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The impact of long-term azithromycin on antibiotic resistance in HIV-associated chronic lung disease

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Abstract

Selection for resistance to azithromycin (AZM) and other antibiotics such as tetracyclines and lincosamides remains a concern with long-term AZM use for treatment of chronic lung diseases (CLD). We investigated the impact of 48 weeks of AZM on the carriage and antibiotic resistance of common respiratory bacteria among children with HIV-associated CLD.

Nasopharyngeal (NP) swabs and sputa were collected at baseline, 48 and 72 weeks from participants with HIV-associated CLD randomised to receive weekly AZM or placebo for 48 weeks and followed post-intervention until 72 weeks. The primary outcomes were prevalence and antibiotic resistance of *Streptococcus pneumoniae* (SP), *Staphylococcus aureus* (SA), *Haemophilus influenzae* (HI), and *Moraxella catarrhalis* (MC) at these timepoints. Mixed-effects logistic regression and Fisher's exact test were used to compare carriage and resistance respectively.

Of 347 (174 AZM, 173 placebo) participants (median age 15 years [IQR =13–18], females 49%),NP carriage was significantly lower in the AZM (n=159) compared to placebo (n=153) arm for SP (18% vs 41%, p<0.001), HI (7% vs 16%, p=0.01), and MC (4% vs 11%, p=0.02); SP resistance to AZM (62% [18/29] vs 13%[8/63], p<0.0001) or tetracycline (60%[18/29] vs 21%[13/63], p<0.0001) were higher in the AZM arm. Carriage of SA resistant to AZM (91% [31/34] vs 3% [1/31], p<0.0001), tetracycline (35% [12/34] vs 13% [4/31], p= 0.05) and clindamycin (79% [27/34] vs 3% [1/31], p<0.0001) was also significantly higher in the AZM arm and persisted at 72 weeks. Similar findings were observed for sputa.

The persistence of antibiotic resistance and its clinical relevance for future infectious episodes requiring treatment needs further investigation.

Keywords: HIV, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, children

Summary: Forty-eight weeks of azithromycin reduced carriage of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* but promoted antibiotic resistance in *S. pneumoniae* and *S. aureus*; antibiotic-resistant *S. aureus* persisted at 72 weeks from randomisation.

Background

Long-term azithromycin (AZM) therapy is commonly used to manage chronic lung diseases (CLD), including cystic fibrosis [1], non-cystic bronchiectasis [2], chronic obstructive pulmonary disease (COPD) [3] and asthma [4]. Evidence suggests that AZM may improve lung function and survival, reduce frequency of acute pulmonary exacerbations, antibiotic administration and hospitalisation in some of these CLDs. These beneficial effects may be mediated by the dual antimicrobial and immunomodulatory properties of AZM [3].

However, AZM use can promote antibiotic resistance in both commensal and potentially pathogenic bacteria in the respiratory tract [1–4], which can be further spread to untreated individuals. AZM can also promote resistance to other antibiotics including tetracyclines, lincosamides and Streptogramins [5]. This is mediated by alteration of drug targets shared by other antibiotics (lincosamides and Streptogramins) and co-location of resistance genes on the same mobile genetic elements (tetracyclines) [5]. In a meta-analysis of CLD patients (COPD, cystic fibrosis, bronchiectasis, and asthma) who received long-term AZM, the risk of bacterial resistance increased 2.7-fold while bacterial colonisation risk was halved in AZM group compared to placebo [6]. None of the trials included in this meta-analysis reported on the persistence of the microbiological effect post-intervention and none included African children or patients with HIV-related CLD. Two later studies that did investigate the persistence of the AZM's microbiological effect post-intervention could not provide robust conclusions due to few participants [2, 7] (mean of 25 per trial arm), short follow up period (4 weeks for one study) [7] and variable timepoints for post-intervention samples [2].

Children with HIV are at high risk of respiratory tract infections. Recent studies have shown that these children also have a high prevalence of CLD, despite anti-retroviral therapy (ART) [8]. The clinical presentation is typically that of chronic cough, reduced exercise tolerance, hypoxia and reduced lung function [8]. Up to a third of these children with HIV included in African studies have CLD with constrictive obliterative bronchiolitis being the dominant cause [8]. As there are currently no treatment guidelines, we conducted a double-blinded, placebo-controlled randomised trial that showed that 48 weeks of once-weekly AZM reduced acute respiratory exacerbations and all-cause hospitalisations in African children with HIV-associated CLD [9]. The microbiological sequelae of long-term AZM have not been previously investigated in a paediatric population with HIV-associated CLD. To address the potential for selection of antibiotic-resistant bacteria in this patient population, we investigated the impact of long-term AZM therapy on the carriage and antibiotic resistance of *Streptococcus pneumoniae* (SP), *Staphylococcus aureus* (SA), *Haemophilus influenzae* (HI) and *Moraxella catarrhalis* (MC) at the 48 weeks (end of therapy) and 72 weeks from randomisation. We also assessed factors associated with carriage and resistance.

Methods

The main results of the BREATHE trial (ClinicalTrials.gov Identifier: NCT02426112) [9] are reported elsewhere. Briefly, individuals with HIV-associated CLD aged 6–19 years and taking ART for at least six months were enrolled from HIV outpatient clinics in Harare, Zimbabwe and Blantyre, Malawi. CLD was defined as forced expiratory volume in 1 second (FEV_1) *z*-score less than -1.0 with no reversibility [<12% improvement in FEV_1 after 200 µg of salbutamol inhaled using a spacer]. Participants were individually randomised to receive weight-based dosing of

AZM (10 to 19.9 kg, 250 mg; 20 to 29.9 kg, 500 mg; 30 to 39.9 kg, 750 mg; and 40 kg or more, 1250 mg) or placebo once-weekly up to 48 weeks, with follow-up for a further 24 weeks post-intervention. Adherence to trial medication was defined as not missing, on average, more than two of the 12 dispensed doses, as assessed by pill count, splitting time in the study into four 12-week periods, according to visit and study medication dispensing schedule [9].

Nasopharyngeal (NP) swabs and sputa were collected from participants at baseline, 48- and 72-week visits. Details of sample collection, handling and transport, culture and antibiotic susceptibility testing (AST) for SP, SA, HI and MC have previously been described [10]. Briefly, susceptibility to AZM, tetracycline and cotrimoxazole was conducted for all four bacterial species using the Kirby-Bauer disk diffusion method. Additionally, AST was done for SP to oxacillin, SA to clindamycin, cefoxitin, and penicillin, HI to amoxicillin-clavulanate, cefuroxime, and ampicillin, and MC to amoxicillin-clavulanate. Inducible clindamycin resistance was assessed as previously reported [11]. SA susceptibility to cefoxitin was tested as a surrogate for methicillin resistance. AST was conducted in accordance with the 2018 Clinical and Laboratory Standards Institute guidelines and breakpoints [12].

Outcomes

The primary outcomes for this study were the difference in the prevalence of SP, SA, HI and MC and their AZM-resistant strains between trial arms at AZM cessation (48 weeks). Secondary outcomes included the differences in the carriage and AZM resistance between trial arms at 72 weeks. We also investigated the effect of long-term AZM on resistance to the additional antibiotics tested at both 48 and 72 weeks. The clinical and socio-demographic factors associated with the carriage of bacteria and AZM-resistant isolates at 48 and 72 weeks; and the effect of adherence to AZM on carriage and resistance (in the AZM arm only) were also assessed.

Statistical analyses

Statistical analyses were conducted in R software version 3.6.2. Bacterial carriage and antibiotic resistance were reported as percentages of total samples cultured and tested for resistance for each trial arm. Fisher's exact test and Mann-Whitney test were used to compare proportions and continuous variables, respectively. Comparisons of bacterial carriage between trial arms at all visits were conducted using mixed-effects logistic regression models, including a random effect for participants, and reported as adjusted odds ratios with 95% confidence intervals in Stata version 15 (StataCorp, Texas, USA). Models were adjusted for site, sex, age category, HIV viral load at enrolment, the season of sampling and visit. A trial arm by time interaction term was included in models to compare trial arms at 48 and 72 weeks, without a trial arm main effect term [13].

Ethical approval and consent to participate

Approval for the main trial was obtained from local regulatory bodies at the study sites and the research ethics committees of the London School of Hygiene and Tropical Medicine, the University of Cape Town, and the Medical and Health Research in Norway. This sub-study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC/REF: 092/2019). Written informed consent and age-appropriate assent were provided by guardians and participants under 18 years, respectively. Older participants (≥18 years) consented independently.

Results

Between June 15, 2016, and September 4, 2018, 347 participants (173 AZM and 174 placebo arm) were enrolled and randomised to AZM or placebo (Figure 1). Eleven participants who were later found to not meet the inclusion criteria for FEV_1 were included in this report. At baseline, participants had a median age of 15 years [IQR = 13–18] with slightly more males than females (51% [177/347] vs 49% [170/347]). The majority of participants were on cotrimoxazole prophylaxis (90% [313/347]) (Table 1). NP and sputum samples were obtained from an average of 97% of all participants at baseline and 48 weeks and 86% at 72 weeks (Figure 1).

Table 1: Baseline Characteristics of study participants

Characteristics	Details	AZM arm N=173	Placebo arm N=174
Demographic Characteristics			
Age in years	Median (IQR)	14.7 (12.6 – 16.8)	15.8 (13.0 – 18.1)
Sex	Female: No. (%)	80 (46.2)	90 (51.7)
Currently in school	No. (%)[a]	146 (84.5)	139 (79.9)
Site	Zimbabwe: No. (%)	120 (69)	121 (70)
	Malawi: No. (%)	53 (31)	53 (30)
HIV Characteristics			
Age in years at diagnosis	Median (IQR)	7.2 (3.5 – 9.9)	8.3 (5.2 – 11.1)
Duration on ART in years	Median (IQR)	5.9 (3.8 – 9.0)	6.4 (3.9 – 8.2)
Age at ART initiation	Median (IQR)	8.2 (5.0 – 11.2)	8.9 (6.7 – 11.6)
HIV viral load log 10 copies/ml	Median (IQR)	2.5 (1.6- 4.0)	2.7 (1.7- 4.1)
HIV viral load suppression	<1000 copies/ml: No. (%)	102 (59.0)	94 (54.0)
CD4 cell count /mm^3	Median (IQR)	601 (417 – 784)	550 (325 – 779)
CD4 count categories	200+ cells/mm: No. (%)	157 (91)	156 (89.7)
	<200 cells/mm: No. (%)	16 (9)	18 (10.3)
Antiretroviral regimen	[l]NNRTI, No. (%)[a]	127 (73)	131 (75)
	[§] PI, No. (%)[a]	46 (27)	42 (25)
Lung function			
FEV1 *z*-score	Median (IQR)	-1.94 (-2.5, -1.4)	-2.0 (-2.4, -1.5)
Clinical Characteristics			
Weight-for-age *z*-score	Median (IQR)	-2.2 (-3.0, -1.4)	-1.9 (-2.8, -1.2)
Underweight	No. (%)[b]	98 (56.6)	83 (47.7)
Height-for-age *z*-score	Median (IQR)	-2.1 (-3.0 , -1.4)	-1.9 (-2.6, -1.3)
Stunted	No. (%)[b]	95 (54.9)	80 (46.0)
History of TB	No. (%)[a]	58 (33.57	39 (22.4)
Admitted for chest problems in last year	No. (%)	3 (1.7)	3 (1.7)
Current cough	No. (%)[a]	13 (7.5)	18 (10.3)
Coughing up sputum	No. (N)[c]	7 (43)	17 (46)
MRC dyspnoea Score	1	89 (51)	96 (55)
	2	64 (37)	62 (36)
	3	12 (7)	11 (6.3)
	4	7 (4)	4 (2.3)
	5	1 (1)	1 (1)
Cotrimoxazole prophylaxis	No. (%)	157 (92)[a]	156 (90)

[a] *Missing value: Currently attending school – n=1 AZM arm; Antiretroviral regimen, n=1, Placebo arm; History of TB– n=1, AZM arm Current cough– n=1, AZM arm; Cotrimoxazole prophylaxis– n=2, AZM arm,* [b] *z-score <-2 ,*[c] *Only asked for those with current cough,* [§] Protease inhibitor *FEV1: Forced Expiratory Volume in one Second;* Participants with missing responses are excluded from that variable. [l]Nonnucleoside Reverse Transcriptase Inhibitor, No. = number of participants, IQR = interquantile range, TB = tuberculosis, MRC =Medical Research Council.

