

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

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55 **Key points**

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

60

61 Findings: In this 2x2 factorial randomized clinical trial of 814 children requiring amoxicillin for
62 community-acquired pneumonia at hospital discharge, antibiotic retreatment within 28 days occurred
63 in 12.6% vs 12.4% of those randomized to lower vs higher doses, respectively, and in 12.5% vs
64 12.5% of those randomized to 3-day vs 7-day amoxicillin duration. Both comparisons met the
65 prespecified 8% noninferiority margin.

66

67 Meaning: Among children with community-acquired pneumonia discharged from an emergency
68 department, observational unit, or inpatient ward, further outpatient treatment with oral amoxicillin
69 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
70 noninferior to 7 days with regard to the need for later antibiotic retreatment.

71 Abstract

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

74 Objective: To determine whether lower dose amoxicillin is noninferior to higher dose, and whether
75 3-day treatment is noninferior to 7 days.

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

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

83 Main Outcomes and Measures: Primary outcome was clinically-indicated antibiotic re-treatment for
84 respiratory infection within 28 days after randomization. The non-inferiority margin was 8%.

85 Secondary outcomes included severity/duration of 9 parent-reported CAP symptoms, 3 antibiotic-
86 related adverse events, and phenotypic resistance in colonizing *Streptococcus pneumoniae* isolates.

87 Results: Of 824 participants randomized, 814 received at least one dose of trial medication (median
88 (IQR) age 2.5 years (1.6-2.7); 423 (52%) male); primary outcome was available for 789 (97%). For
89 lower vs higher dose, respectively, the primary outcome occurred in 12.6% vs 12.4% (difference
90 0.2% [1-sided 95%CI $-\infty$ to 4.0%]) For 3-day vs 7-treatment, the primary outcome occurred in
91 12.5% vs 12.5% (difference 0.1% [1-sided 95%CI $-\infty$ to 3.9]). Both groups demonstrated non-
92 inferiority with no significant interaction between dose and duration (p=0.63). Of the 14 prespecified
93 secondary endpoints, the only significant differences were 3-day vs 7-day treatment for cough
94 duration (median 12d vs 10d; HR 1.2 [95% CI 1.0 to 1.4]; p=0.04) and sleep disturbed by cough

95 (median 4d vs 4d, HR;1.2 [95% CI 1.0 to 1.4]; p=0.03) Among the subgroup of children with severe
96 CAP, for lower vs higher dose the primary endpoint occurred in 17.3% vs 13.5% (difference 3.8%
97 [1-sided 95%CI -∞ to10]; P-value for interaction = 0.28); for 3d vs 7d treatment, the primary
98 endpoint occurred in 16.0% vs 14.8% (difference 1.2% [1-sided 95%CI -∞ to 7.4]; P-value for
99 interaction = 0.82) .

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

105 Trial Registration: ISRCTN76888927.

106

107 **Introduction**

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

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

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

131 **Methods**

132 **Study design**

133 This was a multicenter, randomized, blinded, placebo-controlled, 2x2 factorial, non-inferiority trial
134 conducted in 28 hospitals in the UK and one in Ireland, comparing total daily amoxicillin dose (35-
135 50 mg/kg or 70-90 mg/kg) and duration (3 or 7 days) for treatment of childhood CAP. The trial
136 protocol was approved by West London & GTAC Research Ethics Committee (16/LO/0831)
137 (eAppendix).¹⁶ Parents or legal guardians of participating children provided written informed
138 consent prior to any study procedures.

139 **Participants**

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

154 **Randomization and Blinding**

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

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

169 **Procedures**

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

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

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

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

189 **Outcomes**

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

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

203 **Sample size calculation**

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

210 As it was unclear at trial initiation what the primary endpoint rate would be, data from a pre-planned
211 internal pilot phase were reviewed by the independent data monitoring committee (eMethods 4).
212 After 227 children were enrolled (160 from ED, 67 after inpatient stay), it was noted that disease
213 severity at enrolment was not significantly different among children from each clinical pathway
214 (eMethods 5) and the retreatment endpoint rate of 15% was higher than the 5% rate originally
215 assumed. The data and safety monitoring committee, with support from the trial steering committee,
216 recommended the following amendments: 1) joint analysis of children immediately discharged from
217 ED and discharged after an inpatient stay (eMethods 5); 2) revision of the non-inferiority margin
218 from 4% to 8% to be closer to the most conservative 10% noninferiority margin recommended by
219 the Infectious Diseases Society of America for noninferiority trials in CAP with a mortality endpoint
220 (eMethods 6). For binary clinical endpoints, a noninferiority margin of up to 20% could be
221 acceptable per the Infectious Diseases Society of America²¹

222

223 **Statistical design and analysis**

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

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

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

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

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

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

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

259

260 **Results**

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

264 Of these, 421 (52%) children were male, median (IQR) age was 2.5 years (1.6-3.7) (Table 1). At
265 presentation, 441 (54%) were febrile, 578 (71%) had tachycardia, and 528 (65%) had tachypnea. At
266 randomization, 591 (73%) children were discharged directly from the ED, and 223 (27%) had an
267 inpatient stay of <48 hours (eFigure 1, eTables 3 and 4). 218 (98%) inpatients and 24 (4%) children
268 discharged directly from ED had received beta-lactam antibiotics (100% treated for <48h; 185 (76%)
269 <24h; eTable 5).

