Supplemental Online Content

Bielicki JA, Stöhr W, Barratt S, et al. 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. *JAMA*. doi: 10.1001/jama.2021.17843

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

eTable 1: Features defined as indicating presence of complicated pneumonia

CAP COMPLICATED BY SEPSIS	**CAP WITH SEVERE RESPIRATORY FAILURE**	**CAP WITH LOCAL COMPLICATIONS**
Presence of shock requiring >20ml/kg fluid resuscitation Hypotension as defined by Advanced Paediatric Life Support/European Paediatric Life Support guidelines	Altered mental state (Glasgow Coma Score<14 or AVPU scale <A) Requirement for invasive ventilation or non-invasive ventilatory support	Empyema Pleural effusion Pneumothorax Pulmonary abscess Other complications involving the pleural or pulmonary space
Paediatric intensive care unit admission (direct)		

eMethods 1: Full inclusion and exclusion criteria

CAP-IT recruited children via 2 different pathways:

1. PED group: children who are recruited in the Paediatric Emergency Department (PED) or Paediatric Assessment Unit (PAU). Children in this group will be treated at home with amoxicillin without receiving any in-hospital antibiotics. These children will be entered into the trial either prior to receiving any antibiotic prescription OR after ≤48 hours uninterrupted oral beta-lactam treatment in the community.
2. WARD group: children who are recruited from in-hospital paediatric hospital wards or paediatric assessment units (PAUs) following in-hospital treatment with beta-lactam antibiotics. Children in this group will receive ≤48 hours total treatment with any beta-lactam antibiotic prior to entering the trial. Treatment may start in the community before in-hospital treatment, provided treatment is uninterrupted.

PED Inclusion criteria

1. Age greater than 6 months and weighing 6 - 24kg
2. Clinical diagnosis of CAP at presentation to PED as defined by **all** of the following:
   - Presence of cough (reported by parents/guardians within 96 hours prior to presentation) AND
   - Temperature ≥38^{o}C measured by any method OR parent-reported fever within 48 hours prior to presentation AND
   - Signs of laboured/difficult breathing or focal chest signs at presentation in the PED (i.e. one or more of the following):
     a. Nasal flaring
     b. Chest retractions
     c. Abdominal breathing
     d. Focal dullness to percussion
     e. Focal reduced breath sounds
     f. Crackles with asymmetry
     g. Lobar pneumonia on chest X-ray (if obtained)
3. Prior antibiotic treatment:
   - Not on systemic antibiotic treatment at presentation OR
   - Treated in the community as an outpatient with uninterrupted oral beta-lactam antibiotics for ≤48 hours
4. Decision to treat with oral amoxicillin for CAP on discharge from hospital
5. Parent/guardian willing to accept all possible randomised allocations
6. Available for follow up for the entire study period, parent/guardian willing to be contacted by telephone at day 4, weeks 1, 2 and 3, and attend a face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Informed consent form for trial participation signed by parent/guardian.

PED Exclusion criteria

1. Severe underlying chronic disease with an increased risk of developing complicated CAP including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy

3. Any other known contra-indication to amoxicillin
4. Need for systemic treatment with an antibiotic other than amoxicillin on discharge from hospital
5. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
6. Complicated pneumonia (see below)
7. Receipt of initial antibiotic treatment in hospital in PAU or on the ward
8. Parents/guardians unlikely to reliably complete the diary because of significant language barriers.

WARD Inclusion criteria

1. Age greater than 6 months and weighing 6 - 24kg.
2. Clinical diagnosis of CAP at presentation to hospital as defined by **all** of the following:
    - Presence of cough (reported by parents/guardians within 96 hours prior to presentation) AND;
    - Temperature ≥38ºC measured by any method OR likely fever within 48 hours prior to presentation AND;
    - Signs of laboured/difficult breathing or focal chest signs (i.e. 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 (if obtained)
3. Prior antibiotic treatment including doses administered in hospital:
    - Treated in-hospital only with any oral or intravenous beta-lactam for ≤48 hours after admission
    - Treated initially in the community and subsequently in hospital with any oral or intravenous beta-lactam, without interruption, for ≤48 hours in total
4. Decision to further treat with oral amoxicillin for CAP on discharge from hospital
5. Child is considered fit for discharge at time of randomisation
6. Available for follow-up for the entire study period, parent/guardian willing to be contacted by telephone at weeks 1, 2 and 3 and attend face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Parent/guardian willing to accept all possible randomised allocations
8. Informed consent for trial participation signed by a parent/guardian.

WARD Exclusion criteria

1. Severe underlying chronic disease with an increased risk of complicated CAP including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to taking amoxicillin
4. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
5. Complicated pneumonia (see below)
6. Receipt of antibiotic other than a beta-lactam during admission
7. If treated in the community prior to admission, receipt of a non-beta-lactam antibiotic in the community at presentation
8. Clinically relevant positive blood culture (i.e. positive blood culture and clinical decision to prolong intravenous treatment for more than 48 hours or inappropriate to switch to amoxicillin therapy)
9. Receipt of >48 hours oral or intravenous antibiotic treatment in total
10. Decision to treat with oral antibiotic other than amoxicillin on discharge from hospital
11. Parents/guardians unlikely to reliably complete the diary because of significant language barriers.

eTable 2: Weight bands for dosing of trial medication

WEIGHT BAND	WEIGHT RANGE	MLS PER DAY	MLS PER DOSE (BID)
1	<6.5kg	9	4.5
2	6.5-<8.5	12	6
3	8.5-<10.5	15	7.5
4	10.5-<13.5	19	9.5
5	13.5-<17kg	24	12
6	17-<21kg	30	15
7	21-24kg	33	16.5

Note: body weight in kg.

eMethods 2: Details of adherence assessment

Data on IMP adherence were elicited during follow-up calls and visits, including 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.

eMethods 3: Details of microbiological analysis

At Children's Vaccine Centre (Bristol University) screening cultures for *S. pneumoniae* were performed by plating samples onto streptococcal selective agar COBA plates and incubation at 37°C and 5% CO2. Plates were examined at 24 and 48 hours and suspected alpha-haemolytic colonies confirmed by inhibition on optochin disc and solubility on bile salts. *S. pneumoniae* isolates received by the University of Antwerp underwent phenotypic penicillin-susceptibility testing by microbroth dilution across a dilution range for penicillin of 0.016 to 16 mg/L with interpretation according to EUCAST Clinical Breakpoint Tables v. 10.0. The breakpoints for S. pneumoniae for infections other than meningitis were used as follows:

a) Sensitive: minimal inhibitory concentration (MIC) ≤ 0.064 mg/L
b) Intermediate: considered penicillin non-susceptible, MIC 0.125 to 2 mg/L
c) Resistant: considered penicillin-resistant, MIC > 2 mg/L

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.

eMethods 4: Details of main protocol amendment

- Joint analysis of children presenting and immediately discharged from the emergency department (PED) and children discharged after an inpatient stay of <48 hours (WARD): 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.
- Introduction of a blinded Endpoint Review Committee for adjudication of primary endpoints: Following the pilot phase with a much high primary endpoint rate than originally assumed, the primary endpoint was clarified to guard against the possibility of bias towards the null from a high rate of antibiotic re-prescribing during follow-up unrelated to the target outcome and trial randomisations. A blinded Endpoint Review Committee (ERC) was set up to adjudicate on reported primary endpoints to identify "ERC-adjudicated clinically indicated non-IMP antibiotic

prescribed for respiratory tract infection (including CAP)". The ERC included four independent clinician members (including the independent chair) and reviewed narrative summaries for all cases with non-trial systemic antibiotic prescriptions to identify the reason for prescribing (RTI or other). For RTI prescriptions, the ERC also assessed the likelihood that the retreatment was clinically indicated.

- Revision of the non-inferiority margin from 4% to 8%: Key assumptions in the original sample size calculation were (1) primary endpoint event rate of 5%, (2) non-inferiority (NI) margin of 4% based on 1-sided 95% CI, (3) power of 90% and (4) 15% loss to follow-up. The serious underestimation of the primary endpoint rate resulted in the original NI margin to be considered overly stringent with 8% clinically acceptable. Given the actual estimated primary endpoint rate from the pilot phase of 15%, the 8% NI margin was more conservative on a proportionate scale (8/15, 53%; 4/5, 80%) despite representing an increase.

eMethods 5: Stratification by PED and WARD groups in the CAP-IT trial

1. Background

The original CAP IT proposal and protocol were based on a fully stratified design according to whether children were recruited from the Paediatric Emergency Department (PED group) or from inpatient paediatric hospital wards (WARD group).

The key rationale for this was:

1. the WARD group would tend to include children with more severe community-acquired pneumonia (CAP).

2. children in the PED group would not have received any antibiotic prescription for the current episode, whereas most children in the WARD group would have received inpatient antibiotic treatment.

3. the need for different trial procedures for the two groups, including the consent process, enrolment, and additional data capture during the inpatient period for the WARD group.

Because of these major perceived differences we also proposed conducting separate analyses of the PED and WARD groups, and the sample size was calculated to enable adequate power within each group.

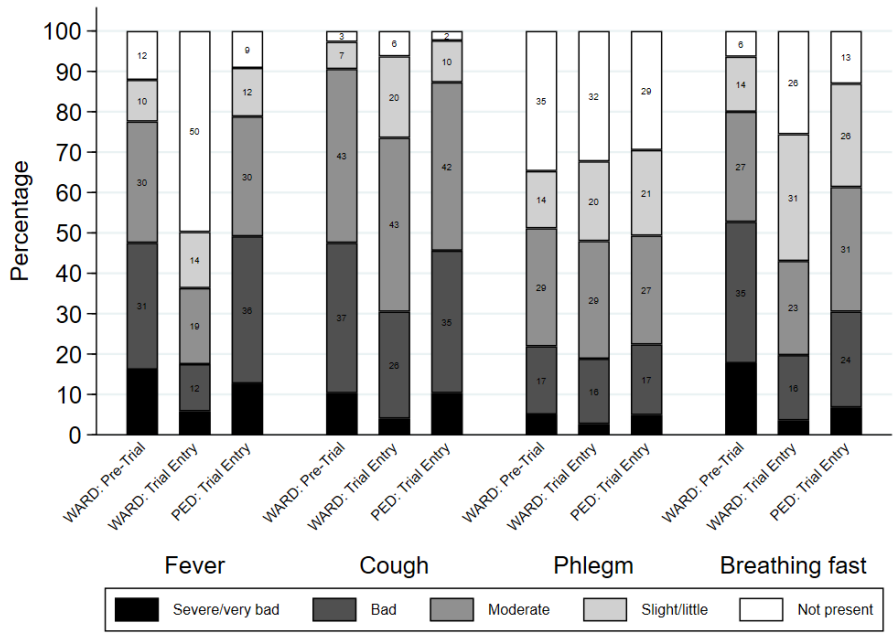
2. Data from the pilot phase

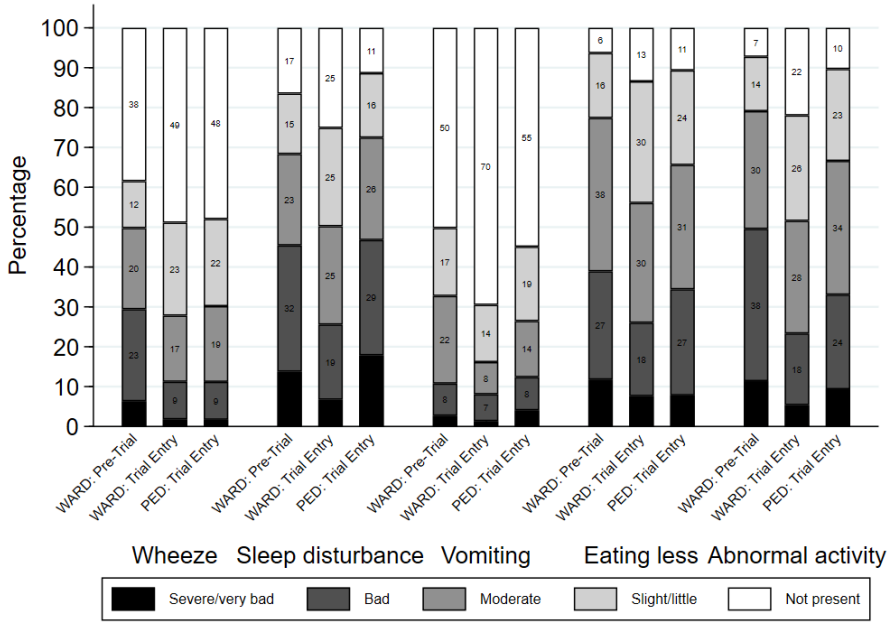
Emerging data from the trial suggested that there is no hard distinction between the PED and WARD groups.