Participants randomised to receive AZM were less likely to carry SP (aOR 0.2, [0.1– 0.4], p < 0.0001), HI (aOR 0.3, [0.1–0.8], $p = 0.01$) or MC (aOR 0.2, [0.1–0.8], $p = 0.02$) (Table 2) in their NP at 48 weeks than placebo. The carriage of any of the four species was lower in the AZM arm at 48 weeks (aOR 0.4, [0.2– 0.7], p = 0.001), but not at 72 weeks, compared to placebo (Table 2). These observations were mirrored in the sputum samples (Table 2).

At 48 weeks, the proportion of SP (62% [18/29] vs 13% [8/63], $p < 0.0001$) or SA (91% [31/34] vs 3% [1/31], $p < 0.0001$) isolates from the NP that were AZM-resistant was higher in the AZM arm than placebo (Figure 2 and 3). However, at 72 weeks, there were no differences in the proportion of AZM-resistant strains, except for AZM-resistant SA (45% [9/20] in the AZM arm vs 4% [1/26] in the placebo arm, $p < 0.001$) (Figure 3). Overall AZM resistance (resistance in any of the four bacterial species) was higher in the AZM arm at 48 weeks (30% [45/154] vs 7% [10/146], $p < 0.0001$) and remained so at 72 weeks (17% [17/102] vs 7% [7/90], $p < 0.0001$) relative to placebo. The above observations were mirrored in sputum samples (Figures 2 and Figure 3).

The proportion of SP and SA in the NP that were tetracycline-resistant was also higher at 48 weeks in the AZM arm than placebo (Figure 2 and Figure 3, Supplementary table S1). Clindamycin resistance in SA was higher in the AZM arm vs. placebo at 48 weeks (79% [27/34] vs 3% [1/31], $p < 0.0001$) and remained higher at 72 weeks in the AZM arm compared to placebo (45% [9/20] vs 0% [0/26], $p < 0.0001$] (Figure 3, Supplementary table S1). Carriage of methicillin-resistant SA remained low (6%) throughout the study in both trial arms (Figure 3, Supplementary table S1). Penicillin (oxacillin) resistance in SP was moderate and indifferent between trial arms however, penicillin resistant SA was higher in AZM than placebo at 72 weeks (Supplementary table S1). Cotrimoxazole resistance levels in SA remained high (~69%), with no clear changes throughout the study period (Supplementary table S1). There was no difference between the trial arms with HI and MC susceptibility to AZM, tetracycline, amoxicillin-clavulanate and cotrimoxazole (Supplementary table S1, Figure S1–S2). There was a universal HI susceptibility to cefuroxime and ampicillin (Supplementary table S1, Figure S1). The above observations were mirrored in sputum samples (Figure 3, Supplementary table S2, Figure S1–S2) except for tetracycline-resistant SP, which did not differ between trial arms at 48 weeks. Also, unlike in the NP, penicillin resistance in sputum SA was similar between trial arms at all visits (Figure 3, Supplementary table S2).

Adherence to AZM was associated with reduced likelihood of sputum SA and overall bacterial carriage at 48 weeks (Supplementary table S3). Adherence was not associated with the carriage of resistant bacteria (Supplementary table S4 and S5). The main factors associated with SP carriage was male sex (NP only) and placebo allocation (NP and sputum) at 48 weeks and age at 72 weeks (Supplementary table S6). Similarly, factors associated with NP and sputum SA carriage were non-adherence to AZM (NP and sputum, Supplementary table S7), viral load suppression (sputum) and season of sampling (Supplementary table S7). Placebo allocation and non-adherence to AZM was associated with increased likelihood of AZM-resistant SP and SA carriage in the NP or sputum (Supplementary table S8 and S9).

Table 2: Nasopharyngeal and sputum bacterial carriage at enrolment, 48 weeks and 72 weeks in participants

NASOPHARYNGEAL SWABS										
	Baseline		**48 weeks**				**72 weeks**			
	AZM (n=168)[1]	**Placebo (n=171)[1]**	**AZM (n=159)[2]**	**Placebo (n=153)[2]**	**aOR (95%CI)**	**P values**	**AZM (n=118)[3]**	**Placebo (n=105)[3]**	**aOR (95%CI)**	**P values**
Streptococcus pneumoniae	74 (44%)	83 (49%)	29 (18%)	64 (41%)	0 .2 [0.1-0.4]	**<0.0001**	41 (35%)	38 (36%)	0.9 [0.4-1.7]	0.681
Staphylococcus aureus	45 (27%)	36 (21%)	34 (21%)	31 (20%)	1.1 [0.5-2.2]	0.882	23 (19%)	26 (25%)	0.7 [0.3-1.7]	0.433
Haemophilus influenzae	21 (13%)	18 (11%)	11 (7%)	24 (16%)	0.3 [0.1-0.8]	**0.011**	13 (11%)	10 (10%)	1.0 [0.4-2.8]	0.964
Moraxella catarrhalis	26 (15%)	21 (12%)	7 (4%)	17 (11%)	0.3 [0.1-0.8]	**0.015**	9 (8%)	7 (7%)	0.9 [0.3-2.9]	0.848
Bacterial carriage (any)	107 (64%)	112 (68%)	63 (43%)	86 (60%)	0.4 [0.2-0.7]	**0.001**	61 (53%)	63 (60%)	0.6 [0.3-1.2]	0.135
SPUTUM										
	Baseline		**48 weeks**				**72 weeks**			
	AZM (n=166)[4]	**Placebo (n=164)[4]**	**AZM (n=148)[5]**	**Placebo (n=143)[5]**	**aOR (95%CI)**	**P values**	**AZM (n=116)[6]**	**Placebo (n=106)[6]**	**aOR (95%CI)**	**P values**
Streptococcus pneumoniae	43 (26%)	38 (23%)	17 (11%)	34 (24%)	0.4 [0.2 -0.8]	**0.008**	20 (17%)	26 (25%)	0.6 [0.3-1.2]	0.122
Staphylococcus aureus	51 (31%)	46 (28%)	46 (31%)	37 (26%)	1.4 [0.7-2.8]	0.323	40 (34%)	37 (34%)	1.1 [0.5-2.3]	0.788
Haemophilus influenzae	4 (2%)	7 (4%)	3 (2%)	19 (13%)	0.1 [0.0-0.4]	**0.002**	6 (5%)	9 (8%)	0.5 [0.1-1.6]	0.221
Moraxella catarrhalis	15 (9%)	15 (9%)	4 (3%)	15 (10%)	0.2 [0.1-0.7]	**0.008**	7 (6%)	7 (7%)	0.9 [0.3-2.8]	0.882
Bacterial carriage (any)	82 (49%)	79 (48%)	62 (42%)	77 (54%)	0.6 [0.3-1.0]	**0.056**	56 (48%)	60 (57%)	0.8 [0.4-1.4]	0.395

[1]Samples not collected from five and three participants in AZM and placebo group at baseline respectively. [2]Samples not collected from five and seven participants in AZM and placebo group at 48 weeks respectively. [3]Samples not collected from 16 and 15 participants in AZM and placebo group at 72 weeks respectively. [4]Sputum samples were not collected from seven and 10 participants in AZM and placebo group at baseline respectively. [5]Sputum samples not collected from 16 and 17 participants in AZM and placebo group at 48 weeks respectively. [6]Sputum samples not collected from 18 and 14 participants in AZM and placebo group at 72 weeks respectively. aOR= adjusted Odd Ratio

Discussion

Our study shows that HIV-infected children with CLD established on ART and cotrimoxazole prophylaxis, who received 48 weeks of AZM therapy, were significantly less likely to carry SP, HI and MC in their NP or sputum compared to placebo at the end of treatment. However, these participants were more likely to carry AZM and tetracycline-resistant SP and SA at 48 weeks. AZM-, clindamycin- and tetracycline-resistant SA remained more prevalent in participants in the AZM arm at 72 weeks.

Our finding of reduced NP and sputum carriage of SP, HI and MC in response to long-term AZM therapy is consistent with previous studies [2, 6]. Similarly, the lack of an effect of long-term AZM therapy on SA carriage observed in our study was also reported in studies conducted in children with chronic suppurative lung disease in Australia and New Zealand [2], and cystic fibrosis in The Netherlands [14], and USA [3]. The reduction in SP, HI and MC prevalence in our study may be related to the almost universal susceptibility of these isolates to AZM at baseline or the consequence of improved alveolar macrophage phagocytic activity [15]. Phagocytosis is generally reduced in chronic lung conditions, especially COPD, but improves with AZM therapy [15]. A survey conducted from 2015 to 2018, the same time period as our study, reported a high SP carriage among children and adults in Malawi regardless of pneumococcal vaccination and HIV status [16]. Our finding that AZM reduced SP carriage may have important implications in reducing the risk of invasive SP disease as well as transmission. The lack of difference between trial arms in the carriage of SP, HI or MC at 72 weeks highlights that the antimicrobial effects of long-term AZM therapy may not be long-lasting. This is corroborated by reports from a randomised controlled trial of AZM among Indigenous Australian, Maori and Pacific Island children aged 1–8 years with chronic suppurative lung disease [2].

Long-term AZM therapy selected for AZM-resistant SP at the end of treatment. This is consistent with other studies that used AZM for both long- [1–3, 14, 17] and short-term [11, 18, 19] treatment periods. AZM resistance occurs soon after exposure, as evidenced by the recovery of resistant strains after a single AZM course or dose [11]. Previous studies revealed clonal expansion of existing resistant strains of SP following exposure to AZM [19]. Studies that involved mass AZM administration for trachoma also noted an increase in resistant SP, which resolved over time [20, 21]. Since the genetic changes that confer macrolide resistance may reduce the fitness of SP strains (their ability to compete with drug-susceptible strains), resistant SP strains were likely to have been displaced by susceptible strains once the antibiotic selective pressure was removed [2]. AZM use did not select for penicillin–resistant SP in our study. Although, we did not determine minimum inhibitory concentrations for the isolates, this non-selection of penicillin-resistant SP is consistent with previous studies that administered AZM for both short [18] and long-term periods [2]. This is important as penicillins remain the first-line treatment for pneumococcal infections in sub-Saharan Africa.

Although the proportion of AZM-resistant SA declined at 72 weeks, AZM-resistant SA isolates remained significantly more common in the AZM arm at this visit. In a cystic fibrosis clinic in the Netherlands, the occurrence of AZM-resistant SA was common enough to warrant discontinuation of long-term AZM therapy among cystic fibrosis patients [1]. In contrast, in Denmark, a low prevalence of SA in cystic fibrosis patients at baseline with a further reduction during treatment with AZM made increase macrolide resistance in SA clinically insignificant [17].

It is possible that the baseline prevalence of SA may influence the effect of long-term AZM therapy on resistance. Additionally, the differences in strength and frequency of dosing of AZM across studies may also contribute to the variations in the observed patterns of resistance. SA is an important pathogen in HIV-infected patients where it causes bacteraemia leading to endocarditis [22]. Staphylococcal bacteraemia is about 17 times more likely to occur in a hospitalised HIV-infected adult than a HIV-negative patient [22]. The increase in AZM-resistant SA which persist beyond six months post-AZM in our setting is therefore concerning.

