise adherence.[97,98]

Antimicrobial resistance was a key secondary outcome in CAP-IT. Colonisation by penicillin-non-susceptible pneumococci at 28 days was similar for both randomisation arms. In general, the observed prevalence of pneumococcal penicillin non-susceptibility and the complete absence of penicillin-resistant pneumococci was in line with the UK being a low-resistance setting. Pneumococcal penicillin resistance alone is unlikely to reflect the full impact of amoxicillin dose and duration on the child nasopharyngeal microflora, including the presence of resistance genotypes. Next-generation sequencing approaches could provide in-depth information about differential changes in the microbiome and resistome with higher or lower amoxicillin dose and shorter or longer treatment duration. However, the interpretation of such analyses is likely to be complex, and will need to take account of the interactions between different pneumococcal subpopulations, as well as between pneumococci and other bacteria in a densely populated niche. An analysis of nasopharyngeal samples obtained in CAP-IT using next-generation sequencing approaches is ongoing.

Several other trials have generated results that complement CAP-IT findings, or are expected to in the near future. In the UK, this includes the primary care-based ARTIC PC (Antibiotics for lower Respiratory Tract Infection in Children presenting in Primary Care) study,[99] a randomised placebo-controlled trial investigating the benefit of a 7-day course of oral amoxicillin in children with possible lower respiratory tract infection (but not considered to have pneumonia clinically). The SAFER (Short-Course Antimicrobial Therapy for Pediatric Community-Acquired Pneumonia) trial[100] in Canada and SCOUT-CAP (Short Course Outpatient Therapy of Community Acquired Pneumonia) study in the USA both target children presenting to EDs but not admitted to hospital, the former comparing 5- and 10-day treatment courses with amoxicillin and the latter a selection of beta-lactams. The SCOUT-CAP study is expected to report on results at the end of 2021. Finally, a Canadian open-label RCT (NCT03031210) is investigating twice-compared with thrice-daily amoxicillin dosing in children treated for pneumonia. The total daily dose in this trial corresponds to the higher total daily dose investigated in CAP-IT.

Implications

For clinical practice, CAP-IT supports routine use of shorter, 3-day, oral amoxicillin courses at current doses for children presenting to hospital with uncomplicated clinically diagnosed CAP for community-based treatment after discharge from acute care. A slightly longer time to resolution of mild cough can be expected in children treated for 3 days, compared with children treated for 7 days.

For research, existing systematic reviews and meta-analyses should be updated to include CAP-IT and other high-income setting trials. A series of relevant trials includes studies already completed or about to complete. Their inclusion, for example in existing Cochrane reviews, would ensure that key reference systematic reviews are relevant globally.

The question of the comparison between two and three times daily dosing of amoxicillin needs to be addressed. However, this may best be tackled by modelling and simulation based on high-quality pharmacokinetic data analysed using modern pharmacometric approaches. Such data are needed from a variety of settings, including low/high prevalence of pneumococcal penicillin resistance, varying pneumococcal vaccine coverage and low-, middle- and high-income settings characterised by varying prevalence of important covariates, such as malnutrition and obesity. Data from adults suggest that gut amoxicillin absorption may be saturable, limiting the expected utility of high-dose regimens.[101]

A proportion of children screened for CAP-IT were identified to be ineligible because the managing clinician was planning treatment with an antibiotic other than amoxicillin. Trial data supporting the use of macrolides (targeting atypical pathogens) or alternative beta-lactams, such as amoxicillin/clavulanate (co-amoxiclav, targeting Gram-negative respiratory pathogens producing beta-lactamases), are lacking.

