Effect of Amoxicillin Dose and Treatment Duration on the Need for Antibiotic Retreatment in Children With Community-Acquired Pneumonia: The CAP-IT Randomized Clinical Trial

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Key points

Question: For children with community-acquired pneumonia discharged from an emergency department, observational unit, or inpatient ward (within 48 hours), is subsequent outpatient treatment with oral amoxicillin at a dose of 35-50 mg/kg/day noninferior to 70-90 mg/kg/day, and for 3 days noninferior to 7 days, with regard to the need for antibiotic retreatment?

Findings: In this 2x2 factorial randomized clinical trial of 814 children requiring amoxicillin for community-acquired pneumonia at hospital discharge, antibiotic retreatment within 28 days occurred in 12.6% vs 12.4% of those randomized to lower vs higher doses, respectively, and in 12.5% vs 12.5% of those randomized to 3-day vs 7-day amoxicillin duration. Both comparisons met the prespecified 8% noninferiority margin.

Meaning: Among children with community-acquired pneumonia discharged from an emergency department, observational unit, or inpatient ward, further outpatient treatment with oral amoxicillin at a dose of 35-50 mg/kg/day was noninferior to a dose of 70-90 mg/kg/day and for 3 days was noninferior to 7 days with regard to the need for later antibiotic retreatment.

Abstract

Importance: The optimal dose and duration of oral amoxicillin for children with community-acquired pneumonia (CAP) are unclear.

Objective: To determine whether lower dose amoxicillin is noninferior to higher dose, and whether 3-day treatment is noninferior to 7 days.

Design, setting, and participants: Multicenter, randomized, blinded, 2x2 factorial non-inferiority trial enrolling 824 children aged ≥6 months, with clinically diagnosed CAP, treated with amoxicillin on discharge from emergency departments and inpatient wards of 29 hospitals in UK and Ireland between February 2017-April 2019, with last trial visit on 21st May 2019.

Intervention(s): Children were randomized 1:1 to oral amoxicillin at lower (n=410, 35-50 mg/kg) or higher (n=404, 70-90mg/kg) daily doses, for shorter (n=413, 3-day) or longer (n=401, 7-day) durations.

Main Outcomes and Measures: Primary outcome was clinically-indicated antibiotic re-treatment for respiratory infection within 28 days after randomization. The non-inferiority margin was 8%. Secondary outcomes included severity/duration of 9 parent-reported CAP symptoms, 3 antibiotic-related adverse events, and phenotypic resistance in colonizing *Streptococcus pneumoniae* isolates.

Results: Of 824 participants randomized, 814 received at least one dose of trial medication (median (IQR) age 2.5 years (1.6-2.7); 423 (52%) male); primary outcome was available for 789 (97%). For lower vs higher dose, respectively, the primary outcome occurred in 12.6% vs 12.4% (difference 0.2% [1-sided 95%CI -∞ to 4.0%]) For 3-day vs 7-treatment, the primary outcome occurred in 12.5% vs 12.5% (difference 0.1% [1-sided 95%CI -∞ to 3.9]). Both groups demonstrated non-inferiority with no significant interaction between dose and duration (p=0.63). Of the 14 prespecified secondary endpoints, the only significant differences were 3-day vs 7-day treatment for cough duration (median 12d vs 10d; HR 1.2 [95% CI 1.0 to 1.4]; p=0.04) and sleep disturbed by cough

(median 4d vs 4d, HR;1.2 [95% CI 1.0 to 1.4]; p=0.03) Among the subgroup of children with severe CAP, for lower vs higher dose the primary endpoint occurred in 17.3% vs 13.5% (difference 3.8% [1-sided 95%CI -∞ to10]; P-value for interaction = 0.28); for 3d vs 7d treatment, the primary endpoint occurred in 16.0% vs 14.8% (difference 1.2% [1-sided 95%CI -∞ to 7.4]; P-value for interaction = 0.82) .

Conclusions and Relevance: Among children with CAP discharged from emergency department or hospital ward (within 48 hours), low dose outpatient oral amoxicillin was noninferior to high dose, and 3-day duration was noninferior to 7 days, with regard to need for antibiotic retreatment. However, disease severity, treatment setting, prior antibiotics received, and acceptability of the noninferiority margin require consideration when interpreting the findings.

Trial Registration: ISRCTN76888927.

Introduction

Children under 5 years old commonly receive oral antibiotics, mainly for respiratory infections.[1,2] In a retrospective cohort study from the UK, the Netherlands, and Belgium, and repeated point prevalence surveys conducted in 28 European emergency departments (ED) between 2014 and 2016, 10% to 40% of children with infection symptoms were diagnosed with possible serious bacterial infections requiring antibiotics, compared to <5% in primary care, and the lower respiratory tract was the second most common focus.[3,4]

Bacteria have been causally implicated in about one third of CAP cases among children <5 years admitted to hospital, with co-detection of viruses and bacteria being common in symptomatic and asymptomatic young children.[5-7] Neither readily available chest radiographs nor inflammatory biomarkers differentiate which children with CAP require antibiotics.[8-10] The lack of predictive diagnostic tests to either rule out or confirm the need for antibiotics means that young children with clinical signs of CAP are likely to continue to be prescribed antibiotics, especially in hospitals. Optimizing antibiotic treatment to minimize drug exposure while achieving high rates of clinical cure would inform essential antibiotic stewardship interventions.

Amoxicillin is widely recommended as the first-line antibiotic for CAP in young children.[11-13] Randomized clinical trial evidence from low- and middle-income countries supports treatment duration of 3-5 days in mild or moderate disease.[14,15] However, the most appropriate total daily dose of oral amoxicillin treatment has not been investigated in any trial, and it is unclear whether evidence supporting 3-day treatment can be generalized from low- and middle-income countries to high-income secondary care settings with differing diagnostic criteria.[11-13] The Community-Acquired Pneumonia: a randomIsed controlled Trial (CAP-IT) aimed to evaluate whether lower dose and shorter amoxicillin treatment were non-inferior to higher dose and longer treatment, respectively, with regard to the need for antibiotic retreatment within 28 days.

Methods

Study design

This was a multicenter, randomized, blinded, placebo-controlled, 2x2 factorial, non-inferiority trial conducted in 28 hospitals in the UK and one in Ireland, comparing total daily amoxicillin dose (35-50 mg/kg or 70-90 mg/kg) and duration (3 or 7 days) for treatment of childhood CAP. The trial protocol was approved by West London & GTAC Research Ethics Committee (16/LO/0831) (eAppendix).[16] Parents or legal guardians of participating children provided written informed consent prior to any study procedures.

Participants

Children were eligible if they were aged ≥6 months, weighed 6-24 kg, were clinically diagnosed with CAP and treatment with amoxicillin monotherapy on discharge from hospital ED, observational unit or inpatient ward was planned. Consistent with British Thoracic Society guidelines, CAP was defined as (1) parent/guardian-reported cough within previous 96 hours, and (2) measured temperature ≥38°C or parent/guardian-reported fever within previous 48 hours, and (3) signs of labored/difficult breathing or focal chest sign(s) (eTable 1).[12] Enrolment took place at discharge if inclusion and exclusion criteria were met (eMethods 2). Exclusion criteria were (1) uninterrupted prior beta-lactam antibiotic treatment >48 hours or any prior non-beta-lactam treatment, (2) severe underlying chronic disease, (3) any contraindications to amoxicillin, including allergy, (4) complicated pneumonia (defined as signs of sepsis or local parenchymal/pleural complications), or (5) bilateral wheezing without focal chest signs. Information on race/ethnicity was collected based on UK Census options through participant self-identification because outcomes for acute infections and respiratory disease in the UK and US have been reported to be poorer among non-White children.[17,18]

Randomization and Blinding

A computer generated randomization list was produced by the trial statistician based on blocks of 8, containing an equal number of the 4 possible combinations of dose and duration in random order. Participants were randomized simultaneously to each of the 2 factorial randomizations in a 1:1 ratio by dispensing the next sequentially numbered set of trial drug bottles. Randomization was stratified by study site and whether or not patients had received any non-trial antibiotics in hospital before being enrolled.