The increase in tetracycline (SP and SA) and clindamycin (SA only) resistance at 48 weeks is not surprising since mobile genetic elements that mediate resistance to macrolides co-carry genes that confer resistance to other antibiotics [23]. Of note, the conjugative transposon Tn916-like element, which carries *tet* (tetracycline resistance) and *erm* genes [23]. The *erm* gene product modifies the bacterial ribosomal target site of macrolides, lincosamides (clindamycin) and streptogramin antibiotics, thereby conferring resistance. These transposons are found in both SP [23] and SA [24]; hence the concurrent increase in resistance to macrolides, lincosamides and tetracyclines with AZM therapy in our study is expected [23]. These mobile genetic elements with multiple resistance genes can be shared between bacterial species and across genera, increasing the overall burden of drug resistance [25].

SP is the most common bacterial cause of community-acquired pneumonia globally [26]. Macrolide-resistant SP is a major concern in the United States and other parts of the world as macrolides have been the first drug of choice in monotherapy for adults for decades [27]. There have been multiple reports of clinical failures resulting from macrolide-resistant SP when patients were treated with macrolides [28]. However, the clinical relevance of macrolide-resistant SP based on AST has remained controversial [28]. This is fuelled by observations that although macrolide-resistant SP, as determined by AST, has been on the rise, an increase in clinical failures due to these isolates has not been observed as frequently as expected (the so-called "*in vitro in vivo"* paradox) [27]. One explanation for this discrepancy is that the current *in vitro* resistance testing methods may not accurately model the action of an antibiotic in the body during an infection [26]. During inflammation, for instance, the level of AZM increases substantially because of intracellular accumulation within macrophages and leukocytes at the site of infection [26]. Furthermore, the potent immunomodulatory properties of macrolides, which influence the resolution of respiratory infections, are not accounted for by the AST method [26].

Although macrolides are not the first-line treatment for SP and SA respiratory infections in Malawi and Zimbabwe (penicillin and tetracyclines are used in Malawi and cotrimoxazole and amoxicillin in Zimbabwe), macrolides are indicated where there is treatment failure following amoxicillin use or in combination with ceftriaxone for severe illness (Malawi). They are also indicated in cases with penicillin allergy or atypical pneumonia in both countries. For SA infections (including those at other body sites, such as skin and soft tissue infections), cloxacillin is the first-line antibiotic; however, clindamycin is indicated in penicillin hypersensitivity. Therefore, the clinical relevance of AZM-resistant SP and SA and clindamycin-resistant SA among study participants and their contacts should be further investigated.

To address concerns about the transmission of AZM-resistant SA to untreated individuals, Tramper-Stranders *et al*., 2007 [29] compared the prevalence of AZM-resistant SA among cystic fibrosis patients on long-term AZM therapy and their household contacts. They found that although there was a higher AZM-resistant SA carriage among the cystic fibrosis patients (69.6%), carriage among household contact (9.6%) was similar to the general population (6.3%) of the Netherlands. Furthermore, the transmission of resistant isolates from the patients to their household contacts could not be proved by genotyping, except for one household. This finding suggests that although the potential risk of transmission of AZM-resistant SA exists, the probability is low. However, this observation may be quite different in an African household.

Taylor et al [30, 4] showed that AZM's ability to reduce acute respiratory exacerbations is mediated by its capacity to reduce airway HI load, which is mirrored in our study. Our finding that AZM-resistant HI and MC strains were uncommon, and similar between trial arms at all visits, is consistent with previous clinical trials of long-term AZM therapy [2,3]. However, other studies of long-term AZM observed an increase in AZM-resistant HI [1,31] and MC [3,31]. The discordance across studies in the observed patterns of HI and MC resistance may be explained by the differences in the dose and duration of AZM used. Also, relatively few isolates of both bacterial species were identified in many studies (including our own) and may have been underpowered to detect resistance in these species.

Huang *et al* [32] observed that acute respiratory exacerbations were associated with an increase in the relative abundance of the bacterial phylum Proteobacteria in patients with COPD. Antibiotic treatment reduced this relative abundance and was associated with resolution of symptoms. Broader changes in the airway microbiome and not only in the specific bacterial species we measured, may modulate the effect of AZM in HCLD. However, microbial dysbiosis may occur in other microbial niches, including the gut, following long-term AZM treatment, and the local and systemic consequences of such dysbiosis requires further study.

Given concerns around the emergence of resistance with long-term AZM therapy, the use of newer macrolide-based drugs that have potent immunomodulatory activity without resistance-promoting antibacterial effect should be considered. Hodge *et al* [33] investigated two new macrolides with limited antibacterial activity against SP, SA, MC and HI. They found that these drugs improve macrophage phagocytosis of bacteria and therefore reduce bacterial carriage and associated acute exacerbations of CLD [33].

The strengths of our study are that it was a double-blinded, individually randomised, placebo-controlled, multicentre study among children with HIV-associated CLD in sub-Saharan African, a previously under-studied population. The study also analysed the persistence of the microbiological effect of long-term AZM therapy six months post-intervention. Furthermore, we also demonstrated that the long-term AZM promoted resistance to other antibiotics (tetracycline and clindamycin). Study limitations include the lack of genomic investigation to delineate the mechanisms underlying antibiotic resistance and determine SP and HI serotypes. Furthermore, 27% of participants' outcomes could not be assessed at 72 weeks due to withdrawal, death and loss to follow-up. However, our findings at this later time point are consistent with previous findings [2]. We could not determine when SA resistance to azithromycin, tetracycline and clindamycin resolved because study concluded at 72 weeks from randomisation.

Another limitation is that the study was not adequately powered to conclude whether AZM induced resistance in HI and MC as the number of isolates recovered from trial participants was low. We did not perform quantitative assessment of minimum inhibitory concentrations (MIC) of antibiotics, which may have identified increases in MIC which did not lead to changes in resistance category.

Long-term AZM therapy reduced the prevalence of SP, HI and MC in African children with HIV-associated CLD while increasing the carriage of AZM and tetracycline-resistant SP and SA at 48 weeks. Inducible clindamycin resistance also increased in SA at 48 weeks. However, these microbiological effects resolved six months post-intervention, except for AZM, tetracycline, and clindamycin resistance in SA. Further studies are needed to determine whether resistance in SA persists beyond 72 weeks. The benefit of reduced acute exacerbations of HIV-associated CLD shown in this study [9], should be weighed against the largely temporary acquisition of antimicrobial resistance to AZM as well as other antibiotics.

Contributors

MPN, FSD and RAF conceived the study. REA conducted laboratory experiments and wrote the first manuscript draft, supervised by MPN and FSD. CB assisted with laboratory experiments. Statistical analysis was conducted by REA, supported by AMR and VS. GM and LN coordinated the trial in Zimbabwe and Malawi, respectively. BW and RH reviewed the manuscript. JOO and RAF are trial PIs. All authors contributed to the manuscript, and all authors have read and approved the final version.

Data sharing

All de-identified data will be available from the University of Cape Town ZivaHub with approval from University of Cape Town ethics committee and a signed data access agreement.

