Title page

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

Authors (alphabetical)

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], Mike Sharland[2]…on behalf of the CAP-IT Trial Team and the PERUKI and GAPRUKI Networks

Affiliations

1. MRC Clinical Trials Unit at UCL, 90 High Holborn, London, UK
2. Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's University of London, London, UK
3. NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK
4. Bristol Children's Vaccine Centre, Schools of Population Health Sciences and of Cellular and Molecular Medicine, University of Bristol, UK
5. Emergency Department, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol, UK
6. Faculty of Health and Applied Sciences, University of the West of England, Bristol, UK
7. Paediatric Emergency Medicine Department, Sidra Medicine, Doha, Qatar
8. School of Medicine, Cardiff University, Cardiff UK
9. Research and Development Nursing Team, Birmingham Women's and Children's Hospital Trust, Steelhouse Lane, Birmingham, UK
10. Paediatric Emergency Medicine Leicester Academic (PEMLA) group, Leicester Hospitals, Leicester, UK
11. SAPPHIRE group, Health Sciences, Leicester University, Leicester, UK
12. Evelina Pharmacy, Guy's and St Thomas' NHS Trust, London, UK

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Correspondence to Michael Sharland, St George's University of London, Cranmer Terrace, London, UK SW17 0RE
Email: msharland@sgul.ac.uk
Phone: 020 8725 5968

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Community acquired pneumonia; children; amoxicillin; antibiotic treatment/Duration; antibiotic treatment/Dose; randomised controlled trial

i. Abstract

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

Objectives: To determine the efficacy, safety and impact on anti-microbial resistance of 3 versus 7 days and lower or higher dose of amoxicillin at hospital discharge in children with uncomplicated CAP.

Design: Multi-centre, randomised, double-blind, 2x2 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 over 6 months, weighing 6-24 kg, with a clinical diagnosis of CAP, in whom the decision had been made to treat with amoxicillin on hospital discharge.

Interventions: Oral amoxicillin syrup at doses of 35-50mg/kg/day versus 70-90mg/kg/day, and three versus seven 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 CAP), other than trial medication, up to 28 days after randomisation. Secondary outcomes included severity and duration of parent-reported CAP symptoms, drug-related adverse events (including thrush, skin rashes, diarrhoea), antimicrobial resistance, and adherence to trial medication.

Results: 824 children were recruited from 29 hospitals. Ten participants received no trial medication and were excluded. Participants (median (IQR) age 2.5 years (1.6-2.7); 52% male) were randomised to either three (413

participants) or seven days (401) of trial medication at either lower (410 participants) or higher (404 participants) doses. There were 51 (12.5%) versus 49 (12.5%) primary endpoints in three versus seven days respectively (difference 0.1% (90%CI -3.8 to 3.9)), and 51 (12.6%) versus 49 (12.4%) in lower versus higher dose arms (difference 0.2%(90%CI -3.7 to 4.0%)); both demonstrating non-inferiority. The seven-day arm had faster resolution than the three-day arm for cough (10 vs 12 days) (p=0.040), with no differences in other symptoms. Adverse events and colonization by penicillin non-susceptible pneumococci were comparable between arms.

Limitations: End-of-treatment swabs were not taken and 28-day swabs only collected on 53% 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% children did not attend the final 28-day visit, we obtained data from general practitioners for the primary endpoint on all but 3% children.

Conclusions: Antibiotic retreatment, adverse events and nasopharyngeal colonization by penicillin non-susceptible pneumococci were similar with higher versus lower amoxicillin dose, and 3-day versus 7-day treatment. Time to resolution of cough and sleep disturbance was slightly longer in children taking 3 days amoxicillin, but all other symptom resolution was similar.

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 sub-study compared parental electronic and paper diary entry is also on-going.

Study registration: ISRCTN registration number ISRCTN76888927; EURACT 2016-000809-36; CTA 00316/0246/001-0006

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ii. Table of Contents

iii. List of figures

iv. List of tables

v. List of abbreviations/glossary

AE	**Adverse event**
AMR	**Antimicrobial Resistance**
AR	**Adverse reaction**
bid/bd	**Twice a day**
BNF	**British National Formulary**
BNFc	**British National Formulary for Children**
BSAC	**British Society of Antimicrobial Chemotherapy**
BTS	**British Thoracic Society**
CAP	**Community Acquired Pneumonia**
CI	**Confidence interval**
CRF	**Case Report Form**
CRP	**C-reactive protein**
ED	**Emergency Department**
EUCAST	**European Committee on Antimicrobial Susceptibility Testing**
GP	**General Practitioner**
IDMC	**Independent Data Monitoring Committee**
IMP	**Investigational medicinal product**
ISRCTN	**International Standard Randomised Controlled Trial Number**
ITT	**Intention-to-treat**
LRTI	**Lower Respiratory Tract Infection**
MedDRA	**Medical Dictionary for Regulatory Activities**
MHRA	**Medicines and Healthcare products Regulatory Agency**
MIC	**Minimal Inhibitory Concentration**
MRC	**Medical Research Council**
MRC CTU at UCL	**Medical Research Council Clinical Trials Unit at University College London**
NHS	**National Health Service**
NICE	**National Institute for Health and Care Excellence**

NIHR	**National Institute for Health Research**
OD	**Once daily**
PAU	**Paediatric Assessment Unit**
PCV	**Pneumococcal Vaccination**
PED	**Paediatric Emergency Department**
PERUKI	**Paediatric Emergency Research in the United Kingdom & Ireland**
PI	**Principal Investigator**
PIS	**Patient Information Sheet**
PK	**Pharmacokinetics**
PKPD	**Pharmacokinetic-pharmacodynamics**
po	**by mouth**
PSI	**Pneumonia Severity Index**
RCT	**Randomised controlled trial**
REC	**Research Ethics Committee**
SAE	**Serious adverse event**
SAP	**Statistical Analysis Plan**
SAR	**Serious adverse reaction**
SD	**Standard deviation**
SPC	**Summary of Product Characteristics**
SSG	**Scientific Strategy Group**
SUSAR	**Suspected unexpected serious adverse reaction**
TDS	**thrice daily**
T>MIC	**Time spent over minimum inhibitory concentration**
TMG	**Trial Management Group**
TMT	**Trial Management Team**
TSC	**Trial Steering Committee**
WHO	**World Health Organization**

vi. Plain English Summary

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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) and number of days (duration) to give.

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. The CAP-IT trial tested whether lower doses and shorter durations of amoxicillin are as good as higher doses and longer durations, and whether these affect the presence of resistant bacteria.

In total, 824 children in United Kingdom and Ireland with pneumonia participated. They received either high or low dose amoxicillin for three days or seven days following discharge from hospital. To ensure that neither doctors of 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 during four weeks after starting the trial medicine. To check for resistant bacteria, a nose swab was collected before starting treatment and again after four weeks.

One in every eight participating children was given additional antibiotics. We found no important difference in this proportion between three days and seven days of amoxicillin, or between lower or higher doses. Whereas children's coughs took slightly longer to go away when they received only three days of antibiotics, there was slightly more rash in children taking seven days. 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.

vii. Scientific Summary

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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, and whilst 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 the British National Formulary for Children (BNFc) and 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 250mg three times daily for children aged 1-5 years, with a total daily dose similar to countries using twice daily dosing. Due 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, 2019 NICE treatment guidelines for childhood pneumonia recommend a 5-day course whereas European and WHO guidance suggests 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 PCV-13 vaccine 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. 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.

While 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 of the CAP-IT trial was to determine: whether for young children with uncomplicated CAP treated after discharge from hospital (1) a three day course of amoxicillin is non-inferior to a seven day course, determined by receipt of clinically indicated systemic antibiotic other than trial medication for respiratory tract infection (including CAP) in the 4 weeks after randomization up to day 28; and (2) lower dose is non-inferior to higher dose amoxicillin under the same conditions.

Secondary objectives evaluated the impact of lower dose and shorter duration of amoxicillin on antimicrobial resistance, severity and duration of parent/guardian-reported CAP symptoms, and specified clinical adverse events

Methods

Trial design

The CAP-IT trial was a multi-centre clinical trial with a target sample size of 800 participants conducted in hospitals in the UK NHS and Ireland. It was a randomised double-blind placebo-controlled 2x2 factorial non-inferiority trial evaluating 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 (ED), assessment/observation units, and inpatient wards.

Children were eligible if they had a diagnosis of uncomplicated CAP, were older than 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 (≥38ºC) in the previous 48 hours, and respiratory distress and/or focal chest signs. Children could have received either no antibiotics or less than 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 contra-indication to amoxicillin; diagnosis of complicated pneumonia (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. Body weight was obtained for all children during eligibility screening to determine dose volume according to seven weight bands. Children were randomised to receive either a lower (35-50mg/kg/day) or higher (70-90mg/kg/day) dose, and to receive either 3 days or 7 days of amoxicillin at the point of discharge from hospital.

Randomisation & blinding

Patients underwent two simultaneous factorial 1:1 randomisations (dose and duration) resulting in allocation to one of the four amoxicillin regimens (low dose, short duration; low dose, long duration; high dose, short duration; 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[1]. Blinded 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, 125mg/5ml and 250mg/5ml. A placebo manufactured to match oral amoxicillin suspension was used to blind the duration. One brand of amoxicillin was used for the first three 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 due to placebo or alternative amoxicillin.

Outcomes

The primary outcome for the CAP-IT trial 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 day 28 final follow-up visit). An expert clinician endpoint review committee 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-reported CAP symptoms (fever, cough, phlegm, fast breathing, wheeze, disturbed sleep, eating/drinking less, interference with normal activity, vomiting), adherence to trial medication, specified clinical adverse events (skin rash, thrush and diarrhoea), and serious adverse events.

Data collection

Data on primary and secondary endpoints were collected on paper CRFs by site staff at trial entry, via telephone contact at day 3, day 7, day 14 and day 21, and at a final face-to-face visit on day 28. For children who did not attend the final face-to-face visit, consent was obtained for the trial team to contact their general practitioner (GP) in order to ascertain whether 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.

[1] Initially stratification was by "PED" or "WARD" group, reflecting whether participants were admitted to in patient wards or observation units or were discharged directly from the emergency department. Following an amendment for the joint analysis of these groups, stratification was effectively based on whether participants had received in-hospital antibiotics prior to randomisation.

Sample size

The sample size was calculated assuming a 15% event rate, 8% non-inferiority margin (on a risk difference scale) assessed against a 2-sided 90% 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 (mITT) 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 from all statistical analyses of randomised patients who did not take any IMP.

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 endpoint. Participants with incomplete primary outcome data were censored at the time of their last contact (including contact with GP). Kaplan-Meier estimates were used to derive the risk difference between the randomised groups for the primary endpoint at day 28.

Four pre-defined sensitivity analyses for the primary outcome were performed: 1) including all systemic antibacterial treatments regardless of reason or indication; 2) limiting to endpoints where either CAP or chest infection (rather than RTI generally) was adjudicated as the reason for treatment; 3) as 2) but also including endpoints where the clinical indication was judged as 'unlikely' by the endpoint review committee; 4) for the duration comparison only, disregarding prescriptions occurring within three days of randomisation because these cannot, by definition, be related to this randomisation.

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

Results

Primary endpoint

Of 814 participants in the analysis population, 100 (12.5%; 90% CI 10.7-14.6%) met the primary endpoint: 51 (12.6%) in the lower dose and 49 (12.4%) in the higher dose arm (difference 0.2%; 90%

CI -3.7 to 4.0%); 51 (12.5%) in the shorter duration and 49 (12.5%) 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.

CAP symptoms

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

Adverse events

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

There was no difference in the 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%; $p=0.055$).

Conclusions

In summary, we found a 3-day treatment course of amoxicillin to be non-inferior to a 7-day course, and lower daily dose to be non-inferior to higher dose, in terms of antibiotic retreatment for respiratory tract infection within 28 days. Time to resolution of parent-reported symptoms was comparable between randomisation arms except for on average two days longer of mild cough in the short compared with the long duration treatment arm. Adverse event rates and healthcare services use within the 28 day follow up period, and penicillin non-susceptible pneumococcal colonization rates at 28 days were similar for both dose and duration randomisation groups. No penicillin-resistant pneumococci were identified in samples from CAP-IT participants. Based on these findings, we would recommend reducing the recommended oral amoxicillin treatment duration from five to three days for children with

uncomplicated pneumonia treated in the ambulatory setting. Current BNF-c 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.

Study registration: ISRCTN registration number ISRCTN76888927; EURACT 2016-000809-36; CTA 00316/0246/001-0006

Funding details: The CAP-IT trial is funded by the NIHR HTA Programme, Antimicrobial Resistance Themed Call, via grant number 13/88/11.

1. Introduction

Note: this chapter includes material that has been adapted from the trial protocol which has been published in BMJ Open. [1]

1.1 Background

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

Of the possible indications in children less than five years old, 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, and whilst 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] Of all antibiotics prescribed for community-acquired infections in the UK, 62% are for CAP. [8] In the United States respiratory symptoms, fever or cough are responsible for a third of all childhood medical visits, and 7-15% of these children will be diagnosed with CAP. [9, 10]

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

The bacterial pathogen most commonly associated with childhood CAP is *Streptococcus pneumoniae,* including in settings with routine pneumococcal vaccination (PCV). [15-18] In 2010 PCV-13 (which covers

13 *S. pneumoniae* serotypes) was introduced in the UK with almost 95% uptake in young children. [19, 20] However, despite an observed impact on invasive pneumococcal disease, a decrease in CAP-related hospital admissions in young children has not been observed. [12, 14, 21, 22]

1.2 What are the current challenges in the management of childhood CAP?

There is no test capable of accurately distinguishing between bacterial and viral CAP. [23] Poor inter-observer agreement for chest x-ray findings casts doubt on their utility 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. [24-26] Diagnosis of bacterial CAP presents a challenge for treating clinicians, who rely largely on clinical criteria. [23] 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, 27-29] while wheezing is negatively associated with radiographic pneumonia and detection of bacteria. [27, 30] Where bacterial CAP is considered the likely diagnosis, this is treated with antibiotics. [10, 31] This diagnostic challenge is particularly problematic in secondary care, where a higher proportion of children presenting with serious bacterial infections are seen, as compared with primary practice. [32, 33]

A further challenge for clinicians is severity assessment. Available validated predictive scoring systems for CAP severity include the Pneumonia Severity Index (PSI) or the CURB-65, but these are not applicable to children. [34, 35] Pneumonia mortality risk scores for children have been developed in low-resource settings, but do not differentiate between viral and bacterial pneumonia. [36, 37] Low oxygen saturation in room air is included as one component in these risk scores, and is an important differentiating factor between non-severe and severe pneumonia. [38-40]

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. [41] According to British Thoracic Society (BTS) guidance, such criteria should trigger clinical review of children treated with oral antibiotics for CAP, [23] including where the following features are present at 48 hours: 1) persistent high fever, 2) increasing or persistently increased effort of breathing, 3) persistent or increasing oxygen requirement to maintain saturations ≥92%. [23] Approximately 15% of children with CAP receive further antibiotics within 28 days of starting treatment due to symptoms which concern parents. [42, 43-45] However, only half of children show recovery from symptoms of acute respiratory illness by day 9-10, while 90% recover by 3.5 weeks after symptom onset. [46-48]

1.3 What are the current management recommendations for childhood CAP?

Amoxicillin is the drug of choice for the treatment of childhood CAP according to the BNFc, BTS and NICE guidelines, as well as several international guidelines, [23, 49-52] 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.

1.3.1 What are the current dose recommendations?

Antibiotic dose selection should be driven by Pharmacokinetic/Pharmacodynamic (PKPD) considerations. The key PKPD parameter for beta-lactams (including amoxicillin) is time spent above the Minimum Inhibitory Concentration (T>MIC; mainly focussed here on pneumococcus). The recommended T>MIC is 40-50% of the dosing interval, however the exact relationship between blood PK and concentrations of amoxicillin in the lungs is unclear. [49, 53] 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. [54] However, there are few data to inform whether three times daily dosing is likely to achieve PKPD parameters better than twice daily dosing. Available data suggest twice daily dosing would be expected to achieve required T>MIC for amoxicillin doses of 25-50mg/kg/day, [54] and a Brazilian group recently demonstrated non-inferiority of twice compared with thrice daily dosing in childhood CAP. [55] Together with a likely improvement in adherence with less frequent administration, twice daily dosing is therefore widely recommended. [49-51, 53] Currently the BNFc recommends amoxicillin 250mg TDS for children aged 1-5 years with CAP, resulting in highly variable dosing between approximately 40-80mg/kg/d depending on the weight of the child, [56] and alternative strategies such as weight-banded dosing may be more appropriate. [57] Furthermore, much higher daily doses of amoxicillin up to 200mg/kg/d are recommended for the treatment of severe infections. [56]

1.3.2 What are the current duration recommendations?

Several large 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. [58, 59] However, these trials enrolled children with symptoms indicative of a viral infection not requiring antibiotics, and generalisability to the UK has therefore been questioned. [23] The BTS recognises that there are no robust data to inform guidance on duration of antibiotic treatment in childhood CAP. [23] The BNFc guidance relevant at the start of this trial recommended a 7-day course, whereas European and WHO guidance suggests a 3 to 5-day course. [49, 56] In 2019, NICE published guidance recommending stopping amoxicillin treatment after 5 days (250mg TDS) for children aged 1-4 years, unless microbiological results suggest a longer course length is needed or the patient is not clinically stable. [52]

1.4 What is the impact of antimicrobial resistance in childhood CAP?

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. [60] Penicillin resistance (MIC >2µg/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. [60] 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. [61]

The relationship between MIC (an in vitro phenomenon) and clinical outcome in CAP is complex, and data on the level of *S. pneumoniae* AMR that reduces amoxicillin effectiveness are limited. Harmonisation of European breakpoints (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. [62] Clinical breakpoints are determined based on a variety of data in addition to efficacy studies. This includes PKPD data, which for penicillin usually take time above 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. [63, 64] These may be passed on to others in the community, especially within childcare settings. [65, 66] Interventions to maintain a low level of AMR amongst 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. [63-74] Experimental models suggest that insufficiently high dosing could promote selection of resistant pathogens, and that while most of the effect on bacterial load is achieved early during antibiotic exposure, resistant isolates emerge after 4-5 days. [75-79] RCTs assessing the effect of antibiotic duration and dose have been called for as they will likely provide the strongest evidence for the relationship between antibiotic exposure and colonisation with resistant bacteria. [80] 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 adherence. [73] 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. [73, 79]

1.5 Trial Rationale

Despite the reduction in incidence of invasive pneumococcal disease since the introduction of the conjugate vaccine, [21] CAP remains one of the most commonly identified and treated childhood infections in the UK. While 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 on AMR of different regimens 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 the CAP-IT trial. A better understanding of the relationship between dose and duration of antibiotic treatment, and the impact on clinical outcomes and AMR would make it possible to formulate improved evidence-based treatment recommendations for childhood CAP.