270 Follow-up data were available for 757 (93%) participants at day 3, and 716 (88%), 676 (83%) and
271 619 (76%) at days 7, 14 and 21, respectively. Final 28-day follow-up was face-to-face for 484 (59%)
272 participants, and 158 (19%) families were contacted by telephone. Including additional information
273 from family physicians on any subsequent antibiotic prescriptions (n=147), the primary endpoint was
274 evaluable for 789 (97%) children, with the remaining 25 providing data up to the point of last
275 contact.

276 **Primary Outcome**

277 For the primary outcome, 139 children received non-trial systemic antibiotic treatment by day 28,
278 with criteria for the primary endpoint met in 100 (12.5%, 90%CI 10.7 to 14.6%) (Figure 2a, eTables
279 6 to 8). There was no significant interaction between randomized factorial groups (p=0.63, Figure
280 2a). The proportions meeting the primary endpoint were 12.6% (51/410) in the lower vs 12.4%
281 (49/404) in the higher dose groups (difference=0.2%, 1-sided 95%CI -∞ to 4.0%, Figure 2b), and
282 12.5% (51/413) in the shorter vs 12.5% (49/401) in the longer duration groups (difference= 0.1%, 1-
283 sided 95%CI -∞ to 3.9%, Figure 2c). Both comparisons satisfied the noninferiority criterion (Figure

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

286 For the pre-specified subgroup analysis among children with severe CAP, the primary endpoint
287 occurred in 31/180 (17.3%) in the lower dose vs 25/188 (13.5%) in the higher dose group (difference
288 3.8% (1-sided 95%CI $-\infty$ to 10); P-value for interaction = 0.28) and in 28/177 (16.0%) in the 3-day
289 group vs 28/191 (14.8%) in the 7-day group (difference 1.2% (1-sided 95% CI $-\infty$ to -7.4); P-value
290 for interaction = 0.82) (Figure 3).

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

304

305 **Secondary Outcomes**

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

308 Cough persisted for longer in the shorter vs longer duration groups (median, 12d vs 10d; HR 1.2
309 [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
310 to 1.3]; p=0.03, eFigures 9 and 11). There was no significant association between dose or duration of
311 amoxicillin and severity of cough symptoms (eFigures 10 and 12).

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

319

320

321 **Adverse Events**

322 Of potentially amoxicillin-related clinical adverse events, diarrhoea was reported in 345 (44%)
323 children after baseline, skin rash in 193 (24%), and oral thrush in 57 (7%). Skin rash occurred in 106
324 (27%) children allocated to longer compared with 87 (22%) children allocated to shorter treatment
325 (22%) (Table 2 and eTable 9). Active trial medication was discontinued early by 47 (6%)
326 participants, while 112 (14%) took fewer doses or a lower volume than prescribed (Table 2, eTable
327 9). The main reasons for early discontinuation were clinical deterioration (n=23), gagging/spitting
328 out (n=7), adverse events (n=6), and clinical improvement (n=3). Children randomized to 3 days of
329 amoxicillin were more likely to complete their full treatment course (98% vs. 91%).

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

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

334 **Discussion**

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

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

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

359 similar to the 10-11% previously observed for amoxicillin-treated lower respiratory tract infection in
360 UK general practice.^{27,30,31}

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

367 **Limitations**

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

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

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

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

386 **Conclusion**

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

393 **Contributors**

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

400

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407 JAB and WS had full access to all the data in the study and take responsibility for the integrity of the
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References