Chapter 5 Conclusions

- For children presenting to acute care settings with uncomplicated, clinically diagnosed, moderate or moderate to severe CAP who can be managed at home, there is no evidence to suggest that a longer 7-day treatment course of oral amoxicillin offers any advantage over a shorter 3-day course, in terms of antibiotic retreatment for respiratory tract infection within 4 weeks. Therefore, the trial supports routine use of 3-day oral amoxicillin courses after discharge from hospital in this population.
- Slightly longer time to resolution of mild cough was observed in children treated for 3 days than in those treated for 7 days. Given the advantages of a shorter duration of treatment for adherence and the observed declining adherence during treatment days 4–7 in the trial, a 3-day course of oral amoxicillin nonetheless appears preferable. This would have the added benefit of greater harmonisation of antibiotic treatment duration guidance between low-/middle-income and high-income settings.
- Similarly, we found that lower total daily doses of oral amoxicillin were non-inferior to higher daily doses, in terms of antibiotic retreatment for respiratory tract infection within 4 weeks. Dosing regimens were also similar in terms of impact on pneumococcal antimicrobial resistance and safety.
- Of note, a weight-banded approach was used for dose selection, resulting in less variability in total daily dose compared with an age-banded approach (as is used in the UK in clinical practice). Based on the age-banded approach, both doses studied in CAP-IT are expected to be prescribed in the UK because of variations in weight within broad age bands.
- Either (lower and higher) total daily dose is feasible to deliver in high-income settings where amoxicillin suspensions of different concentrations are available and are prescribed in preference to solid child-appropriate formulations (i.e. solid forms that are liquid on ingestion or become liquid on administration). As a result, moving between lower and higher total daily doses does not result in greater volumes per dose for treated children.
- However, the situation is different in low- and middle-income settings, where the preferred formulation is dispersible tablets. The lowest-concentration child-appropriate solid formulation supported by the United Nations International Children's Emergency Fund (UNICEF) and WHO contains 250 mg of amoxicillin in a non-divisible dispersible tablet. Administration of this tablet twice a day to young infants (weighing 4–10 kg) gives a wide dose range of 50 (10 kg) to 125 (4 kg) mg/kg per day, with many children expected to receive doses in the higher dose range of CAP-IT. CAP-IT results did not identify any clinically relevant disadvantages to using higher doses; therefore, supporting the continued use of existing dispersible tablets.
- We did not formally compare twice- with thrice-daily dosing. However, we note that children in CAP-IT had good clinical outcomes, with antibiotic retreatment rates and secondary or re-admission rates similar to those described for children with acute lower respiratory tract infections in observational studies in the UK where amoxicillin treatment would generally be given three times daily.

Acknowledgements

We would like to thank all of the patients, their families and the staff from the participating centres for their vital contributions to CAP-IT.

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Sheffield Children's NHS Foundation Trust: Judith Gilchrist (principal investigator), Noreen West, Jayne Evans and Julie Morecombe.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Details of main protocol amendment: joint analysis of paediatric emergency department and ward groups

Initially, PED and ward groups were treated as separate strata because of (1) an expected higher severity of CAP in the ward group, (2) the expected differences in prior receipt of antibiotic for current episode having an impact on the duration of treatment analysis and (3) the need for different trial procedures (i.e. consent process, enrolment and additional data capture during the inpatient period for the ward group). However, based on the pilot phase, the following key aspects emerged and formed the basis for the joint analysis of PED and ward groups. First, in a substantial proportion of participating hospitals, children were first seen in a paediatric assessment unit before either being formally admitted or discharged. This made the distinction between PED and ward less relevant, especially as many paediatric assessment units admitted children for up to 48 hours. Second, although clinical signs and symptoms at presentation to ED were (as expected) worse, on average, in ward children than in PED children, considerable overlap in the two distributions was observed. Third, the duration of prior antibiotic exposure in the ward group was much shorter than anticipated (< 12 hours, 54%; < 24 hours, 75%). Finally, there was no evidence of a difference between the primary end-point rate between PED and ward groups.

Appendix 2 Community-acquired pneumonia symptoms at trial entry by strata

TABLE 27 Community-acquired pneumonia symptoms at trial entry by stratum

	Strata, *n* (%)			
Stratum	**PED (*N* = 591)**	**Ward (*N* = 223)**	***p*-value**	**Total (*N* = 814), *n* (%)**
Fever				
Not present	54 (9.2)	111 (49.8)	< 0.001	165 (20.3)
Slight/little	71 (12.0)	31 (13.9)		102 (12.5)
Moderate	175 (29.7)	42 (18.8)		217 (26.7)
Bad	215 (36.4)	26 (11.7)		241 (29.6)
Severe/very bad	75 (12.7)	13 (5.8)		88 (10.8)
Cough				
Not present	14 (2.4)	14 (6.3)	< 0.001	28 (3.4)
Slight/little	61 (10.3)	45 (20.2)		106 (13.0)
Moderate	246 (41.7)	96 (43.0)		342 (42.1)
Bad	208 (35.3)	59 (26.5)		267 (32.8)
Severe/very bad	61 (10.3)	9 (4.0)		70 (8.6)
Wet cough (phlegm)				
Not present	174 (29.5)	72 (32.3)	0.58	246 (30.3)
Slight/little	125 (21.2)	44 (19.7)		169 (20.8)
Moderate	159 (26.9)	65 (29.1)		224 (27.6)
Bad	103 (17.5)	36 (16.1)		139 (17.1)
Severe/very bad	29 (4.9)	6 (2.7)		35 (4.3)
Breathing faster (shortness of breath)				
Not present	77 (13.1)	57 (25.6)	< 0.001	134 (16.5)
Slight/little	151 (25.6)	70 (31.4)		221 (27.2)
Moderate	182 (30.8)	52 (23.3)		234 (28.8)
Bad	140 (23.7)	36 (16.1)		176 (21.6)
Severe/very bad	40 (6.8)	8 (3.6)		48 (5.9)
Wheeze				
Not present	283 (48.0)	109 (48.9)	0.95	392 (48.2)
Slight/little	129 (21.9)	52 (23.3)		181 (22.3)
Moderate	112 (19.0)	37 (16.6)		149 (18.3)
Bad	56 (9.5)	21 (9.4)		77 (9.5)
Severe/very bad	10 (1.7)	4 (1.8)		14 (1.7)