1.6 Objectives

The primary objectives addressed by the CAP-IT trial were: to determine whether for young children with uncomplicated CAP treated after discharge from hospital (1) a three day course of amoxicillin is non-inferior to a seven day course, determined by receipt of clinically indicated systemic antibiotic other than trial medication for respiratory tract infection (including CAP) in the 4 weeks after randomization up to day 28; and (2) lower dose is non-inferior to higher dose amoxicillin under the same conditions. Secondary objectives evaluated the impact of lower dose and shorter duration of amoxicillin treatment on antimicrobial resistance, severity and duration of parent/guardian-reported CAP symptoms, and specified clinical adverse events

2. Methods

2.1 Trial design

CAP-IT was a multi-centre 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 2x2 factorial non-inferiority trial of amoxicillin dose and duration in young children with CAP (Figure 1).

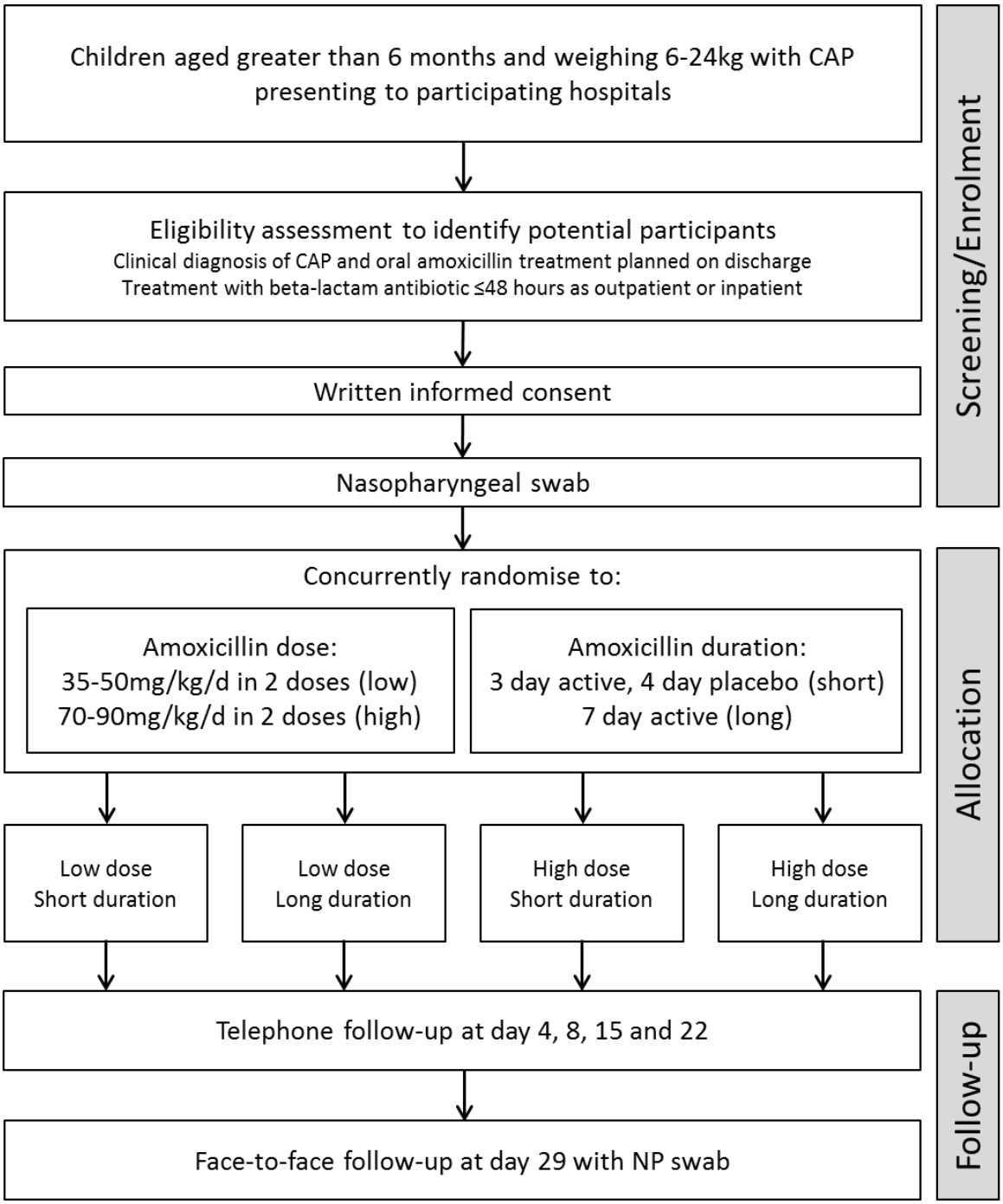


Figure 1: CAP-IT Trial Schema

2.2 Trial setting

Participants were recruited from 28 UK NHS hospitals and one children's hospital in Ireland: Alder Hey Children's Hospital NHS Foundation Trust, Liverpool; Barts Health NHS Trust; Birmingham Women's and Children's NHS Foundation Trust; Brighton and Sussex University Hospitals NHS Trust; Chelsea & Westminster NHS Foundation Trust, London; Children's Health Ireland, Dublin; City Hospitals Sunderland NHS Foundation Trust; Countess of Chester Hospital NHS Foundation Trust; County Durham and Darlington NHS Foundation Trust; Guy's and St Thomas' NHS Foundation Trust; Hull and East Yorkshire Teaching Hospitals NHS Trust; Imperial College Healthcare NHS Trust; King's College Hospital NHS Foundation Trust; The Leeds Teaching Hospitals NHS Trust; Manchester University NHS Foundation Trust; Nottingham University Hospitals NHS Trust; Oxford University Hospitals NHS Foundation Trust; Southport and Ormskirk NHS Trust; Royal Hospital for Children, Glasgow; Sheffield Children's Hospital NHS Foundation Trust; South Tees Hospitals NHS Foundation Trust; St George's University Hospitals NHS Foundation Trust; University Hospitals Bristol NHS Foundation Trust; University Hospital of Derby and Burton NHS Foundation Trust; University Hospitals of Leicester NHS Trust; University Hospitals Lewisham; University Hospital Southampton NHS Foundation Trust and University Hospital of Wales.

Participating sites were tertiary or secondary hospitals with paediatric EDs and inpatient facilities, and were selected in collaboration with Paediatric Emergency Research in the UK & Ireland [81] on the basis of clinical and research infrastructure, experience in clinical research, and likely eligible population size.

2.3 Participants

Patients presenting to participating hospitals were identified in paediatric EDs, 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 and 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, in order to minimise distress. Extensive information and recruitment materials were available for recruiting sites, including printed and video materials (accessible at www.capitstudy.org.uk). The 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 PPI representative and featured a site principle investigator and research nurse as well as graphics to aid explanation of trial procedures. It can be viewed here:

https://vimeo.com/217849985. Families were able to decline participation in the trial, at any time and without providing a reason, without incurring any penalty or affecting clinical management.

2.3.1 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), while the WARD group contained children who received any in-hospital oral or IV 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 less than 48 hours.

2.3.2 Inclusion criteria

Children were eligible if they had a clinical diagnosis of uncomplicated CAP, were older than 6 months, weighed 6-24 kg, and were planned for amoxicillin as the sole antibacterial agent for treatment on discharge. Textbox 1 shows the clinical criteria required for a diagnosis of CAP in the CAP-IT Trial.

Clinical diagnosis of CAP is defined as all of the following:

1. Cough (reported by parents/guardians within 96 hours before presentation) AND
2. Temperature ≥38°C measured by any method OR likely fever within 48 hours before presentation AND
3. Signs of laboured/difficult breathing or focal chest signs (one or more of the following):
   - Nasal flaring
   - Chest retractions
   - Abdominal breathing
   - Focal dullness to percussion
   - Focal reduced breath sounds
   - Crackles with asymmetry
   - Lobar pneumonia on chest x-ray

Textbox 1: Definition of clinical diagnosis of CAP

2.3.3 Exclusion criteria

Children were excluded if they had received 48 hours or more of beta-lactam antibiotics or any non-beta-lactam agents, 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 contra-indication to amoxicillin, complicated pneumonia (shock,

hypotension, altered mental state, ventilatory support, empyema, pneumothorax or pulmonary abscess), or bilateral wheezing without focal chest signs.

2.3.4 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 6-24kg" 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 version 3 for the PED and version 4 for the WARD group, such that they were eligible if they had received a total of ≤48 hours at trial entry as per section 2.3.

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

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

2.4 Interventions

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. Body weight was obtained for all children during eligibility screening and was used to determine dose volume according to seven weight bands (table 1).

Weight range (kg)	Direction
≤ 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 – 20.9	15 ml twice a day
21 – 24	16.5 ml twice a day

Table 1: Weight bands used for dosing of CAP-IT IMP

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

Participants were simultaneously randomised to receive either 3 days 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, due to difficulties in exactly taste-matching the placebo suspension to amoxicillin, one brand of amoxicillin was used for the first three days of treatment followed by a second brand for days 4-7 where duration of treatment was seven 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.

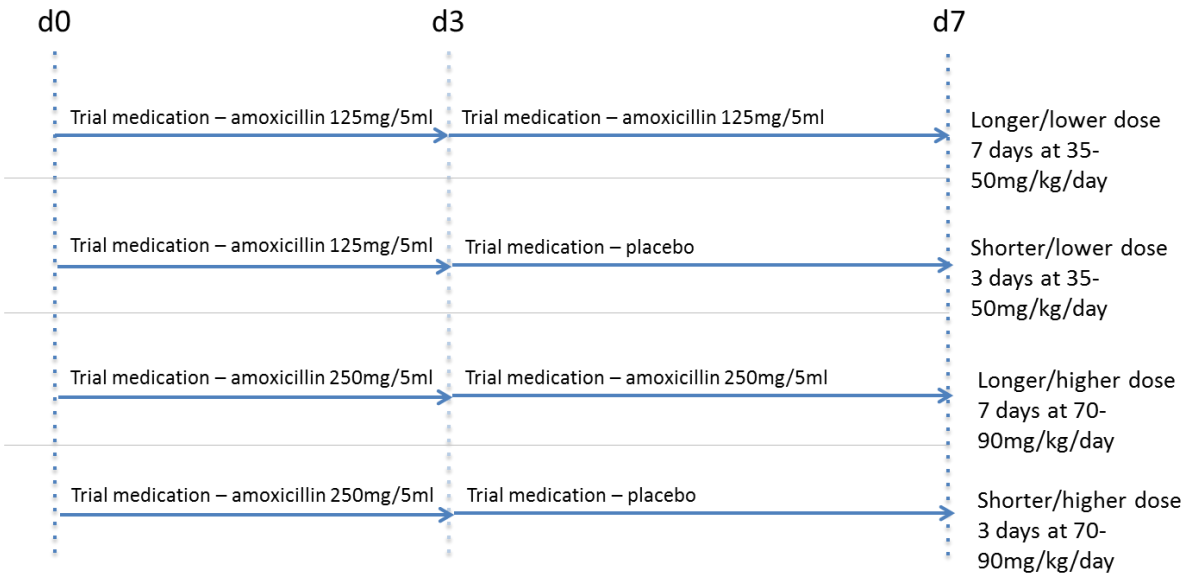


Figure 2: Treatment arms

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

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.

2.4.1 Drug substitutions and discontinuations of trial treatment

Drug substitution to an alternative amoxicillin formulation or another antibiotic was permitted where tolerability issues could not be overcome by improving acceptability (e.g. mixture with formula milk, other liquids, or foods) and where a clinical need for continued treatment persisted. In situations of toxicity, for example if a penicillin allergic reaction was suspected, substitution to 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, where use of a medication with a known major or moderate drug interaction with amoxicillin that was essential for the child's management was necessary, and where the parent/guardian withdrew consent for treatment.

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

2.5 Trial assessments and follow-up

CAP-IT participants were screened as described in section 2.3, 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 endpoints described in section 2.8. The schedule for timing and frequency of assessments is summarised in the trial schedule (table 2) and described below.

2.5.1 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 gender and ethnicity, medical history including review and duration of symptoms (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 (temperature, respiratory rate, heart rate, oxygen saturation in room air) were recorded and a baseline nasopharyngeal swab obtained.

No additional tests were mandated, but results were collected if tests were performed as part of clinical care, including haematology (haemoglobin, platelet count, leukocyte count, neutrophil count, lymphocyte count), biochemistry (C-reactive protein, procalcitonin and electrolytes), virology (rapid testing for RSV and Influenza A/B (any method)), and chest x-ray.

Parents/guardians were provided with trial materials including a symptom diary, participant information sheet (PIS), 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.

2.5.2 Follow-up

Telephone contact was made with participants on days three, seven to nine, 14-16 and 21-23, with a face-to face visit within two days of day 28. At these contacts, primary and secondary endpoints were reviewed, including additional antibiotic treatment, clinical signs and symptoms, adverse treatment effects and IMP adherence. During face-to-face visits (final or unscheduled) an NP swab was collected, and if CAP symptoms were ongoing, physical examination findings and physiological parameters were collected. If a face-to-face visit was not possible for final follow-up, it was attempted by telephone or home visit. If this failed despite reasonable efforts, primary endpoint data were sought through contact with the General Practitioner 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 whether 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, data and samples already collected were included in the analysis unless parents/guardians requested otherwise.

ASSESSMENTS Face to face ■ Telephone □ Face-to-face or Telephone		**DAYS IN TRIAL**						
	Pre-randomisation* **≤48h before randomisation**	Randomisation **D0**	**D3**	Week 1 **D7-9**	Week 2 **d14-16**	Week 3 **d21-23**	Week 4 **d28-30**	**Any acute event**
Trial participation								
Parent/Guardian information sheet†	X	X						
Informed consent		X						
Drug supply dispensing		X						
Adherence questionnaire			X	X				(X)
Adherence review (returned medication)							X	
Clinical assessment								
Medical history†	(X)	X						
Physical examination†	(X)	X					X	X
Symptom review†	(X)	X	X	X	X	X	X	X
EQ-5D		X	X	X			X	X
Use of health services		X		X	X	X	X	X
Laboratory assessment								
Nasopharyngeal swab‡	(X)	X					X	(X)
Haematology	(X)	(X)					(X)	(X)
Biochemistry	(X)	(X)					(X)	(X)
Virology	(X)	(X)					(X)	(X)
Radiological assessment								
Chest X-ray	(X)	(X)						(X)
Parent-completed diary								
Symptom diary			X	X	X			
Ancillary subgroup studies								
Stool sample‡	X	X		X			X	

*(X) indicates tests that may be done if the child's condition requires it or allows it, but are not mandatory; *Assessments in this column only undertaken for potential participants receiving inpatient antibiotic treatment; †may be done any time before enrolment discussion; ‡taken before starting antibiotics where possible.*

Table 2: CAP-IT trial assessment schedule.

2.5.3 Data Collection and Handling

Data were recorded onto 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.

2.6 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 which were grouped into blocks of eight, according to the randomisation list specification. Blinded IMP labels were applied to each kit, which contained the kit 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.

2.7 Blinding

All treating clinicians, parents/guardians and outcome assessors (including Endpoint review committee members) were blinded to the allocated treatment. The use of placebo as well as the permuted block randomisation strategy and blinded drug kits ensured parents and clinic staff remained blinded to amoxicillin duration and dose.

Access to the randomisation list was restricted to trial statisticians and IMP re-packagers, 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 according to the pre-specified statistical analysis plan.

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 blind of the trial team.

2.8 Outcomes

2.8.1 Primary Outcome

The primary outcome for the CAP-IT trial 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 (day 28). Prescription of non-trial medication when the primary reason was (a) illness other than respiratory tract infection, (b) intolerance of or adverse reaction to IMP, (c) parental preference, or (d) administrative error, did not constitute a primary endpoint.

An Endpoint Review Committee (ERC), comprising doctors independent of the trial management group and blinded to randomised allocations, reviewed all cases where a participant was prescribed non-trial systemic antibacterial treatment. The main role of the ERC was to adjudicate, based on all available data, whether 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 categorised as "CAP", "chest infection" or "other respiratory tract infection" and treatment likelihood assessment of "definitely/probably" or "possibly" were regarded as fulfilling the primary endpoint.

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 giving during the follow-up period. This additional information supported the ERC in accurately adjudicating events. Additionally, this allowed the collection of primary outcome data where contact with participants had been lost prior to completion of the follow-up period.

2.8.1.1 Changes to primary endpoint

The primary endpoint definition was clarified in protocol v3.0 to specify "systemic antibacterial" treatments to avoid inclusion of topical antibiotics, which were not of interest. In protocol v4.0, the primary endpoint was refined further, resulting in the definition in section 2.8.1. 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.

2.8.2 Secondary Outcomes

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

2.8.2.1 Morbidity

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

The following CAP symptoms were elicited at baseline, in follow-up calls at day 4, 8, 15, 22, and at the final visit, as well as at unscheduled visits: cough, wet cough (phlegm), breathing faster (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: not present, slight/little, moderate, bad, 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 the following adverse events was collected and graded in the same way as CAP symptoms: diarrhoea, skin rash, and thrush. In addition, adverse events related to the stop of trial medication or the start of non-trial antibiotics were recorded.

Other adverse events meeting the criteria for seriousness (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 according to MedDRA® (version 21.1) and were graded using the Division of Aids Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS AE Grading Table). [82]

2.8.2.2 Antimicrobial Resistance

The antimicrobial resistance secondary endpoint 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, day 29 final visit, and 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 to 16 mg/L, and interpreted according to EUCAST Clinical Breakpoint Tables v10.0 for benzylpenicillin and *S. pneumoniae* (infections other than meningitis): a) sensitive (minimal inhibitory concentration (MIC) ≤ 0.064 mg/L), non-susceptible (MIC 0.125 to 2 mg/L), and c) resistant (MIC > 2 mg/L).[83] The same approach was taken for amoxicillin susceptibility testing (isolates with MIC ≤ 0.5 mg/L = sensitive; MIC > 1 mg/L = resistant). *S. pneumoniae* ATCC49619 was used for quality control.[83]

2.8.2.3 Adherence

Data on IMP adherence were elicited during follow-up calls and the final visit (where follow-up calls were not performed), and at unscheduled visits. At each time-point, parents/guardians were asked whether 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, gagging/spitting out/refusing. Additionally, parents/guardians were asked how many doses of each bottle were either missed or in which the full prescribed volume was not given.

2.9 Sample Size

The sample size was based on demonstrating non-inferiority for the primary efficacy endpoint 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 (the underlying hypothesis with a non-inferiority design), as marginal analyses can then be conducted.

