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Supplementary appendix

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Efficacy of oral amoxicillin–clavulanate or azithromycin for non-severe respiratory exacerbations in children with bronchiectasis (BEST-1): a multicentre, three-arm, double-blind, randomised placebo-controlled trial

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1 Further details of Study Methods

1.1 Duration of antibiotics

When determining the duration of treatment during the conception phase of this placebo-controlled, randomised controlled trial (RCT), we examined current guidelines and sought the views of both paediatric respiratory physicians and parents. At present, guidelines recommend using 10-14 days of antibiotics for treating bronchiectasis exacerbations. Discussions between ourselves and respiratory physician colleagues, as well as feedback from parents, also revealed that 14-days was the longest period deemed acceptable for treating an exacerbation with a placebo with a safety exit at the 7-day mark. Consequently, the 14-day treatment course was chosen for our study protocol

1.2 Additional Procedures

At baseline, and the beginning and end of exacerbations, children had deep nasal swabs collected, which were placed into skim-milk tryptone glucose glycerol broth, and transported to the laboratory for storage at –80°C until testing. Nasal swabs and blood tests were only done when parents consented to blood sample or nasal swab collection. Spirometry was only performed in children aged ≥6-years who were able to perform this test.

1.3 Methods for Antimicrobial susceptibility testing.

Antimicrobial sensitivities for *Streptococcus pneumoniae, Staphylococcus aureus* (Calibrated Dichotomous Susceptibility [CDS] breakpoints)[1] and *Haemophilus influenzae* (European Committee on Antimicrobial Susceptibility Testing [EUCAST] breakpoints) were ascertained by disk diffusion. A disk clearance radius <6mm defined resistance for both *S. pneumoniae* and *S. aureus*. For *H. influenzae*, ampicillin resistance was defined by a clearance diameter <16mm, whereas a clearance diameter of either <10mm or between 10 and 49mm surrounding erythromycin disks identified resistance and intermediate-resistance respectively to azithromycin. Where CDS disk diffusion indicated resistance, E-test (AB bioMe´rieux, France) minimum inhibitory concentrations (MICs; EUCAST, http://www.eucast.org) were used to determine the final resistance profile: *S. pneumoniae* (penicillin resistance: MIC >2 mg/L, intermediate resistance MIC >0.05–2 mg/L; azithromycin resistance: MIC >0·5 mg/L, intermediate resistance MIC >0·25–0·5 mg/L)) and *S. aureus* (azithromycin resistance MIC >2 mg/L, intermediate resistance MIC >1–2 mg/L). EUCAST antibiotic MIC breakpoints have not been validated for *H. influenzae* and were not used. A nitrocephin-based test detected beta-lactamase activity in *H. influenzae* and *Moraxella catarrhalis* isolates.[1]

2 Sample Size

An alpha-level of 0·0245 was used to account for the two, two-sided primary comparisons and an interim analysis. The required sample size of 189 children (63 per arm) provided 84% power for the trial's primary outcomes. As the primary outcome will be obtained in all enrolled children, drop-out was not accounted for in the intention-to-treat (ITT) analyses. With an estimated 20% drop-out, data from 153 children (51 per arm) provides a study power of 75% for the per-protocol (PP) analyses.

Enrolment continued until the study cessation in June 2017 by which time 197 children had been randomised to one of the study drugs. The reason for the final number being higher than planned initially was that all sites continued to enrol children until it was learnt that the minimum sample size was reached and communicated during the 4-6 weekly investigator meetings. The final follow-up for study patients was in December 2017.

The main secondary outcome was Parent Cough-Specific Quality-of-Life (PC-QOL) scores.[2] Based on a between-group difference of 0·9[3] and standard deviation of 0·9, our sample size provided a power of 99·9% (α =0·05, one-sided 95% confidence interval [CI]) for data from at least 102 children (assuming at least 80% retention of children randomised).