- 431 1. Jackson C, Hsia Y, Bielicki JA, et al. Estimating global trends in total and childhood antibiotic
432 consumption, 2011-2015. *BMJ global health*. 2019;4(1):e001241.
- 433 2. Kronman MP, Hersh AL, Feng R, Huang YS, Lee GE, Shah SS. Ambulatory visit rates and antibiotic
434 prescribing for children with pneumonia, 1994-2007. *Pediatrics*. 2011;127(3):411-418.
- 435 3. van de Maat J, van de Voort E, Mintegi S, et al. Antibiotic prescription for febrile children in
436 European emergency departments: a cross-sectional, observational study. *The Lancet Infectious
437 Diseases*. 2019;19(4):382-391.
- 438 4. Verbakel JY, Van den Bruel A, Thompson M, et al. How well do clinical prediction rules perform in
439 identifying serious infections in acutely ill children across an international network of ambulatory
440 care datasets? *BMC Medicine*. 2013;11(1):10.
- 441 5. Jain S, Williams DJ, Arnold SR, et al. Community-Acquired Pneumonia Requiring Hospitalization
442 among U.S. Children. *New England Journal of Medicine*. 2015;372(9):835-845.
- 443 6. O'Brien KL, Baggett HC, Brooks WA, et al. Causes of severe pneumonia requiring hospital
444 admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-
445 control study. *The Lancet*. 2019;394(10200):757-779.
- 446 7. DeMuri GP, Gern JE, Eickhoff JC, Lynch SV, Wald ER. Dynamics of Bacterial Colonization With
447 *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* During Symptomatic
448 and Asymptomatic Viral Upper Respiratory Tract Infection. *Clinical Infectious Diseases*.
449 2017;66(7):1045-1053.
- 450 8. Fancourt N, Deloria Knoll M, Baggett HC, et al. Chest Radiograph Findings in Childhood Pneumonia
451 Cases From the Multisite PERCH Study. *Clinical infectious diseases : an official publication of the
452 Infectious Diseases Society of America*. 2017;64(suppl_3):S262-S270.
- 453 9. Florin TA, Ambroggio L, Brokamp C, et al. Biomarkers and Disease Severity in Children With
454 Community-Acquired Pneumonia. *Pediatrics*. 2020;145(6).
- 455 10. Higdon MM, Le T, O'Brien KL, et al. Association of C-Reactive Protein With Bacterial and
456 Respiratory Syncytial Virus–Associated Pneumonia Among Children Aged <5 Years in the
457 PERCH Study. *Clinical Infectious Diseases*. 2017;64(suppl_3):S378-S386.
- 458 11. Bradley JS, Byington CL, Shah SS, et al. The Management of Community-Acquired Pneumonia in
459 Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric
460 Infectious Diseases Society and the Infectious Diseases Society of America. *Clinical Infectious
461 Diseases*. 2011;53(7):e25-e76.
- 462 12. Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of
463 community acquired pneumonia in children: update 2011. *Thorax*. 2011;66(Suppl 2):ii1-ii23.
- 464 13. Le Saux N, Robinson JL, Canadian Paediatric Society ID, Immunization C. Uncomplicated
465 pneumonia in healthy Canadian children and youth: Practice points for management. *Paediatr Child
466 Health*. 2015;20(8):441-450.
- 467 14. Ginsburg A-S, Mvalo T, Nkwopara E, et al. Amoxicillin for 3 or 5 Days for Chest-Indrawing
468 Pneumonia in Malawian Children. *New England Journal of Medicine*. 2020;383(1):13-23.
- 469 15. Lodha R, Kabra SK, Pandey RM. Antibiotics for community-acquired pneumonia in children.
470 *Cochrane Database of Systematic Reviews*. 2013(6).
- 471 16. Lyttle MD, Bielicki JA, Barratt S, et al. Efficacy, safety and impact on antimicrobial resistance of
472 duration and dose of amoxicillin treatment for young children with Community-Acquired Pneumonia:
473 a protocol for a randomised controlled Trial (CAP-IT). *BMJ Open*. 2019;9(5):e029875.
- 474 17. Lee GE, Lorch SA, Sheffler-Collins S, Kronman MP, Shah SS. National Hospitalization Trends for
475 Pediatric Pneumonia and Associated Complications. *Pediatrics*. 2010;126(2):204-213.
- 476 18. Netuveli G, Hurwitz B, Levy M, et al. Ethnic variations in UK asthma frequency, morbidity, and
477 health-service use: a systematic review and meta-analysis. *Lancet (London, England)*.
478 2005;365(9456):312-317.
- 479 19. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for
480 interpretation of MICs and zone diameters. Version 10.0, 2020. <http://www.eucast.org>. Accessed
481 Please add date.