1. In a substantial proportion of participating hospitals, children are first seen in a Paediatric Assessment Unit (PAU), before either being formally admitted or discharged. This makes the distinction between PED and WARD less relevant, especially as some PAUs admit children for up to 48 hours

2. Although clinical signs and symptoms at presentation to ED were slightly worse on average in WARD than in PED children, there was nevertheless considerable overlap in the two distributions (Figure 1). Also, there was rapid improvement in many WARD children between presentation and enrolment, to the extent that the direction of this difference was reversed.

Figure: Parent-reported symptoms at presentation and at enrolment in original PED and WARD groups





3. The protocol allows for up to 48 hours treatment with a beta-lactam. However, the duration of prior exposure in the WARD group is generally much shorter than this: 55% less than 12 hours, 75% less than 24 hours. Therefore, the impact of pre-treatment on the interpretation of the trial will be less critical.

3. Changes to the protocol: Joint analysis of PED and WARD groups
These issues were extensively discussed at the joint TSC/IDMC meeting in June 2017 and at the separate IDMC and TSC meetings in January 2018. There was consensus and strong support for simplifying the protocol by removing the distinction between the PED and WARD groups (although the difference will remain for some practical aspects of the trial, including how the trial drug is accessed). This change would make the study more generalisable to the broad question of duration and dose of antibiotics for children with CAP. By specifying that out of hospital or inpatient pre-treatment with beta-lactam antibiotics had to be a maximum of 48 hours, very severe cases of CAP requiring prolonged inpatient management and antibiotic treatment were excluded from the trial. The TSC and IDMC also considered that it would be more logical to conduct a single, overall analysis that controls for prior antibiotic exposure rather than the location of enrolment. Furthermore, the TSC and IDMC stressed that the most clinically relevant question of duration and dose of therapy to be given at home would be considered for all children at the point of discharge. This practically resulted a reduced overall sample size since information from all participants was to be considered together in assessing whether the non-inferiority criterion has been met.

4. Further detail for handling of PED and WARD pathways in main trial
The PED and WARD stratification was maintained for practical reasons to facilitate access to trial medication for children managed in different care settings within participating hospitals. Hence, after the amendment children were recruited through two different pathways. Children in either pathway may have had up to 48 hours of oral or parenteral beta-lactam treatment before enrolment.

eMethods 6: Rationale for change in the non-inferiority margin

1. Background
Key assumptions in the original sample size calculation for CAP-IT were:

1. primary endpoint event rate of 5% based on non-UK data.

2. non-inferiority margin of 4%.

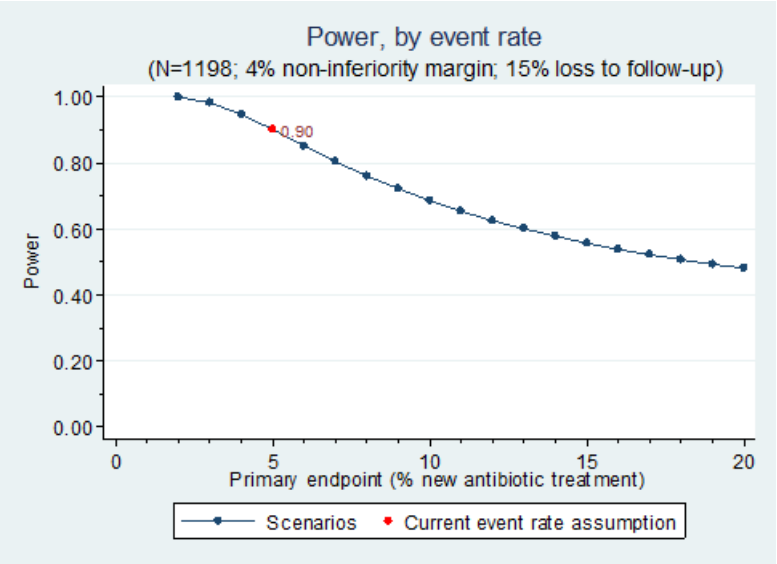
3. expected loss to follow-up of 15%.

The first assumption was highly uncertain due to the paucity of previous trials and observational studies with a similar endpoint in a similar setting. The protocol states: “There is uncertainty in this assumption (as with all trials in a new area), and a key role of the IDMC will be to review the accuracy of this assumption from accumulating data.” Accordingly, the IDMC reviewed unblinded data at their meeting on 15 January 2018.

2. Data from the pilot phase

The estimate of all-cause antibiotic retreatment in the report to the IDMC was 20.3% (95% CI 15.0-27.1) by Kaplan-Meier analysis (i.e. accounting for incomplete follow-up). A considerable proportion of these antibiotic retreatments would be expected to be clinically indicated and for respiratory tract infections. The initial assumption about the primary endpoint event rate was therefore a serious underestimate. The figure below shows how the power decreases as the event rate increases, if the non-inferiority margin remains fixed at 4% (absolute difference). This may seem paradoxical as intuitively there is more information in a trial with a larger number of events. The paradox arises as the risk difference is estimated less precisely the higher the overall event rate.

Figure: Change of statistical power over a range of different event rates



3. Changes to the protocol: Adjustment of the non-inferiority margin to 8%
In their report to the TSC, the IDMC recommended:

"We had an extensive discussion on a document prepared by the Trial Statisticians on a re-examination of the sample size calculation. This was prompted by a much high primary endpoint event rate than originally anticipated. We favour retaining the risk difference as the primary effect measure (rather than switching to an odds ratio) but using a more generous non-inferiority margin."

The rationale for a more generous non-inferiority margin was the need to consider this parameter in the context of the underlying event rate, and to avoid the paradox described in the previous section. The IDMC did not stipulate a new non-inferiority margin, instead this was discussed with the TSC. Various options were discussed, and a consensus was reached to change the margin to 8%, considering both statistical and pragmatic factors. Although this is double the original non-inferiority margin, it is more conservative on a proportionate scale (8/20, 40%; 4/5, 80%).

At the time it was acknowledged that the selection of an 8% non-inferiority margin was arbitrary but conservative considering guidance available at the time for antibiotic trials using similar clinical endpoints. Guidelines from the Infectious Diseases Society of America propose a non-inferiority margin of between 5 and 10% for trials in CAP with mortality endpoints but indicated that margins up to 20% are appropriate for clinical response endpoints.

Considering a rate of the primary outcome to be approximately 15%, an 8% non-inferiority margin assessed against an upper 1-sided 95% CI, and 15% loss to follow-up, 800 children needed to be randomised to achieve 90% power. This was regarded as a minimum sample size. As before, the calculation assumed no interaction between the two factorial randomisations. It was noted that a trial of 800 children was expected to generate 120 endpoints: If these were approximately equally split between two groups being compared, this would constitute strong clinical evidence of non-inferiority while also giving considerable latitude for sensitivity and sub-group analyses.

eMethods 7: Pre-specified sensitivity and subgroup analyses
The primary analysis of the primary endpoint included only those endpoints accepted by the ERC. The following sensitivity analyses for the primary endpoint were pre-defined in the Statistical Analysis Plan:

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" is specified as a reason for this treatment (rather than any respiratory tract infection).
3. As 2) but 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. Starting non-trial antibacterial treatment within the first 3 days from randomisation for any reason cannot by definition be related to the treatment duration randomisation. Sensitivity analyses will be performed ignoring these early endpoints for the comparison of shorter versus longer treatment.

In addition, the following subgroup analysis was also defined:

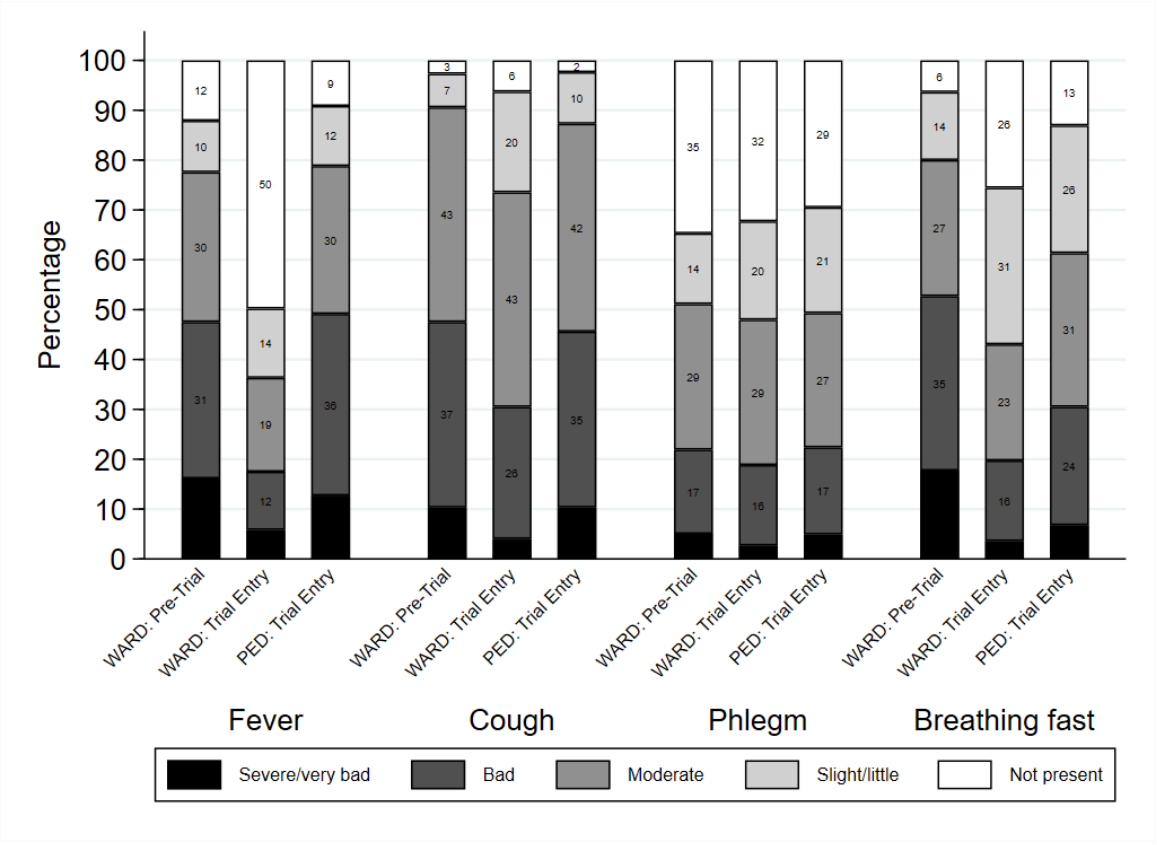
1. A subgroup analysis will consider the severity of CAP at enrolment and the main efficacy analysis repeated, limited to participants at the higher end of the severity spectrum. This is to provide reassurance that an overall null effect (if observed) is not due to a dilution effect arising from the inclusion of children with mild disease, possibly related to viral aetiology. However, there is no widely accepted classification for defining the severity of paediatric CAP in high income settings. Thus, the definition of severe/less severe subgroups will be based on the total number of the following signs/symptoms that are abnormal: respiratory rate, oxygen saturation, chest retractions.