The expected antibiotic re-treatment 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 recommendation for a 10% non-inferiority margin for adult CAP trials [84]. Assuming a 15% event rate, 8% non-inferiority margin (on a risk difference scale) assessed against a 2-sided 90% CI, and 15% loss to follow-up, the sample size was calculated as 800 children in order to achieve 90% power.

2.10 Statistical Methods

2.10.1 Analysis Principles

The primary analysis was performed according to a modified intention-to-treat (mITT) principle, including all patients enrolled, and analysed according to the group to which they were randomised regardless of treatment actually received. One modification to the strict ITT principle pre-specified in the trial statistical analysis plan was exclusion of randomised patients who did not take any IMP. Due 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 which excluded "non-adherent" participants, defined as having taken <80% of scheduled trial medication: (1) based on all trial medication including placebo; (2) based on 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 deviations; SD) or median (with interquartile ranges; IQR) of absolute values and of changes in absolute values from baseline were reported by scheduled 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 endpoints) were not applied, and significance tests should be interpreted in the context of the total number of related comparisons performed.

The primary endpoint was analysed within a non-inferiority framework, where significance testing has no clear role (emphasis instead on confidence intervals). 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 2-sided 90% confidence intervals (rather than the more conventional 95%) to achieve consistency with the reporting of the primary endpoint.

2.10.2 Primary Outcome

The proportion of children meeting the primary endpoint 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 (for example, as a result of a missed final visit) were censored at the time of their last contact. For participants who missed the final visit but who had GP confirmation 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 endpoint, and standard errors and confidence intervals for the risk difference were derived from the estimated standard errors of the individual survival functions.

Lower dose treatment and shorter duration was considered "non-inferior" to higher dose and longer duration treatment, respectively, if the upper limit of the 2-sided 90% confidence interval for the difference in the proportion of children with the primary endpoint 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 confidence intervals.

2.10.3 Sensitivity Analyses

As described in section 2.8.1, the primary analysis only included endpoints 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 endpoint:

1) Including all systemic antibacterial treatments other than trial medication regardless of reason and indication.

2) 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).

3) As (2), above, but also including as an endpoint all systemic antibacterial treatments for CAP or "chest infection" where the clinical indication was "unlikely" as adjudicated by the ERC.

4) Duration randomisation: disregarding systemic antibacterial prescriptions occurring within the first three days from randomisation, as these events cannot be related to the treatment duration randomisation, to allow comparison of shorter versus longer treatment.

2.10.4 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/min for age 1-2 years; >28/min for age 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 endpoints occurring in the two winter seasons spanned by the CAP-IT trial. This was based on Public Health England (PHE) reports of circulating viruses/bacteria in the winter seasons spanned by the CAP-IT trial.

2.10.5 CAP Symptoms

For each symptom specified in section 2.8.2.1, the severity of a symptom was reviewed by number (%) of symptoms in each severity category at each scheduled contact visit and analysed as described for ordered outcomes in section 2.10.1.

Duration of a symptom was measured in time from baseline to resolution, defined as the first day the symptom is reported not present. This was analysed as a time to event outcome as specified in section 2.10.1. Where a symptom was not present at enrolment, participants were excluded from the respective analysis.

2.10.6 Clinical Adverse Events

Solicited clinical adverse events, specified in section 2.8.2.1, 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 section 2.10.1.

Additionally, the number of participants experiencing at least one SAE were compared as a binary outcome (see section 2.10.1).

2.10.7 Antimicrobial Resistance

Descriptive analyses of baseline samples were performed 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-Susceptible, increased exposure/R-Resistant (see section 2.8.2.2).

S. pneumoniae carriage was determined by tabulation of the proportion of samples with positive *S. pneumoniae* culture at final visit, by randomisation group and compared using tests for binary variables, as described in Section 2.10.1. *S. pneumoniae* culture results at 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/I/R categorisation) at the final visit was performed using both cut offs (penicillin and amoxicillin) described in section 2.8.2.2. This analysis was repeated, firstly including only samples with a positive *S. pneumoniae* culture result and secondly including all samples. Randomised groups were compared by tests for binary variables, and cross-tabulation of penicillin resistance at the final visit versus 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.

2.11 Interim Analyses

The trial was reviewed by the CAP-IT Independent Data Monitoring Committee (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.

2.12 Patient and Public Involvement (PPI)

Parents of young children were involved during the development and delivery of the CAP-IT trial. 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, due to difficulties in giving medicine (due to palatability, or challenges with daycare and daytime doses). For the same reasons, parents supported the twice daily dosing of the CAP-IT trial. Multiple PPI representatives reviewed and provided input on the patient information materials, including the CAP-IT information film, to ensure 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.

2.13 Protocol Amendments

CAP-IT protocol version 2 was active when recruitment to the CAP-IT trial 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 (section 2.3.3) and the analysis plan, to which three significant updates were made on the basis of accumulating trial data. Firstly, a stratified analysis was originally planned based on the PED and WARD groups. This was changed to a joint analysis in protocol version 3, due to significant clinical overlap, (please see appendix 1 for more details) Secondly, the primary endpoint definition was made more specific in protocol version 3 and further refined in version 4 (section 2.8.1.1). Finally, the non-inferiority margin was adjusted as the primary endpoint event rate had been substantially under-estimated. The trial and all substantial amendments were approved by the London – West London & GTAC Research Ethics Committee (16/LO/0831).

3. Results

3.1 Participant flow

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

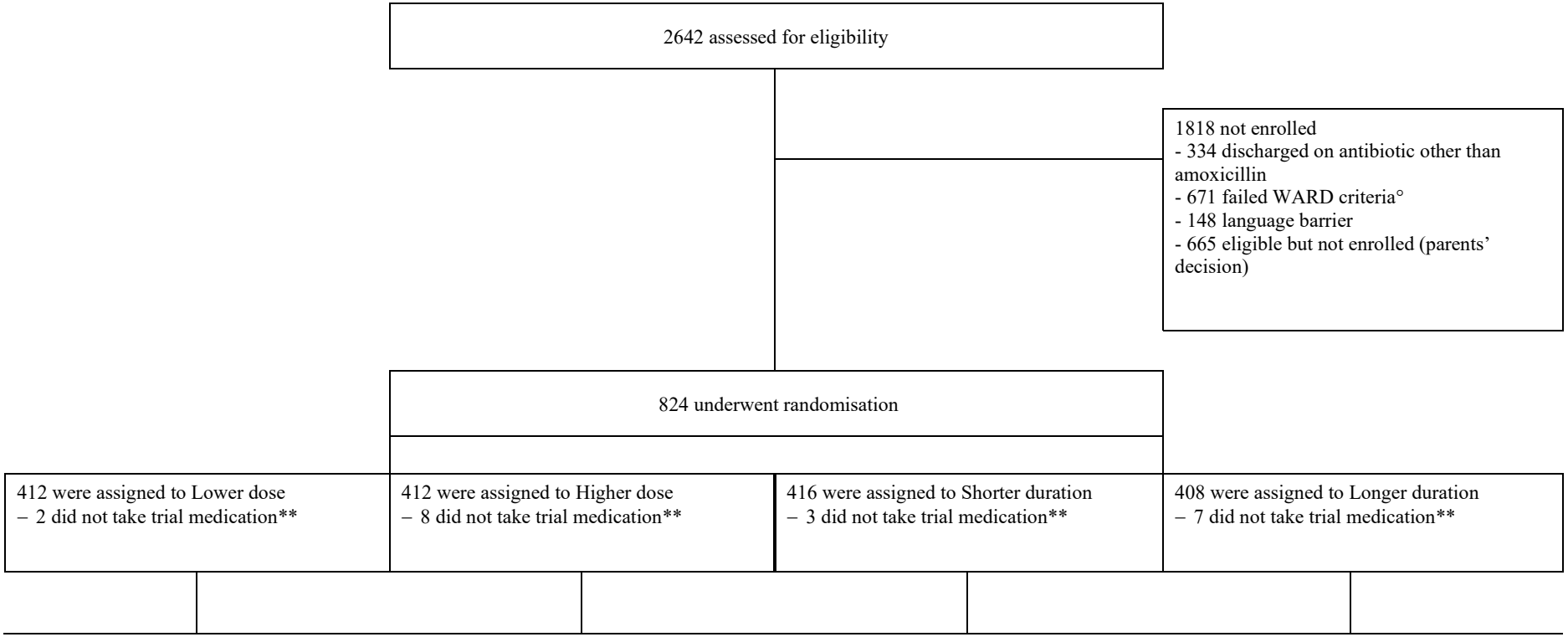
591 participants had no antibiotic pre-treatment at trial entry; 223 (mainly following admission to assessment units of wards) had received beta-lactam antibiotic pre-treatment for no more than 48 hours. The final follow-up visit occurred on 21st May 2019, which was considered the trial end date.

Six participants were randomised in error but were included in the analysis according to the intention to treat principle. Of these, five did not have all the required symptoms to fulfil the criteria for CAP diagnosis (Textbox 1). One patient did not have a cough reported in the previous 96 hours at presentation; two did not have a reported fever in the previous 48 hours at presentation and the final two lacked documentation of signs of laboured/difficult breathing and/or focal chest signs at presentation. Of these final two, one had a chest x-ray result suggestive of lobar pneumonia prior to this being added to the inclusion criteria as part of protocol version 4.0, and the other participant had pneumonia diagnosed on chest x-ray but 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 (see table 3 below).

	Lower N=410	**Higher** N=404	**Shorter** N=413	**Longer** N=401	**Total** N=814
Known violation against 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**

Table 3: Ineligible patients

Participants were well distributed between arms, with 208 (25.6%) receiving three days treatment of lower dose, 202 (24.8%) receiving seven days of lower dose, 205 (25.2%) receiving three days of higher dose and 199 (24.4%) receiving seven days of higher dose (figure 3, table 4).



401 had primary endpoint status fully characterised – 9 withdrew or were lost to follow-up*	388 had primary endpoint status fully characterised – 16 withdrew or were lost to follow-up*	401 had primary endpoint status fully characterised – 12 withdrew or were lost to follow-up*	388 had primary endpoint status fully characterised – 13 withdrew or were lost to follow-up*
410 were included in the analysis	404 were included in the analysis	413 were included in the analysis	401 were included in the analysis

°inpatient stay >48 hours, treated with non-beta-lactam antibiotics as inpatients; * follow-up included up to time of withdrawal or no further contact
**These children have been excluded from all analyses

Figure 3: CONSORT Flow Diagram

	PED N=591	**WARD** N=223	**Total** N=814
Randomisation arm			
Lower + shorter	153 (25.9%)	55 (24.7%)	208 (25.6%)

Lower + longer	150 (25.4%)	52 (23.3%)	202 (24.8%)
Higher + shorter	146 (24.7%)	59 (26.5%)	205 (25.2%)
Higher + longer	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%)

Table 4: Randomisation outcomes: analysis population

3.2 Baseline

3.2.1 Patient Characteristics

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

	Lower N=410	**Higher** N=404	**Shorter** N=413	**Longer** N=401	**Total** N=814
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)
[min - max]	[0.5-8.8]	[0.5-8.5]	[0.5-8.5]	[0.5-8.8]	[0.5-8.8]
Sex					
Male	210 (51%)	211 (52%)	217 (53%)	204 (51%)	421 (52%)
Female	200 (49%)	193 (48%)	196 (47%)	197 (49%)	393 (48%)
Ethnicity					
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%)
Smoker(s) in household?	69 (17%)	62 (16%)	61 (15%)	70 (18%)	131 (16%)

Table 5: Patient characteristics

3.2.2 Medical History

One third of participants (30.7%) reported an underlying diagnosis of asthma or asthma inhaler use within the past month. Eczema was the second most common co-morbidity (20%), 9.6% reported food or drug allergies and 9.1% reported hay fever. Routine vaccinations had been received by 95% of participants, with the remaining 5% either not having had routine vaccinations (3.2%) or not knowing/having been vaccinated outside the UK (1.8%).

	Lower N=410	**Higher** N=404	**Shorter** N=413	**Longer** N=401	**Total** 814
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 (9.1%)
Food or drug allergy	38 (9%)	40 (10%)	37 (9%)	41 (10%)	78 (9.6%)
Eczema	84 (20%)	79 (20%)	78 (19%)	85 (21%)	163 (20%)
Prematurity	43 (10%)	43 (11%)	51 (12%)	35 (9%)	86 (10.6%)
Routine vaccinations?					
Yes	388 (95%)	385 (95%)	394 (95%)	379 (95%)	773 (95%)
No	14 (3%)	12 (3%)	15 (4%)	11 (3%)	26 (3.2%)
Not sure (or vaccinated outside of UK)	8 (2%)	7 (2%)	4 (1%)	11 (3%)	15 (1.8%)
Other underlying disease	37 (9%)	19 (5%)	21 (5%)	35 (9%)	56 (6.9%)

Table 6: Medical history

3.2.3 Vital Parameters and Clinical Signs

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

The most common baseline clinical signs were coryza, reported in 599/814 participants (73.7%), and chest retractions, reported in 483/814 participants (59.4%, table 7). The proportion of other baseline clinical signs were as follows; 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%).

	Lower N=410	**Higher** N=404	**Shorter** N=413	**Longer** N=401	**Total** n=814
Weight (kg)	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)	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	227 (55%)	214 (53%)	221 (54%)	220 (55%)	441 (54%)
Heart rate (bpm)	146 (131, 160)	143 (130, 158)	144 (131, 158)	146 (130, 162)	145 (130, 160)
Abnormal heart rate*	307 (75%)	271 (67%)	282 (68%)	296 (74%)	578 (71%)
Respiratory rate (bpm)	37 (30, 44)	38 (32, 44)	36 (30, 43)	38 (32, 45)	37 (30, 44)
Abnormal respiratory rate**	270 (66%)	258 (64%)	262 (64%)	266 (67%)	528 (65%)
Oxygen saturation (%)	96 (95, 98)	96 (95, 98)	96 (95, 98)	96 (95, 98)	96 (95, 98)
Abnormal oxygen saturation***	18 (4%)	25 (6%)	18 (4%)	25 (6%)	43 (5%)
Nasal flaring	33 (8%)	42 (10%)	35 (9%)	40 (10%)	75 (9.3%)
Chest retractions	239 (58%)	244 (60%)	239 (58%)	244 (61%)	483 (59.4%)
Pallor	82 (20%)	87 (22%)	93 (23%)	76 (19%)	169 (20.9%)
Stridor	4 (1%)	6 (1%)	5 (1%)	5 (1%)	10 (1.2%)
Inflamed/bulging tympanic membrane or middle ear effusion	37 (9%)	35 (9%)	39 (10%)	33 (8%)	72 (9.0%)
Coryza	291 (71%)	308 (76%)	304 (74%)	295 (74%)	599 (73.7%)
Enlarged tonsils or pharyngitis	95 (24%)	86 (22%)	92 (22%)	89 (23%)	181 (22.5%)

Numbers are N (%) or median (IQR). *abnormal respiratory rate: >37/min for age 1-2 years; >28/min for age ≥3 years, **abnormal heart rate: >140/min for age 1-2 years; >120/min for age ≥3 years; ***abnormal oxygen saturation: <92%

Table 7: Vital parameters and clinical signs at presentation by randomisation status.

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

3.2.4 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%), reduced breath sounds in 336 (44%), bronchial breathing in 103 (15%), and dullness to percussion in 59 (13%). The proportions of the four chest examination variables were very similar among the randomisation arms (table 8).

	Lower N=410	**Higher** N=404	**Shorter** N=413	**Longer** N=401	**Total** N=814
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%)

Table 8: Chest examination at presentation by randomisation status

3.2.5 Parent-Reported CAP Symptoms

Parent-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% respectively. Between 80-90% of participants were reported as having sleep disturbance, easting less and interference with normal activity.

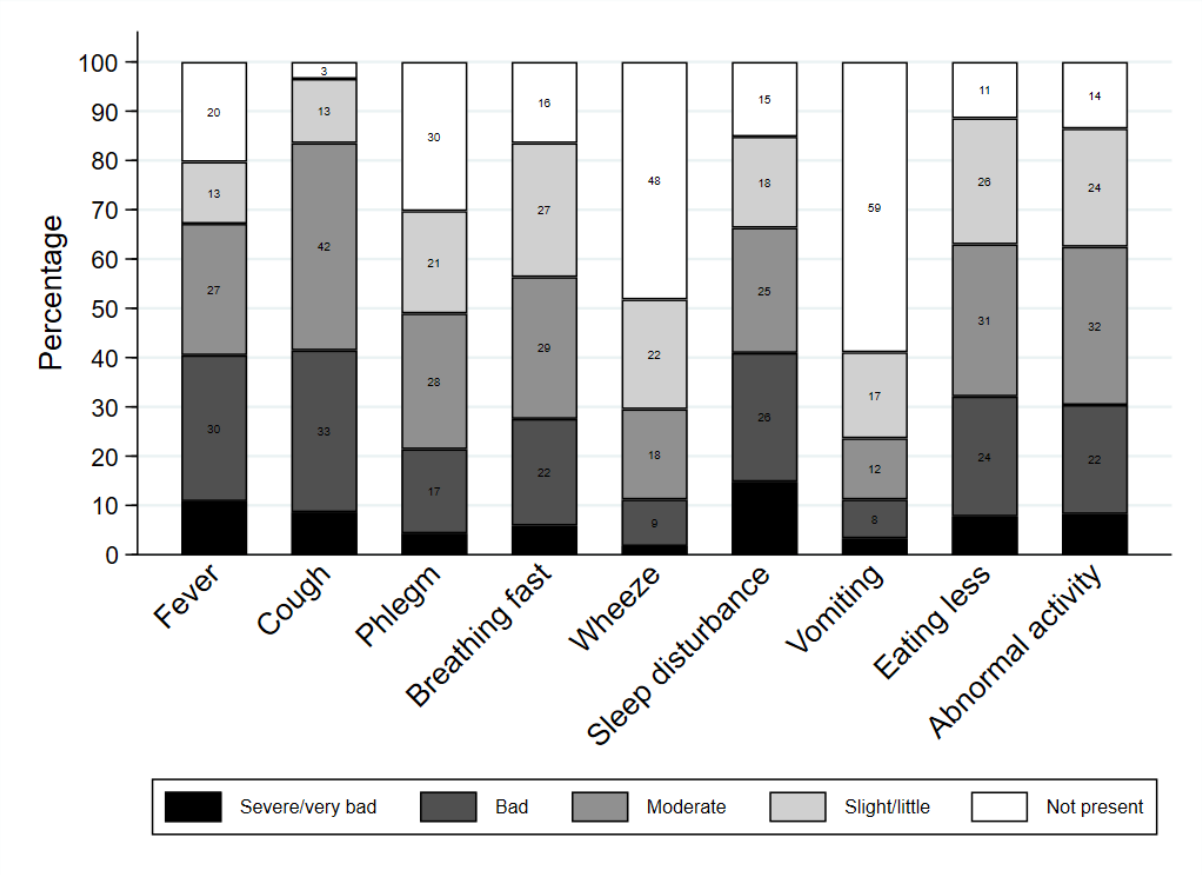


Figure 4: Symptoms at trial entry

Clinical symptoms for patients who received in-hospital antibiotics prior to trial entry (WARD group) were reported by parents/guardians at presentation (pre-trial) and at baseline (trial entry). Figures 5 and 6 show parent-reported clinical symptom severity split by pre-trial and trial entry for the WARD group and including the PED group (trial entry). 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%.