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Figure captions

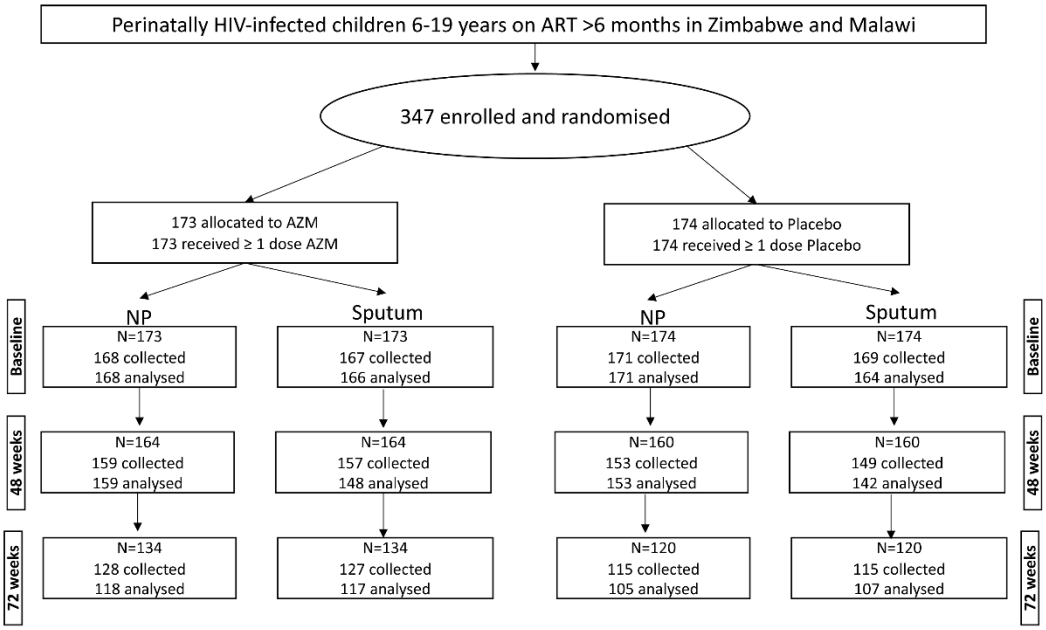

Figure 1

Figure 1: Number of samples collected at each visit flowchart

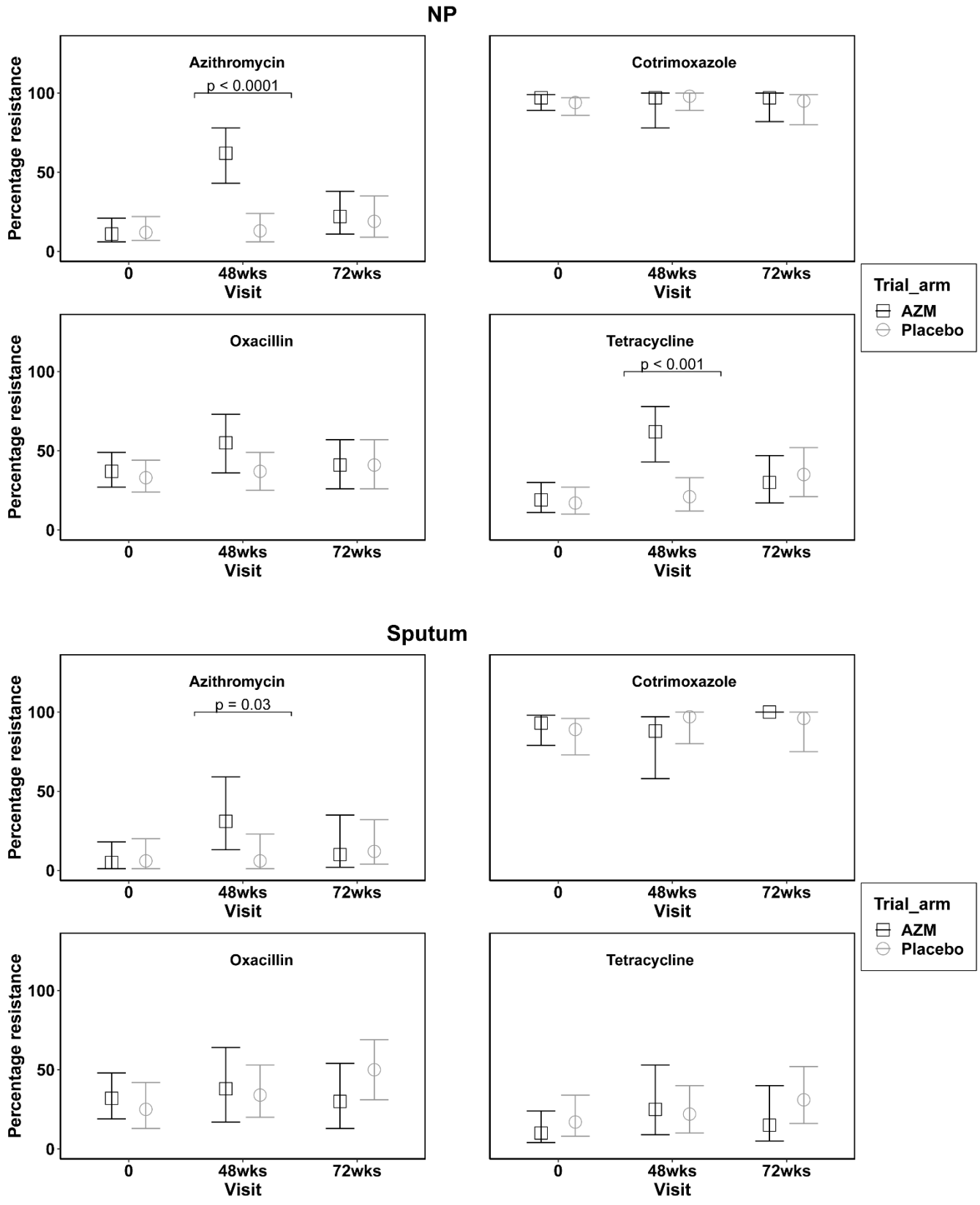

Figure 2: Antibiotic resistance profiles of *Streptococcus pneumoniae* isolated from the nasopharyngeal (NP) and sputum samples at enrolment, 48 weeks and 72 weeks. The x- and y-axes are sampling timepoints and percentage resistance respectively. Number of isolates from NP at each timepoint for AZM vs placebo were– baseline (71 vs 81), 48 weeks (29 vs 63), 72 weeks (37 vs 37). In the sputum, baseline (41 vs 36), 48 weeks (16 vs 32), 72 weeks (20 vs 26). Oxacillin used as a surrogate for penicillin.

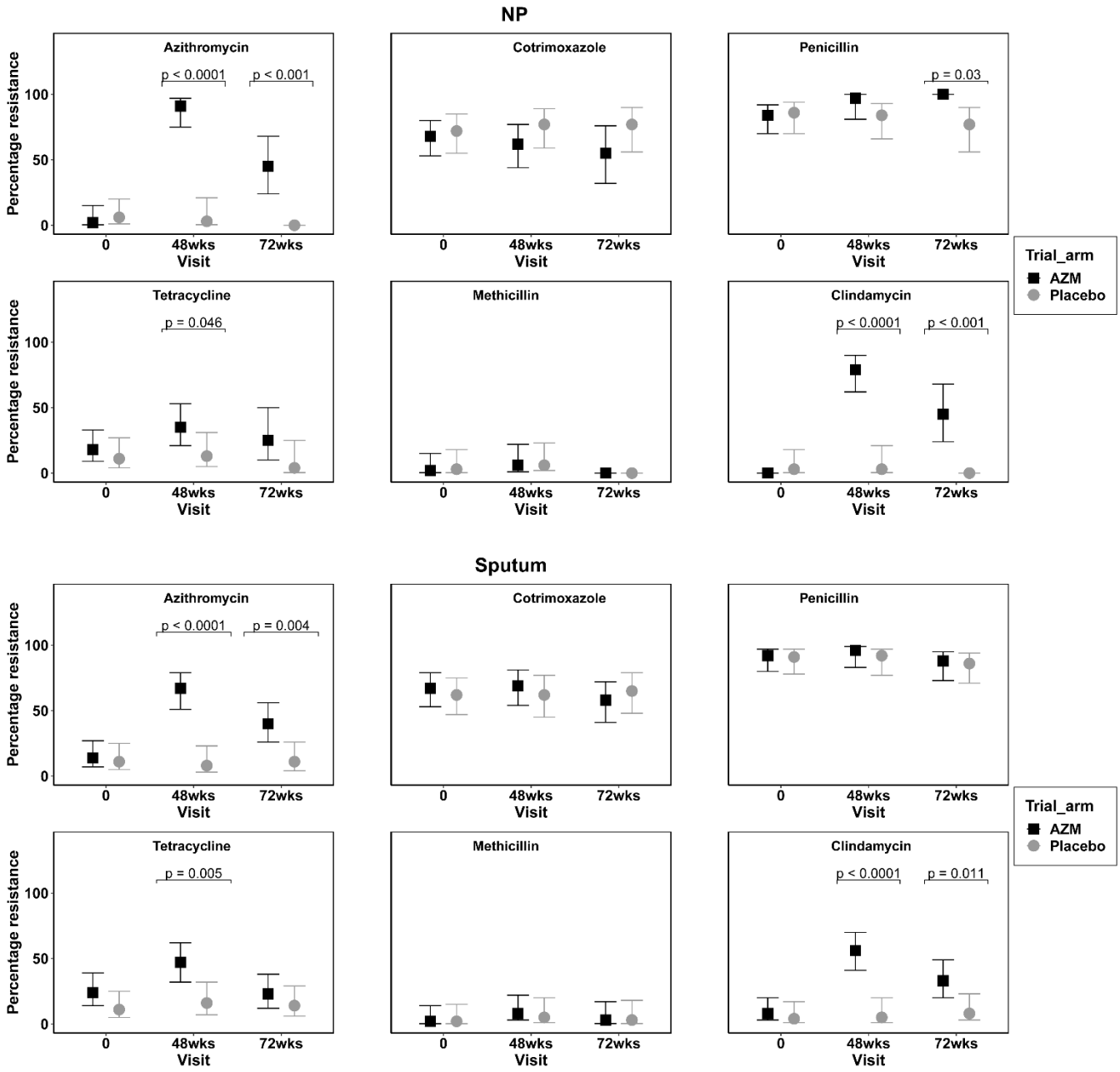

Figure 3: Antibiotic resistance profiles of *Staphylococcus aureus* isolated from the nasopharyngeal and sputum samples at enrolment, 48 weeks and 72 weeks. The x- and y-axes are sampling timepoints and percentage resistance respectively Number of isolates from NP at each timepoint for AZM vs placebo were– baseline (44 vs 36), 48 weeks (34 vs 31), 72 weeks (20 vs 26). In the sputum, baseline (49 vs 45), 48 weeks (45 vs 37), 72 weeks (40 vs 37)

Supplementary Figure captions

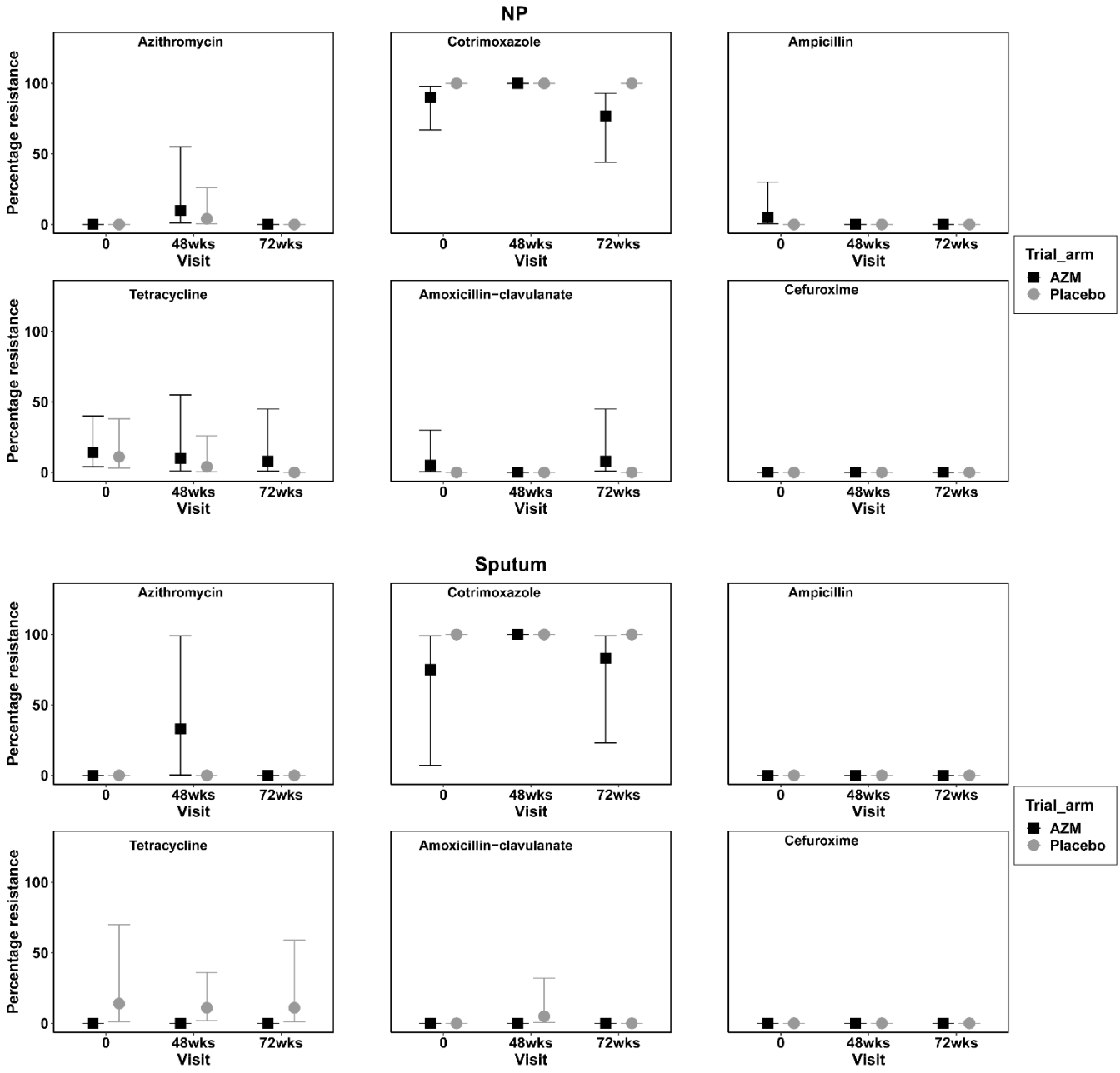

Figure S1: Antibiotic resistance profiles of *Haemophilus influenzae* isolated from the nasopharyngeal (NP) and sputum samples at enrolment, 48 weeks and 72 weeks. The x- and y-axes are sampling timepoints and percentage resistance respectively. Number of isolates from NP at each timepoint for AZM vs placebo were– baseline (21 vs 18), 48 weeks (10 vs 24), 72 weeks (13 vs 8). In the sputum, baseline (4 vs 7), 48 weeks (3 vs 19), 72 weeks (6 vs 9).