Blinding was achieved by independent rebottling, packaging and labelling of 2 amoxicillin brands with trial kits assigned sequential numbers based on the randomization list and delivered ready to dispense to site pharmacies. Lower and higher drug doses were achieved by administering the same volume according to a weight-banded dosing chart (eTable 2) using 125mg/5ml and 250mg/5ml amoxicillin suspension, respectively, which were otherwise of identical appearance, smell and taste. In an effort to ensure blinding for the duration comparison, a single amoxicillin brand was used for the first 3 days followed, by either a different amoxicillin-containing suspension (of the same concentration) or a matching placebo suspension for days 4 to 7.

Procedures

Children were screened against eligibility criteria during ED or hospital admission by trained staff assessing parent/guardian-reported history and physical examination. No radiological or laboratory diagnostic tests were mandated, but results were collected if done as part of routine care. A nasopharyngeal swab for *Streptococcus pneumoniae* carriage and resistance was taken at enrolment prior to administration of study drug.

Follow-up data were collected during scheduled telephone calls 3, 7, 14, and 21 days after discharge, and by face-to-face visit (or telephone call if a visit was not possible) on day 28 and in case of unplanned reattendances or readmissions. At all follow-up contacts, information was collected on CAP symptoms, adverse events, trial medication adherence, and any non-trial antibiotic

prescriptions. Parents/guardians were provided with a diary (paper or electronic) to be completed during the first 14 days, which recorded CAP symptom data plus information on health service utilisation. At the 28-day visit, a repeat nasopharyngeal swab was collected. Primary care physicians were asked about non-trial antibiotic prescriptions if the 28-day visit was missed, provided written consent had been given.

Nasopharyngeal swabs were frozen at below -20^{o}C within 6 hours of being obtained. Samples were batched and sent to the Children's Vaccine Centre, Bristol University, for screening culture. All *S. pneumoniae* isolates were then transferred to the University of Antwerp for confirmatory analysis, and penicillin and amoxicillin susceptibility testing interpreted according to EUCAST Clinical Breakpoint Tables version 10.0 as sensitive, non-susceptible or resistant (eMethods 2).[19]

Outcomes

The primary endpoint was clinically indicated treatment with systemic antibiotics other than trial medication for a respiratory tract infection, including CAP, within 28 days of randomization. All primary endpoints were reviewed by an endpoint review committee, blinded to treatment allocation, to adjudicate whether treatment was (i) clinically indicated and (ii) prescribed for respiratory tract infection.

The secondary endpoints were (i) severity (graded as not present, slight/little, moderate, bad, severe/very bad) and duration (with the first day the symptom is reported not present defined as resolved) of 9 parent-reported CAP symptoms (fever, cough, phlegm, fast breathing, wheezing, disturbed sleep, eating/drinking less, interference with normal activity, vomiting); (ii) potential amoxicillin-related clinical adverse events (diarrhea, thrush, skin rash); (iii) adherence to trial medication (eMethods 2), and (iv) phenotypic penicillin non-susceptibility or resistance at 28 days in nasopharyngeal *S. pneumoniae* isolates (eMethods 3). The prespecified analysis also included serious adverse events (SAEs).

Sample size calculation

The trial was designed to demonstrate non-inferiority of lower dose compared to higher dose, and shorter duration compared to longer duration, in terms of the primary endpoint. The non-inferiority margin was defined as a risk difference of 8%, assessed against a 1-sided 95% CI.[20] Given a 15% antibiotic re-treatment rate based on internal pilot data, 15% loss to follow-up, and assuming no interaction between the dose and duration interventions, the sample size of 800 participants was estimated to achieve 90% power.

As it was unclear at trial initiation what the primary endpoint rate would be, data from a pre-planned internal pilot phase were reviewed by the independent data monitoring committee (eMethods 4). After 227 children were enrolled (160 from ED, 67 after inpatient stay), it was noted that disease severity at enrolment was not significantly different among children from each clinical pathway (eMethods 5) and the retreatment endpoint rate of 15% was higher than the 5% rate originally assumed. The data and safety monitoring committee, with support from the trial steering committee, recommended the following amendments: 1) joint analysis of children immediately discharged from ED and discharged after an inpatient stay (eMethods 5); 2) revision of the non-inferiority margin from 4% to 8% to be closer to the most conservative 10% noninferiority margin recommended by the Infectious Diseases Society of America for noninferiority trials in CAP with a mortality endpoint (eMethods 6). For binary clinical endpoints, a noninferiority margin of up to 20% could be acceptable per the Infectious Diseases Society of America [21]

Statistical design and analysis

The primary analysis included only participants who received trial drug, and patients were analyzed in the groups to which they were randomized. The proportion of children meeting the primary endpoint was obtained from the cumulative incidence at day 28 as estimated by Kaplan-Meier

methods accounting for loss to follow-up. The main effect of each randomization was estimated by collapsing across levels of the other randomization factor, after checking for the absence of statistical interaction between the two randomizations. Other tests for additive interaction were also prespecified for each randomization group with previous systemic antibacterial exposure.

Pre-specified sensitivity analyses included: 1) retreatment regardless of reason or indication; 2) retreatment specifically for CAP or "chest infection"; 3) for duration, considering only retreatments after 3 days from randomization. To provide support that a null result was not due to the inclusion of children with mild infection less likely to benefit from antibiotics, another pre-specified analysis was limited to children with ≥2 abnormal physiological parameters at enrolment, considered the "severe" group (eMethods 7). In addition, 2 post-hoc analyses undertaken were: 1) On-treatment analysis with non-adherence defined as taking <80% of trial medication (all trial medication including placebo, and active drug only) (eMethods 8); 2) Subgroup analysis of children who had not received antibiotics in hospital (most discharged immediately from ED), and those who had received up to 48 hours of beta-lactam treatment in hospital before enrolment (eMethods 9).

Analyses of secondary endpoints were not adjusted for multiple comparisons. Because of the potential for type 1 error due to multiple comparisons, findings for secondary endpoints and analyses should be interpreted as exploratory. Binary outcomes were compared between groups using χ^2 or Fisher exact test and logistic regression. Ordered outcomes were compared using rank tests. Duration of CAP symptoms was analyzed using time-to-event methods, restricted to children with the particular symptom at enrolment, until the first day the symptom was reported not to be present. For all Cox models the proportional-hazards assumption was tested on the basis of Schoenfeld residuals. In none of these tests was the proportionality assumption violated. For secondary end points, all significance tests were performed under the standard null hypothesis of no difference.

Analyses of primary and secondary endpoints were to be based on observed data only taking into account information across all visits, with multiple imputation to be considered if data was missing for >10% of participants.

Data were analyzed using Stata (release 15). Differences in the primary end point are presented with one-sided 95% confidence intervals for the noninferiority analyses, and differences in secondary end points are presented with 2-sided 95% confidence intervals. All statistical tests had a significance threshold of .05.

The data and safety monitoring committee provided oversight of the study and reviewed unblinded data 3 times during the trial.

Results

Between 1st February 2017 and 23rd April 2019, 2642 children were assessed for eligibility, and 824 were randomized (Figure 1). Ten children received no trial medication and were excluded from the analysis, resulting in an analysis population of 814.

Of these, 421 (52%) children were male, median (IQR) age was 2.5 years (1.6-3.7) (Table 1). At presentation, 441 (54%) were febrile, 578 (71%) had tachycardia, and 528 (65%) had tachypnea. At randomization, 591 (73%) children were discharged directly from the ED, and 223 (27%) had an inpatient stay of <48 hours (eFigure 1, eTables 3 and 4). 218 (98%) inpatients and 24 (4%) children discharged directly from ED had received beta-lactam antibiotics (100% treated for <48h; 185 (76%) <24h; eTable 5).

Follow-up data were available for 757 (93%) participants at day 3, and 716 (88%), 676 (83%) and 619 (76%) at days 7, 14 and 21, respectively. Final 28-day follow-up was face-to-face for 484 (59%) participants, and 158 (19%) families were contacted by telephone. Including additional information from family physicians on any subsequent antibiotic prescriptions (n=147), the primary endpoint was evaluable for 789 (97%) children, with the remaining 25 providing data up to the point of last contact.