CAP symptoms at trial entry by strata are shown in Appendix 2, table 27.

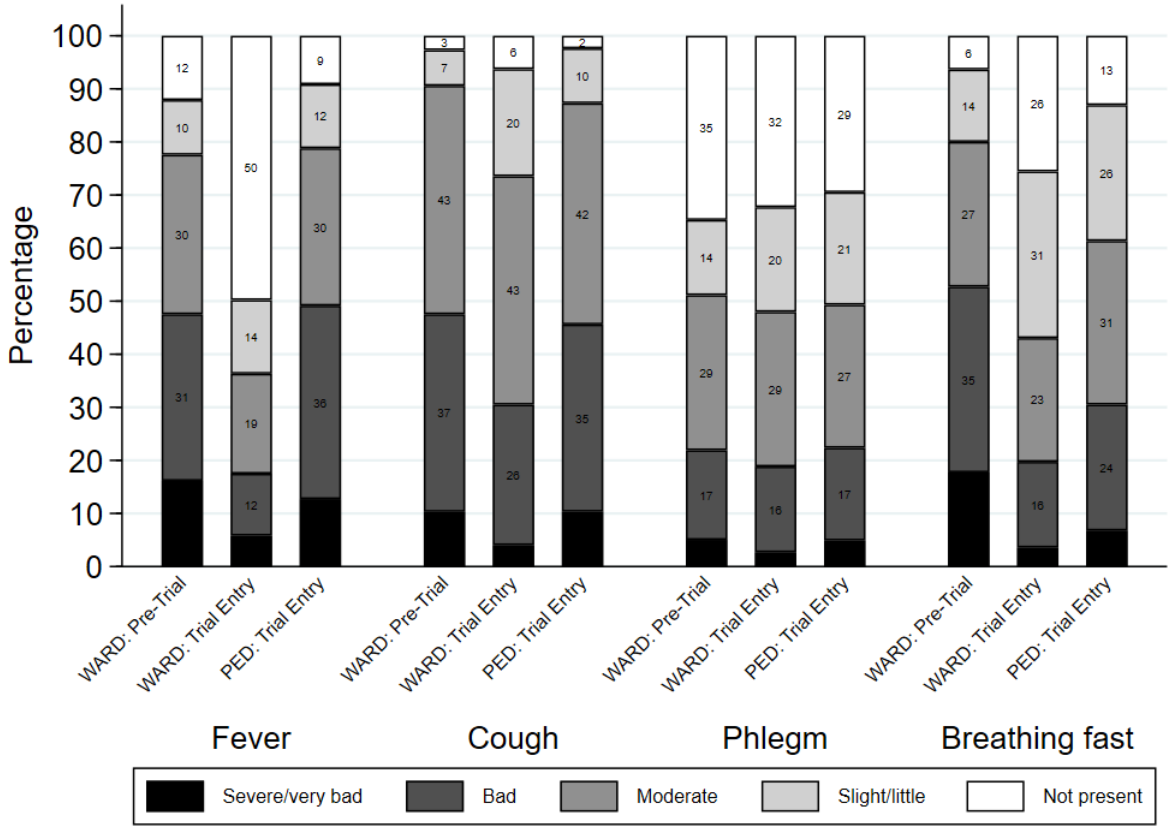


Figure 5: Clinical symptoms at trial entry by group

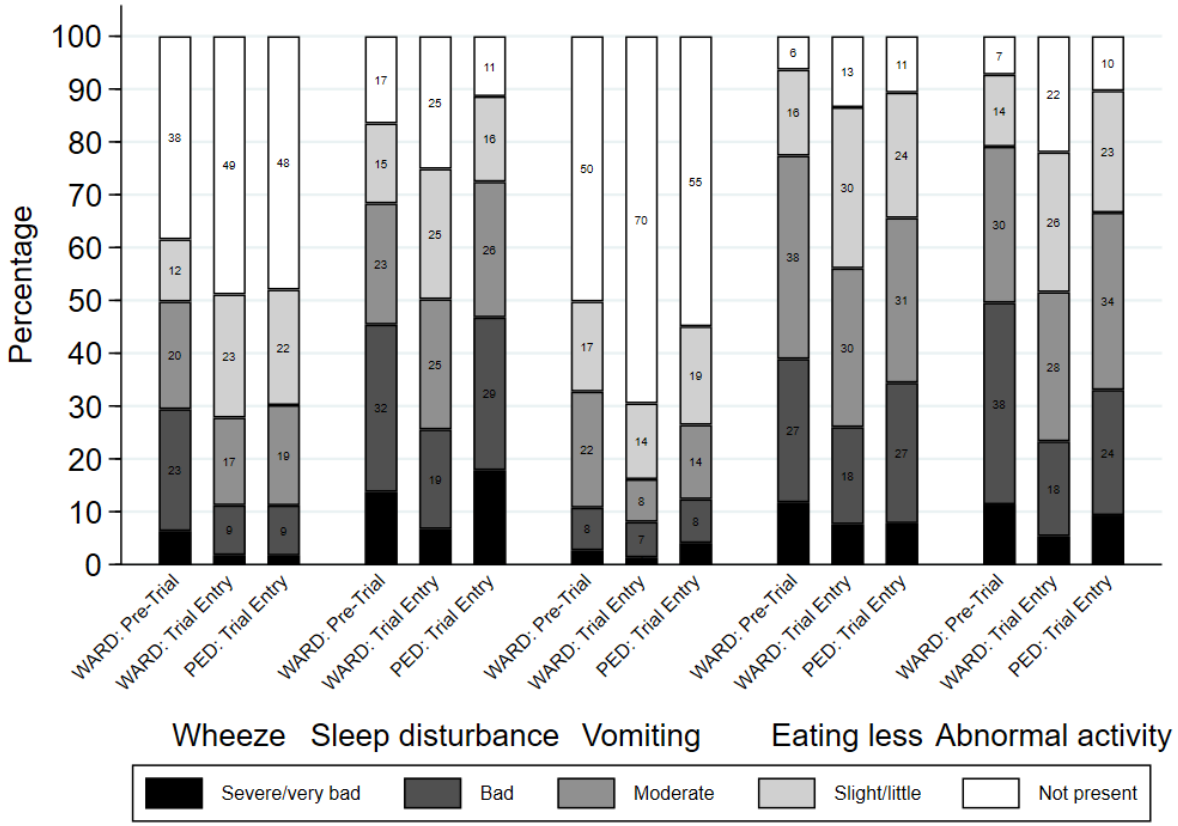


Figure 6: Clinical symptoms at trial entry by group

3.2.6 Clinical Investigations

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

Chest x-rays were the most common investigation and were undertaken in 391 (48%) participants (table 9). Haematology and biochemistry assessments were undertaken in 81 (10%) and 82 (10.1%) participants, respectively, while blood cultures and respiratory specimens were done for 41 (5%) and 46 (5.7%) participants respectively.

	Lower N=192	**Higher** N=199	**Shorter** N=196	**Longer** N=195	**Total** N=391
Result of chest x-ray					
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%)

Table 9: Baseline radiographic findings in participants who had chest x-ray performed

Of the 46 respiratory samples taken, 44 had virology assessment and 11 had bacteriology assessment (table 10). All 11 (100%) of the respiratory samples used for bacteriological assessment resulted in no significant growth.

	Lower N=19	**Higher** N=25	**Shorter** N=24	**Longer** N=20	**Total** N=44
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 + Adenovirus	2 (11%)	1 (4%)	2 (8%)	1 (5%)	3 (7%)
Rhinovirus + Enterovirus	4 (21%)	5 (20%)	5 (21%)	4 (20%)	9 (20%)
Rhinovirus + Enterovirus + Adenovirus	0 (0%)	1 (4%)	0 (0%)	1 (5%)	1 (2%)

Rhinovirus + Enterovirus + 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 10: Baseline respiratory sample virology assessment results

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

3.2.7 Prior Antibiotic Exposure

Two hundred and forty two children (29.7%) received antibiotics for up to 48 hours prior to enrolment, of which 241 were β-lactam antibiotics and one was a macrolide. Amoxicillin was the most common antibiotic taken prior to trial entry (in 209/242; 86.4%), followed by co-amoxiclav (20/242; 8.3%). In children receiving antibiotics prior to enrolment, the median (IQR) number of doses was 2 (1,3), and 55% were enrolled within 12 hours of commencing antibiotic treatment, 24.8% within 12-<24 hours, 12.4% within 24-<36 hours, and 7.9% within 36-≤48 hours, (see table 11 below).

	Lower N=410	**Higher** N=404	**Shorter** N=413	**Longer** N=401	**Total** N=814
Any systemic antibiotic in last 3 months					
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?					
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					
β-lactam	118 (99%)	123 (100%)	123 (100%)	118 (99%)	241 (100%)
Macrolide	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
Name of prior antibiotic					
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	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Prior antibiotic: route					
Intravenous	15 (13%)	10 (8%)	17 (14%)	8 (7%)	100 (41%)
Oral	103 (87%)	110 (89%)	106 (86%)	107 (90%)	85 (35%)
Intravenous + oral	1 (1%)	3 (2%)	0 (0%)	4 (3%)	28 (12%)
Duration of prior antibiotic treatment					
<12 hrs	67 (56%)	66 (54%)	68 (55%)	65 (55%)	133 (55%)
12 - <24 hrs	27 (23%)	33 (27%)	33 (27%)	27 (23%)	60 (25%)
24 - <36 hrs	13 (11%)	17 (14%)	13 (11%)	17 (14%)	30 (12%)
36 - <=48 hrs	12 (10%)	7 (6%)	9 (7%)	10 (8%)	19 (8%)
Data are number (%) or median (IQR)					

Table 11: Prior exposure with antibiotics

3.2.8 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 treatments others than antibiotics in hospital including salbutamol inhalers (58.3%), paracetamol (52.1%), steroids (22.9%), ibuprofen (15.7%) and ipratropium bromide (8.3%).

3.3 Follow-up

Of the 814 patients included in the analysis, 642 (79%) completed the final visit. Where possible this final visit was done face-to-face at hospital or at home, but if this proved impossible (eg parents/guardians unable to attend an appointment), the visit was completed by telephone. Overall, 25% of final visits were performed by telephone, 74% were performed in hospital, and 1% at home. In 172 (21%) participants, the final visit was not conducted with the family. Of these, 11 participants 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; primary outcome data were successfully collected in 144 of these participants. This ensured that primary outcome data were available for 786 (97%), and only 28 children (3%) were considered withdrawn or lost to follow-up, (see table 12 below).

	Lower	**Higher**	**Shorter**	**Longer**	**Total**

	N=410	N=404	N=413	N=401	N=814
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 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	70 (17%)	74 (18%)	84 (20%)	60 (15%)	144 (18%)
Withdrawn/Lost	11 (3%)	17 (4%)	14 (3%)	14 (3%)	28 (3%)

Table 12: Final visit and follow-up data completeness

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. 443 (54%) participants completed all telephone calls and the final visit, with 153 (19%) missing one follow-up visit, 95 (12%) missing two, 51 (6%) missing 3, and 48 (6%) missing four. Twenty-four (3%) participants missed all calls and visits.

	Lower	**Higher**	**Shorter**	**Longer**	**Total**

	N=410	N=404	N=413	N=401	N=814
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%)

Table 13: Participant follow-up rate

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 participants (49.9%), while 227 (27.9%) participants submitted no diary data. Parents/guardians were assigned to complete symptom diaries either electronically (42.5%) or on paper (57.5%) using pseudorandomisation. Summary diary data on completion are presented in table 14.

	Lower N=410	**Higher** N=404	**Shorter** N=413	**L**
Diary status				
completed: all days	201 (49.0%)	205 (50.7%)	212 (51.3%)	194
completed: partly	97 (23.7%)	84 (20.8%)	79 (19.1%)	102
no diary data available	112 (27.3%)	115 (28.5%)	122 (29.5%)	105
Number of days completed				
None	112 (27.3%)	115 (28.5%)	122 (29.5%)	105
1 - 4 days	26 (6.3%)	11 (2.7%)	14 (3.4%)	23
5 - 8 days	27 (6.6%)	32 (7.9%)	33 (8.0%)	26
9 -12 days	44 (10.7%)	41 (10.1%)	32 (7.7%)	53
All 13 days	201 (49.0%)	205 (50.7%)	212 (51.3%)	194
No diary data: reason				
-	298 (72.7%)	289 (71.5%)	291 (70.5%)	296
Withdrawal	7 (1.7%)	2 (0.5%)	5 (1.2%)	4
Paper: no final visit	40 (9.8%)	48 (11.9%)	49 (11.9%)	39
Paper: final visit as call	23 (5.6%)	18 (4.5%)	17 (4.1%)	24
Lost/forgot	21 (5.1%)	19 (4.7%)	24 (5.8%)	16
Technical/Password issue	8 (2.0%)	13 (3.2%)	11 (2.7%)	10
No time	4 (1.0%)	6 (1.5%)	6 (1.5%)	4

Site error		0 (0.0%)	1 (0.2%)	1 (0.2%)	0
unknown		9 (2.2%)	8 (2.0%)	9 (2.2%)	8

Table 14: Parent/guardian diary completion rate

3.4 Adherence

240 (29.5%) participants deviated from the prescribed IMP regimen, including taking fewer doses or lower volume, too many doses or greater volume, or deviation in timing, (table 15).

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

For duration randomisation, 134 (32.4%) participants in the shorter duration arm deviated, compared to 106 (26.4%) participants taking longer duration (p=0.06). A greater proportion of participants in the shorter duration arm did not complete trial treatment (13.3%) compared to the longer duration arm (9.4%) (p=0.015), (see table 15 below).

	Lower N=410	**Higher** N=404	p-value	**Shorter** N=413	**Longer** N=401	p-value	**Total** N=814
Early cessation of trial treatment			0.10			0.015	
Trial treatment completed	355 (86.6%)	366 (90.6%)		358 (86.7%)	363 (90.5%)		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			0.62			0.61	
Days 0 or 1	11 (20%)	4 (11%)		9 (16%)	6 (16%)		15 (16%)
Days 2 or 3	17 (31%)	15 (39%)		16 (29%)	16 (42%)		32 (34%)
Days 4 or 5	22 (40%)	15 (39%)		24 (44%)	13 (34%)		37 (40%)
>= Day 6	5 (9%)	4 (11%)		6 (11%)	3 (8%)		9 (10%)
Bottles received			0.038			0.48	
Taken bottle A but not bottles B/C	30 (7.3%)	16 (4.0%)		21 (5.1%)	25 (6.2%)		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			0.49			0.69	

Yes	86 (21.0%)	77 (19.1%)		85 (20.6%)	78 (19.5%)		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			0.54			0.050	
Yes	104 (25.4%)	95 (23.5%)		113 (27.4%)	86 (21.4%)		199 (24.4%)
No	306 (74.6%)	309 (76.5%)		300 (72.6%)	315 (78.6%)		615 (75.6%)
Overall: Any deviation (incl. too many doses/volume or timing deviations)			0.14			0.033	
Yes	128 (31.2%)	107 (26.5%)		133 (32.2%)	102 (25.4%)		235 (28.9%)
No	282 (68.8%)	297 (73.5%)		280 (67.8%)	299 (74.6%)		579 (71.1%)

Table 15: Adherence to trial medication by randomisation arm

3.5 Primary Outcome

3.5.1 Endpoint 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 (section 2.8.1) and reasons for starting new non-trial antibacterials are given in table 16. Of the 139 participants, 100 (71.9%) met the criteria for a primary endpoint (table 16). Of the 100 participants who had an event which met the criteria for a primary endpoint, "CAP/chest infection" was the most common reason for treatment, accounting for 76 (76%) events (table 16). The ERC adjudicated 38% of the events as definitely/probably clinically indicated, and 62% as possibly indicated (table 17).

	Lower N=74	**Higher** N=65	**Shorter** N=73	**Longer** N=66	**Total** 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/adverse event	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/admin error	1	1	2	0	2

[a]1 bronchiolitis, 2 cough, 1 scarlet fever + tonsillitis.
Four patients had 2 events.

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

The most commonly prescribed antibacterial was oral amoxicillin, prescribed in 49 (49%) of primary endpoints. Oral clarithromycin and co-amoxiclav accounted for 17% and 10% of primary endpoints respectively, while erythromycin, phenoxymethylpenicillin and azithromycin accounted for 7%, 6% and 4% respectively.

Patients who started systemic non trial antibacterials	**Lower**	**Higher**	**Shorter**	**Longer**	**Total**

	N=74	N=65	N=73	N=66	N=139
Had primary endpoint					
Yes	51 (69%)	49 (75%)	51 (70%)	49 (74%)	100 (712%)
No	23 (31%)	16 (25%)	22 (30%)	17 (26%)	39 (28%)
Events which met the criteria for primary endpoint	**Lower**	**Higher**	**Shorter**	**Longer**	**Total**
	N=51	N=49	N=51	N=49	N=100
Primary reason for starting new antibacterials					
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					
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					
Amoxicillin	25 (49%)	24 (49%)	23 (45%)	26 (53%)	49 (49%)
Amoxicillin, iv	0 (0%)	1 (2%)	1 (2%)	0 (0%)	1 (1%)
Azithromycin	3 (6%)	1 (2%)	2 (4%)	2 (4%)	4 (4%)
Azithromycin+Amoxicillin, iv	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Cefuroxime	0 (0%)	1 (2%)	0 (0%)	1 (2%)	1 (1%)
Cefuroxime+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+Azithromycin	2 (4%)	0 (0%)	0 (0%)	2 (4%)	2 (2%)
Co-amoxiclav, iv	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?[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					
Day 0 to 14	29 (57%)	25 (51%)	28 (55%)	26 (53%)	54 (54%)
Day 15 to 28	22 (43%)	24 (49%)	23 (45%)	23 (47%)	46 (46%)

[a] information about prescriber missing in 7 because this was not asked in the beginning of the trial.