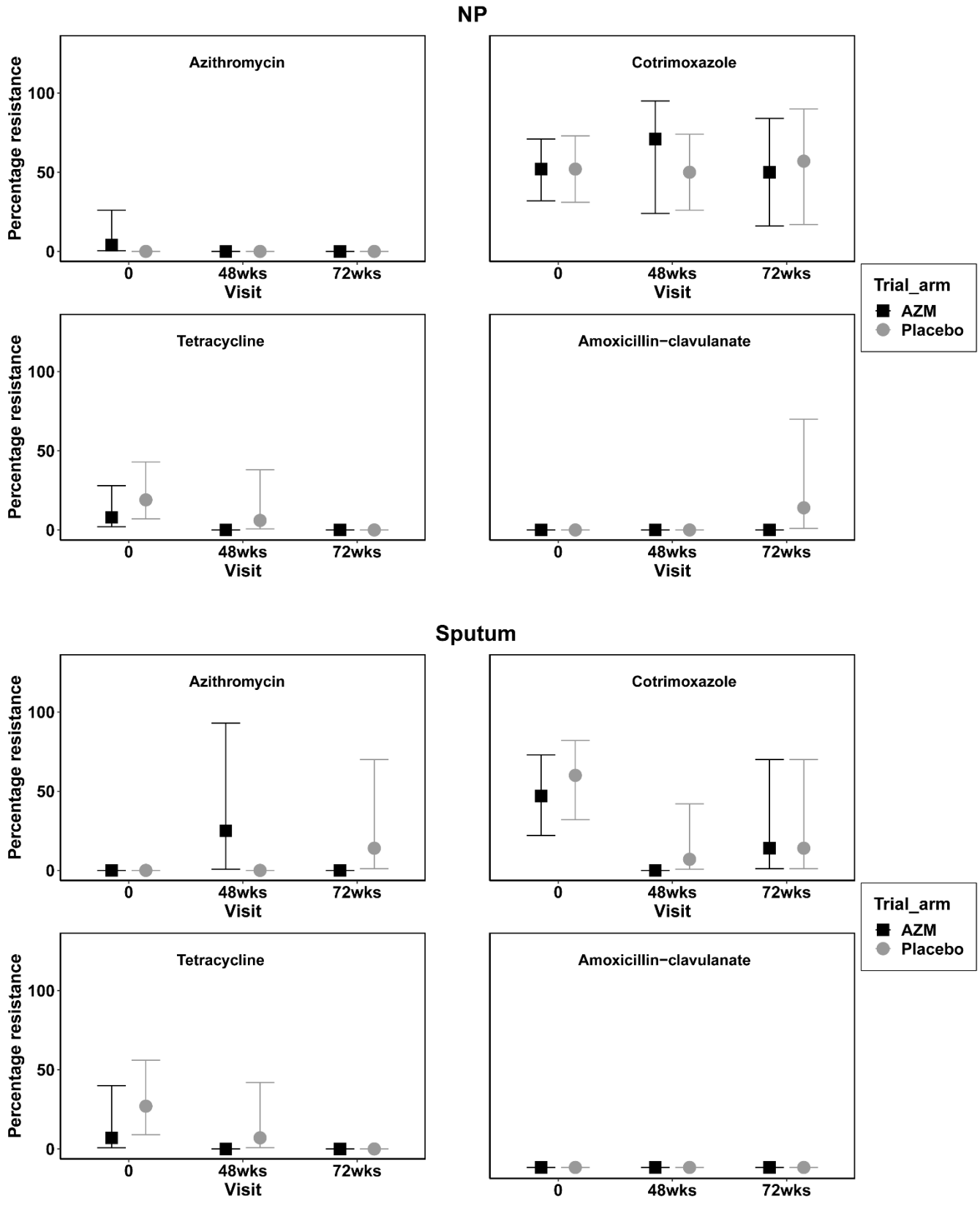

Figure S2: Antibiotic resistance profiles of *Moraxella catarrhalis* isolated from the nasopharyngeal (NP) and sputum samples at enrolment, 48 weeks and 72 weeks. The x- and y-axes are sampling timepoints and percentage resistance respectively. Number of isolates from NP at each timepoint for AZM vs placebo were– baseline (25 vs 21), 48 weeks (7 vs 16), 72 weeks (8 vs 7). In the sputum, baseline (15 vs 15), 48 weeks (4 vs 14), 72 weeks (7 vs 7).ss

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SUPPLEMENTARY TABLES

Table S1. Antibiotic resistance of bacteria isolated from the nasopharyngeal swabs collected at enrolment , 48 weeks and 72 weeks from participants taking azithromycin or placebo.

Carriage	Baseline			48 weeks			72 weeks		
	AZM (n=168)[1]	**Placebo (n=171)[1]**	**P values**	**AZM (n=159)[2]**	**Placebo (n=153)[2]**	**P values**	**AZM (n=118)[3]**	**Placebo (n=105)[3]**	**P values**
Streptococcus pneumoniae (SP)									
Azithromycin resistant SP	8/71 (11%)	10/81 (12%)	1	18/29 (62%)	8/63 (13%)	**<0.001**	8/37 (22%)	7/37 (19%)	1
Tetracycline resistant SP	13/70 (19%)	14/81 (17%)	0.835	18/29 (60%)	13/63 (21%)	**<0.001**	11/37 (30%)	13/37 (35%)	0.804
Cotrimoxazole resistant SP	68/70 (97%)	76/81 (93%)	0.451	28/29 (97%)	62/63 (98%)	0.533	36/37 (97%)	35/37 (95%)	1
[4]Penicillin non-susceptible SP	26/70 (37%)	27/81 (33%)	0.733	16/29 (55%)	23/63 (37%)	0.114	15/37(41%)	15/37 (41%)	1
Staphylococcus aureus (SA)									
Azithromycin resistant SA	1/44 (2%)	2/36 (6%)	0.586	31/34 (91%)	1/31 (3%)	**<0.001**	9/20 (45%)	0/26 (0%)	**<0.001**
Tetracycline resistant SA	8/44 (18%)	4/36 (11%)	0.532	12/34 (35%)	4/31 (13%)	**0.046**	5/20 (25%)	1/26 (4%)	0.072
Cotrimoxazole resistant SA	30/44 (68%)	26/36 (72%)	0.808	21/34 (62%)	24/31 (77%)	0.192	11/20 (55%)	20/26 (77%)	0.204
Penicillin resistant SA	37/44 (84%)	31/36 (86%)	1	33/34 (97%)	26/31 (84%)	0.095	20/20 (100%)	20/26 (77%)	**0.029**
Methicillin resistant SA	1/44 (2%)	1/36 (3%)	1	2/34 (6%)	2/31 (6%)	1	0/20 (0%)	0/26 (0%)	1
Clindamycin resistant SA	0/44 (0%)	1/36 (3%)	0.45	27/34 (79%)	1/31 (3%)	**<0.001**	9/20 (45%)	0/26 (0%)	**<0.001**
Haemophilus influenzae (HI)									
Azithromycin resistant HI	0/21 (0%)	0/18 (0%)	NA	1/10 (10%)	1/24 (4%)	NA	0/13 (0%)	0/8 (0%)	NA
Tetracycline resistant HI	3/21 (14%)	2/18 (11%)	1	1/10 (10%)	1/24 (4%)	0.508	1/13 (8%)	0/9 (0%)	1
Cotrimoxazole resistant HI	19/21 (90%)	18/18 (100%)	0.490	10/10 (100%)	24/24 (100%)	1	10/13 (77%)	9/9 (100%)	0.240
Ampicillin resistant HI	1/21 (5%)	0/18 (0%)	1	0/10 (0%)	0/24 (0%)	1	0/13 (0%)	0/9 (0%)	1

Amoxicillin-clavulanate resistant HI	1/21 (5%)	0/18 (0%)	1	0/10 (0%)	0/24 (0%)	1	1/13 (8%)	0/9 (0%)	1
Cefuroxime resistant HI	0/21 (0%)	0/18 (0%)	NA	0/10 (0%)	0/24 (0%)	NA	0/13 (0%)	0/9 (0%)	NA
Moraxella catarrhalis (MC)									
Azithromycin resistant MC	1/25 (4%)	0/21 (0%)	1	0/7 (0%)	0/16 (0%)	1	0/8 (0%)	0/7 (0%)	1
Tetracycline resistant MC	2/25 (8%)	4/21 (19%)	0.390	0/7 (0%)	1/16 (6%)	1	0/8 (0%)	0/7 (0%)	1
Cotrimoxazole resistant MC	13/25 (52%)	11/21 (52%)	1	5/7 (71%)	8/16 (50%)	0.405	4/8 (50%)	4/7 (57%)	1
Amoxicillin-clavulanate resistant MC	0/25 (0%)	0/21 (0%)	1	0/7 (0%)	0/16 (0%)	1	0/8 (0%)	1/7 (14%)	0.467
All four bacteria									
Macrolide resistant (any)	10 (6%)	12 (7%)	0.826	45 (30%)	10 (7%)	**<0.001**	17 (15%)	7 (7%)	**0.011**
Tetracycline resistant (any)	24 (14%)	23 (14%)	0.742	30 (20%)	18 (13%)	**<0.001**	16 (14%)	13(12%)	0.392

[1]Samples not collected from five and three participants in AZM and placebo group at baseline respectively. [2]Samples not collected from five and seven participants in AZM and placebo group at 48 weeks respectively.[3]Samples not collected from 16 and 15 participants in AZM and placebo group at 72 weeks respectively. [4]Oxacillin used as surrogate for penicillin. Fishers exact test used to compare proportions.

Table S2. Antibiotic resistance of bacteria isolated from the sputa collected at enrolment , 48 weeks and 72 weeks from participants taking azithromycin or placebo.

Carriage	Baseline			48 weeks			72 weeks		
	AZM (n=166)[1]	**Placebo (n=164)[1]**	**P values**	**AZM (n=148)[2]**	**Placebo (n=143)[2]**	**P values**	**AZM (n=116)[3]**	**Placebo (n=106)[3]**	**P values**
Streptococcus pneumoniae (SP)									
Azithromycin resistant SP	2/41 (5%)	2/36 (6%)	1	5/16 (31%)	2/32 (6%)	**0.033**	2/20 (10%)	3/26 (12%)	1
Tetracycline resistant SP	4/41 (10%)	6/35 (17%)	0.499	4/16 (25%)	7/32 (22%)	1	3/20 (15%)	8/26 (31%)	0.302
Cotrimoxazole resistant SP	38/41 (93%)	32/36 (89%)	0.699	14/16 (88%)	31/32 (97%)	0.254	20/20 (100%)	25/26 (96%)	1
[4]Penicillin non-susceptible SP	13/41 (32%)	9/36 (25%)	0.616	6/16 (38%)	11/32 (34%)	1	6/20 (30%)	13/26 (50%)	0.232
Staphylococcus aureus (SA)									
Azithromycin resistant SA	7/49 (14%)	5/45 (11%)	0.762	30/45 (67%)	3/37 (8%)	**<0.001**	16/40 (40%)	4/37 (11%)	**0.004**
Tetracycline resistant SA	12/49 (24%)	5/45 (11%)	0.113	21/45 (47%)	6/37 (16%)	**0.005**	9/40 (23%)	5/37 (14%)	0.382
Cotrimoxazole resistant SA	33/49 (67%)	28/45 (62%)	0.668	31/45 (69%)	23/37 (62%)	0.641	23/40 (58%)	24/37 (65%)	0.641
Penicillin resistant SA	45/49 (92%)	41/45 (91%)	1	43/45 (96%)	34/37 (92%)	0.654	35/40 (86%)	32/37 (86%)	1
Methicillin resistant SA	1/49 (2%)	1/45 (2%)	1	4/45 (8%)	2/37 (5%)	0.685	1/40 (3%)	1/37 (3%)	1
Clindamycin resistant SA	4/49 (8%)	2/45 (4%)	0.679	25/45 (56%)	2/37 (5%)	**<0.001**	13/40 (33%)	3/37 (8%)	**0.011**
Haemophilus influenzae (HI)									
Azithromycin resistant HI	0/4 (0%)	0/7 (0%)	1	1/3 (33%)	0/19 (0%)	0.136	0/6 (0%)	0/9 (0%)	1
Tetracycline resistant HI	0/4 (0%)	1/7 (14%)	1	0/3 (0%)	2/19 (11%)	1	0/6 (0%)	1/9 (11%)	1
Cotrimoxazole resistant HI	3/4 (75%)	7/7 (100%)	0.364	3/3 (100%)	19/19 (100%)	1	5/6 (83%)	9/9 (100%)	0.4
Ampicillin resistant HI	0/4 (0%)	0/7 (0%)	NA	0/3 (0%)	0/19 (0%)	NA	0/6 (0%)	0/9 (0%)	NA
Amoxicillin-clavulanate resistant HI	0/4 (0%)	0/7 (0%)	NA	0/3 (0%)	1/19 (5%)	1	0/6 (0%)	0/9 (0%)	NA