3 General Considerations

3.1 Missing Data

The primary outcome was available for all children, except for one child in the placebo group who was not able to be contacted for 1-month after starting the study medication. As per our *a priori* intention-to-treat analysis plan, this child was deemed to have not resolved before unblinding. For the secondary clinical outcome (PC-QoL), pre and post-treatment data were missing for 37 patients, but we had paired data for 107 children to compare amoxicillin-clavulanate (n=53) to placebo (n=54) and azithromycin (n=53) to placebo (n=54). For other secondary outcomes, we analysed only the data that were available. Children who did not resolve or where the day to resolution was unknown were counted as treatment failures. We compared the between-group exacerbation duration (i.e. days to its resolution) only in the children where the exacerbation episode resolved. This was because children by day-14 who had not returned to their baseline state received open-label antibiotics.

The children who did not have an exacerbation in the 6-months period following treatment with the study medication were censored at 180-days. Real-time polymerase chain reaction (PCR) assays for 18 respiratory viruses, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were performed only on swabs collected on day-1 of treatment at the beginning of an exacerbation.[4] Similarly, only swabs collected at day-1 and day-14 were cultured for respiratory bacterial pathogens. Blood inflammatory markers (white blood cell counts and C-reactive protein) were analysed only for the children who were consented for a blood test and a sample was obtained on day-1 and day-14 of treatment for an exacerbation. Changes in lung function between day-1 and day-14 as determined by forced expiratory volume 1-second percentage (FEV_1%) predicted was limited to children able to perform spirometry.

3.2 Interim Analyses and Data Monitoring

An independent data monitoring committee (iDMC) was in place throughout the study and met regularly. An interim analysis was undertaken by Dr. Stephanie Yerkovich when 50% of the sample size was achieved. The results were presented to the iDMC on the 16th of July 2016 and it was deemed that these did not meet the pre-determined stopping rules criteria.[5]

3.3 Protocol changes from the original trial methods publication

In the published RCT protocol,[5] we planned to recruit children from Brisbane, Darwin, Auckland, Sydney, Perth and Melbourne. However, due to change of circumstances with investigators at Melbourne and Sydney, these sites were omitted from this RCT. In the published protocol we had planned to report odds ratio and number-needed-to-treat for benefit (NNT-B), but while doing the statistical analysis plan, we decided to use generalised linear regression to detect relative risk of resolution and report the same along with NNT-B. We decided to present relative risk rather than odds ratio to better align the results with the sample size calculation (which was formulated in terms of difference in risk between groups).The relative risk of resolution of the active medication compared to placebo was defined as significant if it was >1, the 95%CI did not cross 1 and the p-value was <0.0245. We also used a generalised linear model to define the risk difference and to calculate the NNT-B including 95%CIs.

4 Sensitivity and Secondary Analyses

As reported in the published trial protocol,[5] we undertook a PP analysis for primary and secondary outcomes (Tables S1-S3). We also undertook a post-hoc analysis based on age group (≤5 or >5-years) and virus identified on day-1 of treatment for the exacerbation (present or absent) for both the primary and secondary outcomes. The primary outcome analyses are presented in Table S1, duration of exacerbation presented in Table S2 and the other secondary outcomes in Table S4. When considering global statistical significance, the comparison with amoxicillin-clavulanate was formally statistically significant after accounting for both pairwise comparisons and the interim analysis (as p<0·0245).

4.1 Primary outcome (Table S1)

In the PP analysis, we excluded the children who exited the study protocol because of medication refusal or intolerance (amoxicillin-clavulanate =3, azithromycin =6 and placebo =4). In PP sensitivity analyses, amoxicillin-clavulanate and azithromycin were both superior to placebo, with the risk of resolution being 1·48 (95% CI 1·08, 2·04) and 1·42 (95% CI 1·03, 1·97) respectively. The NNT-B for resolution of exacerbation by Day-14 was similar to that for the ITT analyses, but with less wide 95%CIs; NNT-B was 5 (95% CI 3, 19) and 6 (95%CI 3, 42) for amoxicillin-clavulanate and azithromycin respectively. The odds ratio for resolution for the amoxicillin-clavulanate group was 2·44 (95% CI 1·20, 4·96, p=0·014) and for the azithromycin group it was 2·07 (95% CI 1·04, 4·11, p=0·039).

4.2 Duration of exacerbation (Table S2)

As with the ITT analysis, the exacerbation duration in the amoxicillin-clavulanate group was significantly shorter than the placebo group (p=0·02). Exacerbation duration was also shorter for children who received amoxicillin-clavulanate compared to placebo in the subgroup where a virus or an atypical bacterial pathogen was identified on day-1 of treating an exacerbation (p=0·02).