Table 17: ERC primary endpoint adjudication results

3.5.2 Analysis of primary endpoint: overall

Overall, 100 participants in the 814 analysis population met the primary endpoint during the follow-up period, a cumulative proportion of 12.5% (90% CI 10.7-14.6%), as estimated with Kaplan-Meier methods.

3.5.3 Analysis of primary endpoint: dose randomisation

The observed number of primary endpoints was similar in the lower dose randomisation arm (51, 12.6%) and in the higher dose arm (49, 12.4%). The estimated risk difference at day 28 was 0.2% (90% CI -3.7-4.0%), meeting the criterion for non-inferiority (Figure 8).

3.5.4 Analysis of primary endpoint: duration randomisation

51 (12.5%) participants experienced a primary endpoint in the shorter duration arm, and 49 (12.5%) in the longer duration arm. The estimated risk difference at day 28 was 0.1% (90% CI -3.8-3.9%), again satisfying the non-inferiority criterion (figure 9).

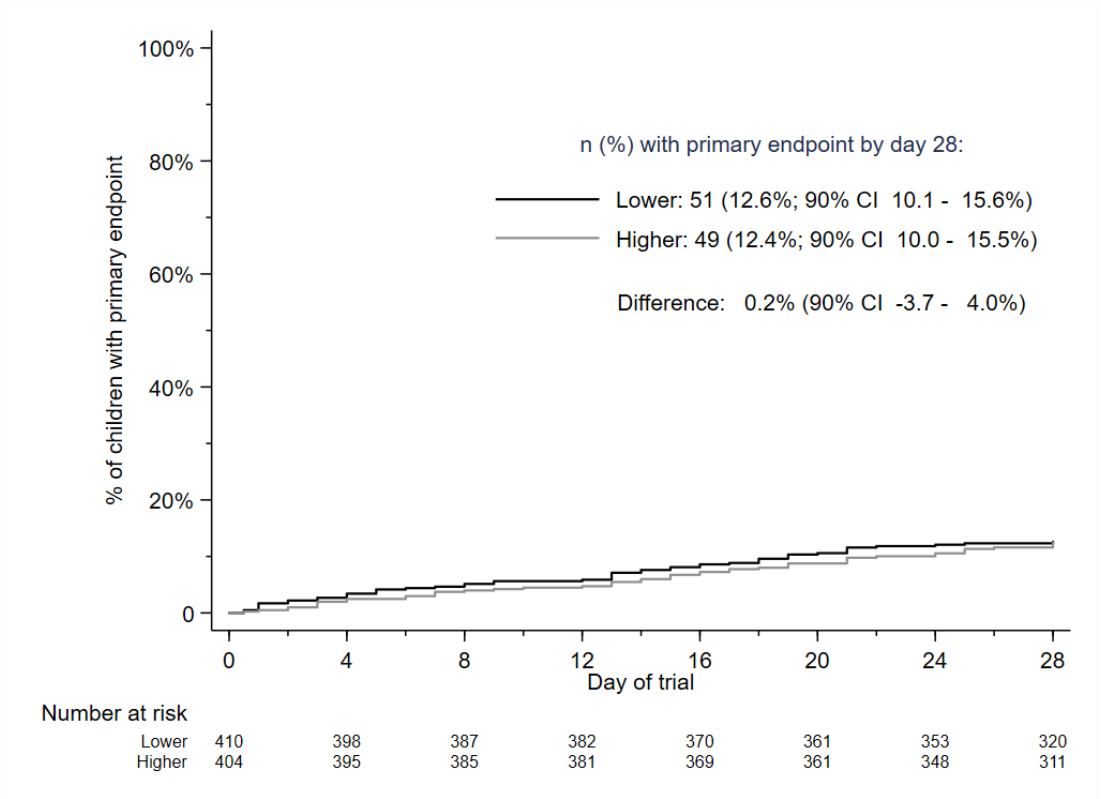


Figure 7: Kaplan-Meier curve for primary endpoint: dose randomisation

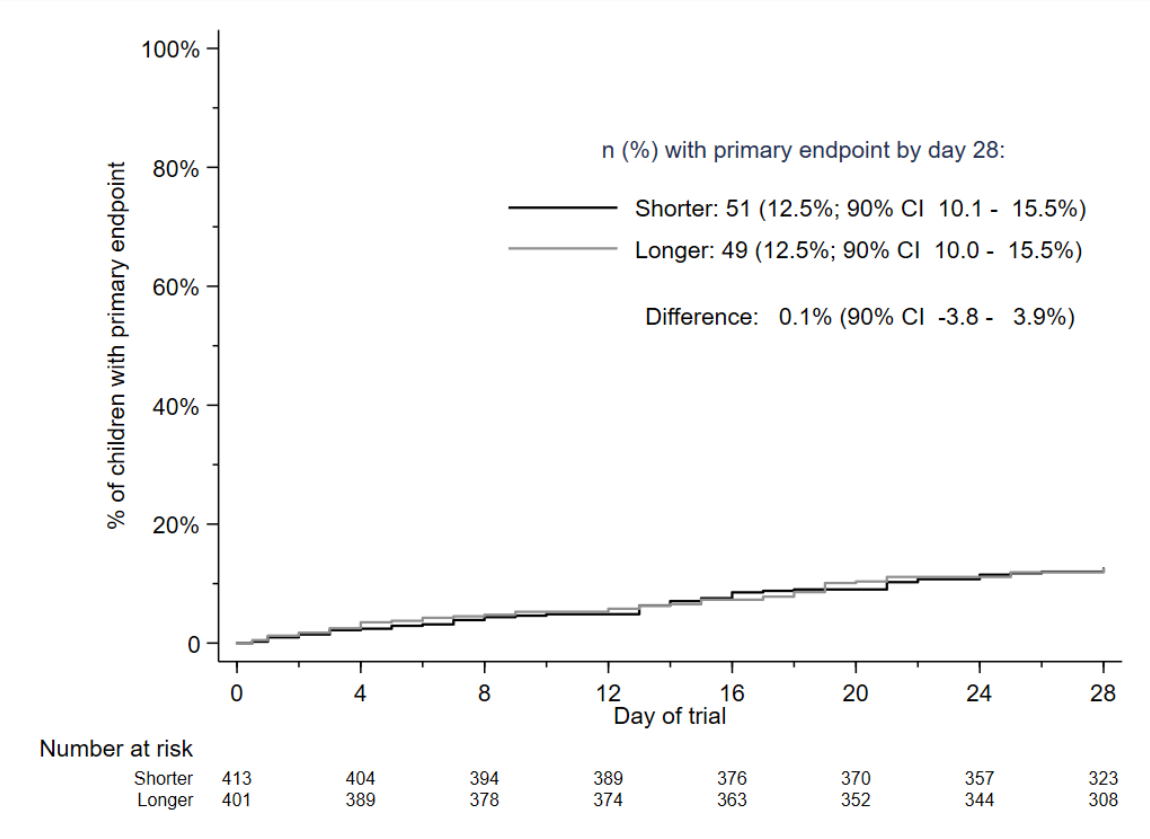


Figure 8: Kaplan-Meier curve for primary endpoint: duration randomisation

3.5.5 Interaction effects

The outcomes for the analyses of interaction effects between the two randomisations (dose and duration), between pre-exposure to antibiotics and dose randomisation and between pre-exposure and duration randomisation are shown in figures 9, 10 and 11.

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 duration randomisation arm and pre-exposure to antibiotics (p=0.592). This justifies analysis of the "main effects" for the two randomisations (figure 7 and figure 8).

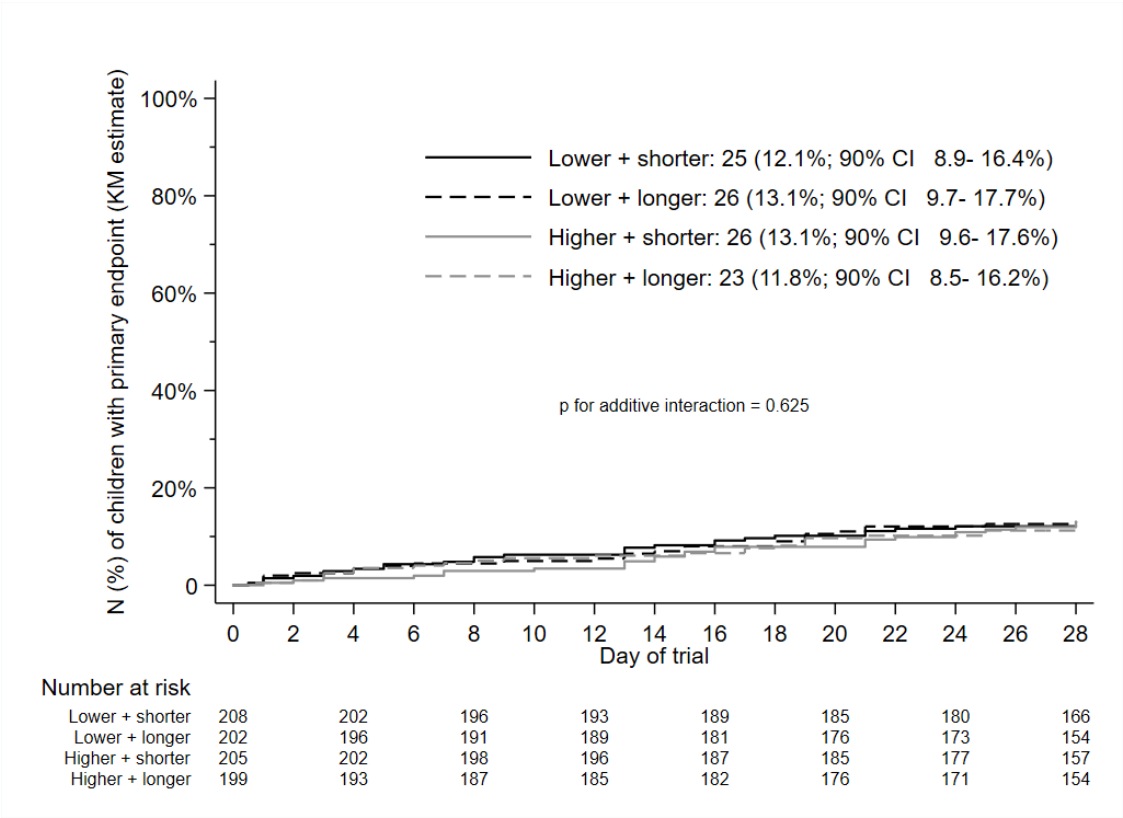


Figure 9: Kaplan Meier curve for analysis of interaction between the two randomisations

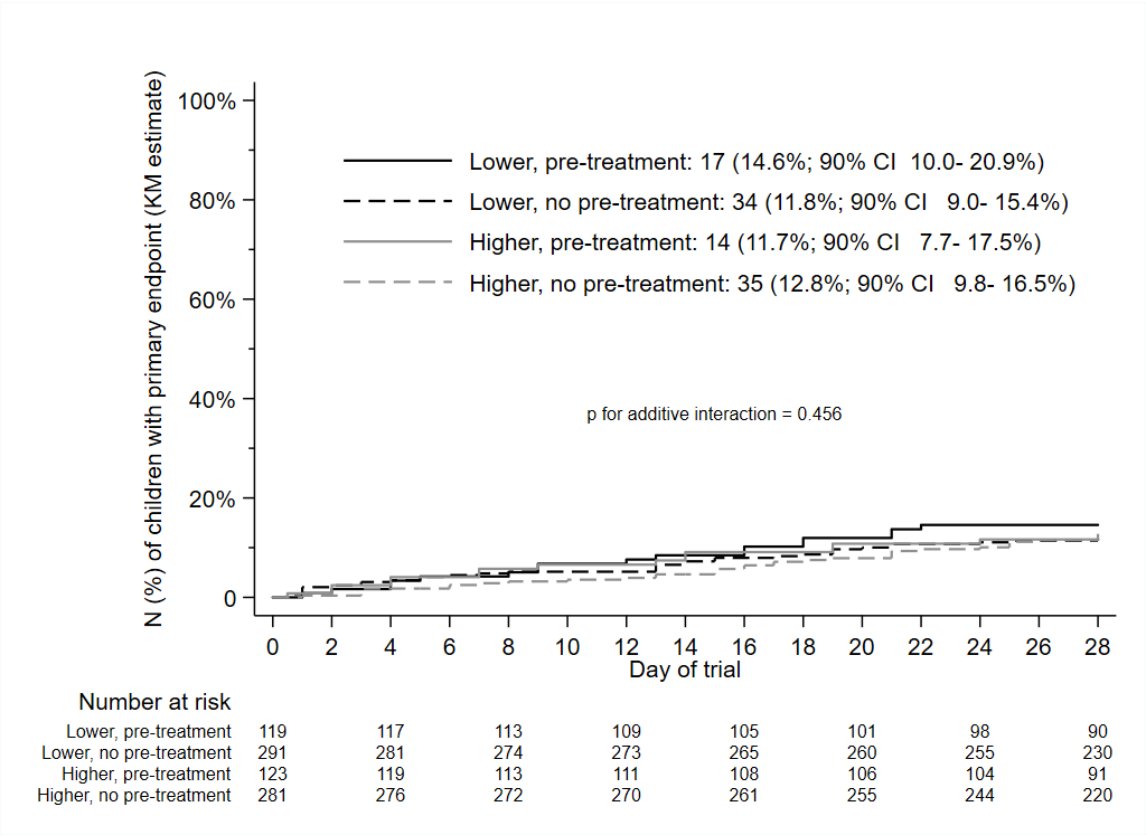


Figure 10: Kaplan Meier curve for analysis of interaction between pre-treatment with antibiotics and dose randomisation

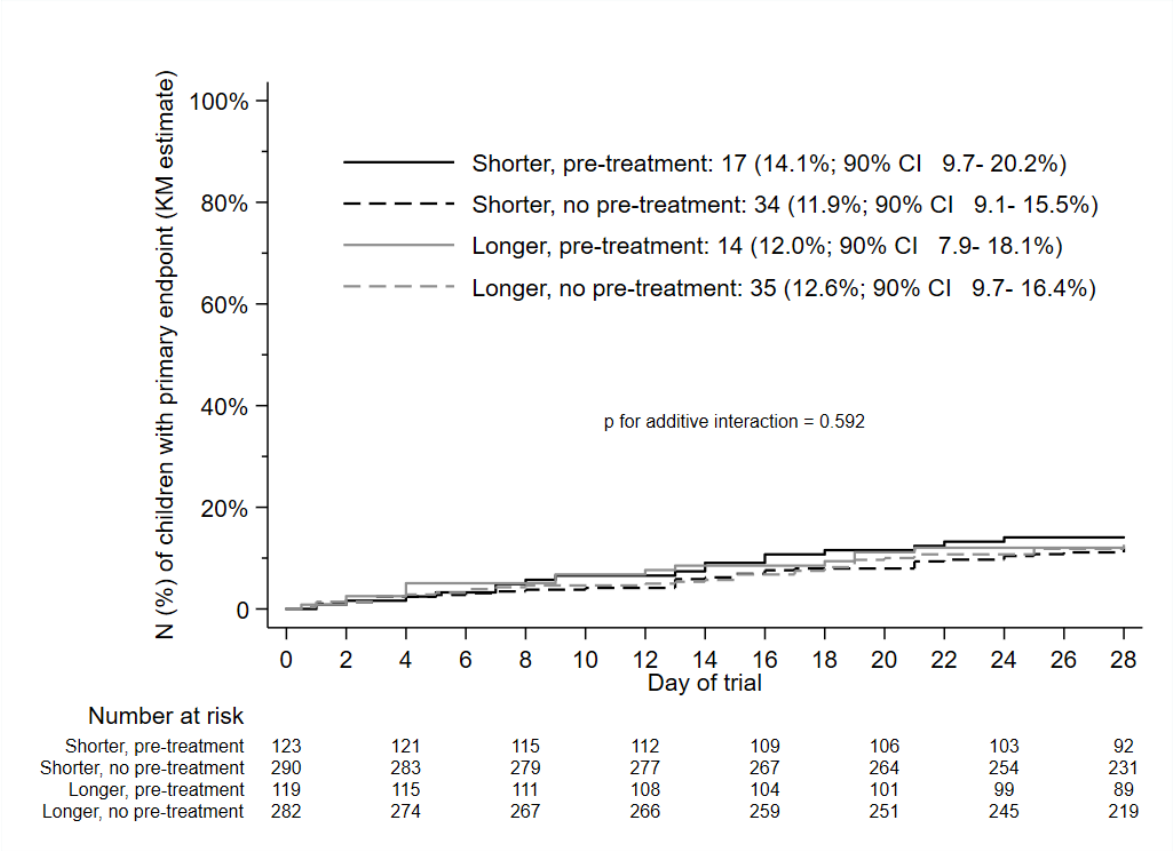


Figure 11: Kaplan Meier curve for analysis of interaction between pre-treatment with antibiotics and duration randomisation

3.6 Primary endpoint sensitivity analyses

Results for 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.

3.6.1 All systemic antibacterial treatments

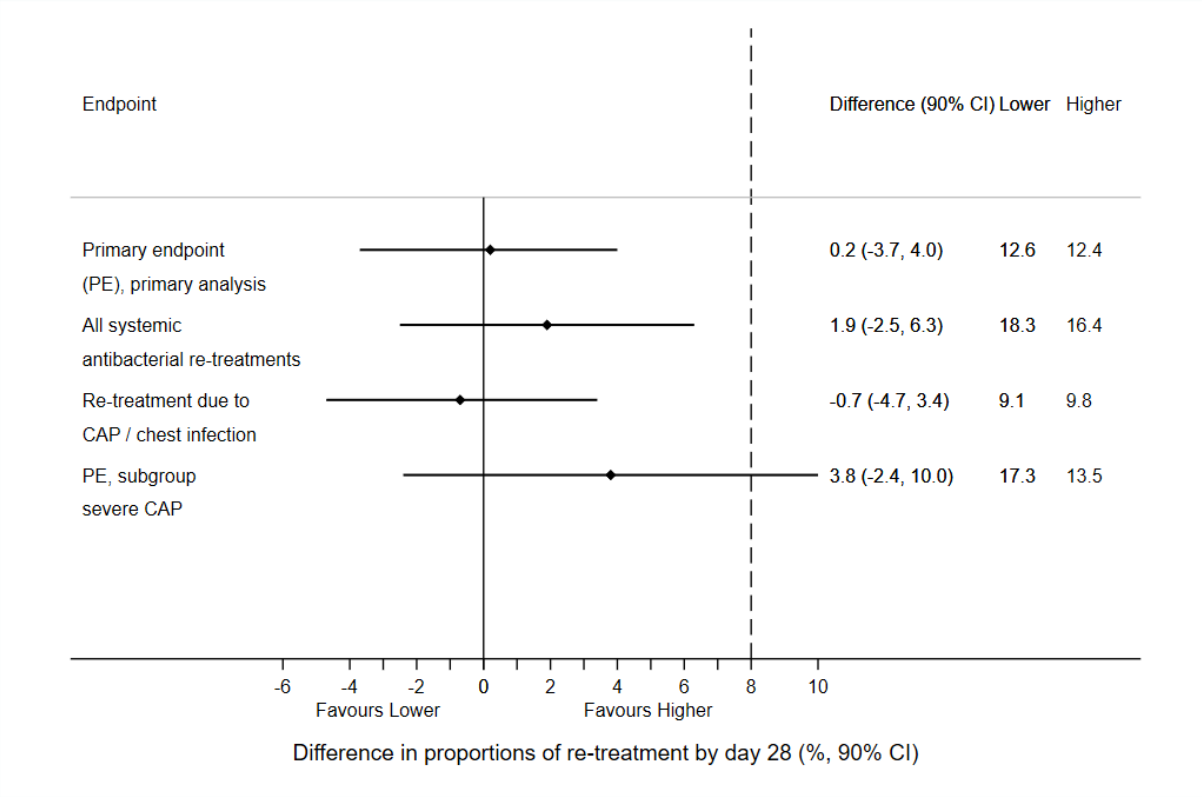
The first sensitivity analysis repeated the primary analysis but considered all systemic antibacterial treatments other than trial medication regardless of reason and indication. The total number of participants experiencing an endpoint in this analysis was 139/814 (17.4%; 90% CI 15.3– 19.7%).