Primary Outcome

For the primary outcome, 139 children received non-trial systemic antibiotic treatment by day 28, with criteria for the primary endpoint met in 100 (12.5%, 90%CI 10.7 to 14.6%) (Figure 2a, eTables 6 to 8). There was no significant interaction between randomized factorial groups (p=0.63, Figure 2a). The proportions meeting the primary endpoint were 12.6% (51/410) in the lower vs 12.4% (49/404) in the higher dose groups (difference=0.2%, 1-sided 95%CI -∞ to 4.0%, Figure 2b), and 12.5% (51/413) in the shorter vs 12.5% (49/401) in the longer duration groups (difference= 0.1%, 1-sided 95%CI -∞ to 3.9%, Figure 2c). Both comparisons satisfied the noninferiority criterion (Figure

3). There were no significant interactions between use of antibiotics in the preceding 48 hours and either dose (p=0.46) or duration randomizations (p=0.59) (eFigure 2).

For the pre-specified subgroup analysis among children with severe CAP, the primary endpoint occurred in 31/180 (17.3%) in the lower dose vs 25/188 (13.5%) in the higher dose group (difference 3.8% (1-sided 95%CI -∞ to10); P-value for interaction = 0.28) and in 28/177 (16.0%) in the 3-day group vs 28/191 (14.8%) in the 7-day group (difference 1.2% (1-sided 95% CI -∞ to -7.4); P-value for interaction = 0.82) (Figure 3).

Post-hoc on-treatment analysis of 693 children who took 80% or more doses showed non-inferiority for lower dose (lower vs higher, 9.5% vs 10.2%; difference=-0.7%, 1-sided 95%CI -∞ to 3.1%) and shorter duration (shorter vs longer, 10.5% vs 9.2%, difference= 1.3%, 1-sided 95%CI -∞ to 5.1%) (eFigures 3 and 4). In addition, in the subgroup of 591 children without prior inpatient antibiotics, the primary endpoint occurred in 11.7% in the lower dose group vs 12.8% in the higher dose group (difference= -1.5%, 1-sided 95%CI -∞ to 3.0%) and in 11.5% in the shorter duration group vs 12.9% in the longer duration group (difference= -1.4%, 1-sided 95%CI -∞ to 3.1%). Among the 223 children enrolled following inpatient antibiotic treatment, the corresponding rates were 15.3% in the lower dose group vs 11.5% in the higher dose group (difference= 3.7%, 1-sided 95%CI -∞ to 11.4%) and 15.2% in the shorter duration group vs 11.3% in the longer duration group (difference= 3.9%, 1-sided 95%CI -∞ to 11.5%) (eFigures 5 to 8); neither comparison met the noninferiority criterion. Post-hoc interaction tests for these subgroups were not statistically significant (p=0.37 with dose randomization; p=0.32 with duration randomization).

Secondary Outcomes

Resolution of vomiting, fever, fast breathing, wheeze, interference with normal activity, reduced appetite and phlegm production was not significantly different between groups by dose or duration.

Cough persisted for longer in the shorter vs longer duration groups (median, 12d vs 10d; HR 1.2 [90% CI 1.0 to 1.4]; p=0.04), as did sleep disturbed by cough (median 4d vs 4d; HR 1.2 [90% CI 1.0 to 1.3]; p=0.03, eFigures 9 and 11). There was no significant association between dose or duration of amoxicillin and severity of cough symptoms (eFigures 10 and 12).

A baseline nasopharyngeal sample was obtained in 647 participants, of which 272 (42%) were colonized by *S. pneumoniae* with penicillin non-susceptibility identified in 46 (16.9%) samples. At the final visit, 437 children provided a sample, of which 129 (29.5%) were positive for *S. pneumoniae* and penicillin non-susceptibility was identified in 21 samples. No penicillin-resistant pneumococci were identified, and there was no significant difference in day 28 pneumococcal carriage or penicillin non-susceptibility according to the dose or duration of amoxicillin (Table 3 and eTables 11-14).

Adverse Events

Of potentially amoxicillin-related clinical adverse events, diarrhoea was reported in 345 (44%) children after baseline, skin rash in 193 (24%), and oral thrush in 57 (7%). Skin rash occurred in 106 (27%) children allocated to longer compared with 87 (22%) children allocated to shorter treatment (22%) (Table 2 and eTable 9). Active trial medication was discontinued early by 47 (6%) participants, while 112 (14%) took fewer doses or a lower volume than prescribed (Table 2, eTable 9). The main reasons for early discontinuation were clinical deterioration (n=23), gagging/spitting out (n=7), adverse events (n=6), and clinical improvement (n=3). Children randomized to 3 days of amoxicillin were more likely to complete their full treatment course (98% vs. 91%).

In total, 43 (5%) children experienced a SAE; all were hospitalizations and most (37, 86%) were due to respiratory illness (Table 2 and eTable 9). One SAE (hospital admission for intravenous treatment

because of vomiting on day 2, higher dose, shorter duration) was classified as related to trial medication. There were no deaths.

Discussion

In this pragmatic trial evaluating dose and duration of amoxicillin for treatment of childhood CAP on discharge from ED or an inpatient ward, antibiotic retreatment rates for respiratory tract infection within 4 weeks were noninferior among those randomized to lower versus higher dose amoxicillin, and among those randomized to 3-day versus 7-day course of treatment.

Noninferiority was confirmed in all pre-specified sensitivity analyses. For the prespecified subgroup of children with severe disease at baseline, the confidence interval was within the noninferiority margin for the duration comparison; however for the dose comparison it did not meet the noninferiority criterion, although the test for interaction by CAP severity at baseline was not statistically significant. The results were consistent with noninferiority in all post-hoc on-treatment analyses, including only children taking >80% of trial drug. In a post-hoc subgroup analysis, separating children discharged from ED and those requiring inpatient hospitalization, the confidence interval was within the noninferiority margin only for the larger ED group; it did not meet the noninferiority criterion for the children discharged after inpatient treatment, although the test for interaction by previous receipt of antibiotics were not statistically significant.

There are few trials that have compared different durations of the same antibiotic for treatment of CAP in adults or children, and none to our knowledge have compared both dose and duration in the same trial for childhood CAP.[15,22-28] The recently completed Canadian SAFER trial comparing 5-day with 10-day high-dose oral amoxicillin treatment for childhood CAP on discharge from ED, found comparable clinical cure rates in both groups (89% in 5-day and 84% in 10-day group) at 2-3 weeks.[27] Similarly, 3-day beta-lactam therapy was recently reported to be non-inferior to 8-day treatment in adults hospitalized with CAP in non-critical care wards.[28] As in this trial, retreatment with non-trial antibiotics was part of the composite primary endpoint in the SAFER trial and provides a reasonable and important endpoint for high resource settings where mortality and critical illness from childhood CAP are low.[29] Retreatment rates in both the current trial and SAFER are

similar to the 10-11% previously observed for amoxicillin-treated lower respiratory tract infection in UK general practice.[27,30,31]

In this trial, amoxicillin was prescribed in 2 instead of 3 divided daily doses, an approach endorsed by patient representatives in the design phase and consistent with international guidance.[11,32-34] The trial findings suggest that a lower total daily amoxicillin dose may be used in twice daily dosing regimens, especially when prevalence of penicillin-resistant pneumococci is low. Observations of saturability of amoxicillin gut absorption limiting the achievement of desired amoxicillin exposure when using high oral doses at low administration frequency require further investigation.[35]

Limitations

This trial has several limitations. First, it is not possible to unequivocally identify children likely to benefit from antibiotics. Biomarkers and chest radiographs have been shown to have questionable discriminatory ability and are discouraged by some guidelines.[8-12] Although children with a mixed picture of CAP and obstructive airway disease were included, those with wheezing but without clinical signs of CAP were not included, and only 16% children received bronchodilators or steroids, compared to the 48% bronchodilator use observed in the most recent UK pediatric pneumonia audit.[36] Children commonly show a mixed pattern of disease (bacterial, viral with/without airway obstruction), and some antibiotic retreatment may have been for self-limiting disease, unlikely to respond to antibiotics.