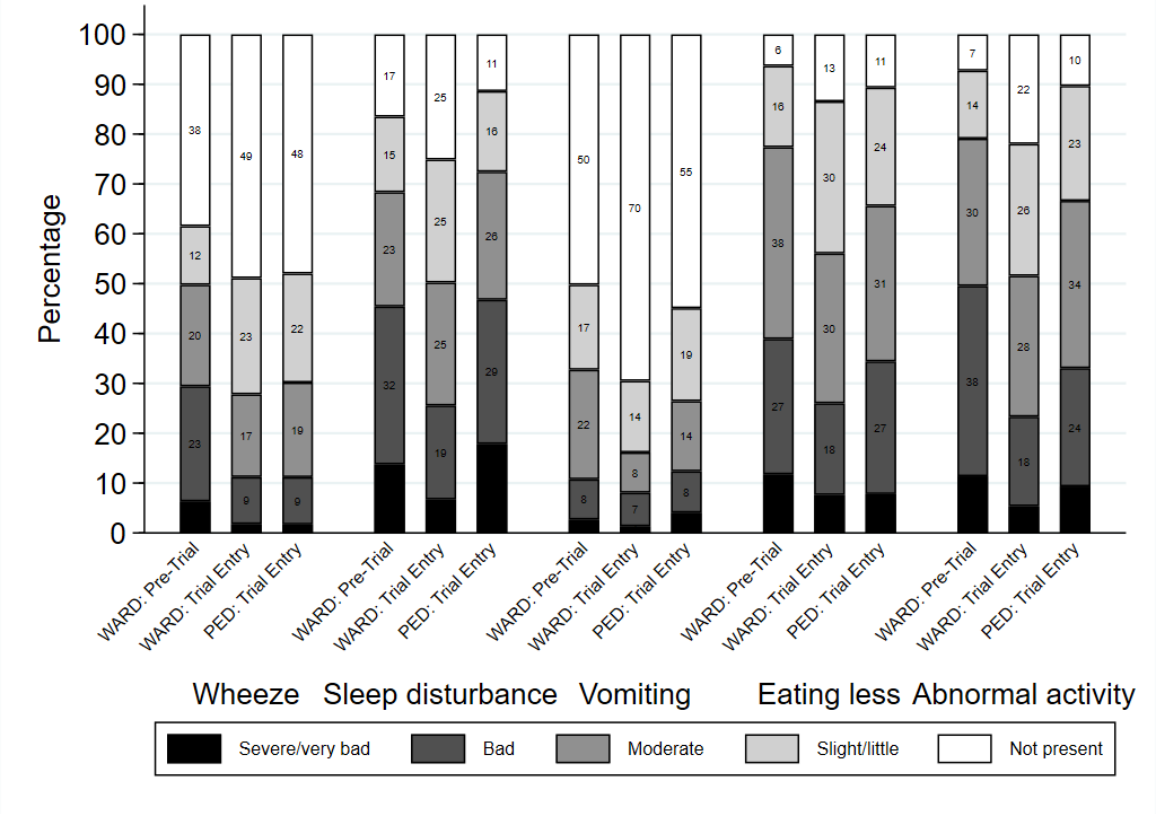
eMethods 8: Post-hoc on-treatment analysis
Overall non-adherence to trial medication, for the purposes of the on-treatment analysis of the primary endpoint, is defined as having taken less than 80% of trial medication as scheduled (i.e. more than 2 doses not taken or taken at smaller volume). However, switch from trial medication to non-trial antibiotics due to deterioration will not be regarded as non-adherence. The on-treatment analysis will exclude participants who were non-adherent to trial medication using two approaches: 1) non-adherence based on all trial medication including placebo, and 2) non-adherence based on active drug only.

eMethods9: Post-hoc subgroup analysis by PED and WARD pathways
The PED pathway 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 pathway 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 in hospital subsequently, without interruption, for a total of less than 48 hours. This subgroup analysis will evaluate the primary endpoint rate within each subgroup for each of the two randomizations.

eResults

eFigures 1 a and b: CAP symptoms at pre-trial entry in WARD, and at trial entry in PED and WARD





eTable 3: Participant characteristics at presentation, by dose and duration randomisations

		Total (n=814)	**Lower** (n=410)	**Higher** (n=404)	**Shorter** (n=413)	**Longer** (n=401)
Characteristics	Age (y)	2.5 (1.6,3.7)	2.5 (1.6, 3.7)	2.4 (1.6, 3.7)	2.5 (1.7, 3.7)	2.5 (1.5, 3.7)
	Male sex	421 (52%)	210 (51%)	211 (52%)	217 (53%)	204 (51%)
	Ethnicity					
	White	554 (68%)	275 (67%)	279 (69%)	283 (69%)	271 (68%)
	Asian or British Asian	106 (13%)	55 (13%)	51 (13%)	53 (13%)	53 (13%)
	Black or Black British	76 (9%)	40 (10%)	36 (9%)	40 (10%)	36 (9%)
	Mixed/other	78 (10%)	40 (10%)	38 (9%)	37 (9%)	41 (10%)
Medical history	Asthma or inhaler use within past month	255 (31%)	119 (29%)	136 (34%)	125 (30%)	130 (32%)
	Allergy or eczema	229 (28%)	115 (28%)	114 (28%)	108 (26%)	121 (30%)
	Prematurity	86 (11%)	43 (10%)	43 (11%)	51 (12%)	35 (9%)
	Other underlying disease	56 (7%)	37 (9%)	19 (5%)	21 (5%)	35 (9%)
	Routine vaccinations					
	Yes	773 (95%)	388 (95%)	385 (95%)	394 (95%)	379 (95%)
	No	26 (3%)	14 (3%)	12 (3%)	15 (4%)	11 (3%)
	Unknown	15 (2%)	8 (2%)	7 (2%)	4 (1%)	11 (3%)
History of current complaint	Duration of cough (d)	4 (2, 7)	4 (2, 6)	4 (2, 7)	4 (2, 7)	4 (2, 6)
	Duration of fever (d)	3 (1, 4)	3 (2, 4)	3 (1, 4)	3 (2, 4)	2 (1, 4)
	Systemic antibiotics in last 3 months	129 (16%)	64 (16%)	65 (16%)	66 (16%)	63 (16%)
	Systemic antibiotics in last 48 hrs	242 (30%)	119 (29%)	123 (30%)	123 (30%)	119 (30%)
	<12 hrs	100 (12%)	50 (12%)	50 (12%)	53 (13%)	47 (12%)
	12 - <24 hrs	85 (10%)	39 (10%)	46 (11%)	43 (10%)	42 (10%)
	≥24 hrs	57 (7%)	30 (7%)	27 (7%)	27 (7%)	30 (7%)
Clinical examination	Weight (kg)	13.5 (11.2,16.4)	13.6 (11.2,16.8)	13.3 (11.1,16.2)	13.8 (11.5,16.4)	13.2 (10.9,16.4)
	Temperature (°C)	38.1 (37.2, 38.8)	38.1 (37.3, 38.9)	38.0 (37.2, 38.6)	38.0 (37.1, 38.7)	38.1 (37.3, 38.8)
	Abnormal temperature	441 (54%)	227 (55%)	214 (53%)	221 (54%)	220 (55%)
	Heart rate (beats/min)	145 (130,160)	146 (131,160)	143 (130,158)	144 (131,158)	146 (130,162)
	Abnormal heart rate	578 (71%)	307 (75%)	271 (67%)	282 (68%)	296 (74%)
	Respiratory rate (breaths/min)	37 (30,44)	37 (30, 44)	38 (32, 44)	36 (30, 43)	38 (32, 45)
	Abnormal respiratory rate	528 (65%)	270 (66%)	258 (64%)	262 (64%)	266 (67%)
	Oxygen saturation (%)	96 (95,98)	96 (95, 98)	96 (95, 98)	96 (95, 98)	96 (95, 98)
	Abnormal oxygen saturation	43 (5%)	18 (4%)	25 (6%)	18 (4%)	25 (6%)
	Nasal flaring	75 (9%)	33 (8%)	42 (10%)	35 (9%)	40 (10%)
	Chest retractions	483 (59%)	239 (58%)	244 (60%)	239 (58%)	244 (61%)
	Pallor	169 (21%)	82 (20%)	87 (22%)	93 (23%)	76 (19%)
	Dullness to percussion Absent	380 (86%)	194 (86%)	186 (86%)	198 (86%)	182 (86%)
	Unilateral	59 (13%)	32 (14%)	27 (13%)	31 (13%)	28 (13%)
	Bilateral	3 (1%)	0 (0%)	3 (1%)	1 (<1%)	2 (1%)
	Bronchial breathing Absent	546 (82%)	283 (82%)	263 (82%)	276 (83%)	270 (81%)
	Unilateral	103 (15%)	53 (15%)	50 (16%)	49 (15%)	54 (16%)
	Bilateral	17 (3%)	10 (3%)	7 (2%)	8 (2%)	9 (3%)
	Reduced breath sounds Absent	389 (50%)	202 (52%)	187 (49%)	202 (51%)	187 (50%)
	Unilateral	336 (44%)	168 (43%)	168 (44%)	174 (44%)	162 (43%)
	Bilateral	46 (6%)	20 (5%)	26 (7%)	20 (5%)	26 (7%)
	Crackles crepitations Absent	134 (17%)	69 (17%)	65 (17%)	71 (18%)	63 (16%)
	Unilateral	562 (71%)	287 (71%)	275 (70%)	290 (72%)	272 (69%)
	Bilateral	100 (13%)	48 (12%)	52 (13%)	42 (10%)	58 (15%)

Note: Results are number (%) or median (IQR). 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%.