The difference in exacerbation duration between the azithromycin and placebo groups was not significant in the PP analyses or any of the subgroup analyses.

4.3 Virus and atypical organisms (Table S3)

We have also presented the details of different viruses and atypical bacterial pathogens identified at the beginning of treatment of exacerbation in the three arms**.**

4.4 PC-QoL and spirometry (Table S4)

The improvement in FEV_1% predicted between day-1 and day-14 of treatment in the amoxicillin-clavulanate group was significant, compared to placebo in the PP analyses. Improvement in FEV_1% predicted was also significant in those receiving amoxicillin-clavulanate compared with placebo for children aged >5-years and if either a respiratory virus or atypical bacterial pathogens were detected on day-1 of starting treatment for an exacerbation. There were no other significant changes in FEV_1% predicted found for the other subgroups. Similarly, no significant between group-differences were identified in the secondary PC-QoL and laboratory outcomes in either amoxicillin-clavulanate compared to placebo or azithromycin compared to placebo analyses.

4.5 Time-to-next-exacerbation (Figure S1)

Time-to-next exacerbation (in days) was not statistically different for either antibiotic compared to placebo in any of the subgroup analyses – see the Kaplan-Meyer curve in Figure S1. The time (in days) to next exacerbation for each patient was collected individually from the day of resolution. The denominator used for this outcome was confined to children whose exacerbations had resolved within the 14-day period when the study medications were being received. This was because those whose exacerbations failed to resolve after 14-days of receiving the study medication were then prescribed open-label antibiotics (amoxicillin-clavulanate) as per the study protocol. Including children treated with open-label antibiotics would therefore no longer represent the true effect of the study treatments, including the placebo medication. The children who did not have an exacerbation after the study intervention were censored at day-180 (6-months), which was the end of the follow-up period for the study.

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6 Data Sharing

As per our institutions' policy involving Indigenous children from Australia and New Zealand, and in accordance with national guidelines, we are unable to share data without specific individual consent. As this was not obtained, we are prevented from sharing individual data with others.

7 Tables and Figure

7.1 Table S1: Relative risk for resolution (1^0 outcome) using per-protocol analyses and post-hoc subgroups (age, virus/atypical bacterial pathogens)

Subgroup for primary outcome	RR for resolution (95% CI)	p-value
ITT Population		
Amoxicillin-clavulanate (n=63)	1·50 (1·08, 2·09)	0·02
Azithromycin (n=67)	1·41 (1·01, 1·97)	0·04
PP population		
Amoxicillin-clavulanate (n=60)	1·48 (1·08, 2·04)	0·02
Azithromycin (n=61)	1·42 (1·03, 1·97)	0·03
Age >5-years		
Amoxicillin-clavulanate (n=42)	1·60 (1·08, 2·37)	0·02
Azithromycin (n=40)	1·33 (0·87, 2·04)	0·19
Age ≤5-years		
Amoxicillin-clavulanate (n=21)	1·31 (0·72, 2·38)	0·37
Azithromycin (n=27)	1·53 (0·9, 2·62)	0·12
Virus or atypical bacteria present		
Amoxicillin-clavulanate (n=32)	1·49 (0·95, 2·33)	0·08
Azithromycin (n=34)	1·29 (0·81, 2·07)	0·29
Virus or atypical bacteria absent		
Amoxicillin-clavulanate (n=17)	1·66 (1·01, 2·74)	0·05
Azithromycin (n=17)	1·66 (1·01, 2·74)	0·05

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RR, relative risk.

7.2 Table S2: Duration of exacerbation and time-to-next exacerbation after treatment with study medication in children whose exacerbation resolved