For the dose comparison the estimated risk difference at day 28 was 1.9% (90% CI -2.5– 6.3%); for the duration comparison it was 1.0% (90% CI -3.4– 5.4%). For both comparisons the upper limit of the 90% confidence interval was less than the non-inferiority margin of 8%, supporting the observations of the primary endpoint analysis.

3.6.2 Treatment events for CAP/ 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 endpoint in this analysis was 76/814 (9.4%; 90% CI 7.9– 11.3%).

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



PE: Primary endpoint

Figure 12: Forest plot summarising sensitivity and subgroup analyses outcomes in terms of difference in proportions of re-treatment by day 28 for the dose randomisation

3.6.3 All treatment events for CAP/ 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 endpoint in this analysis was 78/814 (9.7%; 90% CI 8.1– 11.6%).

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

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

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

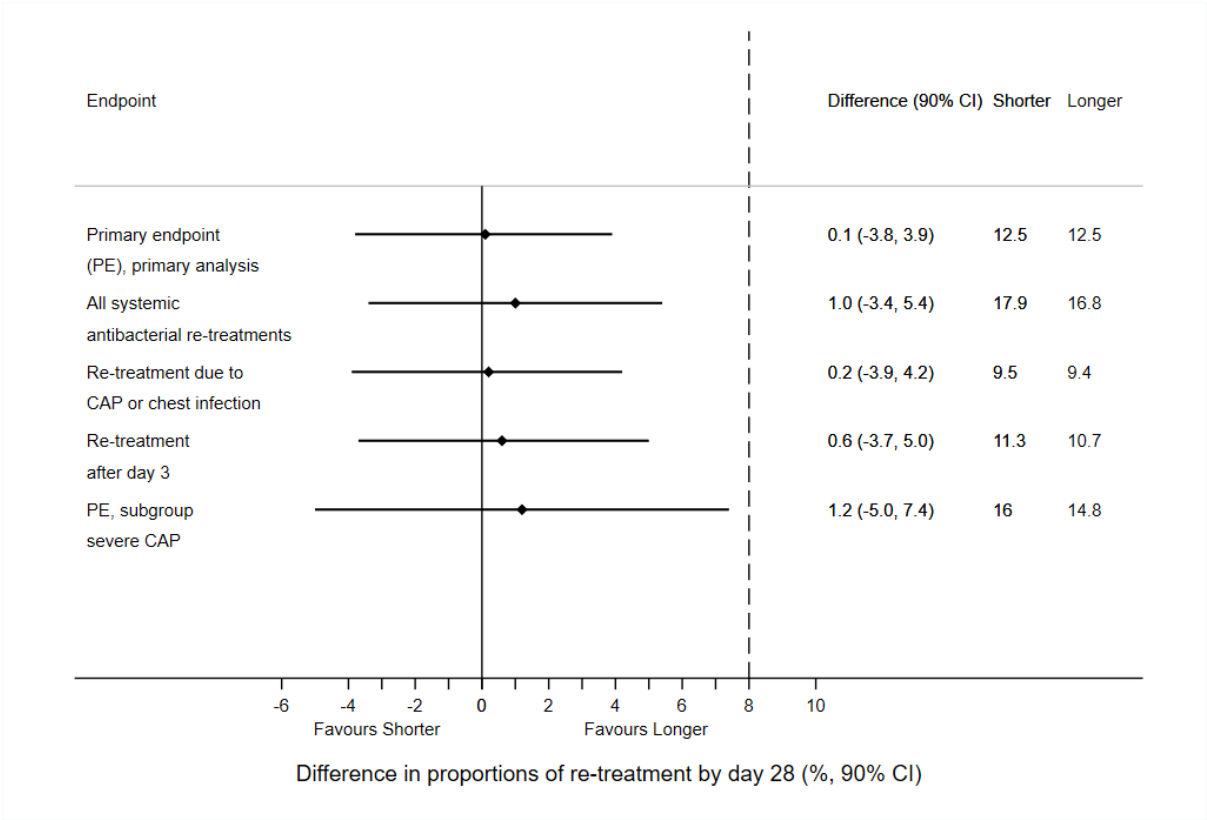


Figure 13: Forest plot summarising sensitivity and subgroup analyses outcomes in terms of difference in proportions of re-treatment by day 28 for the duration randomisation

3.7 On-treatment Analyses

The on-treatment analyses gave very similar results to the primary analysis, and 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).

3.8 Subgroup Analyses

3.8.1 Participants with severe CAP

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%) had none of these abnormalities at presentation, 291 (35.7%) had one, 341 (41.9%) had two and 27 (3.3) had three. 368 (45.2%) were included in the subgroup analysis.

	Lower N=410	**Higher** N=404	p-value	**Shorter** N=413	**Longer** N=401	p-value	**Total** N=814
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 abnormality	180 (43.9%)	188 (46.5%)	0.45	177 (42.9%)	191 (47.6%)	0.17	368 (45.2%)

Table 18: Abnormalities at presentation considered for subgroup analysis for severe CAP

Fifty six (15.4%) experienced a primary endpoint. There was no significant difference between the arms for either the dose (p=0.283) or the duration (p=0.821) comparison. For duration, the estimated risk difference at day 28 was 1.2% (90% CI -5.0-7.4%) (figure 14). For the dose randomisation the estimated difference at day 28 was 3.8% (90% CI -2.4- 10.0%). This is consistent with no effect, although the 90% confidence interval crossed the non-inferiority margin (figure 15).

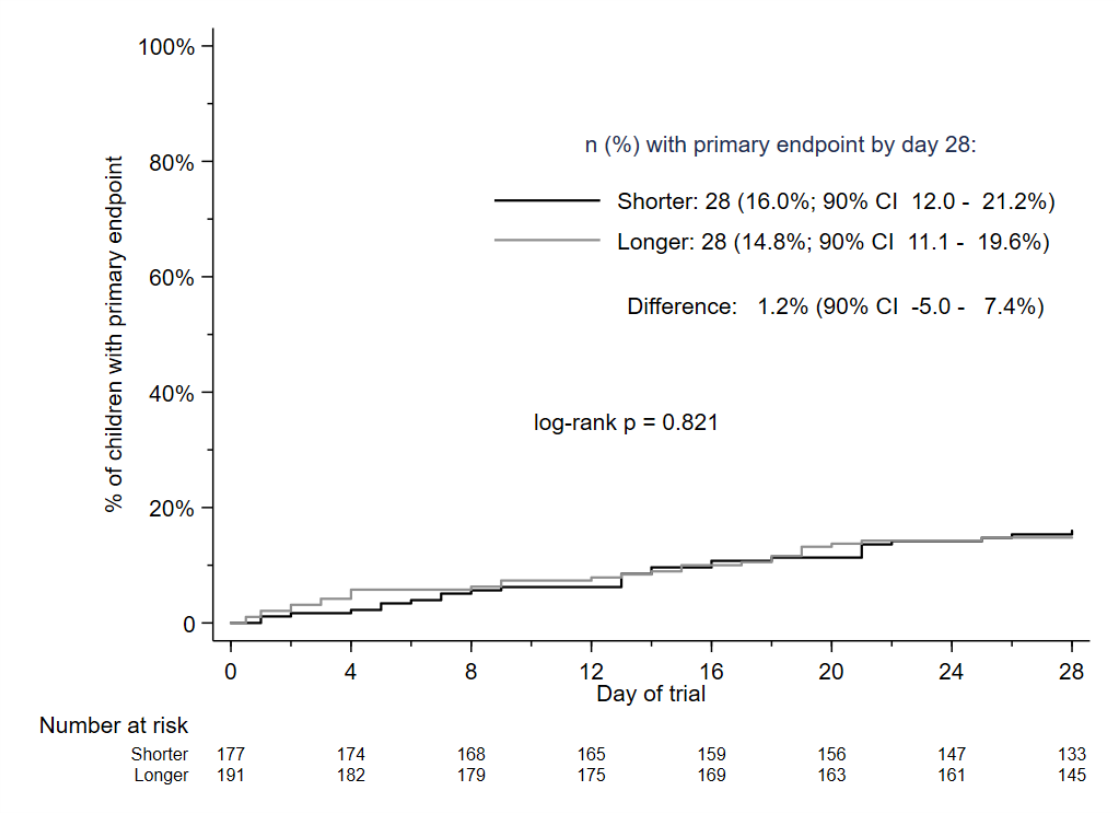


Figure 14: Kaplan Meier curve for severe CAP subgroup primary analysis for duration randomisation

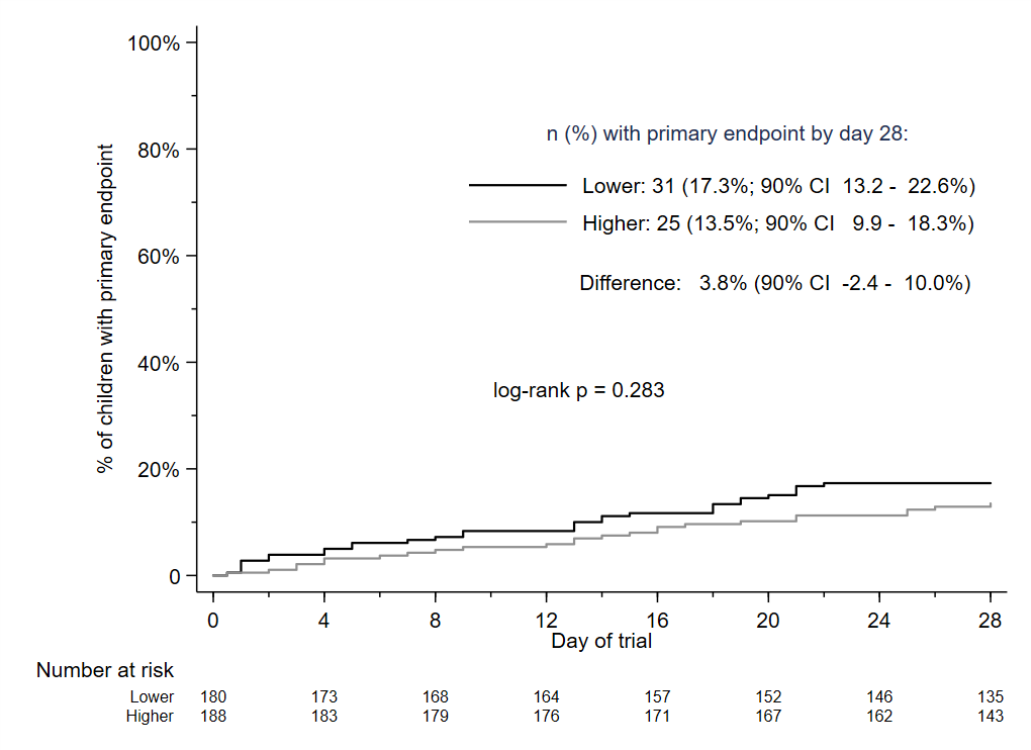


Figure 15: Kaplan Meier curve for severe CAP subgroup primary analysis for dose randomisation

3.8.2 Seasonal effect

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

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

3.9 *S. 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, final visit, and any unscheduled visits during follow-up.

3.9.1 Availability of nasopharyngeal culture results

Of the 814 participants in the analysis population, 647 (79%) had a nasopharyngeal sample taken at baseline, while 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 and 61 (7%) who had just a final visit sample. 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).

	PED	**WARD**		**Total**
	N=591	N=223	p-value	N=814
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			0.84	
None	75 (13%)	31 (14%)		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: # of culture samples available			0.37	
0	490 (95%)	186 (97%)		676 (95%)
1	22 (4%)	6 (3%)		28 (4%)

2	4 (1%)	0 (1%)	4 (1%)

Table 19: Availability of nasopharyngeal culture results

3.9.2 *S. pneumoniae* carriage

Of the baseline sample cultures, 272/647 (42%) were culture positive for *S. pneumoniae,* and of the final visit sample cultures 129/437 (30%) were positive. In participants with a culture result at both baseline and final visit, 75/376 (20%) were positive for *S. pneumoniae* at both visits, 100/376 (27%) were positive at baseline only and 40/376 (11%) were positive at the final visit only. The remaining 161/376 (43%) were negative at both visits (table 20).

	Lower	**Higher**	p-value	**Shorter**	**Longer**	p-value	**Total**
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 *							
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%)

*Table 20: S. pneumoniae carriage. Notes: *patients with culture results at both time-points.*

3.9.3 *S. pneumoniae* penicillin non-susceptibility

No penicillin-resistant pneumococcal isolates were identified in the CAP-IT trial. Of participants with a baseline culture result (either positive or negative), penicillin non-susceptibility was detected in the samples of 45/647 (7%) participants, 17% of *S. pneumoniae*-positive samples. For those with a final visit culture result (positive or negative) penicillin non-susceptibility was detected in the samples of 21 (5%) participants, 16% of *S. pneumoniae*-positive samples. Of participants with positive or negative culture results at both baseline and final visit, 23 (6%) participants had pneumococcal penicillin non-susceptibility

identified only in the baseline sample, 11 (3%) only in the final visit sample and seven (2%) in both baseline and final visit samples. In the remaining 335 (89%) participants penicillin resistance was not identified in either sample culture.

There was no evidence for a difference between penicillin non-susceptibility in the lower and higher dose randomisation groups, either in baseline or at the final visit sample culture, or between the shorter and longer duration baseline cultures (table 23). At the final visit, penicillin non-susceptibility was slightly more frequent in pneumococcal isolates in the shorter duration (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. pneumonia*-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), in which penicillin non-susceptibility was detected in 22% (n=14) of participants in the shorter duration randomisation arm and 11% (n=7) of participants in the longer duration randomisation arm (p=0.10).

3.9.4 *S. pneumoniae* amoxicillin resistance/non-susceptibility

Of participants with a baseline culture result (either positive or negative), amoxicillin non-susceptibility or resistance was detected in the samples of 7 (2%) participants. For those with a final visit culture result (positive or negative), this was detected in the samples of four (1%) participants. Of participants with positive or negative culture results at both baseline and final visit, one (<1%) of participants had resistance identified only in the baseline sample, two (1%) only in the final visit sample and one (<1%) in both baseline and final visit samples. In the remaining 361 (99%) participants, neither amoxicillin non-susceptibility nor resistance was identified in any samples.

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

	Lower	**Higher**	p-value	**Shorter**	**Longer**	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*						
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*						
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%)	

*Table 21: Penicillin and amoxicillin resistance/non-susceptibility in all participants with a culture result, either negative or positive for S. pneumoniae. *In patients with culture results at both time-points*

3.10 CAP symptoms

Parent/guardian-reported symptom data were elicited at telephone follow-up calls and through parental/guardian completion of a daily diary up to day 14. The proportion of participants for whom parent-reported symptom data from any source were available reduced from day 3 (93%), day 7 (88%), day 14 (83%) to day 21 and day 2 (both 76%, figure 16).

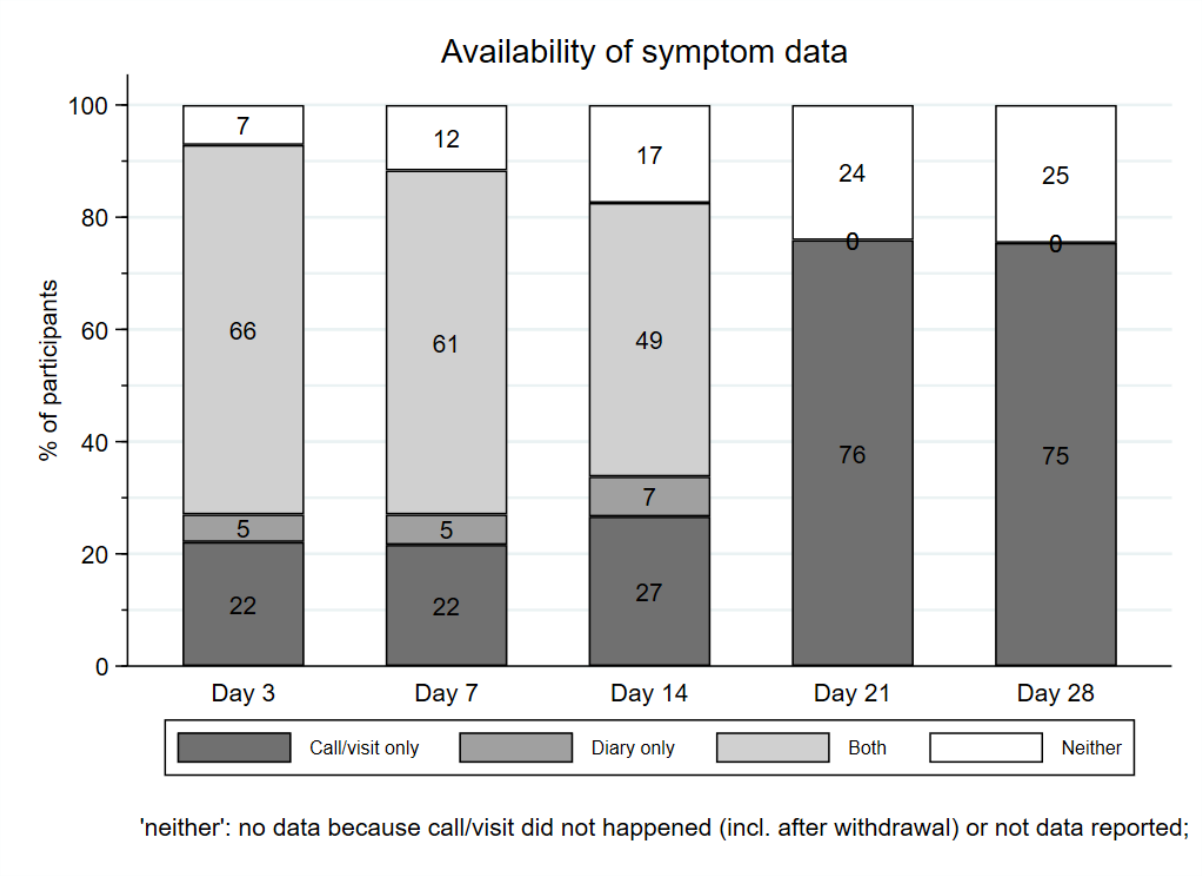


Figure 16: Availability of symptom data over time, by data source. 'neither': no data because call/visit did not happen or no data reported

3.10.1 Time to resolution of CAP symptoms: overall

Severity was elicited for nine CAP symptoms, each of which was analysed separately in terms of time to resolution. Because multiple comparisons were performed the p-value from each individual analysis needs to be interpreted cautiously. Participants were only included in the analysis 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 with a median of 1 day and 2 days, respectively. The remaining symptoms had a median time to resolution of between 3 and 5 days.