Cefuroxime resistant HI	0/4 (0%)	0/7 (0%)	NA	0/3 (0%)	0/19 (0%)	NA	0/6 (0%)	0/9 (0%)	NA
Moraxella catarrhalis (MC)									
Azithromycin resistant MC	0/15 (0%)	0/15 (0%)	1	1/4 (25%)	0/14 (0%)	0.222	0/7 (0%)	1/7% (14%)	1
Tetracycline resistant MC	1/15 (7%)	4/15 (27%)	0.330	0/4 (0%)	1/14 (7%)	1	0/7 (0%)	0/7 (0%)	1
Cotrimoxazole resistant MC	7/15 (47%)	9/15 (60%)	0.715	0/4 (0%)	1/14 (7%)	1	1/7% (14%)	1/7% (14%)	1
Amoxicillin-clavulanate resistant MC	0/15 (0%)	0/15 (0%)	NA	0/4 (0%)	0/14 (0%)	NA	0/7 (0%)	0/7 (0%)	NA
All four bacteria									
Macrolide resistant (any)	9 (5%)	7 (4%)	0.795	36 (24%)	5 (3%)	**<0.001**	18 (16%)	8 (8%)	**0.025**
Tetracycline resistant (any)	17 (10%)	16 (10%)	1	25 (17%)	15 (10%)	**0.008**	12 (10%)	13 (12%)	1

[1]Samples not collected from seven and 10 participants in AZM and placebo group at baseline respectively. [2]Samples not collected from 16 and 17 participants in AZM and placebo group at 48 weeks respectively.[3]Samples not collected from 18 and 14 participants in AZM and placebo group at 72 weeks respectively. [4]Oxacillin used as surrogate for penicillin. Fishers exact test used to compare proportions.

Table S3: Nasopharyngeal and sputum bacterial carriage at enrolment, 48 weeks and 72 weeks in participants taking azithromycin, by adherence to azithromycin

	NASOPHARYNGEAL SWABS												
	Baseline (n=168)[1]			**48 weeks (n=159)[2]**					**72 weeks (n=118)[3]**				
	Total (n=168)	**Adherent (n=124)[1]**	**Non-adherent (n=44)[1]**	**Total (n=159)**	**Adherent (n=122)[2]**	**Non-adherent (n=37)**	**aOR (95%CI)**	**P value**	**Total (n=118)**	**Adherent (n=94)[3]**	**Non-adherent (n=24)[3]**	**aOR (95%CI)**	**P value**
Streptococcus pneumoniae	74 (44%)	58 (47%)	16 (36%)	29 (18%)	22 (18%)	7 (19%)	1·5 [0·4-5·2]	0·529	41 (35%)	34 (36%)	7 (29%)	1·4 [0·4-4·8]	0·554
Staphylococcus aureus	45 (27%)	33 (27%)	12 (27%)	34 (21%)	20 (16%)	14 (38%)	0·4 [0·1-1·2]	0·609	23 (19%)	19 (20%)	4 (17%)	2·2 [0·5-9·6]	0·293
Haemophilus influenzae	21 (13%)	15 (12%)	6 (14%)	11 (7%)	8 (7%)	3 (8%)	0·8 [0·2-4·0]	0·814	13 (11%)	10 (11%)	3 (13%)	0·9 [0·2-4·5]	0·975
Moraxella catarrhalis	26 (15%)	18 (15%)	8 (18%)	7 (4%)	4 (3%)	3 (8%)	0·6 [0·1-3·4]	0·537	9 (8%)	4 (4%)	5 (21%)	0·2 [0·0-0·98]	**0·048**
Bacterial carriage (any)	107 (64%)	78 (61%)	29 (63%)	63 (43%)	45 (35%)	18 (49%)	1·1 [0·4-2·6]	0·912	61 (53%)	49 (48%)	12 (39%)	1·7 [0·6-5·1]	0·310
	SPUTUM												
	Baseline (n=166)[1]			**48 weeks (n=148)[2]**					**72 weeks (n=116)[3]**				
	Total (n=166)[4]	**Adherent (n=122)[4]**	**Non-adherent (n=44)[4]**	**Total (n=148)[5]**	**Adherent (n=114)[5]**	**Non-adherent (n=34)[5]**	**aOR (95%CI)**	**P values**	**Total (n=117)[6]**	**Adherent (n=93)[6]**	**Non-adherent (n=24)[6]**	**aOR (95%CI)**	**P values**
Streptococcus pneumoniae	43 (26%)	36 (30%)	7 (16%)	17 (11%)	13 (11%)	4 (12%)	0·6 [0·2-2·6]	0·491	20 (17%)	16 (17%)	4 (17%)	0·8 [0·2-3·1]	0·750
Staphylococcus aureus	51 (31%)	40 (33%)	11 (25%)	46 (31%)	29 (25%)	17 (50%)	0·2 [0·1-0·6]	**0·004**	40 (34%)	32 (34%)	8 (33%)	1·0 [0·3-3·6]	0·972
Haemophilus influenzae	4 (2%)	2 (2%)	2 (5%)	3 (2%)	2 (2%)	1 (3%)	0·6 [0·0-14·2]	0·756	6 (5%)	5 (5%)	1 (4%)	5·4 [0·3-83·7]	0·229
Moraxella catarrhalis	15 (9%)	11 (9%)	4 (9%)	4 (3%)	2 (2%)	2 (6%)	0·3 [0·0-2·6]	0·257	7 (6%)	5 (5%)	2 (8%)	0·9 [0·1-6·7]	0·896
Bacterial carriage (any)	82 (49%)	60 (47%)	22 (48%)	62 (42%)	41 (32%)	21 (57%)	0·2 [0·1-0·6]	**0·003**	56 (48%)	45 (44%)	11 (35%)	1·3 [0·4-4·0]	0·634

[1]Samples not collected from three and two participants in adherent and non-adherent group at baseline respectively. [2]Samples not collected from five participants in adherent at 48 weeks. [3]Samples not collected from nine and seven participants in adherent and non-adherent group at 72 weeks respectively. [4]Samples not collected from five and two participants in adherent and non-adherent group at baseline respectively.

[5]Samples not collected from 13 and three participants in adherent and non-adherent groups at 48 weeks respectively. [6]Samples not collected from 11 and seven participants in adherent and non-adherent group at 72 weeks respectively. aOR= adjusted Odd Ratio. Comparisons of bacterial carriage between trial arms at all visits were conducted using mixed-effects logistic regression models, including a random effect for participants. Models were adjusted for site, sex, age category, HIV viral load at enrolment, the season of sampling and visit. A trial arm by time interaction term was included in models to compare trial arms at 48 and 72 weeks, without a trial arm main effect term.

Table S4: Antibiotic resistance of nasopharyngeal bacterial isolates at enrolment , 48 weeks and 72 weeks in participants taking azithromycin, by adherence to azithromycin

	Baseline (n=168)[1]				48 weeks(n=159)[2]				72 weeks (n=118)[3]			
	Total (n=168)	**Adherent (n=122)[1]**	**Non-adherent (n=44)[1]**	**P values**	**Total (n=159)**	**Adherent (n=122)[2]**	**Non-adherent (n=37)**	**P values**	**Total (n=118)**	**Adherent (n=94)[3]**	**Non-adherent (n=24)[3]**	**P values**
Streptococcus pneumoniae (SP)												
Azithromycin resistant SP	8/71 (11%)	6/56 (11%)	2/15 (13%)	0·673	18/29 (62%)	14/22 (64%)	4/7 (57%)	1	8/37 (22%)	7/30 (23%)	1/7 (14%)	1
Tetracycline resistant SP	13/70 (19%)	8/55 (15%)	5/15 (33%)	0·133	18/29 (62%)	14/22 (64%)	4/7 (57%)	1	11/37 (30%)	9/30 (30%)	2/7 (29%)	1
Cotrimoxazole resistant SP	68/70 (97%)	53/55 (96%)	15/15 (100%)	1	28/29 (97%)	21/22 (95%)	7/7 (100%)	1	36/37 (97%)	29/30 (97%)	7/7 (100%)	1
[4]Penicillin non-susceptible SP	26/70 (37%)	20/55 (36%)	6/15 (40%)	1	16/29 (55%)	12/22 (54%)	4/7 (57%)	1	15/37(41%)	12/30(40%)	3/7 (43%)	1
Staphylococcus aureus (SA)												
Azithromycin resistant SA	1/44 (2%)	1/33 (3%)	0/11 (0%)	1	31/34 (91%)	18/20 (90%)	13/14 (93%)	1	9/20 (45%)	7/17 (41%)	2/3 (67%)	0·566
Tetracycline resistant SA	8/44 (18%)	6/33 (18%)	2/11 (18%)	1	12/34 (35%)	6/20 (30%)	6/14 (43%)	0·487	5/20 (25%)	4/17 (24%)	1/3 (33%)	1
Cotrimoxazole resistant SA	30/44 (68%)	22/33 (67%)	8/11 (72%)	1	21/34 (62%)	12/20 (60%)	9/14 (64%)	1	11/20 (55%)	9/17 (53%)	2/3 (67%)	1
Penicillin resistant SA	37/44 (84%)	28/33 (84%)	9/11 (82%)	1	33/34 (97%)	20/20 (100%)	13/14 (93%)	0·412	20/20 (100%)	17/17 (100%)	3/3 (100%)	1
Methicillin resistant SA	1/44 (2%)	1/33 (3%)	0/11 (0%)	1	2/34 (6%)	1/20 (5%)	1/14 (7%)	1	0/20 (0%)	0/17 (0%)	0/3 (0%)	1
Clindamycin resistant SA	0/44 (0%)	0/33 (0%)	0/11 (0%)	1	27/34 (79%)	17/20 (85%)	10/14 (71%)	0·4099	9/20 (45%)	7/17 (41%)	2/3 (67%)	0·566
Haemophilus influenzae (HI)												
Azithromycin resistant HI	0/21 (0%)	0/15 (0%)	0/6 (0%)	NA	1/10 (10%)	1/7 (14%)	0/3 (0%)	NA	0/13 (0%)	0/10 (0%)	0/3 (0%)	NA
Tetracycline resistant HI	3/21 (14%)	3/15 (20%)	0/6 (0%)	0·526	1/10 (10%)	1/7 (14%)	0/3 (0%)	1	1/13 (8%)	1/10 (10%)	0/3 (0%)	1

Cotrimoxazole resistant HI	19/21 (90%)	14/15 (93%)	5/6 (83%)	0·5	10/10 (100%)	7/7 (100%)	3/3 (100%)	1	10/13 (77%)	7/10 (70%)	3/3 (100%)	0·528
Ampicillin resistant HI	1/21 (5%)	1/15 (67%)	0/6 (0%)	1	0/10 (0%)	0/7 (0%)	0/3 (0%)	1	0/13 (0%)	0/10 (0%)	0/3 (0%)	1
Amoxicillin-clavulanate resistant HI	1/21 (5%)	1/15 (7%)	0/6 (0%)	1	0/10 (0%)	0/7 (0%)	0/3 (0%)	1	1/13 (8%)	1/10 (10%)	0/3 (0%)	1
Cefuroxime resistant HI	0/21 (0%)	0/15 (0%)	0/6 (0%)	NA	0/10 (0%)	0/7 (0%)	0/3 (0%)	NA	0/13 (0%)	1/10 (10%)	0/3 (0%)	NA
Moraxella catarrhalis (MC)												
Azithromycin resistant MC	1/25 (4%)	1/17 (6%)	0/8 (0%)	1	0/7 (0%)	0/4 (0%)	0/3 (0%)	1	0/8 (0%)	0/3(0%)	0/5 (0%)	1
Tetracycline resistant MC	2/25 (8%)	0/17 (0%)	2/8 (25%)	0·093	0/7 (0%)	0/4 (0%)	0/3 (0%)	1	0/8 (0%)	0/3 (0%)	0/5 (0%)	1
Cotrimoxazole resistant MC	13/25 (52%)	7/17 (41%)	6/8 (75%)	0·202	5/7 (71%)	3/4 (75%)	2/3 (67%)	1	4/8 (50%)	2/3 (67%)	2/5 (40%)	1
Amoxicillin-clavulanate resistant MC	0/25 (0%)	0/17 (0%)	0/8 (0%)	1	0/7 (0%)	0/4 (0%)	0/3 (0%)	1	0/8 (0%)	0/3 (0%)	0/5 (0%)	1
All four bacteria												
Macrolide resistant (any)	10 (6%)	8 (6%)	2 (7%)	1	45 (30%)	30 (68%)	15 (83%)	0·348	17 (15%)	14 (32%)	3 (27%)	1
Tetracycline resistant (any)	24 (14%)	17 (22%)	7 (25%)	0·797	30 (20%)	21 (48%)	9 (50%)	1	16 (14%)	13 (30%)	3 (27%)	1

[1]Samples not collected from three and two participants in adherent and non-adherent group at baseline respectively. [2]Samples not collected from five participants in adherent at 48 weeks. [3]Samples not collected from nine and seven participants in adherent and non-adherent group at 72 weeks respectively. [4]Oxacillin used as surrogate for penicillin. NA is Not applicable. Fishers exact test used to compare proportions.