- 482 20. US Department of Health and Human Services, Food and Drug Administration, Center for Drug
483 Evaluation and Research. *Community-Acquired Bacterial Pneumonia: Developing Drugs for*
484 *Treatment. Guidance for Industry*. 2020.
- 485 21. America IDSo. Position Paper: Recommended Design Features of Future Clinical Trials of
486 Antibacterial Agents for Community-Acquired Pneumonia. *Clinical Infectious Diseases*.
487 2008;47(Supplement_3):S249-S265.
- 488 22. Haider BA, Lassi ZS, Bhutta ZA. Short-course versus long-course antibiotic therapy for non-severe
489 community-acquired pneumonia in children aged 2 months to 59 months. *Cochrane Database of*
490 *Systematic Reviews*. 2008(2).
- 491 23. López-Alcalde J, Rodriguez-Barrientos R, Redondo-Sánchez J, et al. Short-course versus long-course
492 therapy of the same antibiotic for community-acquired pneumonia in adolescent and adult outpatients.
493 *Cochrane Database of Systematic Reviews*. 2018(9).
- 494 24. Pakhale S, Mulpuru S, Verheij TJM, Kochen MM, Rohde GGU, Bjerre LM. Antibiotics for
495 community-acquired pneumonia in adult outpatients. *Cochrane Database of Systematic Reviews*.
496 2014(10).
- 497 25. Tansarli GS, Mylonakis E. Systematic Review and Meta-analysis of the Efficacy of Short-Course
498 Antibiotic Treatments for Community-Acquired Pneumonia in Adults. *Antimicrobial agents and*
499 *chemotherapy*. 2018;62(9).
- 500 26. Greenberg D, Givon-Lavi N, Sadaka Y, Ben-Shimol S, Bar-Ziv J, Dagan R. Short-course antibiotic
501 treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind,
502 randomized, placebo-controlled trial. *The Pediatric infectious disease journal*. 2014;33(2):136-142.
- 503 27. Pernica JM, Harman S, Kam AJ, et al. Short-Course Antimicrobial Therapy for Pediatric Community-
504 Acquired Pneumonia: The SAFER Randomized Clinical Trial. *JAMA Pediatr*. 2021;175(5):475-482.
- 505 28. Dinh A, Ropers J, Duran C, et al. Discontinuing beta-lactam treatment after 3 days for patients with
506 community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised,
507 placebo-controlled, non-inferiority trial. *The Lancet*. 2021;397(10280):1195-1203.
- 508 29. Madhi SA, Wals PD, Grijalva CG, et al. The Burden of Childhood Pneumonia in the Developed
509 World: A Review of the Literature. *The Pediatric infectious disease journal*. 2013;32(3):e119-e127.
- 510 30. Berni E, Scott LA, Jenkins-Jones S, et al. Non-Response to Antibiotic Treatment in Adolescents for
511 Four Common Infections in UK Primary Care 1991–2012: A Retrospective, Longitudinal Study.
512 *Antibiotics*. 2016;5(3):25.
- 513 31. Currie CJ, Berni E, Jenkins-Jones S, et al. Antibiotic treatment failure in four common infections in
514 UK primary care 1991-2012: longitudinal analysis. *BMJ : British Medical Journal*. 2014;349:g5493.
- 515 32. Esposito S, Cohen R, Domingo JD, et al. Antibiotic therapy for pediatric community-acquired
516 pneumonia: do we know when, what and for how long to treat? *The Pediatric infectious disease*
517 *journal*. 2012;31(6):e78-85.
- 518 33. World Health Organization. Revised WHO classification and treatment of childhood pneumonia at
519 health facilities: evidence summaries. In. Geneva, Switzerland: WHO Press; 2014.
- 520 34. Llor C, Hernández S, Bayona C, et al. A study of adherence to antibiotic treatment in ambulatory
521 respiratory infections. *International Journal of Infectious Diseases*. 2013;17(3):e168-e172.
- 522 35. de Velde F, de Winter BCM, Koch BCP, van Gelder T, Mouton JW, consortium obotC-N. Non-linear
523 absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical
524 breakpoints. *Journal of Antimicrobial Chemotherapy*. 2016;71(10):2909-2917.
- 525 36. Legg J, Rampton C. *British Thoracic Society Paediatric Pneumonia Audit 2016/2017 Report*. British
526 Thoracic Society;2018.
- 527

528 **Figure legends**

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

530

531 °inpatient stay >48 hours, treated with non-beta-lactam antibiotics as inpatients; * follow-up

532 included up to time of withdrawal

533

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

536

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

540

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

543

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

550

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%)

554

555 Note: Results are number (%) unless median (IQR)^a indicated. Abnormal parameters: Temperature $\geq 38^{\circ}\text{C}$; Respiratory
556 rate: $>37/\text{min}$ for age 1-2 years; $>28/\text{min}$ for age ≥ 3 years; Heart rate: $>140/\text{min}$ for age 1-2 years; $>120/\text{min}$ for age ≥ 3
557 years; Oxygen saturation: $<92\%$. For race and ethnicity, other includes Middle Eastern/North African (n=12), Latin
558 American (n=3) and children with missing data (n=3).
559

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

Outcome	Amoxicillin dose				Amoxicillin duration			
	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; ^aincluding non-adherence to placebo; ^bignoring non-adherence to placebo; ^cNo 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

Outcome	Amoxicillin dose				Amoxicillin duration			
	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
<i>S. pneumoniae</i> 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

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. The data stratified by randomization groups can be found in eTable 11.