Subgroup for Secondary outcome	Median duration of exacerbation	p-value compared to placebo	Time-to next-exacerbation	p-value compared to placebo
ITT Population				
Placebo (n=67)	10-days	-	89-days	-
Amoxicillin-clavulanate (n=63)	7-days	0·02	89-days	1
Azithromycin (n=67)	8-days	0·24	83-days	0·86
PP population				
Placebo (n=63)	10-days	-	89-days	-
Amoxicillin-clavulanate (n=60)	7-days	0·02	89-days	1
Azithromycin (n=61)	8-days	0·24	83-days	0·86
Age >5-years				
Placebo (n=44)	8-days	-	102-days	-
Amoxicillin-clavulanate (n=42)	7-days	0·60	105-days	0·93
Azithromycin (n=40)	8-days	1	166-days	0·08
Age ≤5-years				
Placebo (n=23)	11-days	-	56-days	-
Amoxicillin-clavulanate (n=21)	7-days	0·06	73-days	0·74
Azithromycin (n=27)	7-days	0·07	83-days	0·57
Virus or atypical bacteria present				
Placebo (n=21)	11-days	-	94-days	
Amoxicillin-clavulanate (n=32)	7-days	0·02	65-days	0·59
Azithromycin (n=34)	8-days	0·19	68-days	0·64

Virus or atypical bacteria absent				
Placebo (n=33)	7-days		77-days	-
Amoxicillin-clavulanate (n=17)	9-days	0·32	102-days	0·47
Azithromycin (n=17)	7-days	1	71-days	0·86

Abbreviations: ITT, intention-to-treat; PP, per-protocol.

7.3 Table S3: Identification of viruses and atypical bacteria on day-1 of treatment

	Amoxicillin-clavulanate (n=49)	Azithromycin (n=51)	Placebo (n=54)
Rhinovirus	18 (37%)	21 (41%)	14 (26%)
Influenza	1 (2%)	3 (6%)	2 (4%)
Human metapneumovirus	0 (0%)	1 (2%)	1 (2%)
Parainfluenza	5 (10%)	2 (4%)	0 (0%)
Respiratory syncytial virus	3 (6%)	1 (2%)	0 (0%)
Adenovirus	1 (2%)	0 (0%)	1 (2%)
Human bocavirus-1	0 (0%)	1 (2%)	0 (0%)
Human polyomavirus	4 (8%)	2 (4%)	1 (1%)
Human coronaviruses	5 (10%)	2 (4%)	4 (8%)
Enterovirus	2 (4%)	4 (8%)	0 (0%)
Atypical bacterial pathogens	1 (2%)	5 10%)	2 (4%)

7.4 Table S4: Quality of life and laboratory parameters using per protocol analyses and post-hoc subgroups (age and virus)

ITT Population	**Amoxicillin-clavulanate (n=63)**				**Azithromycin (n=67)**				**Placebo (n=67)**		
	D1	D14	Change D1 to D14 (Day-14 minus day-1)	Difference in change compared to Placebo*	D1	D14	Change D1 to D14 (Day-14 minus day1)	Difference in change compared to Placebo*	D1	D14	Change D1 to D14 (Day-14 minus day-1)
PC-QoL n=160	4·6 (2·9 - 5·7)	6·5 (5·2 - 7)	0·8 (0·2 - 2·1)	0·1 (-0·6, 0·7)	4·1 (3·2 - 5·2)	6·5 (5·0 - 6·9)	1·3 (0·4 - 2·3)	0·63 (-0·0, 1·3)	4·6 (3·7 - 5·7)	5·6 (4·4 - 6·8)	0·7 (0·1 - 1·5)
WBC n=40	9·3 (6·8 - 11·2)	8·3 (6·4 -11·2)	0·1 (-2·4 - 2·5)	-0·8 (-3·6, 2·0)	9·2 (6·7 - 9·8)	7·8 (7·0 - 12·8)	0 (-0·2 - 0·7)	-0·9 (-4·5, 2·7)	9·0 (7·6 - 10·3)	8·9 (7·1 - 10·5)	1·0 (-1·4 - 2·6)
CRP n=43	2·3 (2·0-7·1)	2·0 (2·0-2·0)	-0·4 (-5·6-0·2)	3·7 (-4·6,12·0)	2·0 (2·0-2·2)	2·0 (2·0-2·0)	0·0 (0·0-0·0)	3·7 (-2·4,9·8)	5·7 (2·0-15·0)	2·0 (2·0-2·0)	-4·2 (-13·0- 0·0)
FEV_1 % predicted n=28	81·0 (73·0 -89·0)	90·5 (81·0 - 98·5)	10·0 (5·0 - 11·0)	10·0 (3·9, 16·1)	92·0 (76·0 - 98·0)	94·0 (87·0 - 96·0)	2·0 (-1·6 - 3·0)	2·0 (-5·0, 9·0)	86·0 (79·0 - 96·0)	91·0 (84·0 - 102·0)	0 (-1·0 - 4·0)
PP Population	**Amoxicillin-clavulanate (n=60)**				**Azithromycin (n=61)**				**Placebo (n=63)**		
PC-QoL n=160	4·6 (3·2 - 5·7)	6·6 (5·2 - 7)	0·7 (0·0 - 2·1)	0·04 (-0·6, 0·7)	4·1 (3·3 - 5·2)	6·5 (5·0 - 6·9)	1·4 (0·4 - 2·4)	0·63 (-0·0, 1·3)	4·5 (3·3 - 5·7)	5·6 (4·4 - 6·8)	0·7 (0·1 - 1·6)
WBC n=40	9·3 (6·8 - 11·2)	8·3 (6·4 - 11·2)	0·1 (-2·4 - 2·5)	-0·8 (-3·6, 2·0)	9·2 (6·7 - 9·8)	7·4 (6·7 - 12·6)	0 (-0·2 - 0·7)	-0·9 (-4·52, 2·72)	9·0 (7·2 - 10·4)	8·9 (7·1 - 10·5)	1·0 (-1·4 - 2·6)
CRP n=43	2·3 (2·0-7·1)	2·0 (2·0-2·0)	-0·4 (-5·6-0·2)	3·7 (-4·6,12·0)	2·0 (2·0-2·2)	2·0 (2·0-2·0)	0·0 (0·0-0·0)	3·7 (-2·4,9·8)	5·7 (2·0-15·0)	2·0 (2·0-2·0)	-4·2 (-13·0- 0·0)