eTable 4: Chest x-ray results at trial entry as reported by sites

	Lower	Higher	Shorter	Longer
	N=192	N=199	N=196	N=195
Result of chest x-ray				
Suggestive of pneumonia: lobar infiltrate	65 (33.9%)	69 (34.7%)	64 (32.7%)	70 (35.9%)
Suggestive of pneumonia: patchy infiltrate	72 (37.5%)	82 (41.2%)	84 (42.9%)	70 (35.9%)
Unsure if suggestive of pneumonia	21 (10.9%)	16 (8.0%)	15 (7.7%)	22 (11.3%)
Other diagnosis	7 (3.6%)	5 (2.5%)	6 (3.1%)	6 (3.1%)
No finding/not suggestive of pneumonia	27 (14.1%)	27 (13.6%)	27 (13.8%)	27 (13.8%)

eTable 5: Inpatient management for children in the WARD group

	Lower	Higher	Shorter	Longer	Total
	N=107	N=116	N=114	N=109	N=223
Any supportive measures?	56 (52%)	65 (56%)	59 (52%)	62 (57%)	121 (54%)
-Oxygen?	50 (47%)	60 (52%)	54 (47%)	56 (51%)	110 (49%)
-Nasogastric feeds or fluids?	4 (4%)	2 (2%)	2 (2%)	4 (4%)	6 (3%)
-Parenteral fluids?	5 (5%)	14 (12%)	9 (8%)	10 (9%)	19 (9%)
-Chest physiotherapy?	3 (3%)	3 (3%)	3 (3%)	3 (3%)	6 (3%)
-Other supportive measures?	0	0	0	0	0
Any non-antibiotic treatments given?	86 (80%)	97 (84%)	91 (80%)	92 (84%)	183 (82%)
-Salbutamol inhaled?	57 (53%)	73 (63%)	60 (53%)	70 (64%)	130 (58%)
-Steroids?	24 (22%)	27 (23%)	25 (22%)	26 (24%)	51 (23%)
-Salbutamol IV?	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
-Other non-antibiotic treatments	54 (50%)	67 (58%)	59 (52%)	62 (57%)	121 (54%)

eTable 6: Prior exposure to antibiotics

	Lower	Higher	Shorter	Longer	Total
	N=410	N=404	N=413	N=401	N=814
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)
Time since first antibiotic					
<12 hrs	50 (42%)	50 (41%)	53 (43%)	47 (39%)	100 (41%)
12 - <24 hrs	39 (33%)	46 (37%)	43 (35%)	42 (35%)	85 (35%)
24 - <36 hrs	12 (10%)	16 (13%)	14 (11%)	14 (12%)	28 (12%)
>=36 hrs	18 (15%)	11 (9%)	13 (11%)	16 (13%)	29 (12%)
Time since first antibiotic	13.6 (5.0, 24.6)	13.9 (5.7, 23.0)	13.0 (5.0, 22.7)	14.0 (6.6, 24.6)	13.9 (5.6, 23.6)
Prior antibiotic: route					
Intravenous	15 (13%)	10 (8%)	17 (14%)	8 (7%)	25 (10%)
Oral	103 (87%)	110 (89%)	106 (86%)	107 (90%)	213 (88%)
Intravenous + oral	1 (1%)	3 (2%)	0 (0%)	4 (3%)	4 (2%)
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%)

eTable 7: Summary of ERC review

	Lower	Higher	Shorter	Longer
	N=410	N=404	N=413	N=401
Number of re-treatment events reviewed	76	67	77	66
By participant:				
Any retreatment reviewed by the ERC				
yes	74 (18.0%)	65 (16.1%)	73 (17.7%)	66 (16.5%)
no	336 (82.0%)	339 (83.9%)	340 (82.3%)	335 (83.5%)
# of ERC events per participant				
1	72 (97%)	63 (97%)	69 (95%)	66 (100%)
2	2 (3%)	2 (3%)	4 (5%)	0 (0%)

eTable 8: Reasons for starting non-trial systemic antibacterials, as adjudicated by the ERC

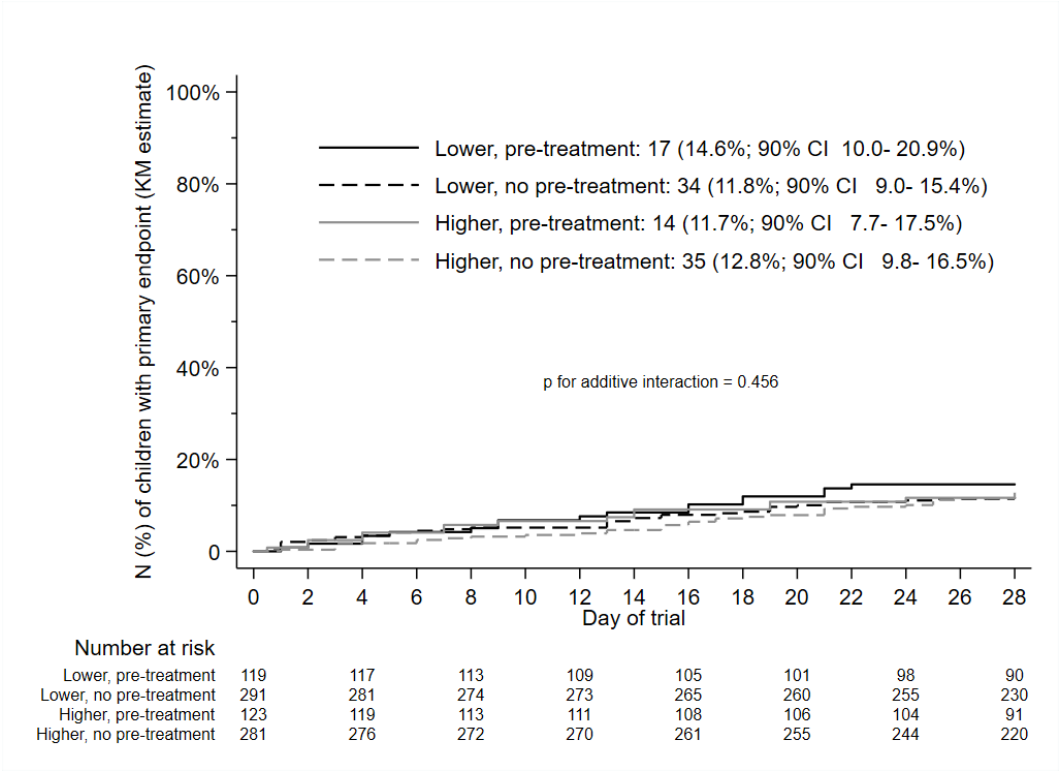
	Lower	Higher	Shorter	Longer
	N=74	N=65	N=73	N=66
CAP / Chest Infection	38	40	40	38
Other respiratory tract infection	19	12	18	13
Otitis Media	7	3	6	4
URTI	7	2	4	5
Tonsillitis	3	5	5	3
Other [a]	2	2	3	1
Other bacterial infection	8	7	9	6
Skin Infection	2	2	3	1
Urinary Tract Infection	2	2	3	1
Cellulitis	1	2	2	1
Scarlet Fever	1	1	0	2
Nail Infection	1	0	0	1
Salmonella Gastroenteritis	1	0	1	0
Other illness / injury	4	2	3	3
Appendicitis	1	0	1	0
Asthma	0	1	0	1
Bronchospasm/ Asthma	1	0	1	0
Dental Abscess	0	1	1	0
Lymphadenitis	1	0	0	1
Prophylaxis	1	0	0	1
Intolerance to IMP/adverse event	3	5	5	3
Vomiting	1	4	4	1
Diarrhoea	1	0	0	1
Rash	0	1	0	1
Refusing IMP	1	0	1	0
Parental preference	3	0	0	3
Pharmacy/admin error	1	1	2	0

eTable 9: Description of the primary endpoint

Patients who started systemic non trial antibacterials	Lower	Higher	Shorter	Longer
	N=51	N=49	N=51	N=49
Primary reason for starting new antibacterials				
CAP / Chest Infection	37 (73%)	39 (80%)	39 (76%)	37 (76%)
Otitis Media	5 (10%)	3 (6%)	4 (8%)	4 (8%)
Tonsillitis	3 (6%)	5 (10%)	5 (10%)	3 (6%)
URTI	5 (10%)	2 (4%)	3 (6%)	4 (8%)
Other respiratory tract infection	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Clinical indication				
Definitely/Probably	19 (37%)	19 (39%)	19 (37%)	19 (39%)
Possibly	32 (63%)	30 (61%)	32 (63%)	30 (61%)
First new antibiotic				
Amoxicillin	25 (49%)	24 (49%)	23 (45%)	26 (53%)
Amoxicillin, iv	0 (0%)	1 (2%)	1 (2%)	0 (0%)
Azithromycin	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Azithromycin+Amoxicillin, iv	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Cefuroxime	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Cefuroxime+Clarithromycin	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Clarithromycin	8 (16%)	9 (18%)	13 (25%)	4 (8%)
Co-amoxiclav	5 (10%)	5 (10%)	2 (4%)	8 (16%)
Co-amoxiclav+Azithromycin	2 (4%)	0 (0%)	0 (0%)	2 (4%)
Co-amoxiclav, iv	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Erythromycin	3 (6%)	4 (8%)	3 (6%)	4 (8%)
Phenoxymethylpenicillin	2 (4%)	4 (8%)	4 (8%)	2 (4%)
Who prescribed?				
CAP-IT Investigator	3 (6%)	3 (7%)	3 (6%)	3 (7%)
Other hospital doctor	18 (38%)	16 (36%)	17 (36%)	17 (37%)
GP	24 (50%)	25 (56%)	27 (57%)	22 (48%)
Other	3 (6%)	1 (2%)	0 (0%)	4 (9%)
Time new antibiotic started				
Day 1 to 15	29 (57%)	25 (51%)	28 (55%)	26 (53%)
Day 16 to 29	22 (43%)	24 (49%)	23 (45%)	23 (47%)

eFigures 2 a and b: Primary endpoint, analysis of interactions

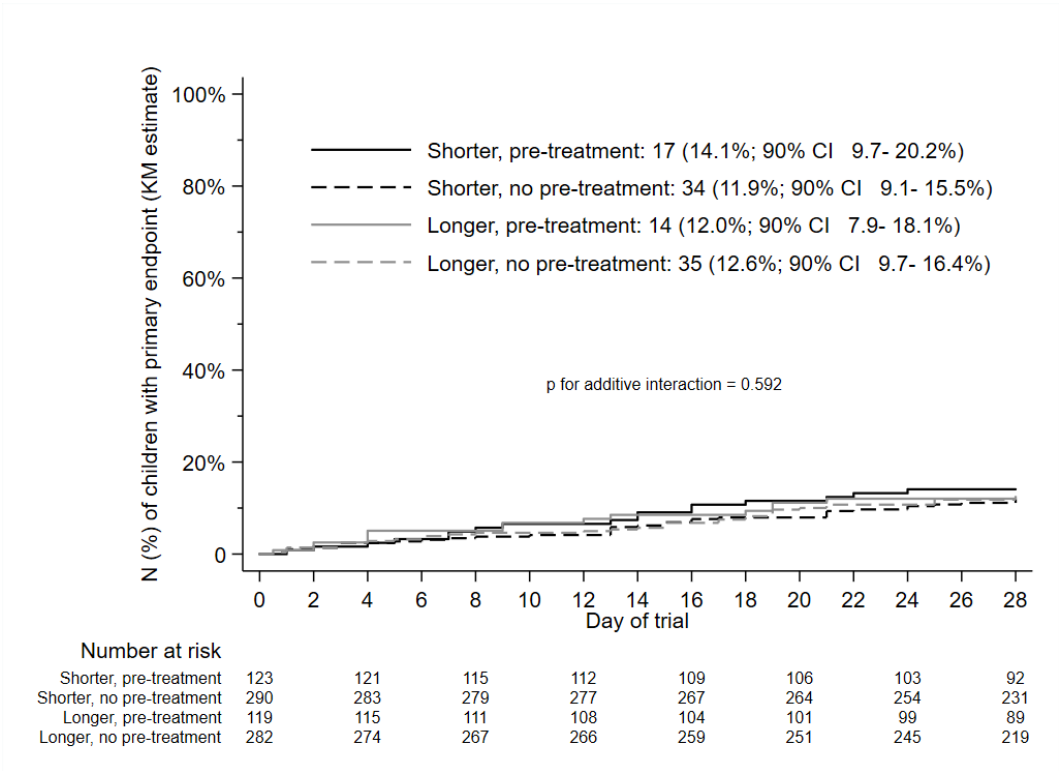
a) Interaction between pre-treatment with antibiotics and dose randomisation