Second, the trial findings do not inform total treatment duration for children initially admitted to hospital. Optimal total treatment duration may differ for children requiring prolonged intravenous treatment as inpatients. Only 13% of children receiving inpatient treatment in this trial received antibiotics intravenously, consistent with UK recommendations.[12]

Third, the trial was not powered to investigate noninferiority of lower dose and shorter duration of home-based oral amoxicillin treatment in the subgroup of children discharged after an inpatient stay,

and the tests for interaction may have been similarly underpowered. Fourth these findings should not be considered generalizable to children with very severe disease including those with underlying co-morbidities who may benefit from higher dose or longer treatment.

Conclusion

Among children with community-acquired pneumonia discharged from an emergency department, observational unit, or ward (within 48 hours), outpatient treatment with oral amoxicillin at 35-50 mg/kg/day was noninferior to 70-90 mg/kg/day, and for 3 days was noninferior to 7 days with regard to the need for further antibiotic retreatment. However, the underlying disease severity, treatment setting and antibiotics received prior to discharge, and acceptability of the noninferiority margin should be considered when interpreting the findings.

Contributors

JAB, DD, DMG and MS designed and managed the study with input from WS, MDL, SB and KS. MDL, DR, KS, SB and NN contributed to on-site implementation of the study and data collection and management. AF, JJRR and SMK carried out microbiological analyses. WS and DD analyzed the data with JAB, DMG, MS and MDL contributing to data interpretation. JAB and WS wrote the first draft, and DD, DMG and MS revised the manuscript. All authors read and approved the final version.

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JAB and WS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Sharing Statement: See supplement.

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Figure legends

Figure 1: Patient recruitment, randomization, and follow-up in the CAP-IT trial

°inpatient stay >48 hours, treated with non-beta-lactam antibiotics as inpatients; * follow-up included up to time of withdrawal

Figure 2: Kaplan-Meier curves of time to experiencing the primary endpoint for (a) the four separate groups, (b) the amoxicillin dose randomization, and (c) the amoxicillin duration randomization.

The primary endpoint is clinically indicated treatment with systemic antibiotics other than trial medication for a respiratory tract infection within 4 weeks of randomization. Median observation time not reported since > 75% of participants were observed for the 28-day entire period.

Figure 3: Sensitivity and subgroup analyses for the primary endpoint for (a) the amoxicillin dose and (b) duration randomizations.

The primary analysis as well as three pre-specified analyses are shown for both randomizations: including all systemic antibacterial retreatments, only retreatments for CAP or chest infection and by severe CAP subgroups. In addition, a post hoc subgroup analysis by prior inpatient antibiotic exposure is shown. A sensitivity analysis including only retreatments after day 3 is shown for the duration randomization. One-sided 95% confidence intervals are shown with the lower bound extending to -100%.

551 **Tables**

552

553 **Table 1: Participant characteristics at baseline or presentation (for inpatients)**

		Amoxicillin dosing and duration			
		Lower + shorter (n=208)	**Lower + longer** (n=202)	**Higher + shorter** (n=205)	**Higher + longer** (n=199)
Demographics	Age[a] (y)	2.5 (1.7, 3.7)	2.6 (1.6, 3.9)	2.5 (1.7, 3.8)	2.3 (1.4, 3.6)
	Male sex	110 (53%)	100 (50%)	107 (52%)	104 (52%)
	Female sex	98 (47%)	102 (50%)	98 (48%)	95 (48%)
	Race & Ethnicity				
	White	139 (67%)	136 (67%)	144 (70%)	135 (68%)
	Asian or British Asian	32 (15%)	23 (11%)	21 (10%)	30 (15%)
	Black or Black British	20 (10%)	20 (10%)	20 (10%)	16 (8%)
	Multiracial	15 (7%)	17 (8%)	14 (7%)	14 (7%)
	Other	2 (1%)	6 (3%)	6 (3%)	4 (2%)
Medical history	Asthma or inhaler use within past month	54 (26%)	65 (32%)	71 (35%)	65 (33%)
	Allergy or eczema	52 (25%)	63 (31%)	56 (27%)	58 (29%)
	Prematurity	26 (13%)	17 (8%)	25 (12%)	18 (9%)
	Other underlying disease	16 (8%)	21 (10%)	5 (2%)	14 (7%)
	Routine vaccinations				
	Yes	198 (95%)	190 (94%)	196 (96%)	189 (95%)
	No	8 (4%)	6 (3%)	7 (3%)	5 (3%)
	Unknown	2 (1%)	6 (3%)	2 (1%)	5 (3%)
History of current complaint	Duration of cough[a] (d)	4 (2, 7)	4 (2, 6)	4 (3, 7)	4 (2, 7)
	Duration of fever[a] (d)	2 (2, 4)	3 (1, 4)	3 (2, 4)	2 (1, 4)
	Systemic antibiotics in last 3 months	30 (14%)	34 (17%)	36 (18%)	29 (15%)
	Systemic antibiotics in last 48 hrs	61 (29%)	58 (29%)	62 (30%)	61 (31%)
	<12 hrs	34 (56%)	33 (57%)	34 (55%)	32 (52%)
	12 - <24 hrs	15 (25%)	12 (21%)	18 (29%)	15 (25%)
	≥24 hrs	12 (19%)	13 (23%)	10 (16%)	14 (23%)
Clinical examination	Weight[a] (kg)	13.9 (11.5, 16.5)	13.4 (11.2, 17.0)	13.8 (11.5, 16.4)	13.0 (10.7, 15.9)
	Temperature[a] (°C)	38.2 (37.3, 38.8)	38.0 (37.2, 38.9)	37.9 (37.0, 38.6)	38.1 (37.4, 38.7)
	Abnormal temperature	121 (58%)	106 (52%)	100 (49%)	114 (57%)
	Heart rate[a] (beats/min)	146 (133, 160)	146 (130, 161)	140 (129, 153)	146 (131, 162)
	Abnormal heart rate	154 (74%)	153 (76%)	128 (62%)	143 (72%)
	Respiratory rate[a] (breaths/min)	38 (30, 44)	37 (30, 44)	36 (30, 42)	40 (32, 46)
	Abnormal respiratory rate	138 (66%)	132 (65%)	124 (61%)	134 (68%)
	Oxygen saturation[a] (%)	96 (95, 98)	96 (95, 98)	97 (95, 98)	96 (94, 98)
	Abnormal oxygen saturation	7 (3%)	11 (5%)	11 (5%)	14 (7%)
	Nasal flaring	18 (9%)	15 (7%)	17 (8%)	25 (13%)
	Chest retractions	117 (57%)	122 (60%)	122 (60%)	122 (61%)
	Pallor	48 (23%)	34 (17%)	45 (22%)	42 (21%)
	Dullness to percussion Absent	105 (85%)	89 (86%)	93 (87%)	93 (85%)
	Unilateral	18 (15%)	14 (14%)	13 (12%)	14 (13%)
	Bilateral	0 (0%)	0 (0%)	1 (1%)	2 (2%)
	Bronchial breathing Absent	146 (83%)	137 (80%)	130 (82%)	133 (82%)
	Unilateral	23 (13%)	30 (18%)	26 (16%)	24 (15%)
	Bilateral	6 (3%)	4 (2%)	2 (1%)	5 (3%)
	Reduced breath sounds Absent	108 (54%)	94 (49%)	94 (48%)	93 (50%)
	Unilateral	82 (41%)	86 (45%)	92 (47%)	76 (41%)
	Bilateral	10 (5%)	10 (5%)	10 (5%)	16 (9%)

	Crackles/crepitations	Absent	37 (18%)	32 (16%)	34 (17%)	31 (16%)
		Unilateral	147 (72%)	140 (70%)	143 (72%)	132 (68%)
		Bilateral	20 (10%)	28 (14%)	22 (11%)	30 (16%)

Note: Results are number (%) unless median (IQR)[a] indicated. Abnormal parameters: Temperature ≥ 38°C; Respiratory rate: >37/min for age 1-2 years; >28/min for age ≥3 years; Heart rate: >140/min for age 1-2 years; >120/min for age ≥3 years; Oxygen saturation: <92%. For race and ethnicity, other includes Middle Eastern/North African (n=12), Latin American (n=3) and children with missing data (n=3).