FEV_1 % predicted n=28	80·5 (73·0 - 88·0)	90·5 (81·0 - 98·5)	10·0 (5·0 - 11·0)	10·0 (3·9, 16·1)	92·0 (76·0 - 98·0)	94·0 (83·0 - 96·0)	2·0 (-1·6 - 3·0)	2·0 (-5·0, 0·0)	87·5 (82·0 - 96·0)	91·0 (84·0 - 102·0)	0 (-1·0 - 4·0)
Age >5-years	**Amoxicillin-clavulanate (n=42)**				**Azithromycin (n=42)**				**Placebo (n=44)**		
PC-QoL n=101	4·6 (2·8 - 5·7)	6·6 (4·6 - 7·0)	0·9 (0·2 - 2·7)	0·2 (-0·8, 1·1)	4·3 (3·4 - 5·1)	6·6 (5·9 - 7)	1·0 (0·4 - 2·1)	0·4 (-0·3, 1·2)	5·0 (3·5 - 6·0)	5·8 (4·4 - 6·8)	0·7 (0·1 - 1·6)
WBC n=26	9·3 (5·9 - 11·2)	8·1 (6·4 - 9·3)	-0·4 (-2·4 - 2·5)	-0·9 (-5·6, 3·8)	6·7 (6·2 - 7·6)	6·7 (6·2 - 7·4)	0 (-0·2 - 0)	-2·4 (-7·4, 2·7)	8·9 (7·6 - 9·9)	8·3 (7·1 - 9·4)	0·7 (-1·6 - 1·8)
CRP n=43	2·0 (2·0 - 6·7)	2·0 (2·0 - 2·4)	-0·15 (-5·4 - 0·2)	3·9 (-2·2, 10·0)	2·0 (2·0 - 2·2)	2·0 (2·0 - 2·0)	0 (-0·2 - 0)	na	6·0 (2·0 - 10·0)	2·0 (2·0 - 2·8)	-4·2 (-10·2 - 0)
FEV_1 % predicted n=28	81·0 (73·0 - 89·0)	90·5 (81·0 - 98·5)	10·0 (5·0 - 11·0)	10·0 (3·2, 16·8)	92·0 (76·0 - 98·0)	91·2 (85·0 - 95·5)	2·0 (-1·6 - 3·0)	2·0 (-7·0, 11·0)	87·5 (80·5 - 95·5)	91·0 (84·0 - 102·0)	0 (-1·0 - 4·0)
Age ≤5-years	**Amoxicillin-clavulanate (n=27)**				**Azithromycin (n=21)**				**Placebo (n=23)**		
PC-QoL n=59	4·4 (3·6 - 5·7)	6·7 (5·7 - 7)	0·7 (0·2 - 2·1)	0 (-1·1, 1·1)	3·8 (3·2-5·2)	6·4 (4·8- 6·9)	1·8 (0·7 - 3·2)	1·1 (-0·36, 2)	4·3 (3·8-5·1)	5·2 (4·4-6·8)	0·7 (0·2 - 1·3)
WBC n=18	10·1 (8·9 - 11·7)	9·7 (6·6 -11·3)	0·5 (-1·6 - 0·8)	-2·4 (-8·1, 3·3)	9·3 (8·6 - 11·7)	12·6 (8·2 - 12·9)	0·35 (-2·4 - 2·2)	-2·5 (-9·7, 4·7)	10 (6·1 - 11·2)	10·2 (7·9 - 14·1)	2·6 (-1·4 - 3·0)
CRP n=15	6·0 (3·0 - 11·6)	2·0 (2·0 - 2·0)	-0·4 (-9·6 - -1·3)	-5·1 (-35·6, 25·4)	2·0 (2·0 - 2·0)	2·0 (2·0 - 2·0)	0 (0 - 0)	na	2·0 (2·0 - 21·0)	2·0 (1·0 - 2·0)	0 (-22·0 - 0)