continued

TABLE 27 Community-acquired pneumonia symptoms at trial entry by stratum (*continued*)

Stratum	Strata, *n* (%)		*p*-value	Total (*N* = 814), *n* (%)
	PED (*N* = 591)	Ward (*N* = 223)		
Sleep disturbed by cough				
Not present	67 (11.4)	56 (25.1)	< 0.001	123 (15.2)
Slight/little	95 (16.2)	55 (24.7)		150 (18.5)
Moderate	151 (25.7)	55 (24.7)		206 (25.4)
Bad	170 (28.9)	42 (18.8)		212 (26.1)
Severe/very bad	105 (17.9)	15 (6.7)		120 (14.8)
Vomiting (including after cough)				
Not present	324 (54.9)	155 (69.5)	0.003	479 (58.9)
Slight/little	110 (18.6)	32 (14.3)		142 (17.5)
Moderate	83 (14.1)	18 (8.1)		101 (12.4)
Bad	49 (8.3)	15 (6.7)		64 (7.9)
Severe/very bad	24 (4.1)	3 (1.3)		27 (3.3)
Eating/drinking less				
Not present	63 (10.7)	30 (13.5)	0.073	93 (11.4)
Slight/little	140 (23.7)	68 (30.5)		208 (25.6)
Moderate	184 (31.2)	67 (30.0)		251 (30.9)
Bad	157 (26.6)	41 (18.4)		198 (24.4)
Severe/very bad	46 (7.8)	17 (7.6)		63 (7.7)
Interference with normal activity				
Not present	61 (10.3)	49 (22.0)	< 0.001	110 (13.5)
Slight/little	136 (23.1)	59 (26.5)		195 (24.0)
Moderate	198 (33.6)	63 (28.3)		261 (32.1)
Bad	140 (23.7)	40 (17.9)		180 (22.1)
Severe/very bad	55 (9.3)	12 (5.4)		67 (8.2)

Appendix 3 On-treatment analysis of the primary end point

The on-treatment analyses of the primary end point excluded participants who took < 80% of trial medication as scheduled (e.g. when patients missed two doses of medication, when a smaller volume of medication was taken). When patients switched from medication to non-trial antibiotics because of deterioration this was not regarded as non-adherence. For each randomised comparison, non-adherence was analysed in two ways: (1) based on all trial medication including placebo and (2) based on active drug only (*Figures 21–24*).