Number at risk

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

b) Interaction between pre-treatment with antibiotics and duration randomisation

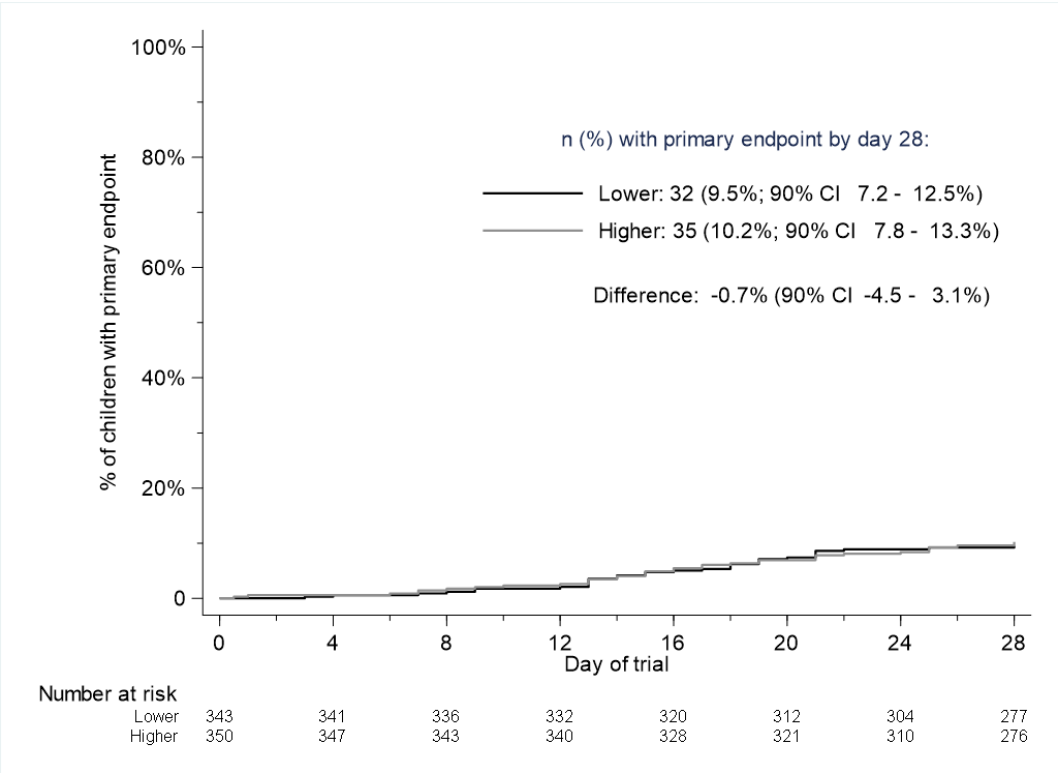


Number at risk

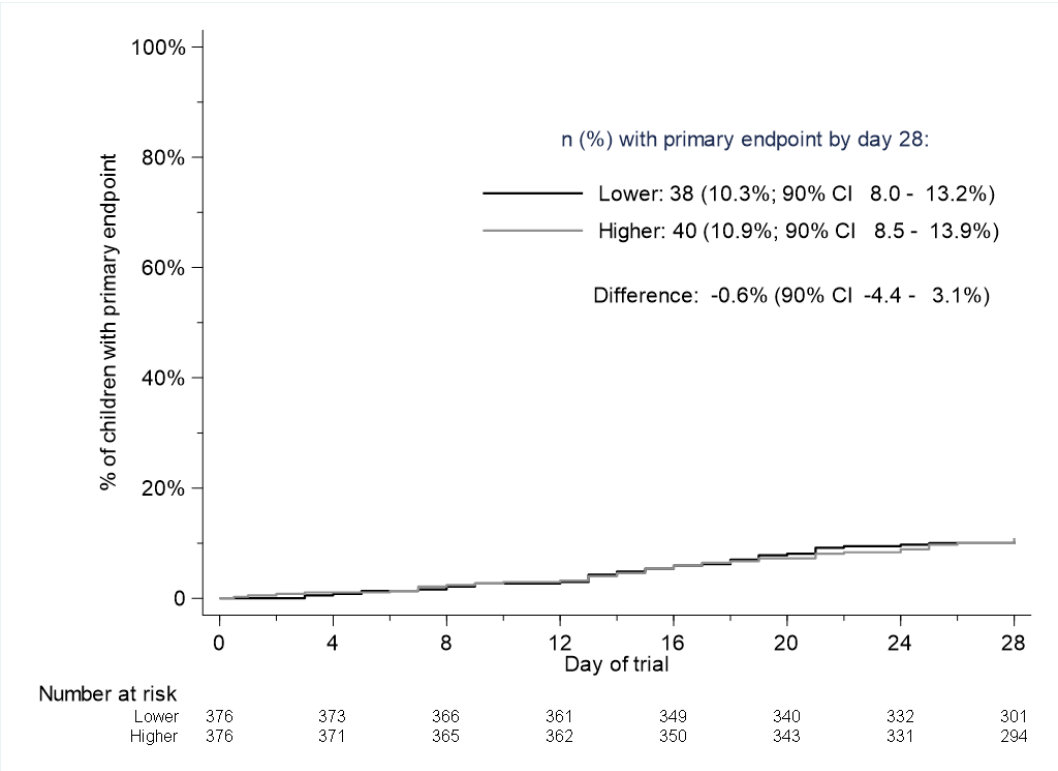
Shorter, pre-treatment	123	121	115	112	109	106	103	92
Shorter, no pre-treatment	290	283	279	277	267	264	254	231
Longer, pre-treatment	119	115	111	108	104	101	99	89
Longer, no pre-treatment	282	274	267	266	259	251	245	219