FEV_1 % predicted, n=0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Virus or atypical bacteria present	**Amoxicillin-clavulanate (n=34)**				**Azithromycin (n=32)**				**Placebo (n=21)**		
PC-QoL n=78	3·9 (2·6 - 5·6)	6·7 (5·4 - 7·0)	1·2 (0·0 - 2·7)	0·4 (-0·1, 1·7)	4·0 (3·1 - 5·2)	6·6 (5·0 - 6·9)	1·8 (0·4 - 3·1)	1·0 (-0·5, 2·4)	4·8 (3·0 - 5·9)	6·1 (5·0 - 6·9)	0·8 (0·2 - 1·9)
WBC n=21	9·9 (7·4 - 12·2)	8·4 (6·4 - 11·3)	1·7 (0·1 - 2·5)	0·4 (-6·4, 5·6)	9·8 (7·6 - 10·7)	7·4 (6·2 - 8·2)	-0·2 (-4·8 - 0)	-1·4 (-8·1, 5·3)	9·0 (7·9 - 10·0)	9·5 (7·4 - 12·3)	1·2 (0·9 - 3·0)
CRP n=18	5·8 (2·0 - 11·6)	2·0 (2·0 - 2·0)	-4·7 (-6- -0·3)	-1·0 (-10·5, 8·6)	2·1 (2·0 - 3·5)	2·0 (2·0 - 2·0)	0 (-0·2 - 0)	n/a	9·6 (2·0 - 15·0)	2·0 (2·0 - 2·0)	-5·4 (-7·8 - 0)
FEV_1 % predicted n=12	86·0 (80·0 - 87·0)	90·0 (90·0 - 98·0)	19·0 (10·0 - 20·0)	19·0 (13·0, 24·9)	94·0 (92·0 - 98·0)	95·0 (85·5 - 98·5)	2·0 (2·0 - 3·0)	2·0 (-1·3, 5·3)	85·0 (82·5 - 92·5)	88·5 (84·0 - 99·0)	0 (-1·0 - 1·0)
Virus or atypical bacteria absent	**Amoxicillin-clavulanate (n=17)**				**Azithromycin (n=17)**				**Placebo (n=33)**		
PC-QoL n=58	5·3 (4·2 - 5·8)	6·6 (5·5 - 6·9)	0·6 (0·2 - 1·2)	0·2 (-0·6, 1·0)	4·7 (3·9 - 5·2)	6·3 (4·8 - 6·3)	1·0 (0·5 - 1·2)	0·6 (-0·3, 1·5)	4·4 (3·7 - 5·6)	4·8 (3·7 - 6·1)	0·4 (-0·3 - 1·2)
WBC n=21	9·3 (4·9 - 11·2)	7·6 (6·2 - 9·3)	-0·6 (-2·4 - 0·4)	-0·1 (-6·6, 6·4)	8·6 (6·7 - 9·3)	10·0 (7 - 12·8)	0·4 (0 - 2·2)	-1·2 (-6·7, 9·1)	9·6 (6·8 - 11·3)	8·7 (7·1 - 9·9)	0 (-2·7 - 2·5)
CRP n=22	2·6 (2·0 - 13·0)	2·0 (2·0 - 2·4)	0 (-11·0 - 1·3)	0 -(49·7, 49·7)	2·0 (2·0 - 2·0)	2·0 (2·0 - 2·0)	0 (0 - 0)	n/a	5·0 (2·0 - 23·0)	2·0 (2·0 - 5·0)	0 (-22·3 - 0)
FEV_1 % predicted n=16	84·5 (73·0 - 95·0)	84·5 (75·0 - 99·0)	5·0 (2·0 - 10·0)	4·0 (-4·5, 12·5)	90·0 (76·0 - 93·0)	88·4 (83·0 - 95·0)	-1·6 (-7·0 - 20·0)	-2·6 (-16·5, 11·3)	92·0 (79·0 - 105·0)	96·0 (72·0 - 107·0)	1·0 (-1·0 - 4·9)