Table 2: Adherence and adverse events in lower (35 to 50 mg/kg per day) and higher (70 to 90 mg/kg per day) dose and shorter (3-day) and longer (7-day) duration groups

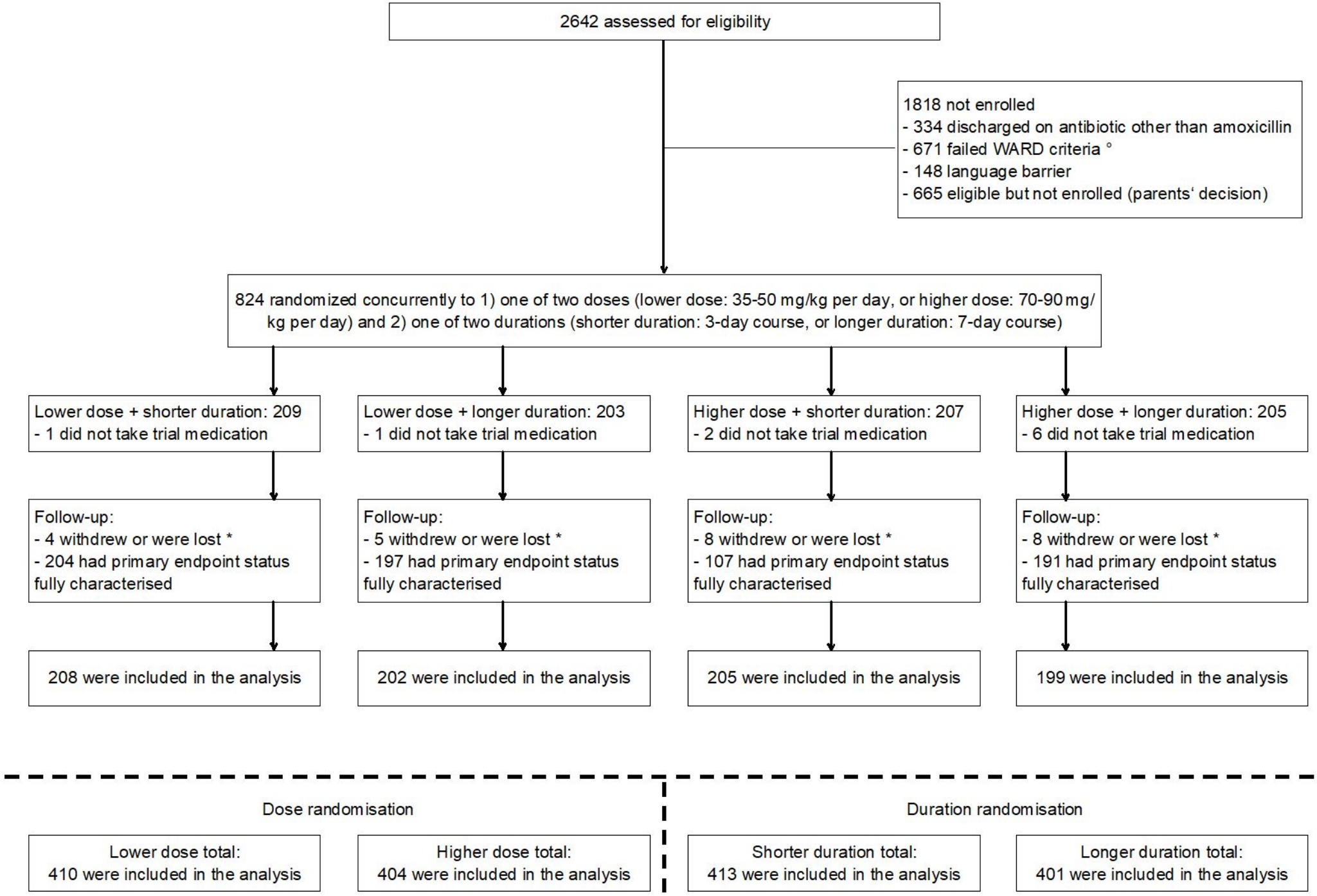
	Amoxicillin dose				Amoxicillin duration			
Outcome	**Lower** (n=410)	**Higher** (n=404)	**Difference (95% CI)**	**p value**	**Shorter** (n=413)	**Longer** (n=401)	**Difference (95% CI)**	**p value**
Adherence: complete course taken								
All treatment [a]	355 (87%)	366 (91%)	-4% (-8 to -0%)	.07	358 (87%)	363 (91%)	-4% (-8 to 1%)	.09
Active treatment only [b]	383 (93%)	384 (95%)	-2% (-5 to 2%)	.32	404 (98%)	363 (91%)	7% (4 to 10%)	<.001
Adherence: all doses taken and all volumes as prescribed								
All treatment [a]	306 (75%)	309 (76%)	-2% (-8 to 4%)	.54	300 (73%)	315 (79%)	-6% (-12 to -0%)	.05
Active treatment only [b]	352 (86%)	350 (87%)	-1% (-6 to 4%)	.75	387 (94%)	315 (79%)	15% (11 to 20%)	<.001
Clinical possibly drug-related adverse events post enrolment								
Diarrhoea	168 (42%)	177 (45%)	-4% (-10 to 3%)	.31	187 (46%)	158 (41%)	6% (-1 to 12%)	.11
Oral thrush	27 (7%)	30 (8%)	-1% (-5 to 3%)	.60	25 (6%)	32 (8%)	-2% (-6 to 2%)	.26
Rash	94 (23%)	99 (25%)	-2% (-8 to 4%)	.52	87 (22%)	106 (27%)	-6% (-12 to -0%)	.06
Serious adverse event, any [c]	23 (6%)	20 (5%)	1% (-2 to 4%)	.67	25 (6%)	18 (4%)	2% (-2 to 5%)	.32