eFigures 3 a and b: On-treatment analysis of dose randomisation

a) Non-adherence based on all trial medication including placebo

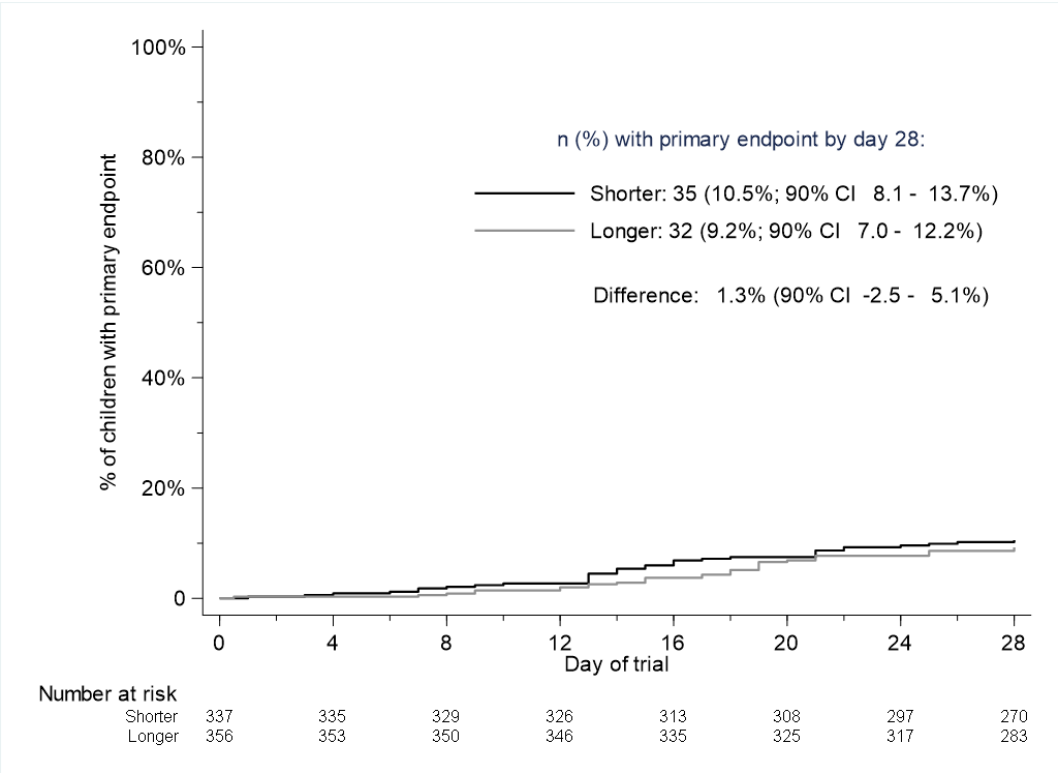


b) Non-adherence based on active trial drug only

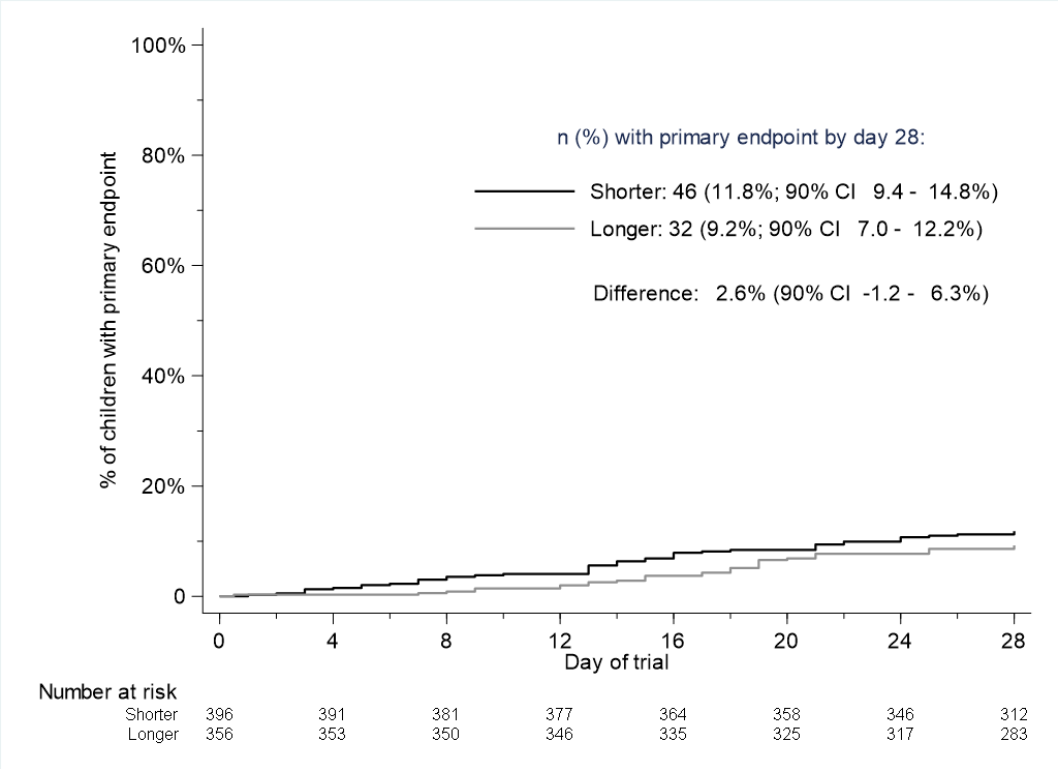


eFigures 4 a and b: On-treatment analysis of duration randomisation

a) Non-adherence based on all trial medication including placebo

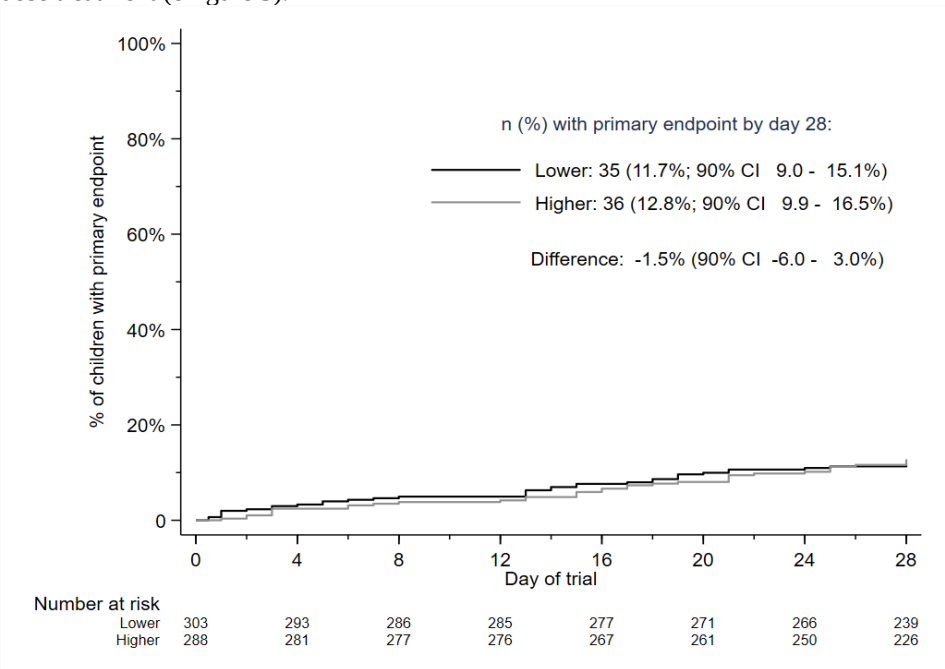


b) Non-adherence based on active trial drug only



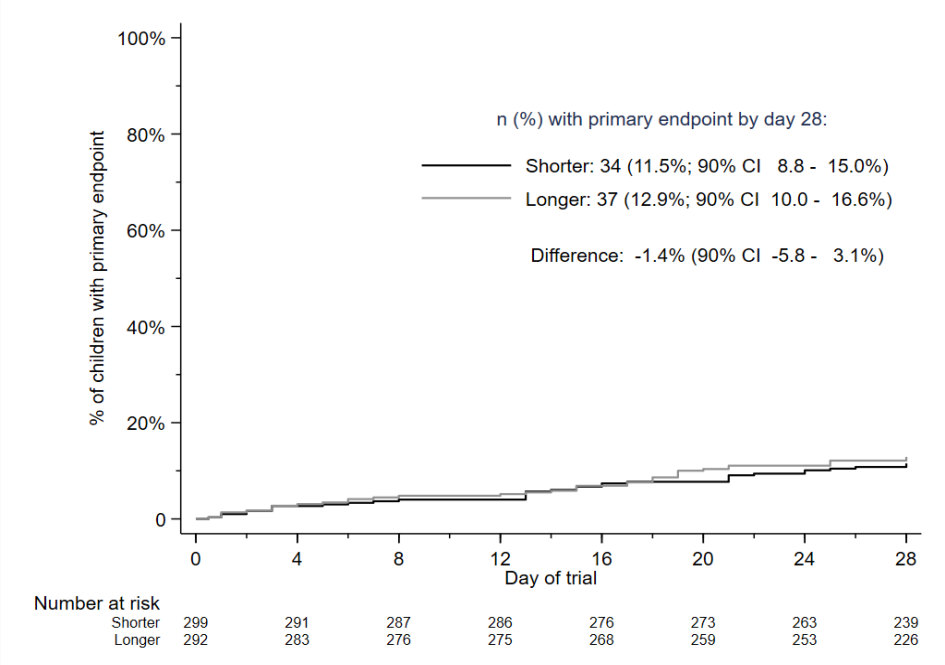
eFigure 5: Primary endpoint analysis for dose randomisation in PED pathway

Among 591 children in the PED pathway, primary endpoints occurred in 71 (12.2%) of children. Primary endpoint rates were 35/303 (11.7%) versus 36/288 (12.8%) in the lower dose and higher dose amoxicillin treatment groups (difference -1.5% (90%CI -6.0 to 3.0%)). For children in the PED pathway, lower dose treatment was therefore noninferior to higher dose treatment (eFigure 5).



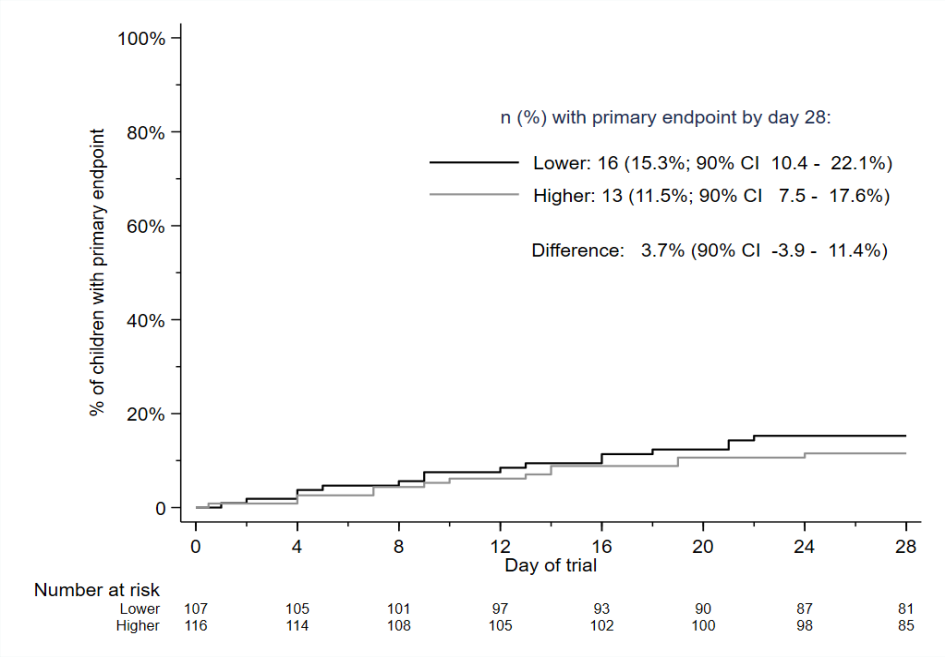
eFigure 6: Primary endpoint analysis for duration randomisation in PED pathway

Primary endpoint rates were 34/299 (11.5%) versus 37/292 (12.9%) in the 3-day and 7-day treatment groups (difference -1.4% (90%CI -5.8 to 3.1)). For children in the PED pathway, shorter treatment duration was therefore noninferior to longer treatment duration (eFigure 6).



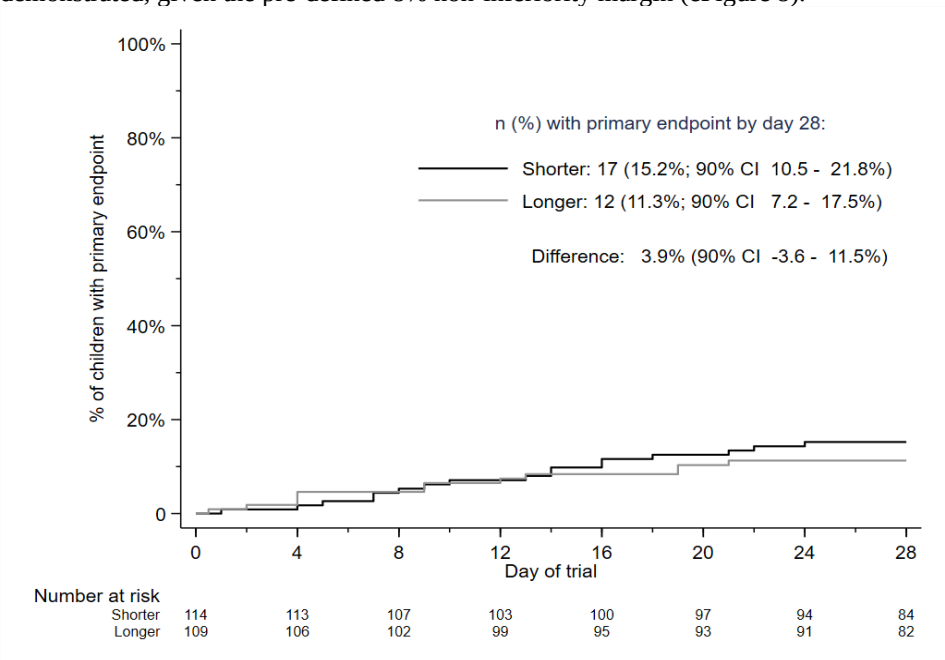
eFigure 7: Primary endpoint analysis for dose randomisation in WARD pathway

Among 223 children in the WARD pathway, primary endpoints occurred in 29 (13.3%) of children. Primary endpoint rates were 16/107 (15.3%) versus 13/116 (11.5%) participants in the lower dose and higher dose amoxicillin treatment groups (difference 3.7% (90%CI -3.9 to 11.4%)). For children in the WARD pathway with a much smaller sample size and consequent loss of statistical power, noninferiority of lower dose treatment to higher dose treatment therefore could not be demonstrated, given the pre-defined 8% non-inferiority margin (eFigure 7).



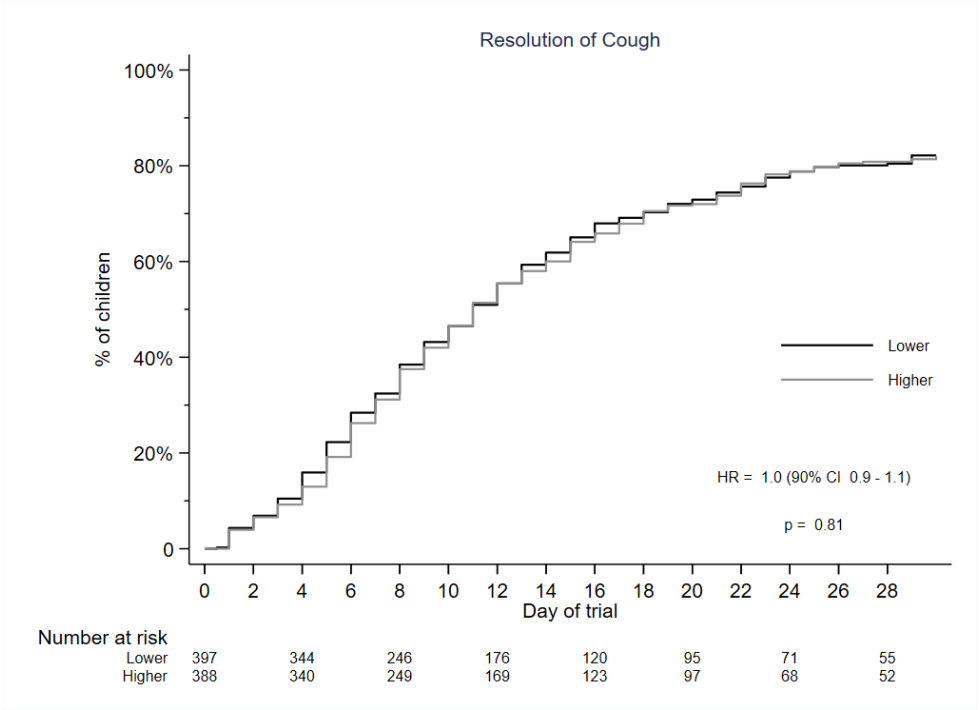
eFigure 8 Primary endpoint analysis for duration randomisation in WARD pathway

Primary endpoint rates were and 17/114 (15.2%) versus 12/109 (11.3%) in the 3-day and 7-day treatment groups (difference 3.9% (90%CI -3.6 to 11.5)). For children in the WARD pathway with a much smaller sample size and consequent loss of statistical power, noninferiority of shorter duration treatment to longer duration treatment therefore could not be demonstrated, given the pre-defined 8% non-inferiority margin (eFigure 8).