Data presented are medians (25-75th percentile). *To compare difference between groups, median regression with 95% CI is reported.

Abbreviations: D1, day 1; D14, day 14;CI, confidence interval; CRP, C-reactive protein; FEV_1 %, forced expiratory volume in one-second percent; ITT, intention-to-treat; PC-QoL, parent cough-specific quality-of-life; PP, per-protocol; WBC, white blood cell count.

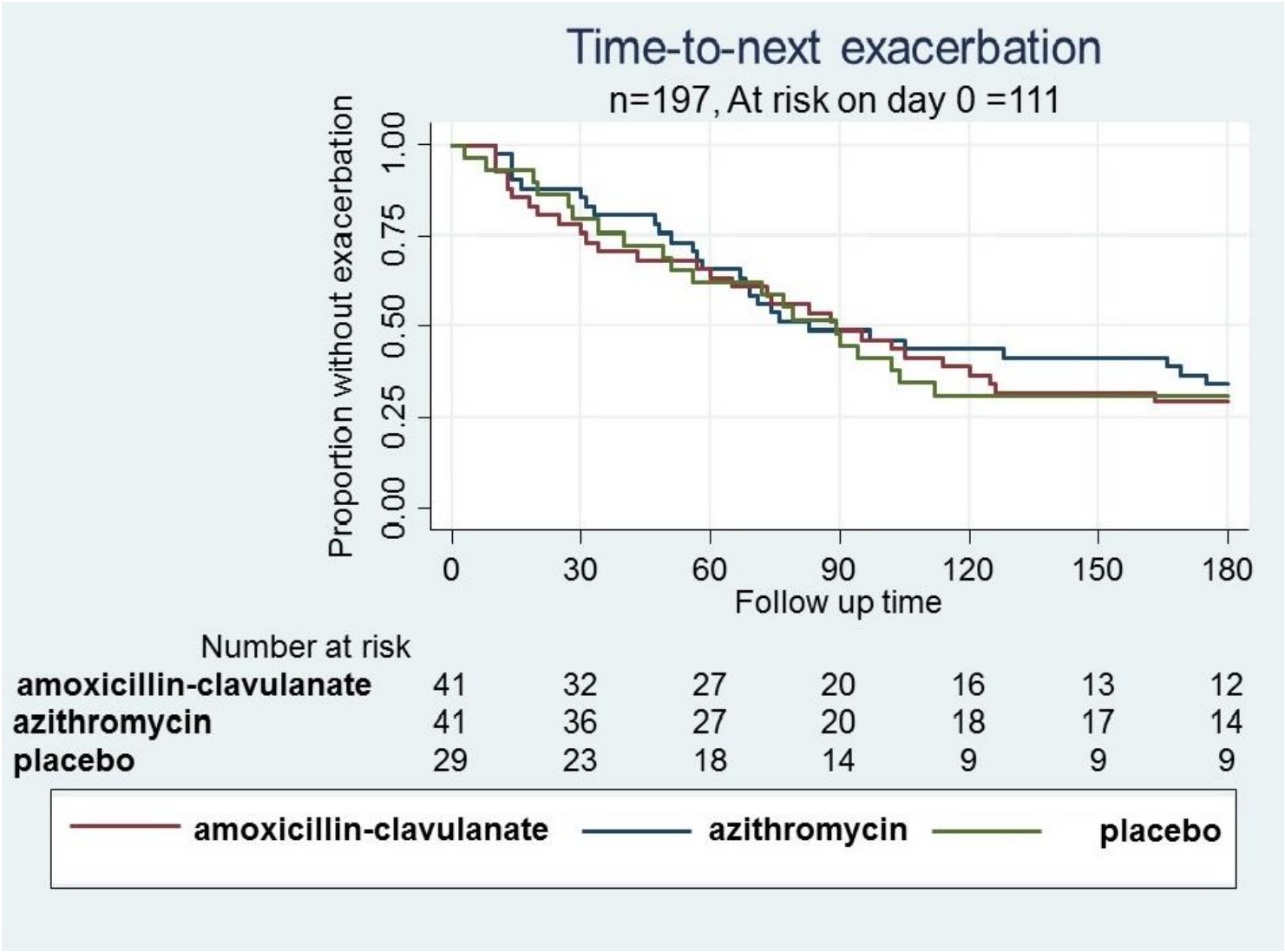
7.5 Table S5: Nasal swab bacteriology on day-1 and day-14 of study medication, analysis adjusted for variability in bacterial prevalence at Day-1.