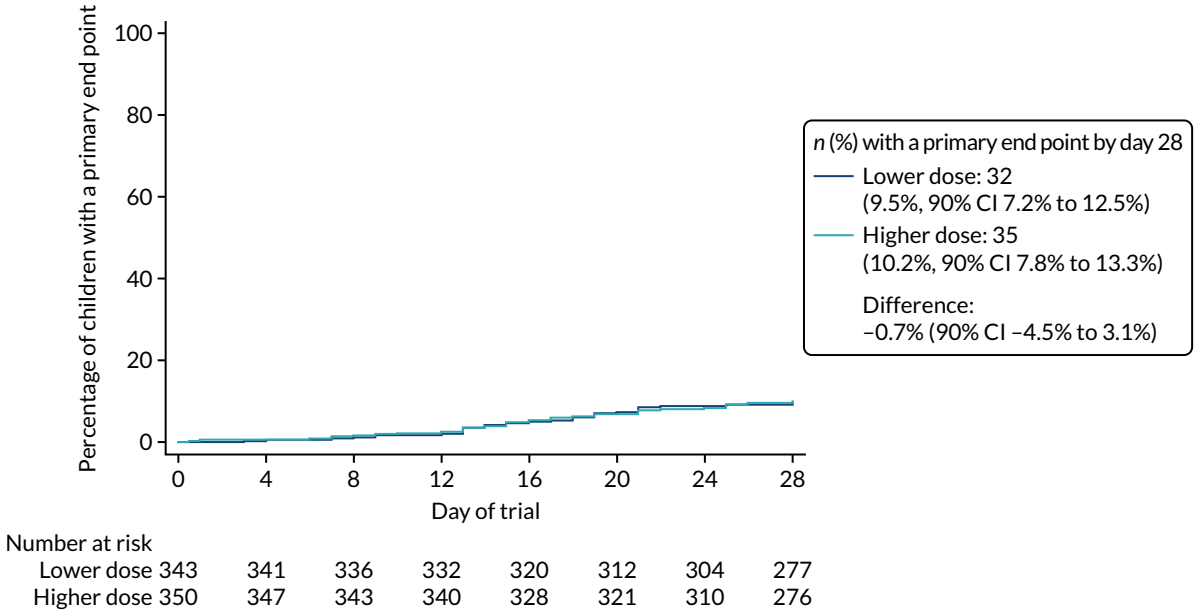


FIGURE 21 Dose randomisation: participants who took at least 80% of all trial medication, including placebo.