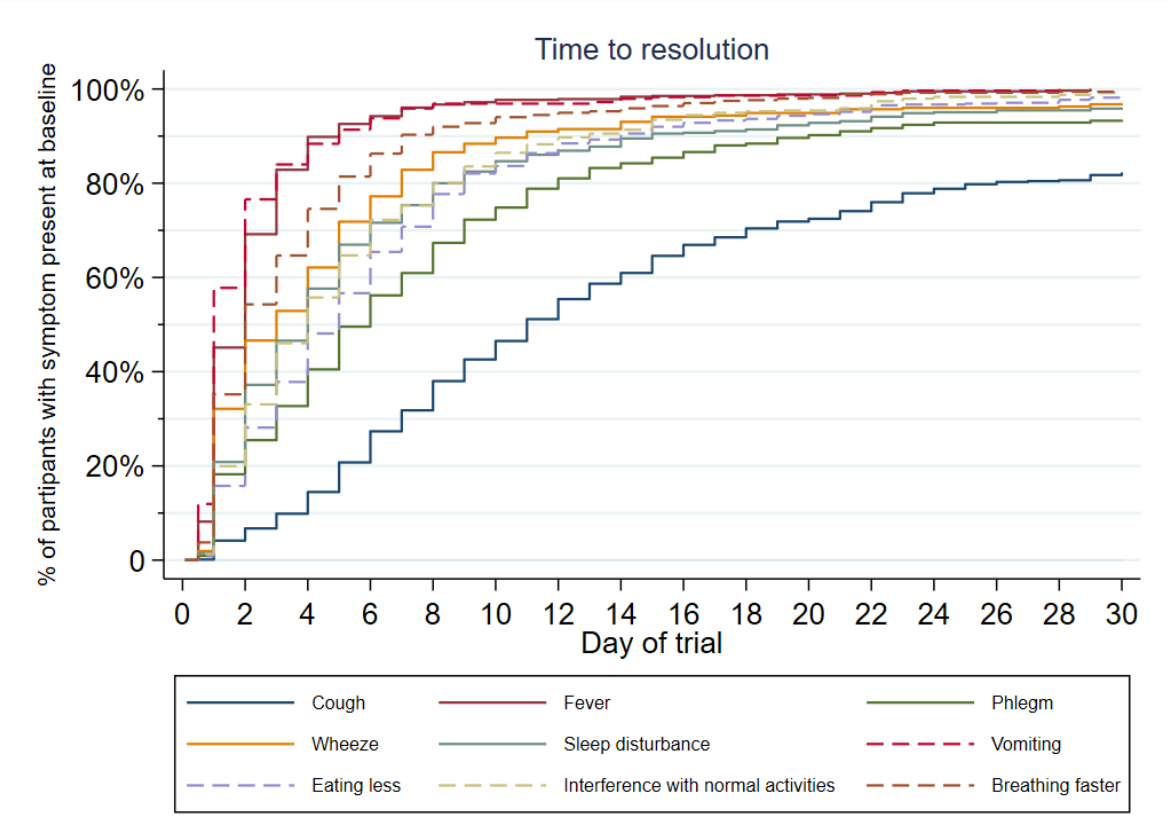


Figure 17: Kaplan Meier curves for time to symptom resolution across all randomisation arms. Participants excluded if symptom not present at enrolment.

3.10.2 Time to resolution of CAP symptoms: dose randomisation

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

3.10.3 Time to resolution of CAP 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, 19).

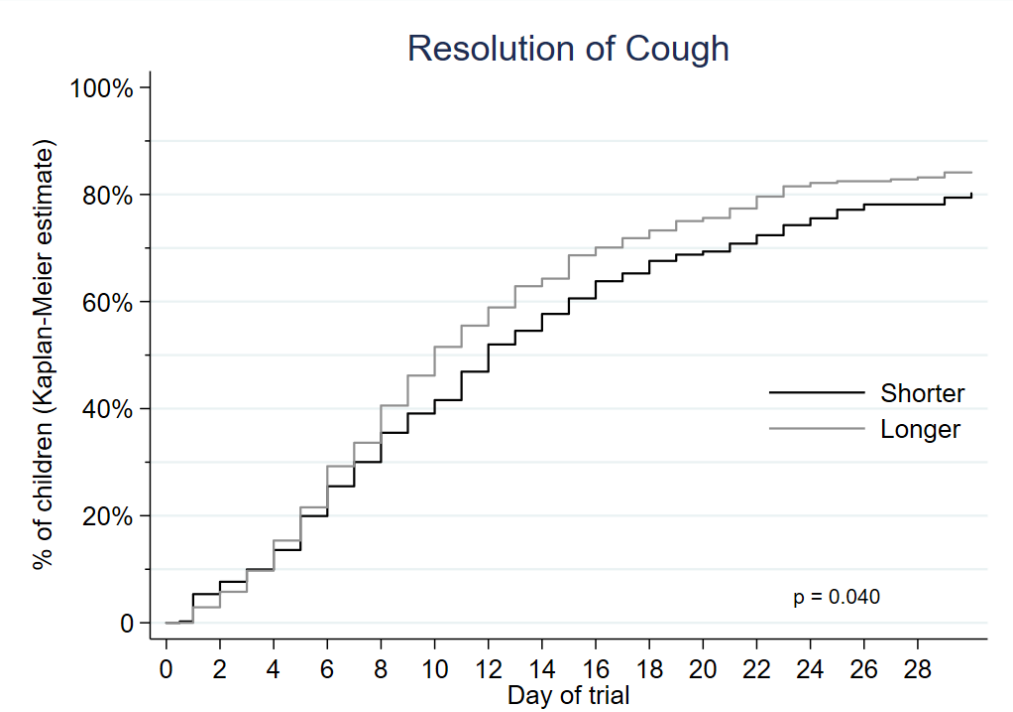


Figure 18: Kaplan-Meier curve for time to resolution of cough in the duration randomisation groups. Participants excluded if symptom not present at enrolment.

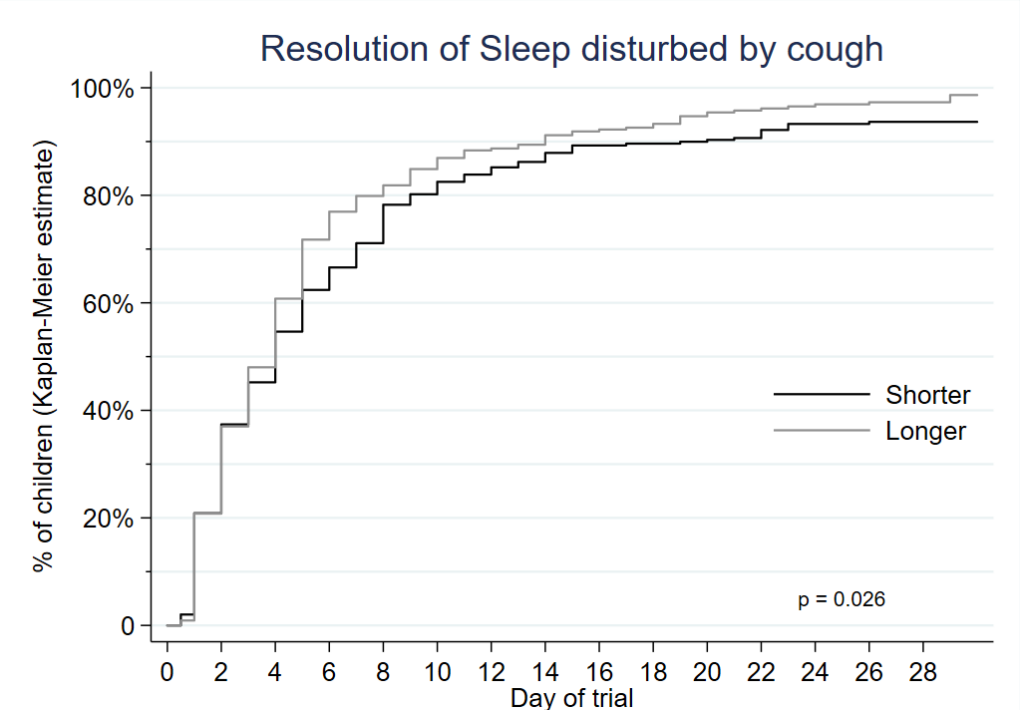


Figure 19: Kaplan-Meier curve for time to resolution of sleep disturbed by cough in the duration randomisation groups. Participants excluded if symptom not present at enrolment.

3.10.4 Sensitivity analysis for duration randomisation

As symptom resolution within the first three days from randomisation cannot by definition be related to the treatment duration randomisation, a pre-specified sensitivity analysis was performed changing the time origin to day four for the comparison of shorter versus longer treatment.

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

3.11 Adverse events

3.11.1 Serious Adverse Events

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

Of the 43 SAEs, 42 (98%) were hospitalisations and one (2%) was classified as life-threatening (table 23). This participant experienced an exacerbation of asthma, unrelated to the trial medication, and required intubation and transfer to a paediatric intensive care unit. Respiratory events were the most common diagnoses in 35/43 SAEs (81%). Of these, 16 (37%) were classified as respiratory distress, eight (19%) were lower respiratory tract infection, five (12%) were pneumonia and the remaining six were asthma (3 (7%)), bronchiolitis (2 (5%)) and influenza (1 (2%)). Most SAEs occurred between days 1-4 (29 (67%)).

	Lower N=410	**Higher** N=404	p-value	**Shorter** N=413	**Longer** N=401	p-value	**Total** N=814
# SAEs per participant			0.67			0.32	
0	387 (94.4%)	384 (95.0%)		388 (93.9%)	383 (95.5%)		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

Table 22: Summary of serious adverse events

The SAR was a diagnosis of vomiting, originally classified by the site investigator as unlikely related to IMP. However, upon 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.

	Shorter N=25	**Longer** N=18	**Lower** N=23	**Higher** N=20	**Total** N=43
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					2 (5%)
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%)
Day of hospitalisation[a]					
Day 0-3	20 (80%)	9 (50%)	16 (70%)	13 (65%)	29 (67%)
Day 4-7	0	2 (11%)	1 (4%)	1 (5%)	2 (5%)
Day 8-14	2 (8%)	1 (6%)	1 (4%)	2 (10%)	3 (7%)
Day 15-21	0	2 (11%)	0	2 (10%)	2 (5%)
Day 22-28	3 (12%)	4 (22%)	5 (22%)	2 (10%)	7 (16%)
Event grade					
Grade 1	11 (44%)	4 (22%)	9 (39%)	6 (30%)	15 (35%)
Grade 2	6 (24%)	9 (50%)	7 (30%)	8 (40%)	15 (35%)
Grade 3	8 (32%)	3 (17%)	6 (26%)	5 (25%)	11 (26%)

Grade 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

Table 23: SAE details

3.11.2 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 adverse event, 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 for 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 for a difference between shorter and longer duration in terms of prevalence after baseline, with 106 (27.4%) participants ever having skin rash after baseline in the longer duration arm and 87 (21.5%) in the shorter arm (p=0.055).

Additionally, when considering skin rash severity during the treatment period only, there was evidence for a difference between the shorter and longer duration arms. The longer duration arm experienced greater skin rash severity compared to the short arm at day 3 (p=0.019) and at day 7 (p=0.005), (figure 20). There

was no evidence for a difference between dose randomisation arms in terms of skin rash severity during the treatment period and there was no evidence for a difference in severity during the treatment period between the dose or duration randomisation arms for diarrhoea or oral thrush, (see table 24 below)

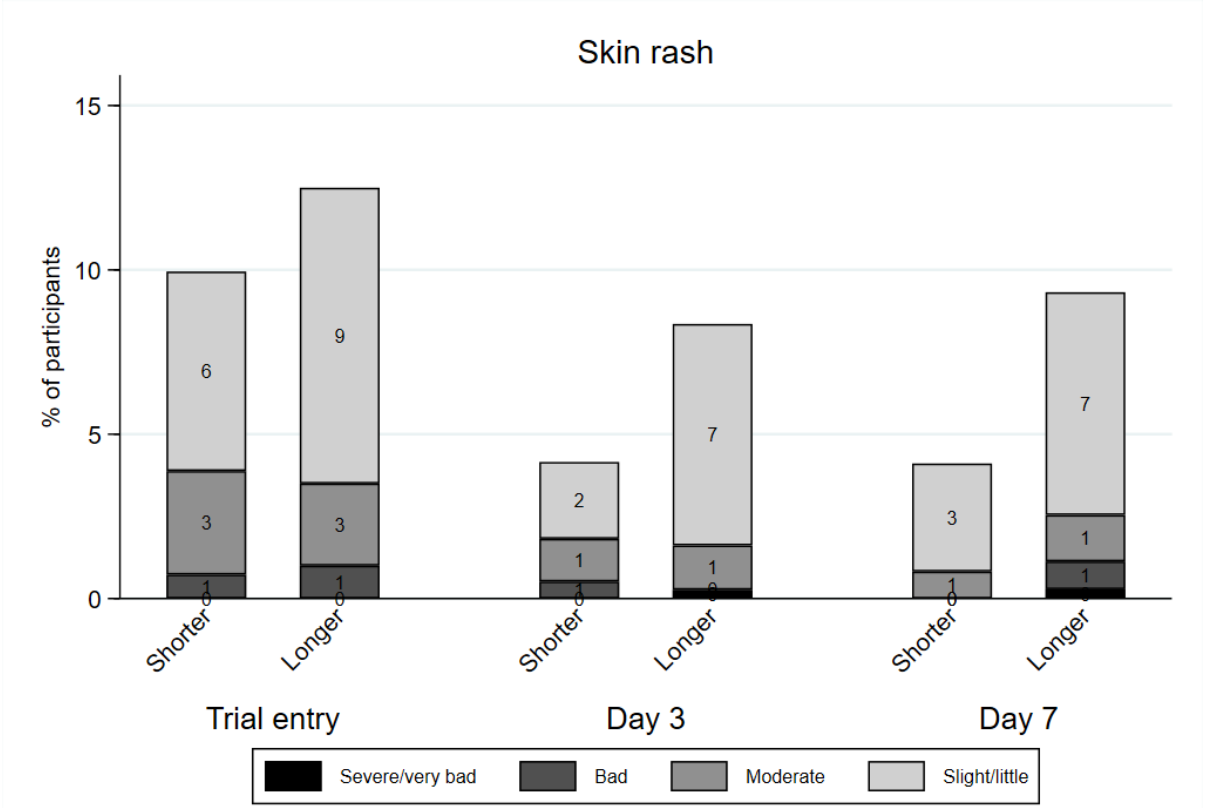


Figure 20: Skin rash severity during treatment period: duration randomisation

	Lower N=410	Higher N=404	Shorter N=413	Longer N=401	Total N=814
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=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=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=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=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=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=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=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=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=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

Table24: Prevalence of diarrhoea, oral thrush and skin rash after baseline

3.12 Health care services

Utilisation of health care services was unrelated to randomisation arm. Hospital admissions and visits to the emergency department without admission were reported in 46 (5.7%) and 43 (5.3%) participants, respectively, while a larger proportion reported using any health care service (304, 37.3%), (see table 25 below).

	Lower	**Higher**		**Shorter**	**Longer**		**Total**
	N=410	N=404	**p-value**	N=413	N=401	**p-value**	N=814
Ever admitted to hospital?			0.80			0.27	
Yes	24 (5.9%)	22 (5.4%)		27 (6.5%)	19 (4.7%)		46 (5.7%)
No	386 (94.1%)	382 (94.6%)		386 (93.5%)	382 (95.3%)		768 (94.3%)
Ever visit to A&E (without admission)?			0.84			0.23	
Yes	21 (5.1%)	22 (5.4%)		18 (4.4%)	25 (6.2%)		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?			0.55			0.75	
Yes	149 (36.3%)	155 (38.4%)		152 (36.8%)	152 (37.9%)		304 (37.3%)
No	261 (63.7%)	249 (61.6%)		261 (63.2%)	249 (62.1%)		510 (62.7%)

Table25: Health care service utilisation

3.13 Daily activities and childcare

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

	Lower N=298	**Higher** N=289	p-value	**Shorter** N=291	**Longer** N=296	p-value	**Total** N=441
Child missed school, day care or nursery: ever			0.18			0.43	
Yes	152 (71.0%)	174 (76.7%)		159 (72.3%)	167 (75.6%)		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	4 (0, 5)	4 (2, 6)	0.14	4 (0, 6)	4 (2, 6)	0.62	4 (0, 6)
Parent missed work: ever			0.92			0.71	
Yes	128 (64.0%)	136 (63.6%)		127 (62.9%)	137 (64.6%)		264 (63.8%)
No	72 (36.0%)	78 (36.4%)		75 (37.1%)	75 (35.4%)		150 (36.2%)
Days parent missed work	3 (0, 4)	3 (0, 5)	0.43	3 (0, 4)	3 (0, 5)	0.20	3 (0, 5)
Parent missed other activities: ever			0.97			0.84	
Yes	50 (33.6%)	56 (33.7%)		53 (34.2%)	53 (33.1%)		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	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			0.54			0.98	
Yes	73 (36.3%)	72 (33.5%)		73 (34.9%)	72 (34.8%)		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	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							

Table26: Daily activities and childcare

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 paediatric emergency department, 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.