Table S5: Sputum carriage and antibiotic resistance at enrolment , 48 weeks and 72 weeks in participants taking azithromycin, by adherence to azithromycin

Carriage	Baseline (n=166)[1]				48 weeks				72 weeks			
	Total (n=166)[1]	Adherent (n=122)[1]	Non-adherent (n=44)[1]	P values	Total (n=148)[2]	Adherent (n=114)[2]	Non-adherent (n=34)[2]	P values	Total (n=117)[3]	Adherent (n=93)[3]	Non-adherent (n=24)[3]	P values
Streptococcus pneumoniae (SP)												
Azithromycin resistant SP	2/41 (5%)	2/34 (6%)	0/7 (0%)	1	5/16 (31%)	4/12 (33%)	1/4 (25%)	1	2/20 (10%)	2/16 (13%)	0/4 (0%)	1
Tetracycline resistant SP	4/41 (10%)	4/34 (12%)	0/7 (0%)	1	4/16 (25%)	3/12 (25%)	1/4 (25%)	1	3/20 (15%)	1/16 (6%)	2/4 (50%)	0·088
Cotrimoxazole resistant SP	38/41 (93%)	31/34 (91%)	7/7 (100%)	1	14/16 (88%)	10/12 (83%)	4/4 (100%)	1	20/20 (100%)	16/16 (100%)	4/4 (100%)	1
[4]Penicillin non-susceptible SP	13/41 (32%)	12/34 (35%)	1/7 (14%)	0·399	6/16 (38%)	4/12 (33%)	2/4 (50%)	0·604	6/20 (30%)	5/16 (31%)	1/4 (25%)	1
Staphylococcus aureus (SA)												
Azithromycin resistant SA	7/49 (14%)	5/38 (13%)	2/11 (18%)	0·647	30/45 (67%)	17/29 (59%)	13/16 (81%)	0·189	16/40 (40%)	13/32 (41%)	3/8 (38%)	1
Tetracycline resistant SA	12/49 (24%)	9/38 (24%)	3/11 (27%)	1	21/45 (47%)	15/29 (52%)	6/16 (38%)	0·533	9/40 (23%)	8/32 (25%)	1/8 (13%)	0·655
Cotrimoxazole resistant SA	33/49 (67%)	27/38 (71%)	6/11 (54%)	0·466	31/45 (69%)	21/29 (72%)	10/16 (63%)	0·519	23/40 (58%)	18/32 (56%)	5/8 (63%)	1
Penicillin resistant SA	45/49 (92%)	36/38 (95%)	9/11 (81%)	0·214	43/45 (96%)	27/29 (93%)	16/16 (100%)	0·531	35/40 (86%)	27/32 (84%)	8/8 (100%)	0·563
Methicillin resistant SA	1/49 (2%)	1/38 (3%)	0/11 (0%)	1	4/45 (8%)	2/29 (7%)	2/16 (13%)	0·608	1/40 (3%)	1/32 (3%)	0/8 (0%)	1

Clindamycin resistant SA	4/49 (8%)	3/38 (8%)	1/11 (9%)	1	25/45 (56%)	14/29 (48%)	11/16 (69%)	0·224	13/40 (33%)	11/32 (34%)	2/8 (25%)	1
Haemophilus influenzae (HI)												
Azithromycin resistant HI	0/4 (0%)	0/2 (0%)	0/2 (0%)	1	1/3 (33%)	1/2 (50%)	0/1 (0%)	1	0/6 (0%)	0/5 (0%)	0/1 (0%)	1
Tetracycline resistant HI	0/4 (0%)	0/2 (0%)	0/2 (0%)	1	0/3 (0%)	0/2 (0%)	0/1 (0%)	1	0/6 (0%)	0/5 (0%)	0/1 (0%)	1
Cotrimoxazole resistant HI	3/4 (75%)	2/2 (100%)	1/2 (50%)	1	3/3 (100%)	2/2 (100%)	1/1 (100%)	1	5/6 (83%)	4/5 (80%)	1/1 (100%)	1
Ampicillin resistant HI	0/4 (0%)	0/2 (0%)	0/2 (0%)	NA	0/3 (0%)	0/2 (0%)	0/1 (0%)	NA	0/6 (0%)	0/5 (0%)	0/1 (0%)	NA
Amoxicillin-clavulanate resistant HI	0/4 (0%)	0/2 (0%)	0/2 (0%)	1	0/3 (0%)	0/2 (0%)	0/1 (0%)	1	0/6 (0%)	0/5 (0%)	0/1 (0%)	1
Cefuroxime resistant HI	0/4 (0%)	0/2 (0%)	0/2 (0%)	NA	0/3 (0%)	0/2 (0%)	0/1 (0%)	NA	0/6 (0%)	0/5 (0%)	0/1 (0%)	NA
Moraxella catarrhalis (MC)												
Azithromycin resistant MC	0/15 (0%)	0/11 (0%)	0/4 (0%)	1	1/4 (25%)	1/2 (50%)	0/2 (0%)	1	0/7 (0%)	0/5 (0%)	0/2 (0%)	1
Tetracycline resistant MC	1/15 (7%)	0/11 (0%)	1/4 (25%)	0·267	0/4 (0%)	0/2 (0%)	0/2 (0%)	1	0/7 (0%)	0/5 (0%)	0/2 (0%)	1
Cotrimoxazole resistant MC	7/15 (47%)	6/11 (55%)	1/4 (25%)	0·569	0/4 (0%)	0/2 (0%)	0/2 (0%)	1	1/7% (14%)	1/5 (20%)	0/2 (0%)	1
Amoxicillin-clavulanate resistant MC	0/15 (0%)	0/11 (0%)	0/4 (0%)	NA	0/4 (0%)	0/2 (0%)	0/2 (0%)	NA	0/7 (0%)	0/5 (0%)	0/2 (0%)	NA
All four bacteria												
Macrolide resistant (any)	9 (5%)	7 (12%)	2 (9%)	1	36 (24%)	22 (55%)	14 (70%)	0·402	18 (16%)	15 (33%)	3 (27%)	1
Tetracycline resistant (any)	17 (10%)	13 (22%)	4 (18%)	1	25 (17%)	18 (45%)	7 (35%)	0·581	12 (10%)	9 (20%)	3 (27%)	0·686

[1]Samples not collected from three and two participants in adherent and non-adherent group at baseline respectively. [2]Samples not collected from five participants in adherent at 48 weeks. [3]Samples not collected from nine and seven participants in adherent and non-adherent group at 72 weeks respectively. [4]Oxacillin used as surrogate for penicillin. NA is Not applicable. Fishers exact test used to compare proportions.

Table S6: Factors associated with carriage of *Streptococcus pneumoniae* isolates at 48 weeks and 72 weeks in trial participants

	NASOPHARYNGEAL SWABS											
	48 weeks						72 weeks					
			Univariate analysis		Multivariate analysis				Univariate analysis		Multivariate analysis	
Variable	No. observations (n=312)#	No. isolates (n=93)*	Adjusted Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value	No. observations (n=223)§	No. isolates (n=79)ω	Adjusted Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value
Site												
Malawi	31% (96)	41% (38)	Reference		Reference		20% (44)	23% (18)	Reference		Reference	
Zimbabwe	69% (216)	59% (55)	0.52 [0.31–0.87]	0.012	0.55 [0.22–1.35]	0.195	80% (179)	77% (61)	0.75 [0.38–1.48]	0.397	1.05 [0.32–3.44]	0.936
Sex												
Female	48% (151)	57% (53)	Reference		Reference		45% (100)	52% (41)	Reference		Reference	
Male	52% (161)	43% (40)	0.61 [0.37–0.99]	0.049	0.52 [0.28–0.96]	0.038	55% (123)	48% (38)	0.64 [0.37–1.12]	0.118	0.62 [0.32–1.18]	0.148
Season of sampling												
May-Oct-Dry	58% (180)	56% (52)	Reference		Reference		37% (82)	35% (28)	Reference		Reference	
Nov-Apr-Rainy	42% (132)	44% (41)	1.11 [0.68–1.81]	0.679	0.97 [0.53–1.75]	0.922	63% (141)	65% (51)	1.09 [0.62–1.95]	0.761	0.91 [0.47–1.75]	0.768
Weight-for-age-z-score												
Not underweight	51% (158)	49% (45)	Reference		Reference		47% (104)	51% (40)	Reference		Reference	
underweight	49% (149)	51% (46)	1.12 [0.69–1.83]	0.647	1.56 [0.85–2.91]	0.158	53% (117)	49% (39)	0.8 [0.46–1.39]	0.428	0.92 [0.47–1.79]	0.795
Age at enrolment												
6-9y	9% (28)	10% (9)	Reference		Reference		11% (24)	19% (15)	Reference		Reference	
10-12y	20% (61)	22% (20)	1.03 [0.4–2.76]	0.33	1.12 [0.37–3.49]	0.24	18% (41)	15% (12)	0.25 [0.08–0.7]	0.04	0.28 [0.08–0.86]	0.1
13-16y	43% (133)	47% (44)	1.04 [0.45–2.6]		1.14 [0.43–3.18]		43% (96)	42% (33)	0.31 [0.12–0.78]		0.31 [0.11–0.84]	
17-19y	29% (90)	22% (20)	0.6 [0.24–1.58]		0.55 [0.19–1.63]		28% (62)	24% (19)	0.27 [0.1–0.7]		0.29 [0.09–0.84]	