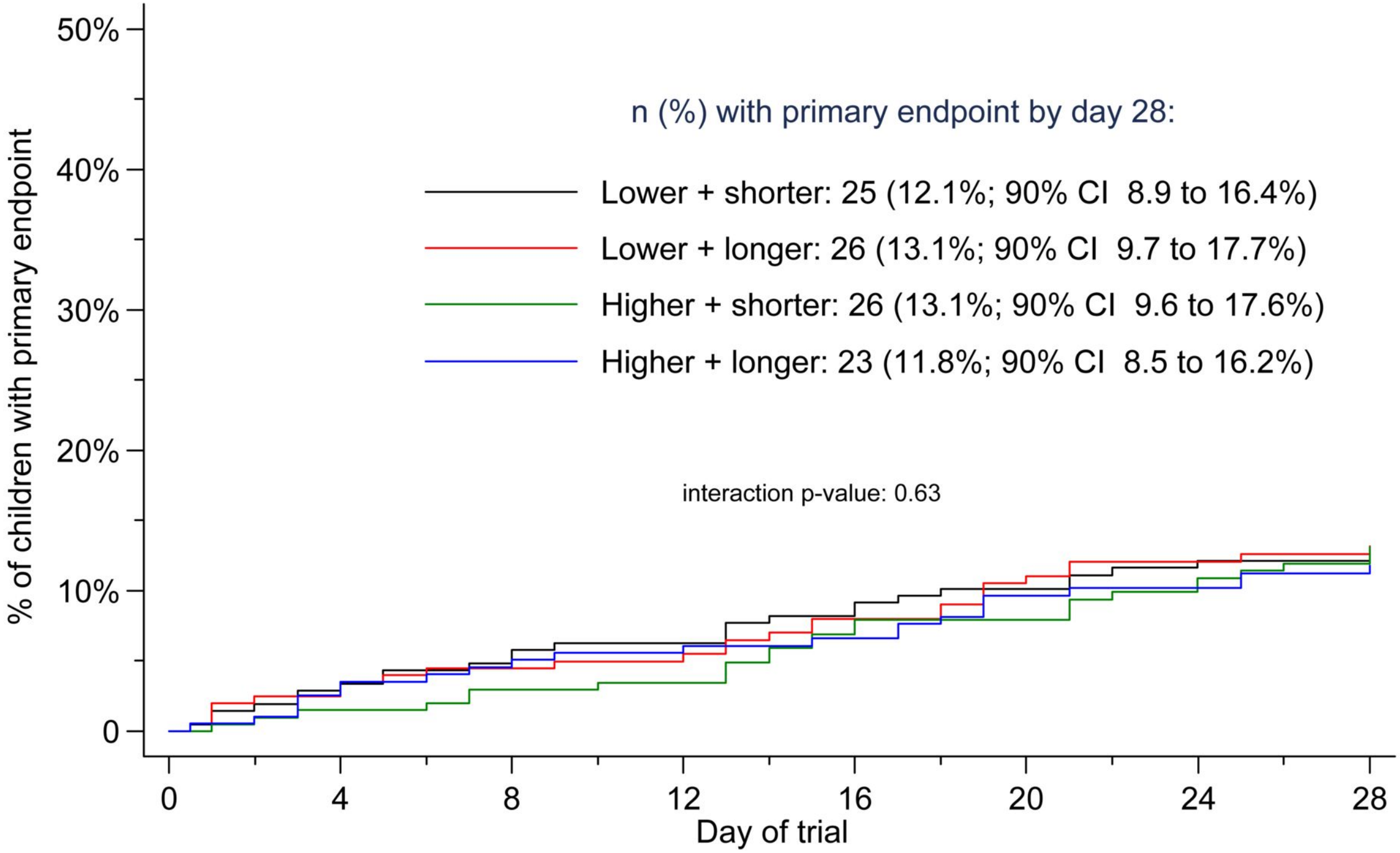
Note: courses were considered complete when trial drug was been taken on all 7 days; [a]including non-adherence to placebo; [b]ignoring non-adherence to placebo; [c]No participant had more than one SAE, all SAEs were hospitalizations (most for respiratory distress), no deaths. The data stratified by randomization groups can be found in eTable 10.

Table 3: *S. pneumoniae* and antimicrobial resistance on day 28 in lower (35 to 50 mg/kg per day) and higher (70 to 90 mg/kg per day) dose and shorter (3-day) and longer (7-day) duration groups

	Amoxicillin dose				Amoxicillin duration			
Outcome	**Lower** (n=410)	**Higher** (n=404)	**Difference (95% CI)**	**p value**	**Shorter** (n=413)	**Longer** (n=401)	**Difference (95% CI)**	**p value**
Culture sample available	224/410 (55%)	213/404 (53%)	2% (-5 to 9%)	.58	205/413 (50%)	232/401 (58%)	-8% (-15 to -1%)	.02
S. pneumoniae colonization	66/224 (29%)	63/213 (30%)	0% (-9 to 8%)	.98	65/205 (32%)	64/232 (28%)	4% (-4 to 13%)	.35
Penicillin MIC [a]								
0.016	18 (27%)	10 (16%)		.49	15 (23%)	13 (20%)		.56
0.032	35 (53%)	44 (70%)			36 (55%)	43 (67%)		
0.064	1 (2%)	0			0	1 (2%)		
0.125	4 (6%)	1 (2%)			3 (5%)	2 (3%)		
0.25	6 (9%)	5 (8%)			8 (12%)	3 (5%)		
0.5	0	1 (2%)			1 (2%)	0		
1	2 (3%)	1 (2%)			1 (2%)	2 (3%)		
2	0	1 (2%)			1 (2%)	0		
Penicillin-non-susceptibility [b]								
a) including all samples	12/224 (5%)	9/213 (4%)	1% (-3 to 5%)	.58	14/205 (7%)	7/232 (3%)	4% (-0 to 8%)	.06
b) in positive samples	12/66 (18%)	9/63 (14%)	4% (-9 to 17%)	.55	14/65 (22%)	7/64 (11%)	11% (-2 to 23%)	.10
Amoxicillin MIC [a]								
0.016	42 (64%)	43 (68%)		.61	40 (62%)	45 (70%)		.21
0.032	14 (21%)	11 (17%)			12 (18%)	13 (20%)		
0.064	4 (6%)	5 (8%)			7 (11%)	2 (3%)		
0.125	2 (3%)	0			1 (2%)	1 (2%)		
0.25	2 (3%)	2 (3%)			3 (5%)	1 (2%)		
0.5	0	0			0	0		
1	2 (3%)	1 (2%)			1 (2%)	2 (3%)		
2	0	1 (2%)			1 (2%)	0		
Amoxicillin-resistance/non-susceptibility [c]								
a) including all samples	2/224 (1%)	2/213 (1%)	0% (-2 to 2%)	>.99	2/205 (1%)	2/232 (1%)	0% (-2 to 2%)	>.99
b) in positive samples	2/66 (3%)	2/63 (3%)	0% (-6 to 6%)	>.99	2/65 (3%)	2/64 (3%)	0% (-6 to 6%)	>.99

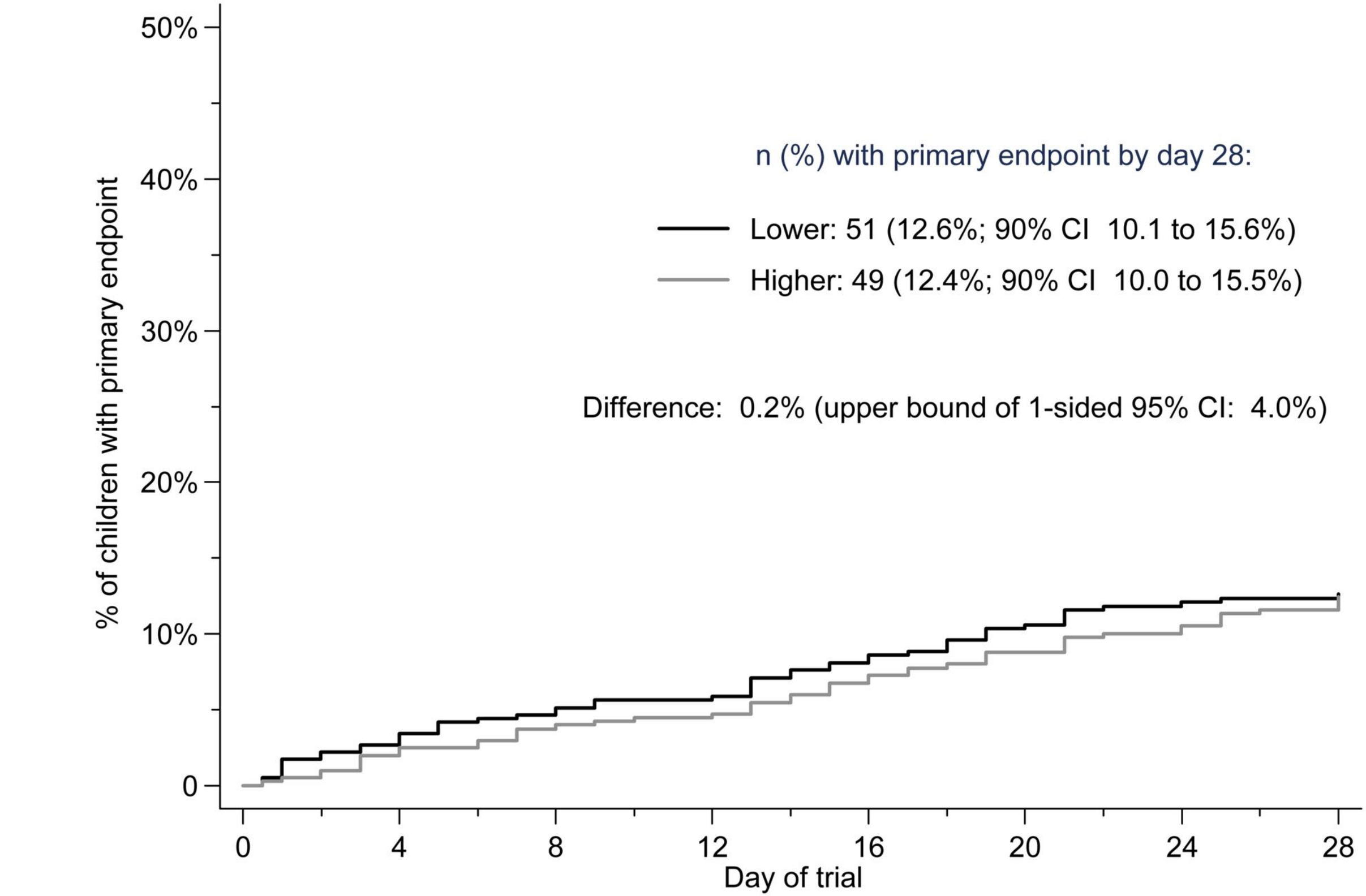
570 Notes: [a] minimal inhibitory concentration. [b] Breakpoints for penicillin: MIC ≤ 0.064 mg/L = sensitive; MIC 0.125 to 2 mg/L = non-susceptible; MIC > 2
571 mg/L = resistant. [c] Breakpoints for amoxicillin: MIC ≤ 0.5 mg/L = sensitive; MIC >0.5 - 1 mg/L = non-susceptible; MIC > 1 mg/L = resistant. The data
572 stratified by randomization groups can be found in eTable 11.