	Start of treatment for exacerbation			**End of exacerbation treatment**				***adjusted**		***adjusted**
	Day-1			**Day-14**						
Number (%)	Amox-clav (n=63)	Azithro (n=67)	Placebo (n=67)	Amox-clav (n=63)	Azithro (n=67)	Placebo (n=67)	Amox-clav vs Placebo ***p-value***	Amox-clav vs Placebo ***p-value***	Azithro vs Placebo ***p-value***	Azithro vs Placebo ***p-value***
Swab pairs	39 (62)	42 (63)	47 (70)	39 (62)	42 (63)	47 (70)				
Streptococcus pneumoniae	4 (10)	7 (17)	11 (23)	1 (3)	3 (7)	6 (13)	0·09	0·828	0·38	0·922
Azithromycin-resistant	1 (25)	1 (14)	4 (36)	0 (0)	3 (100)	2 (33)	0·50	na	0·06	0·500
Penicillin-resistant	0 (0)	0 (0)	2 (18)	0 (0)	1 (33)	2 (33)	0·50	na	1·0	na
Haemophilus influenzae	4 (10)	5 (12)	13 (28)	0 (0)	2 (5)	6 (13)	0·02	0·096	0·19	0·340
Azithromycin-resistant	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	na	na	na	na
Ampicillin-resistant	1 (25)	0 (0)	3 (23)	0 (0)	0 (0)	1 (17)	na	na	0·54	na
Moraxella catarrhalis	12 (31)	18 (43)	14 (30)	6 (15)	1 (2)	15 (32)	0·08	0·020	<0·001	<0·001
B-lactamase positive	12 (100)	17 (94)	14 (100)	6 (100)	1 (100)	15 (100)	na	na	na	na
Staphylococcus aureus	7 (18)	5 (12)	8 (17)	5 (13)	3 (7)	15 (32)	0·04	0·004	0·004	0·002
Azithromycin-resistant	2 (29)	1 (20)	3 (38)	2 (40)	2 (67)	3 (20)	0·37	na	0·01	na

Methicillin-resistant	3 (43)	2 (40)	1 (13)	2 (40)	0 (0)	2 (13)	0·20	na	0·50	na
Any of the above pathogens	20 (51)	22 (52)	32 (68)	11 (28)	8 (19)	32 (68)	<0·001	<0·001	<0·001	<0·001
Azithromycin-resistant (any)	3 (15)	2 (9)	7 (22)	2 (18)	5 (63)	5 (16)	0·84	0·161	0·006	0·006

Amox-clav- amoxicillin-clavulanate, Azithro- azithromycin.
***adjusted for baseline bacteriology:** using a generalised linear model for the binomial family and an identity link to report risk differences. An exact logistic regression model was used where cell numbers were low.

7.6 Figure S1: Time-to-next exacerbation after treatment with study medication in children whose exacerbation resolved



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