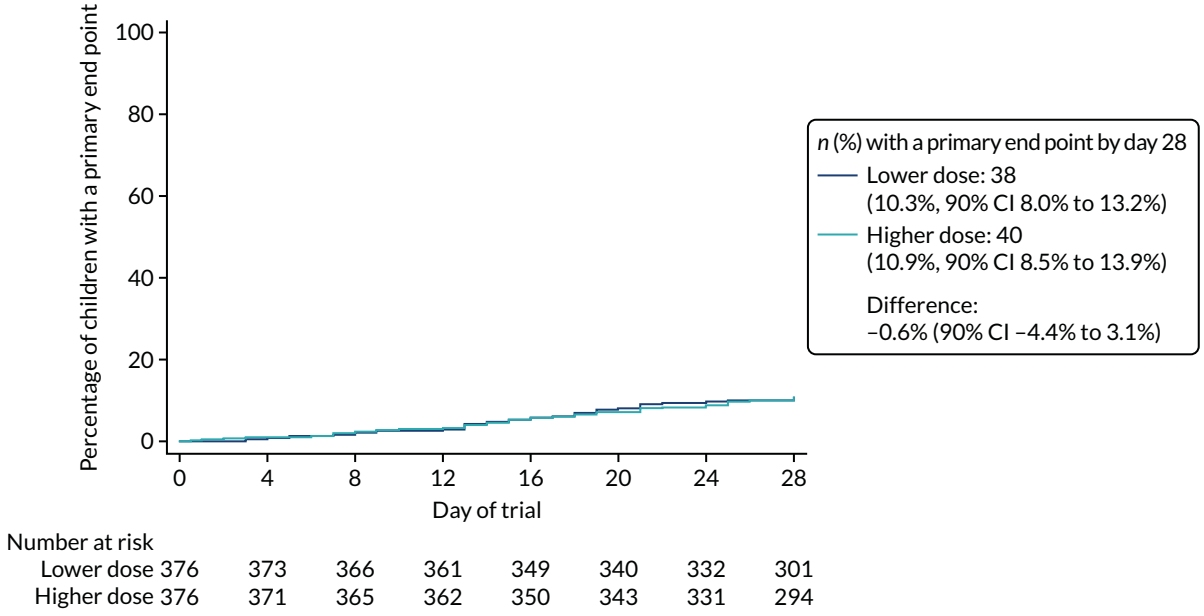
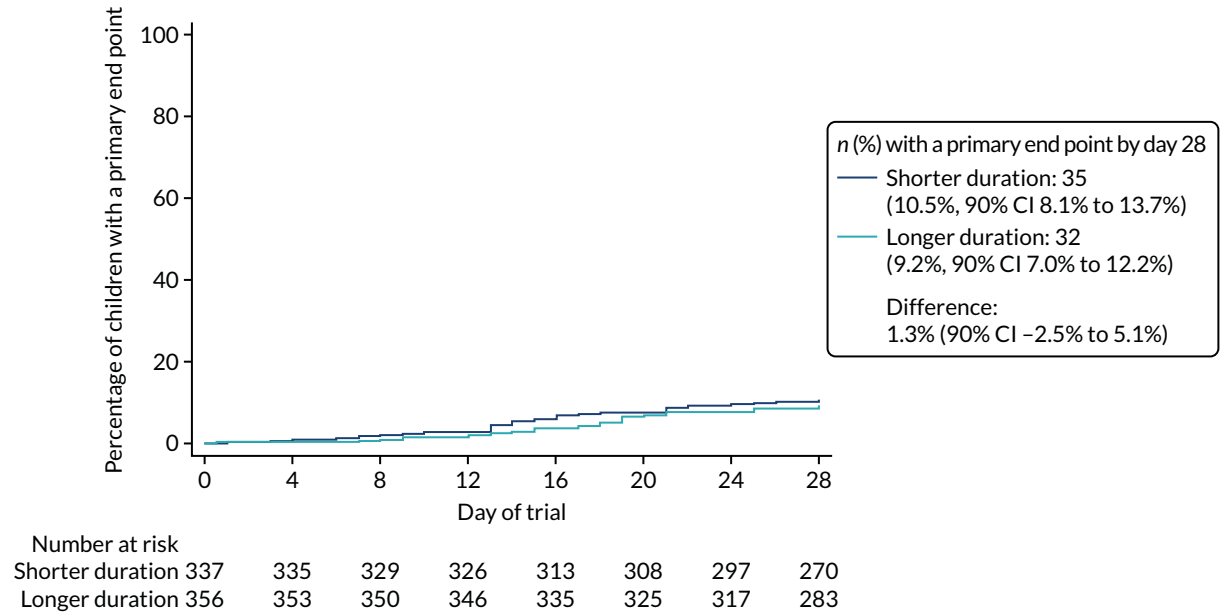
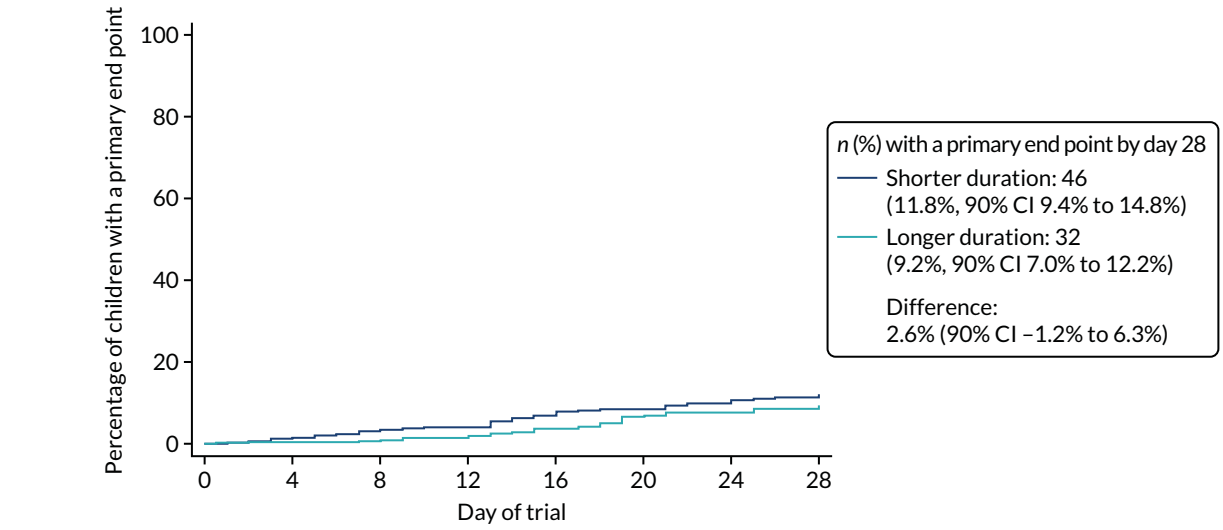


FIGURE 22 Dose randomisation: participants who took at least 80% of active trial drug.



Number at risk								
Shorter duration	337	335	329	326	313	308	297	270
Longer duration	356	353	350	346	335	325	317	283

FIGURE 23 Duration randomisation: participants who took at least 80% of all trial medication, including placebo.



Number at risk								
Shorter duration	396	391	381	377	364	358	346	312
Longer duration	356	353	350	346	335	325	317	283

FIGURE 24 Duration randomisation: participants who took at least 80% of active trial drug.

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