2642 assessed for eligibility
1818 not enrolled
- 334 discharged on antibiotic other than amoxicillin
- 671 failed WARD criteria °
- 148 language barrier
- 665 eligible but not enrolled (parents' decision)
824 randomized concurrently to 1) one of two doses (lower dose: 35-50 mg/kg per day, or higher dose: 70-90 mg/kg per day) and 2) one of two durations (shorter duration: 3-day course, or longer duration: 7-day course)
Lower dose + shorter duration: 209
- 1 did not take trial medication
Lower dose + longer duration: 203
- 1 did not take trial medication
Higher dose + shorter duration: 207
- 2 did not take trial medication
Higher dose + longer duration: 205
- 6 did not take trial medication
Follow-up:
- 4 withdrew or were lost *
- 204 had primary endpoint status fully characterised
Follow-up:
- 5 withdrew or were lost *
- 197 had primary endpoint status fully characterised
Follow-up:
- 8 withdrew or were lost *
- 107 had primary endpoint status fully characterised
Follow-up:
- 8 withdrew or were lost *
- 191 had primary endpoint status fully characterised
208 were included in the analysis
202 were included in the analysis
205 were included in the analysis
199 were included in the analysis
Dose randomisation
Lower dose total:
410 were included in the analysis
Higher dose total:
404 were included in the analysis
Duration randomisation
Shorter duration total:
413 were included in the analysis
Longer duration total:
401 were included in the analysis



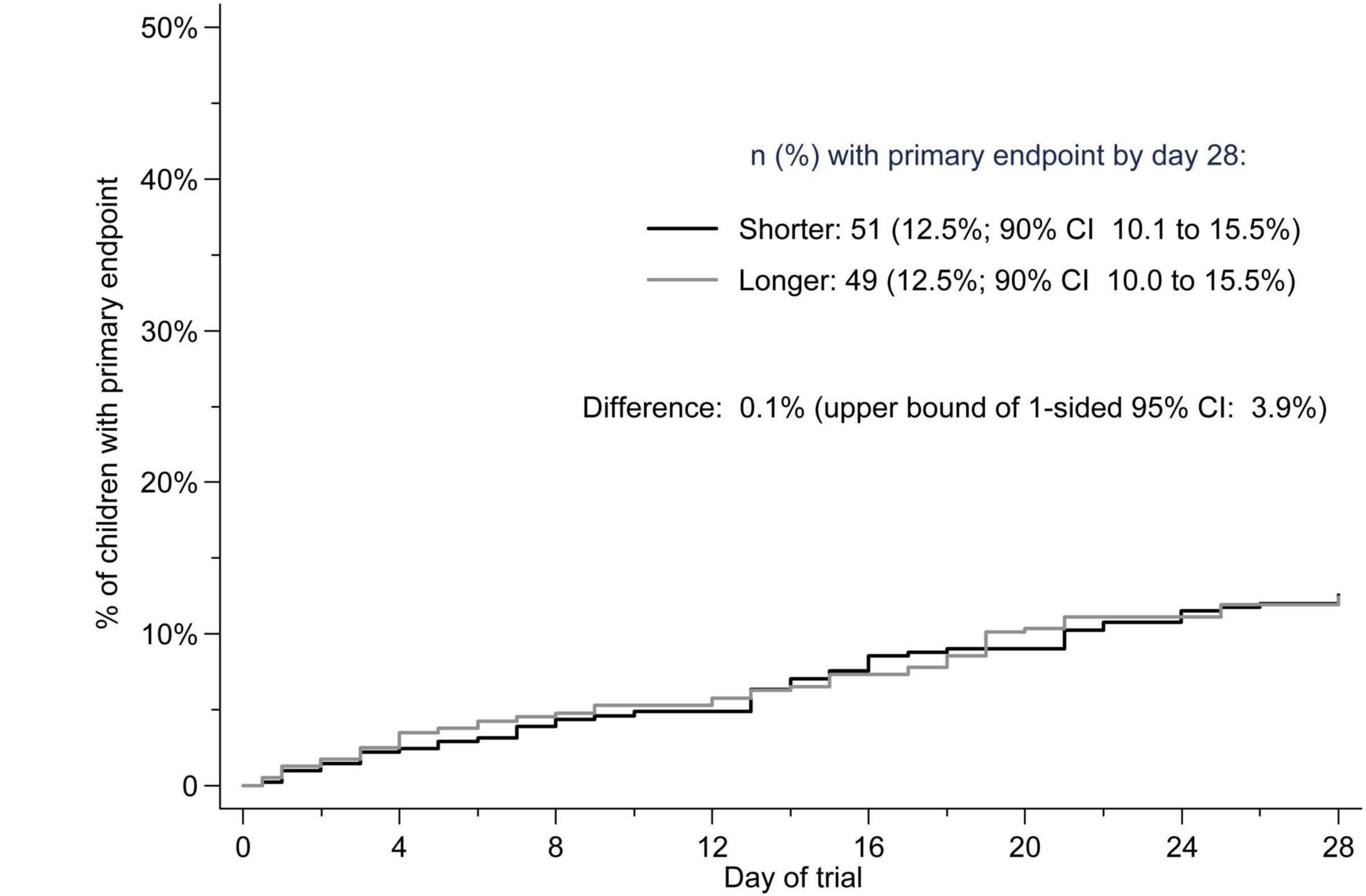
Number at risk

Lower + shorter	208	202	196	193	189	185	180	166
Lower + longer	202	196	191	189	181	176	173	154
Higher + shorter	205	202	198	196	187	185	177	157
Higher + longer	199	193	187	185	182	176	171	154