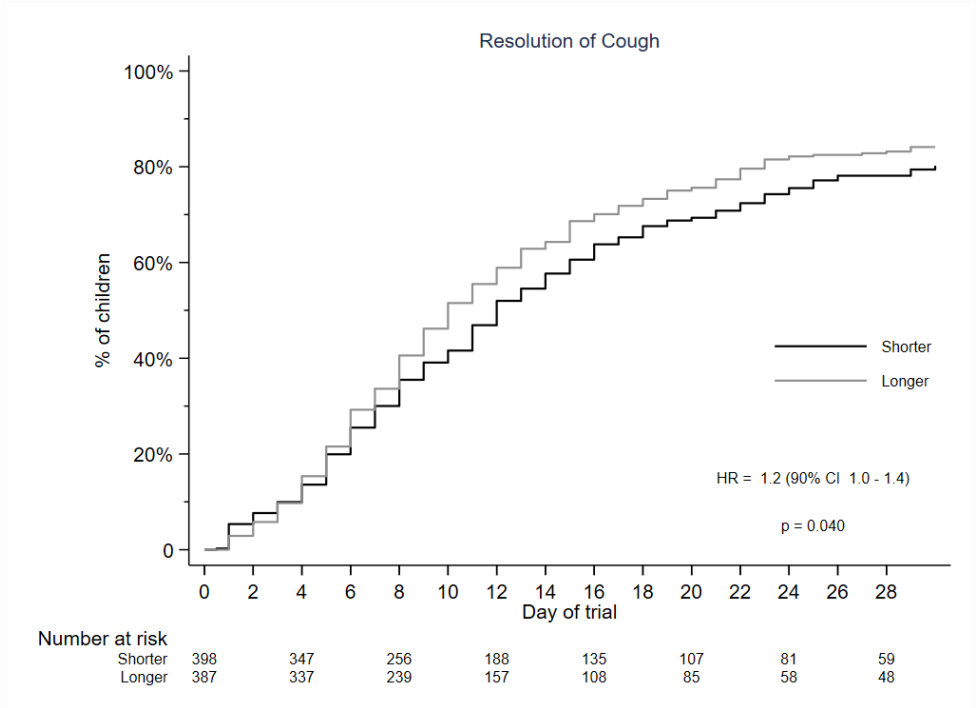


eFigures 9 a and b: Time to resolution of cough by randomisation group

a) Cough resolution: dose randomisation

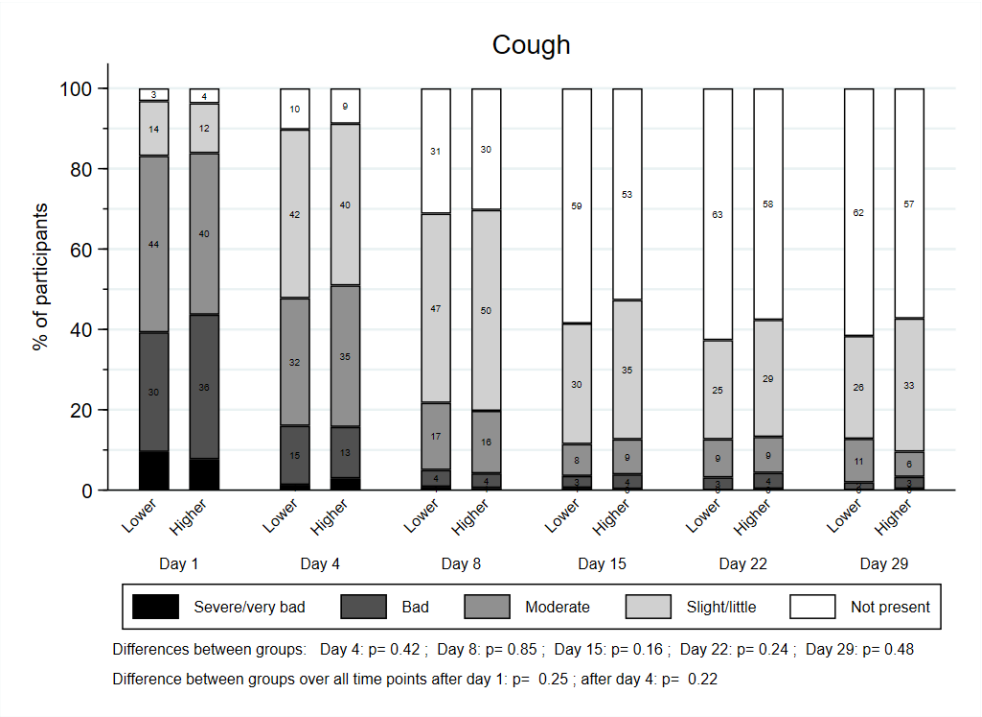


b) Cough resolution; duration randomisation

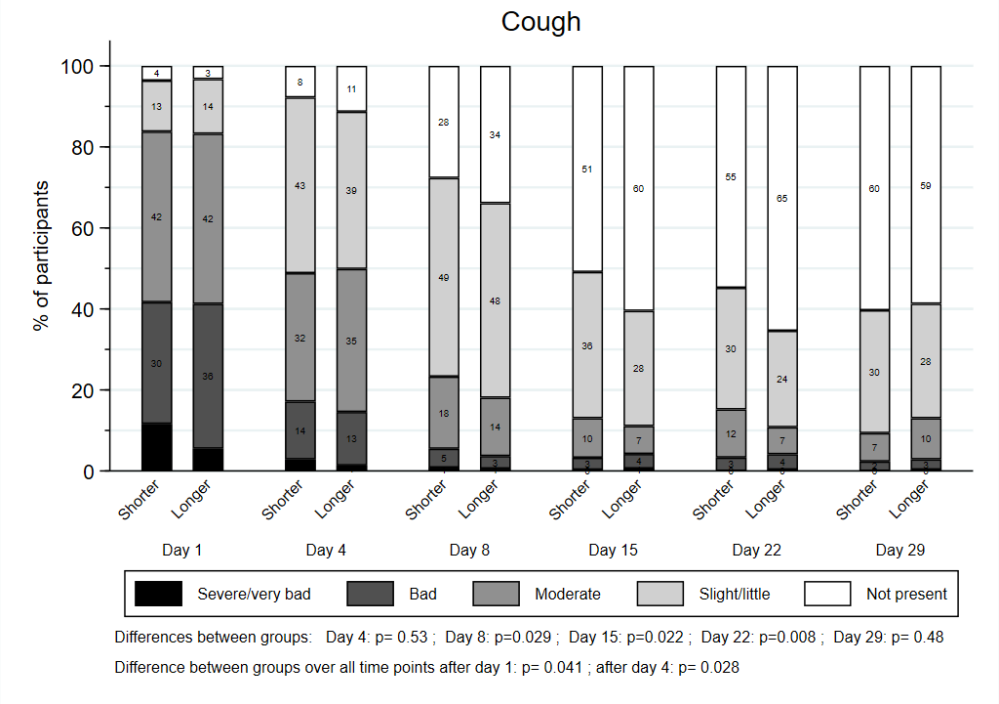


eFigures 10 a and b: Cough prevalence and severity by randomisation group and time point

a) Cough prevalence and severity: dose randomisation

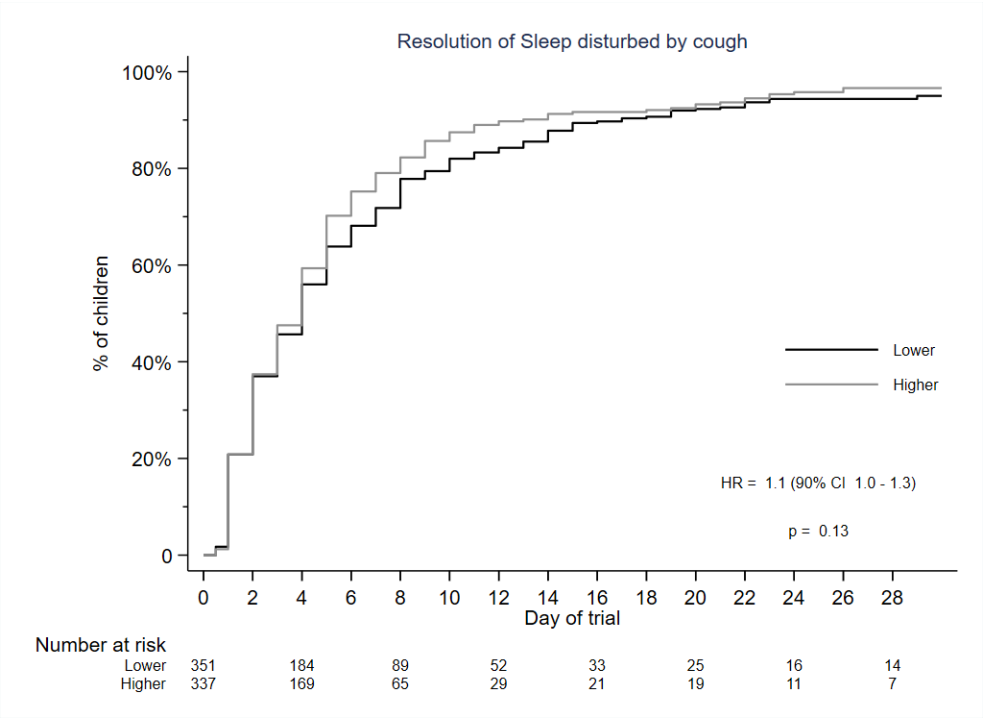


b) Cough prevalence and severity: duration randomisation

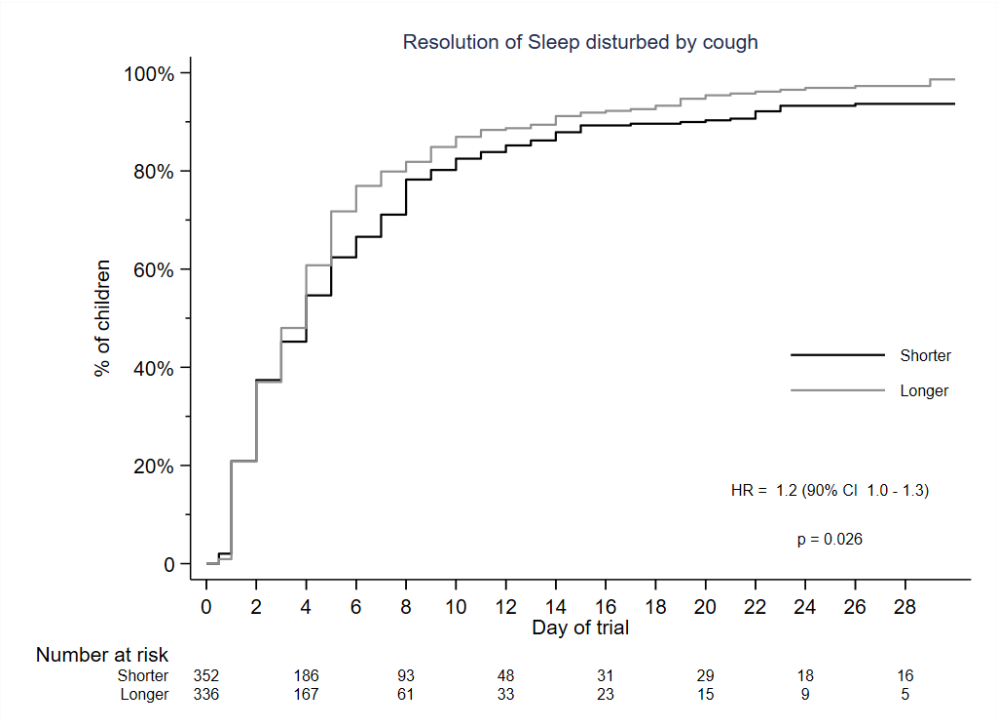


eFigures 11 a and b: Time to resolution of sleep disturbed by cough by randomisation group