4.1 Limitations

In contrast to the majority of trials addressing optimal antibiotic treatment duration and dose of a single drug for childhood pneumonia, the CAP-IT trial was conducted in a high-income setting where the expected mortality, even from moderate-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.[85]

To further guard against bias, an independent endpoint review committee comprised of experienced clinicians adjudicated all antibiotic retreatments during the trial period regarding the reason (respiratory tract infection or other) and clinical indication. Of note, the primary endpoint could be ascertained in 97% of CAP-IT trial participants either at final follow-up or through contact with the general practitioner. We therefore consider the impact of loss-to-follow up negligible.

We aimed to exclude children for whom antibiotics would not be expected to have any beneficial effect, primarily those likely to have obstructive airway disease only. A mixed picture, however, was common for hospitalised children, with 16% 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 to the 48% bronchodilator use observed in the most recent UK paediatric pneumonia audit, the use of salbutamol or steroids was therefore low in CAP-IT, indicating that there was a strong clinical suspicion of CAP likely to benefit from antibiotics in enrolled children. [86]

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 colonization rates at or shortly after the end of antibiotic treatment is expected to be very low whereas significant recolonization or regrowth was expected (and observed) by 28 days. Finally, we considered penicillin-resistant pneumococcal colonization at final follow-up to be the most relevant population- and individual-level resistance marker, as children colonized 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.[87]

4.2 Generalisability

Children were enrolled in the trial based on clinically diagnosed pneumonia requiring antibiotic treatment with amoxicillin, and are likely typical of children treated for pneumonia with amoxicillin in paediatric emergency departments. 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.[88, 89] 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 emergency department. Only 13% of screened children were not approached due to physician preference for an antibiotic other than amoxicillin at discharge, in keeping with guidance suggesting amoxicillin 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-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, consistent with reported low penicillin-resistance levels in Northern Europe.[90] Our findings for effectiveness of lower versus higher amoxicillin dose, and impacts on resistance, may therefore 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 World Health Organization and other international recommendations was used in the CAP-IT trial rather than administration in three daily doses as recommended by the British National Formulary for Children. This was selected as it is known to maximise adherence,

which would be particularly important in children allocated to lower dose and shorter duration arms. In addition, patient representatives involved in the design phase indicated this approach to be particularly family friendly, with an additional midday dose often being most challenging in terms of practicality in day care settings and adherence. 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 the CAP-IT trial had rates of antibiotic retreatment and secondary or re-hospitalisation similar to those described in observational studies conducted in settings with standard administration of amoxicillin in three doses.[42, 88, 91, 92]

4.3 Interpretation

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 pneumococcal conjugate vaccines and in an era with lower pneumococcal penicillin resistance.[93, 94] Two recent relevant trials conducted in Malawi investigated 3-day vs 5-day and 3-day vs placebo amoxicillin treatment of young HIV-uninfected children with non-severe pneumonia.[95, 96] 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 versus 3-day treatment. The latter 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 UK primary care reported in large observational studies, but has not previously been described for children with CAP seen in emergency departments or discharged from hospital after a short stay. Similarly, the secondary or re-hospitalisation 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 3-day and 7-day treatment durations, despite two-day slower resolution of mainly mild cough on average in the shorter duration arm. We did not identify any differences between lower and higher dose amoxicillin 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 either 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 daycare or school and work, respectively, 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.[97] 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 allowing children to return to usual activities and will maximise adherence.[98, 99]

Antimicrobial resistance was a key secondary outcome in CAP-IT. Colonization by penicillin-non-susceptible pneumococci at 28 days was similar for both randomisation arms. In general, 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 are likely to generate results that will complement CAP-IT findings. In the UK, the primary care-based ARTIC-PC study, a randomised placebo-controlled trial investigating the benefit of a seven-day course of oral amoxicillin in children with possible lower respiratory tract infection (but not considered to have pneumonia clinically), has completed recruitment. The SAFER trial in Canada and SCOUT-CAP in the United States both target children presenting to emergency departments but not admitted to hospital and are comparing 5-day with 10-day treatment courses with amoxicillin and one of a selection

of beta-lactams, respectively. Both trials are expected to report on results at the end of 2020 or first half of 2021. Finally, another Canadian open-label randomised controlled trial 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.

4.4 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 community-acquired pneumonia for community-based treatment after discharge from acute care. A slightly longer time to resolution of mild cough could 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 twice 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/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. [100]

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.

5. Conclusions

- For children presenting to acute care settings with uncomplicated, clinically diagnosed, moderate or moderate-severe community-acquired pneumonia 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 four weeks. The trial therefore 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 three days compared with seven days. Given the advantages of a shorter duration of treatment for adherence and the observed declining adherence during treatment days four to seven in the trial, a 3-day oral amoxicillin course 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 four weeks. Dosing regimens also were 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 due to variations in weight within broad age-bands.
- Either 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 (solid forms that are liquid upon ingestion or become liquid upon 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 UNICEF and WHO contains 250 mg amoxicillin in a non-divisible dispersible tablet. Administration of this tablet twice a day to young infants (weighing 4 to <10kg) in a wide dose range of 50 (10kg)-125 (4kg) mg/kg per day with many children expected to receive doses in the higher dose range of CAP-IT. The CAP-IT trial results did not identify any clinically relevant disadvantages to using higher doses, thus supporting the continued use of existing dispersible tablets.

- We did not formally compare twice with thrice daily dosing. However, we note that children in the CAP-IT study 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 settings in which amoxicillin treatment would generally be given three times daily.

Contributions of Authors

Sam Barratt (Clinical Trials Manager), contributed to compiling data and drafting the report

Julia A Bielicki (Consultant in Paediatric Infectious Diseases), drafted the report

David Dunn (Professor of Medical Statistics) performed statistical analyses

Saul Faust (Professor of Paediatric Immunology and Infectious Diseases) contributed to drafting the report

Adam Finn (Professor of Paediatrics) performed resistance analyses

Diana Gibb (Professor, Epidemiology), drafted the report

Lynda Harper (Clinical Project Manager) contributed to drafting the report

Pauline Jackson (Paediatric nurse) contributed to drafting the report

Mark D Lyttle (Consultant in Paediatric Emergency Medicine) contributed to drafting the report

Colin Powell (Consultant in Paediatric Emergency Medicine) contributed to drafting the report

Louise Rogers (Clinical Research Sister) contributed to drafting the report

Damian Roland (Consultant in Paediatric Emergency Medicine) contributed to drafting the report

Michael Sharland (Professor of Paediatric Infectious Diseases), drafted the report

Wolfgang Stöhr (Senior Medical Statistician) performed statistical analyses

Kate Sturgeon (Senior Research Nurse) contributed to drafting the report

Elia Vitale (Senior Paediatric Clinical Research Nurse) contributed to drafting the report

Mandy Wan (Paediatric Clinical Trials Pharmacist) contributed to drafting the report

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Trial Steering Committee (TSC)

Elizabeth Molyneux (Chair), Chris Butler, Alan Smyth, Catherine Pritchard (Patient and Public Involvement)

Independent Data Monitoring Committee (IDMC)

Tim Peto (Chair), Simon Cousens and Stuart Logan

Independent Endpoint Review Committee (ERC)

Alasdair Bamford (Chair), Anna Turkova, Anna Goodman and Felicity Fitzgerald

Trial Management Group (TMG)

Mike Sharland (Chair), Julia Bielicki, Mark Lyttle, Colin Powell, Paul Little, Saul Faust, Adam Finn, Julie Robotham, Mandy Wan, David Dunn, Wolfgang Stöhr, Lynda Harper, Sam Barratt, Nigel Klein, Louise Rogers, Elia Vitale and Diana Gibb

Investigator Sites

Alder Hey Children's Hospital NHS Foundation Trust, Liverpool: Dan Hawcutt (PI), Matt Rotheram, Liz D Lee and Rachel Greenwood-Bibby

Birmingham Children's Hospital**:** Stuart Hartshorn (PI), Deepthi Jyothish, Louise Rogers and Juliet Hopkins

Bristol Royal Hospital for Children: Mark Lyttle (PI), Stefania Vergnano, Lucie Aplin, Pauline Jackson, Gurnie Kaur, Beth Pittaway, Michelle Ross, Sarah Sheedy, Alice Smith, and Yesenia Tanner

Chelsea & Westminster NHS Foundation Trust, London: James Ross (PI), Poonam Patel, Nabila Burney, Hannah Fletcher, Jaime Carungcong, Kribashnie Nundlall

City Hospitals Sunderland NHS Foundation Trust: Niall Mullen (PI), Rhona McCrone and Paul P Corrigan

Countess of Chester Hospital: Susie Holt (PI), John Gibbs, Caroline Burchett, Caroline Lonsdale and Sarah De-Beger

Darlington Memorial Hospital**:** Godfrey Nyamugunuduru (PI), John Furness (former PI) and Dawn Eggington

Derbyshire Children's Hospital, Derby**:** Gisela Robinson (PI), Lizzie Starkey and Mel Hayman

Evelina London Children's Hospital: Anastasia Alcock (PI), Dani Hall (former PI), Ronny Cheung, Alyce B Sheedy and Mohammad Ahmad

James Cook University Hospital, Middlesbrough**:** Arshid Murad (PI), Katherine Jarman and Joanna Green

John Radcliffe Hospital, Oxford: Tanya Baron (PI), Chris Bird (former PI), Shelley Segal and Sally Beer

King's College Hospital, London: Fleur Cantle (PI), Hannah Eastman, Raine Astin-Chamberlain, Paul Riozzi and Hannah Cotton

Leeds Children's Hospital**:** Sean O'Riordan (PI), Alice Downes, Marjorie Allen and Louise Conner

Leicester Hospitals**:** Damian Roland (PI), Srini Bandi and Rekha Patel

Nottingham University Hospitals NHS Trust: Chris Gough (PI), Megan McAulay and Louise Conner

Southport and Ormskirk NHS Trust: Sharryn Gardner (PI), Zena Haslam, Moira Morrison

Our Lady's Children's Hospital Crumlin, Dublin**:** Michael Barrett (PI) and Madeleine Niermeyer

Royal Alexandra Children's Hospital, Brighton**:** Emily Walton (PI), Akshat Kapur and Vivien Richmond

Royal Hospital for Children, Glasgow: Steven Foster (PI), Ruth Bland, Ashleigh Neil, Barry Milligan and Helen Bannister

Royal London Hospital**:** Ben Bloom (PI), Ami Parikh, Olivia Boulton, Imogen Skene

Royal Manchester Children's Hospital: Katherine Potier (PI), Fiona Poole, Jill L Wilson

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

St George's Hospital, London: Paul Heath (PI), Yasser Iqbal, Malte Kohns, Elena Stefanova, Elia Vitale

St Mary's Hospital, London: Ian Maconochie (PI), Suzanne Laing, Rikke Jorgensen

University Hospitals Lewisham: Maggie Nyirenda (PI), Anastasia Alcock, Samia Pilgrim, Emma Gardiner

University Hospital of Wales, Cardiff: Jeff Morgan (PI), Colin VE Powell (former PI), Jennifer Muller and Gail Marshall

Southampton Children's Hospital: Katrina Cathie (PI), Jane Bayreuther, Ruth Ensom, Emily Cornish

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 is used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

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Appendices

Appendix 1: Details of main protocol amendment – joint analysis of PED and WARD groups

Initially PED and WARD 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 impacting on the duration of treatment analysis, (3) the need for different trial procedures (consent process, enrolment, additional data capture during inpatient period for 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: (1) In a substantial proportion of participating hospitals, children were first seen in a Paediatric Assessment Unit (PAU), before either being formally admitted or discharged. This made the distinction between PED and WARD less relevant, especially as many PAUs admitted children for up to 48 hours. (2) Although clinical signs and symptoms at presentation to ED were (as expected) worse on average in WARD vs PED children, considerable overlap in the two distributions was observed. (3) Duration of prior antibiotic exposure in the WARD group was much shorter than anticipated: 54% less than 12 hours, 75% less than 24 hours. (4) There was no evidence of a difference between the primary endpoint rate between PED and WARD.

Appendix 2: Table 27: CAP symptoms at trial entry by strata

	PED N=591	WARD N=223	p-value	Total N=814
Fever			<0.001	
Not present	54 (9.2%)	111 (49.8%)		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			<0.001	
Not present	14 (2.4%)	14 (6.3%)		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)			0.58	
Not present	174 (29.5%)	72 (32.3%)		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)			<0.001	
Not present	77 (13.1%)	57 (25.6%)		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			0.95	
Not present	283 (48.0%)	109 (48.9%)		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%)
Sleep disturbed by cough			<0.001	
Not present	67 (11.4%)	56 (25.1%)		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)			0.003	
Not present	324 (54.9%)	155 (69.5%)		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			0.073	
Not present	63 (10.7%)	30 (13.5%)		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			<0.001	
Not present	61 (10.3%)	49 (22.0%)		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 endpoint

The on-treatment analyses of the primary endpoint excluded participants who took less than 80% of trial medication as scheduled (i.e. more than 2 doses not taken or taken at smaller volume; switch from trial medication to non-trial antibiotics due to deterioration 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.

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

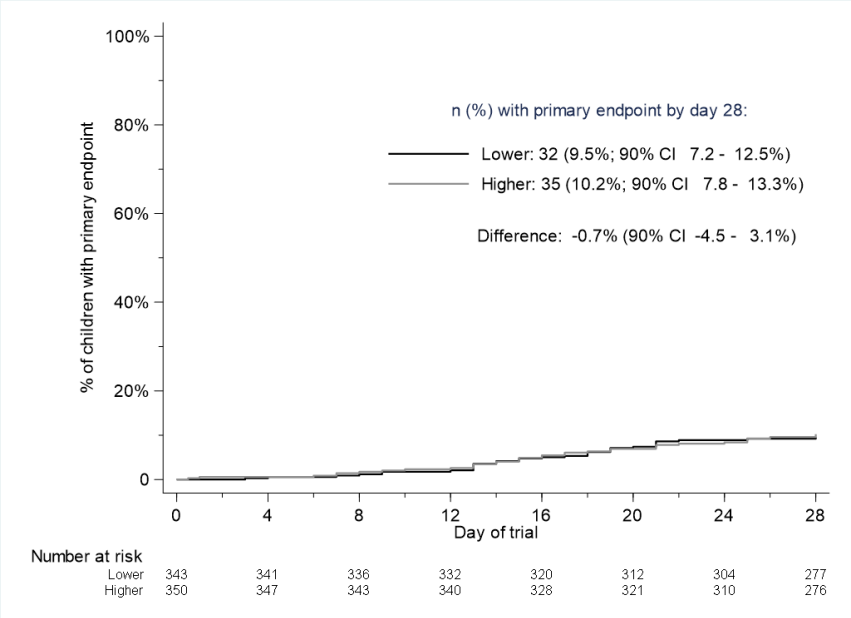

Figure 22: Dose randomisation, participants who took at least 80% of active trial drug

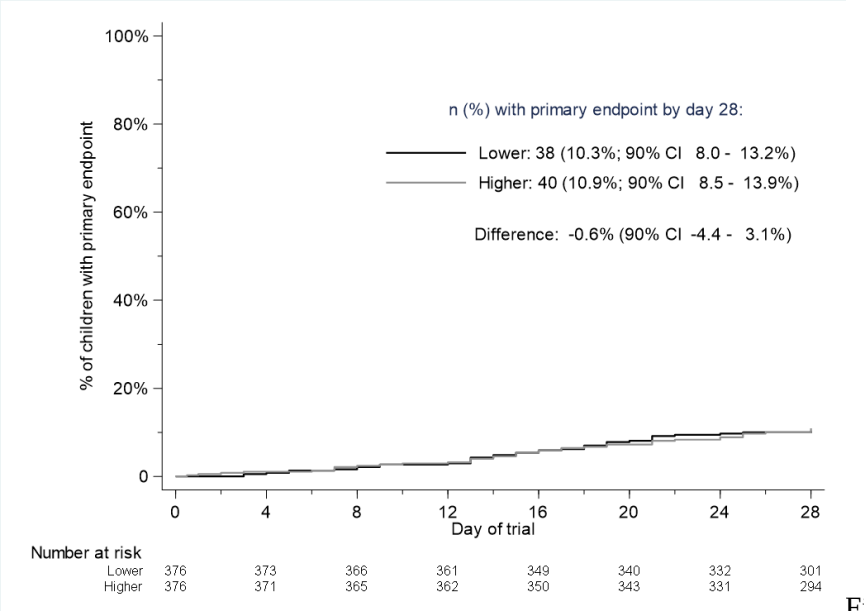

Figure 23: Duration randomisation, participants who took at least 80% of all trial medication including placebo

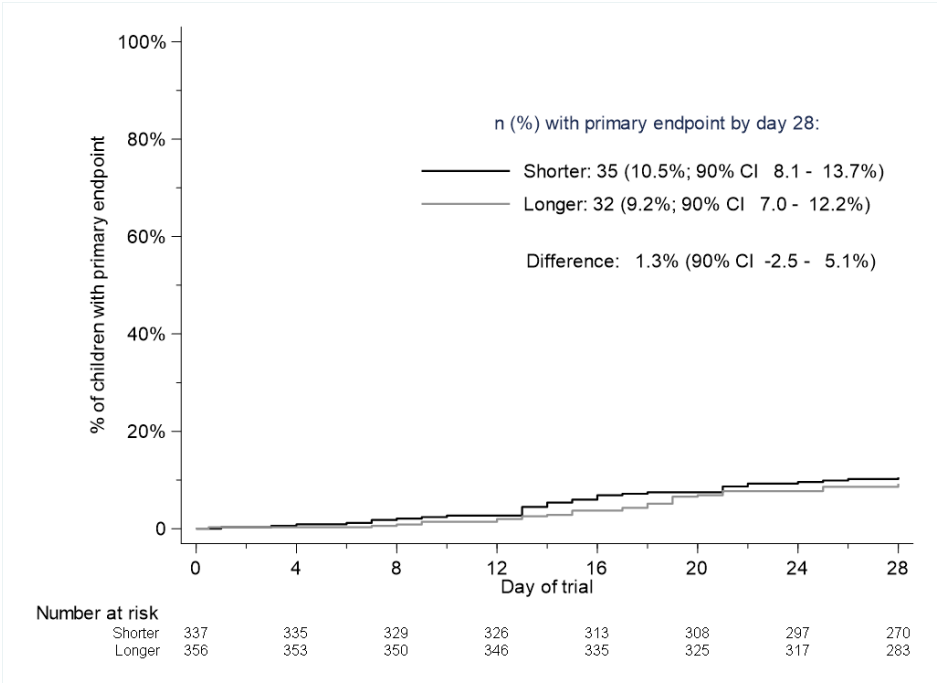

Figure 24: Duration randomisation, participants who took at least 80% of active trial drug