Number at risk

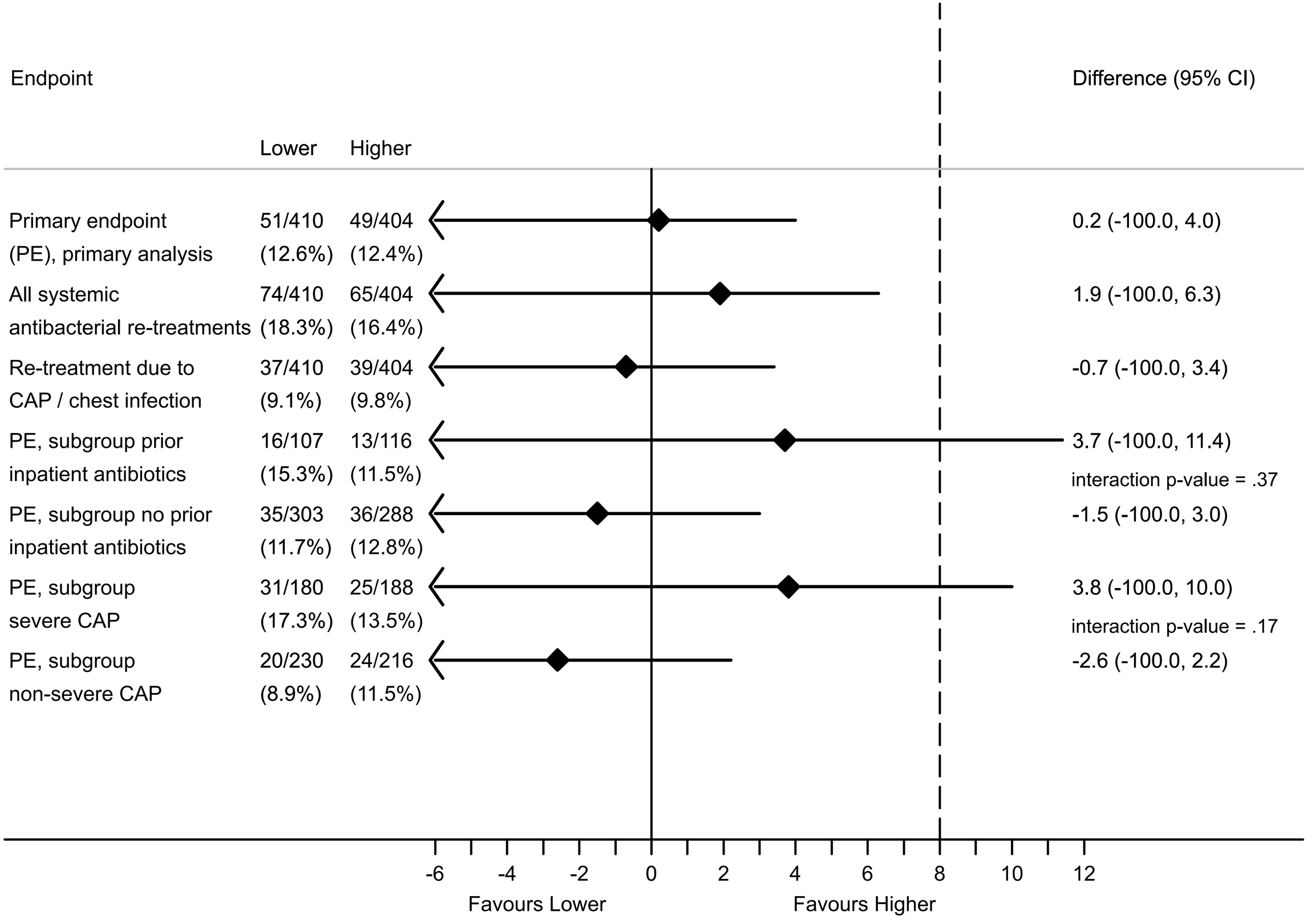
Lower	410	398	387	382	370	361	353	320
Higher	404	395	385	381	369	361	348	311



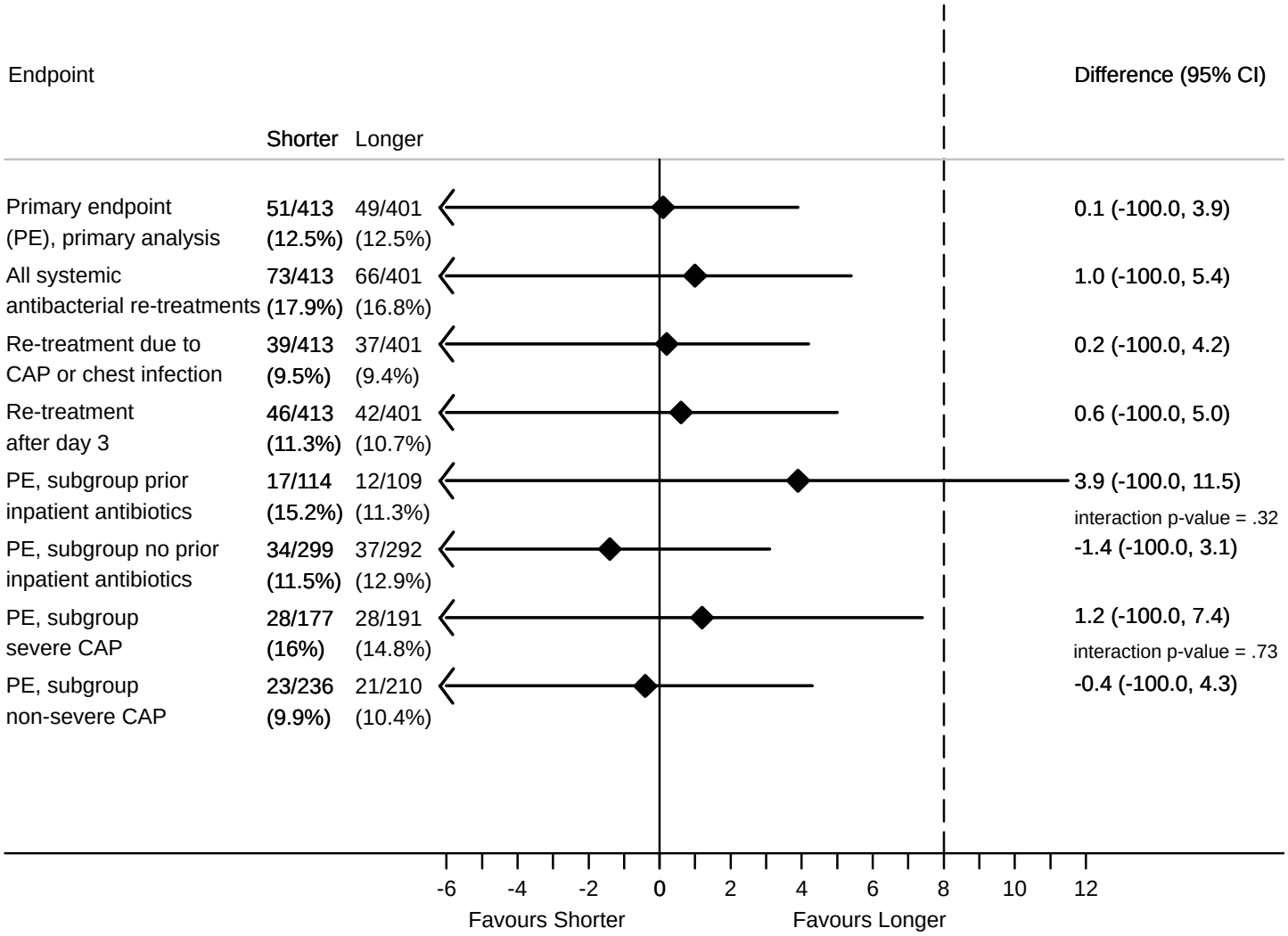
Number at risk

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

Endpoint	Lower	Higher	Difference (95% CI)
Primary endpoint (PE), primary analysis	51/410 (12.6%)	49/404 (12.4%)	0.2 (-100.0, 4.0)
All systemic antibacterial re-treatments	74/410 (18.3%)	65/404 (16.4%)	1.9 (-100.0, 6.3)
Re-treatment due to CAP / chest infection	37/410 (9.1%)	39/404 (9.8%)	-0.7 (-100.0, 3.4)
PE, subgroup prior inpatient antibiotics	16/107 (15.3%)	13/116 (11.5%)	3.7 (-100.0, 11.4)
			interaction p-value = .37
PE, subgroup no prior inpatient antibiotics	35/303 (11.7%)	36/288 (12.8%)	-1.5 (-100.0, 3.0)
PE, subgroup severe CAP	31/180 (17.3%)	25/188 (13.5%)	3.8 (-100.0, 10.0)
			interaction p-value = .17
PE, subgroup non-severe CAP	20/230 (8.9%)	24/216 (11.5%)	-2.6 (-100.0, 2.2)



Difference in proportions of re-treatment by day 28 for dose comparison (%, 1-sided 95% CI)



Difference in proportions of re-treatment by day 28 for duration comparison (%, 1-sided 95% CI)