a) Disturbed sleep resolution: dose randomisation

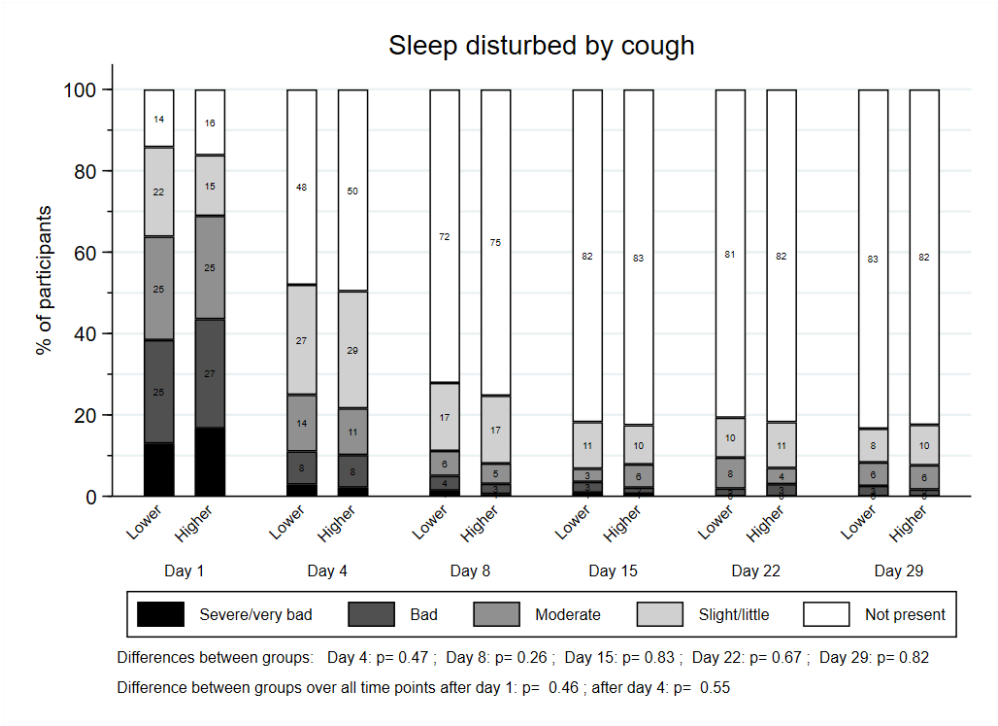


b) Disturbed sleep resolution: duration randomisation

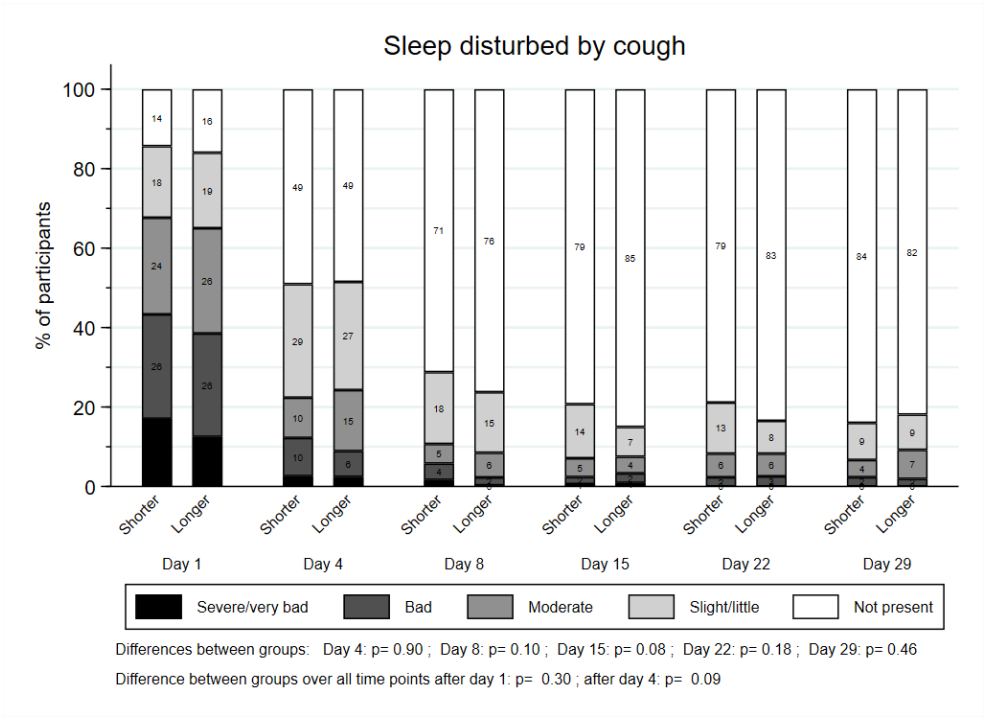


eFigures 12 a and b: Prevalence and severity of sleep disturbed by cough by randomisation group and time point

a) Disturbed sleep prevalence and severity: dose randomisation



b) Disturbed sleep prevalence and severity: duration randomisation



eTable 10: Adherence and adverse events, by 4 randomized groups

Outcome	Lower + shorter (n=208)	Lower + longer (n=202)	Higher + shorter (n=205)	Higher + longer (n=199)
Adherence: complete course taken				
All treatment [a]	173 (83.2%)	182 (90.1%)	185 (90.2%)	181 (91.0%)
Active treatment only [b]	201 (96.6%)	182 (90.1%)	203 (99.0%)	181 (91.0%)
Adherence: all doses taken and never smaller than prescribed volume				
All treatment [a]	146 (70.2%)	160 (79.2%)	154 (75.1%)	155 (77.9%)
Active treatment only [b]	192 (92.3%)	160 (79.2%)	195 (95.1%)	155 (77.9%)
Clinical possibly drug-related adverse events post enrolment				
Ever diarrhoea	97 (47.5%)	71 (35.9%)	90 (45.0%)	87 (45.8%)
Ever oral thrush	12 (5.9%)	15 (7.6%)	13 (6.5%)	17 (8.9%)
Ever skin rash	48 (23.5%)	46 (23.4%)	39 (19.5%)	60 (31.6%)
Serious adverse event, ever [c]	14 (6.7%)	9 (4.5%)	11 (5.4%)	9 (4.5%)

Note: a including non-adherence to placebo; b ignoring non-adherence to placebo; c No participant had more than one SAE, all SAEs were hospitalisations, no deaths.

eTable 11: *S. pneumoniae* and antimicrobial resistance on day 28, by 4 randomized groups

Outcome	**Lower + shorter** (n=208)	**Lower + longer** (n=202)	**Higher + shorter** (n=205)	**Higher + longer** (n=199)
Culture sample available	102/208 (57%)	122/202 (69%)	103/205 (60%)	110/199 (61%)
S. pneumoniae colonization	34/102 (33%)	32/122 (26%)	31/103 (30%)	32/110 (29%)
Penicillin MIC [a]				
0.016	9 (26%)	9 (28%)	6 (19%)	4 (13%)
0.032	18 (53%)	17 (53%)	18 (58%)	26 (81%)
0.064	0	1 (3%)	0	0
0.125	2 (6%)	2 (6%)	1 (3%)	0
0.25	4 (12%)	2 (6%)	4 (13%)	1 (3%)
0.5	0	0	1 (3%)	0
1	1 (3%)	1 (3%)	0	1 (3%)
2	0	0	1 (3%)	0
Penicillin-non-susceptibility [b] a) including all samples	7/102 (7%)	5/122 (4%)	7/103 (7%)	2/110 (2%)
b) in positive samples	7/34 (21%)	5/32 (16%)	7/31 (23%)	2/32 (6%)
Amoxicillin MIC [a]				
0.016	20 (59%)	22 (69%)	20 (65%)	23 (72%)
0.032	8 (24%)	6 (19%)	4 (13%)	7 (22%)
0.064	2 (6%)	2 (6%)	5 (16%)	0
0.125	1 (3%)	1 (3%)	0	0
0.25	2 (6%)	0	1 (3%)	1 (3%)
0.5	0	0	0	0
1	1 (3%)	1 (3%)	0	1 (3%)
2	0	0	1 (3%)	0
Amoxicillin-resistance/non-susceptibility [c] a) including all samples	1/102 (1%)	1/122 (1%)	1/103 (1%)	1/110 (1%)
b) in positive samples	1/34 (3%)	1/32 (3%)	1/31 (3%)	1/32 (3%)

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 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

eTable 12: *S. pneumoniae* carriage

	Lower	Higher		Shorter	Longer		Total
			p-value			p-value	
Baseline Positive	133/327 (41%)	139/320 (43%)		132/317 (42%)	140/330 (42%)		272/647 (42%)
Final Visit Positive	66/224 (29%)	63/213 (30%)	0.98	65/205 (32%)	64/232 (28%)	0.35	129/437 (30%)
Summary: pneumococcal carriage *	n=194	n=182		n=171	n=205		n=376
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%)

Notes: *patients with culture results at both time-points.

eTable 13: Penicillin non-susceptibility in patients with available culture result (positive or negative)

	Lower	Higher		Shorter	Longer		Total
			p-value			p-value	
Baseline	25/327 (8%)	21/320 (7%)		24/317 (8%)	22/330 (7%)		46/647 (7%)
Final visit	12/224 (5%)	9/213 (4%)	0.58	14/205 (7%)	7/232 (3%)	0.063	21/437 (5%)
Summary: Penicillin non-susceptibility *	n=194	n=182		n=171	n=205		n=376
Never	175 (90%)	166 (91%)		151 (88%)	190 (93%)		341 (91%)
Baseline only	10 (5%)	9 (5%)		9 (5%)	10 (5%)		19 (5%)
Final visit only	6 (3%)	3 (2%)		6 (4%)	3 (1%)		9 (2%)
Both	3 (2%)	4 (2%)		5 (3%)	2 (1%)		7 (2%)

eTable 14: Penicillin non-susceptibility in patients with a culture positive for S. *pneumoniae*

	Lower	**Higher**		**Shorter**	**Longer**		**Total**
			p-value			p-value	
Baseline	25/133 (19%)	21/139 (15%)		24/132 (18%)	22/140 (16%)		46/272 (17%)
Final visit	12/66 (18%)	9/63 (14%)	0.55	14/65 (22%)	7/64 (11%)	0.10	21/129 (16%)
Summary: **Penicillin non-susceptibility ***	n=34	n=36		n=36	n=34		n=70
never	24 (71%)	31 (86%)		26 (72%)	29 (85%)		55 (79%)
Baseline only	3 (9%)	0 (0%)		2 (6%)	1 (3%)		3 (4%)
Final visit only	4 (12%)	1 (3%)		3 (8%)	2 (6%)		5 (7%)
Both	3 (9%)	4 (11%)		5 (14%)	2 (6%)		7 (10%)