Viral load suppression at enrolment												
Suppressed (<1000 copies/ml)	58% (177)	53% (48)	Reference		Reference		60% (130)	57% (45)	Reference		Reference	
Unsuppressed (>1000 copies/ml)	42% (130)	47% (43)	1.33 [0.81–2.18]	0.259	1.51 [0.82–2.78]	0.186	40% (88)	43% (34)	1.19 [0.68–2.08]	0.545	1.5 [0.78–2.91]	0.227
Adherence and Trial arm												
Adherence AZM	39% (122)	24% (22)	Reference		Reference		42% (94)	43% (34)	Reference		Reference	
Adherence Placebo	37% (114)	49% (46)	3.07 [1.71–5.65]	0.0002	4.1 [2.14–8.14]	<0.0001	38% (94)	38% (30)	0.98 [0.53–1.81]	0.92	1.01 [0.52–1.99]	0.85
Not Adherent AZM	12% (37)	8% (7)	1.06 [0.39–2.63]		0.53 [0.14–1.71]		11% (24)	9% (7)	0.73 [0.26–1.87]		0.6 [0.17–1.91]	
Not Adherent Placebo	13% (39)	19% (18)	3.9 [1.79–8.57]		2.93 [1.15–7.48]		9% (21)	10% (8)	1.09 [0.39–2.85]		0.86 [0.28–2.54]	
MRC dyspnoea score												
< 2	65% (204)	57% (53)	Reference		Reference		71% (159)	65% (51)	Reference		Reference	
2 and above	35% (108)	43% (40)	1.68 [1.01–2.76]	0.043	1.07 [0.46–2.42]	0.877	29% (64)	36% (28)	1.65 [0.9–2.99]	0.101	1.81 [0.69–4.85]	0.227
ART regimen												
ATV/LPV/PI	26% (81)	29% (27)	Reference		Reference		31% (70)	32% (25)	Reference		Reference	
EFV/NVP	74% (230)	71% (65)	0.79 [0.46–1.37]	0.39	0.51 [0.26–1]	0.049	69% (153)	68% (54)	0.98 [0.55–1.79]	0.951	1.06 [0.54–2.08]	0.876
Duration of ART at baseline												
6m-<2y	10% (31)	15% (13)	Reference		Reference		8% (18)	13% (10)	Reference		Reference	
2y-<4y	18% (53)	21% (18)	0.71 [0.29–1.79]	0.21	0.84 [0.29–2.41]	0.35	16% (35)	17% (13)	0.47 [0.14–1.49]	0.34	0.71 [0.19–2.62]	0.58
4y-<6y	21% (64)	21% (18)	0.54 [0.22–1.34]		0.58 [0.21–1.61]		21% (46)	19% (15)	0.39 [0.12–1.17]		0.44 [0.13–1.5]	
6y+	51% (154)	44% (38)	0.45 [0.2–1.03]		0.48 [0.19–1.25]		55% (119)	51% (40)	0.41 [0.14–1.1]		0.6 [0.19–1.9]	
Adherence to study drug												
Adherence	76% (236)	73% (68)	Reference				80% (178)	81% (64)	Reference			
Not Adherent	24% (76)	27% (25)	1.21 [0.69–2.1]	0.499			20% (45)	19% (15)	0.89 [0.44–1.76]	0.743		

Trial arm								
Azithromycin	51% (159)	31% (29)	Reference		53% (118)	52% (41)	Reference	
Placebo	49% (153)	69% (64)	3.22 [1.94–5.45]	<0.0001	47% (105)	48% (38)	1.07 [0.61–1.85]	0.822
BMI-for-age z-score								
Wasted	20% (62)	16% (15)	Reference		24% (54)	23% (18)	Reference	
Normal	80% (245)	84% (76)	1.41 [0.76–2.75]	0.295	76% (167)	77% (61)	1.15 [0.61–2.23]	0.67
Height-for-age z-score								
Not stunted	46% (140)	52% (47)	Reference		43% (94)	41% (32)	Reference	
Stunted	54% (167)	48% (44)	0.71 [0.43–1.16]	0.168	57% (127)	59% (47)	1.14 [0.65–2]	0.649

#Missing values: Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (10), BMI-for-age z-score (5), Height-for-age z-score (5). *Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (2), Duration of ART at baseline (1), BMI-for-age z-score (2), Height-for-age z-score (2). §Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (5), Duration of ART at baseline (5), BMI-for-age z-score (2), Height-for-age z-score (2). ωMissing values: Duration of ART at baseline (1). ℑMissing values: Season of sampling (1), Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (9), BMI-for-age z-score (5), Height-for-age z-score (5). ϑMissing values: Viral load suppression at enrolment (1), Duration of ART at baseline (2). ΨMissing values: Season of sampling (2), Weight-for-age-z-score (1), Viral load suppression at enrolment (5), Duration of ART at baseline (6), BMI-for-age z-score (1), Height-for-age z-score (1). $\mathcal{M}$Missing values: Weight-for-age-z-score (1), Viral load suppression at enrolment (1), Duration of ART at baseline (4), BMI-for-age z-score (1), Height-for-age z-score (1). BMI-for-age z-score and Height-for-age z-score were not included in the multivariate analysis because of colinearity. Adherence to study drug and Trial arm were colinear with Adherence and Trial arm hence excluded from multivariate analysis. Statistical model applied is generalised logistic regression.

Table S6: Factors associated with carriage of *Streptococcus pneumoniae* isolates at 48 weeks and 72 weeks in trial participants cont'd

SPUTUM

Variable	48 weeks						72 weeks					
	No. observations (n=290)ℑ	No. isolates (n=51)ϑ	Univariate analysis		Multivariate analysis		No. observations (n=224)Ψ	No. isolates (n=46)ℳ	Univariate analysis		Multivariate analysis	
			Adjusted Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value			Adjusted Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value
Site												
Malawi	29% (83)	35% (18)	Reference		Reference		25% (56)	30% (14)	Reference		Reference	
Zimbabwe	71% (207)	65% (33)	0.68 [0.36–1.32]	0.247	0.74 [0.24–2.25]	0.593	75% (168)	70% (32)	0.67 [0.33–1.41]	0.28	0.5 [0.12–1.91]	0.315
Sex												
Female	49% (142)	51% (26)	Reference		Reference		46% (104)	48% (22)	Reference		Reference	
Male	51% (148)	49% (25)	0.91 [0.49–1.66]	0.751	0.92 [0.43–1.97]	0.826	54% (120)	52% (24)	0.95 [0.5–1.83]	0.881	0.63 [0.29–1.38]	0.253
Season of sampling												
May-Oct-Dry	58% (167)	57% (29)	Reference		Reference		37% (82)	41% (19)	Reference		Reference	
Nov-Apr-Rainy	42% (122)	43% (22)	1.04 [0.56–1.9]	0.908	0.89 [0.43–1.81]	0.747	63% (140)	59% (27)	0.79 [0.41–1.55]	0.491	0.85 [0.4–1.86]	0.678

Weight-for-age-z-score												
Not underweight	53% (150)	51% (26)	Reference		Reference		50% (111)	42% (19)	Reference		Reference	
underweight	47% (135)	49% (25)	1.08 [0.59–1.99]	0.794	1.18 [0.56–2.52]	0.66	50% (112)	58% (26)	1.5 [0.78–2.94]	0.23	1.42 [0.64–3.24]	0.391
Age at enrolment												
6-9y	9% (27)	10% (5)	Reference		Reference		10% (23)	11% (5)	Reference		Reference	
10-12y	19% (56)	16% (8)	0.73 [0.22–2.66]	0.88	0.86 [0.22–3.66]	0.53	20% (44)	11% (5)	0.46 [0.11–1.85]	0.41	0.5 [0.1–2.34]	0.7
13-16y	43% (125)	47% (24)	1.05 [0.38–3.37]		1.74 [0.56–6.35]		44% (98)	50% (23)	1.12 [0.39–3.68]		0.97 [0.3–3.67]	
17-19y	28% (82)	27% (14)	0.91 [0.31–3.06]		1.31 [0.38–5.07]		26% (59)	28% (13)	1.04 [0.34–3.62]		0.87 [0.23–3.52]	
Viral load suppression at enrolment												
Suppressed (<1000 copies/ml)	57% (162)	50% (25)	Reference		Reference		58% (127)	49% (22)	Reference		Reference	
Unsuppressed (>1000 copies/ml)	43% (123)	50% (25)	1.4 [0.76–2.59]	0.283	1.55 [0.74–3.26]	0.241	42% (92)	51% (23)	1.6 [0.83–3.11]	0.163	1.63 [0.75–3.57]	0.217
Adherence and Trial arm												
Adherence AZM	39% (114)	25% (13)	Reference		Reference		42% (93)	35% (16)	Reference		Reference	

Adherence Placebo	36% (105)	57% (29)	2.96 [1.47–6.26]	0.012	3.82 [1.76–8.82]	0.002	38% (84)	46% (21)	1.58 [0.77–3.33]	0.61	1.62 [0.72–3.74]	0.56
Not Adherent AZM	11% (34)	8% (4)	1.04 [0.28–3.18]		0.73 [0.14–2.8]		11% (24)	9% (4)	0.95 [0.25–2.94]		0.81 [0.16–3.24]	
Not Adherent Placebo	13% (37)	10% (5)	1.21 [0.37–3.5]		0.77 [0.18–2.77]		10% (23)	11% (5)	1.4 [0.41–4.15]		1.65 [0.43–5.8]	
MRC dyspnoea score												
< 2	66% (192)	59% (30)	Reference		Reference		68% (153)	67% (31)	Reference		Reference	
2 and above	34% (98)	41% (21)	1.47 [0.78–2.73]	0.221	1.73 [0.63–4.69]	0.283	32% (71)	33% (15)	1.06 [0.52–2.1]	0.86	0.5 [0.13–1.7]	0.294
ART regimen												
ATV/LPV/PI	25% (73)	25% (13)	Reference		Reference		30% (68)	30% (14)	Reference		Reference	
EFV/NVP	75% (216)	75% (38)	0.99 [0.5–2.03]	0.967	0.72 [0.32–1.7]	0.446	70% (156)	70% (32)	0.96 [0.48–1.99]	0.906	0.85 [0.38–1.97]	0.697
Duration of ART at baseline												
6m-<2y	9% (27)	20% (10)	Reference		Reference		9% (19)	14% (6)	Reference		Reference	
2y-<4y	17% (49)	14% (7)	0.28 [0.09–0.86]	0.026	0.26 [0.07–0.88]	0.014	16% (34)	14% (6)	0.48 [0.13–1.81]	0.47	0.5 [0.11–2.19]	0.45
4y-<6y	22% (61)	27% (13)	0.46 [0.17–1.26]		0.33 [0.1–1.05]		23% (50)	26% (11)	0.61 [0.19–2.07]		0.65 [0.17–2.49]	
6y+	51% (144)	39% (19)	0.26 [0.1–0.66]		0.17 [0.06–0.51]		53% (115)	45% (19)	0.43 [0.15–1.36]		0.39 [0.11–1.43]	

Adherence to study drug								
Adherence	76% (219)	82% (42)	Reference		79% (177)	80% (37)	Reference	
Not Adherent	24% (71)	18% (9)	0.61 [0.27–1.28]	0.214	21% (47)	20% (9)	0.91 [0.39–1.99]	0.828
Trial arm								
Azithromycin	51% (148)	33% (17)	Reference		52% (117)	43% (20)	Reference	
Placebo	49% (142)	67% (34)	2.43 [1.3–4.67]	0.006	48% (107)	57% (26)	1.56 [0.81–3.03]	0.183
BMI-for-age z-score								
Wasted	20% (56)	24% (12)	Reference		22% (48)	20% (9)	Reference	
Normal	80% (229)	76% (39)	0.75 [0.37–1.61]	0.443	78% (175)	80% (36)	1.14 [0.52–2.7]	0.754
Height-for-age z-score								
Not stunted	44% (125)	47% (24)	Reference		42% (94)	49% (22)	Reference	
Stunted	56% (160)	53% (27)	0.85 [0.47–1.58]	0.612	58% (129)	51% (23)	0.69 [0.36–1.34]	0.27

#Missing values: Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (10), BMI-for-age z-score (5), Height-for-age z-score (5). *Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (2), Duration of ART at baseline (1), BMI-for-age z-score (2), Height-for-age z-score (2). §Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (5), Duration of ART at baseline (5), BMI-for-age z-score (2), Height-for-age z-score (2). ωMissing values: Duration of ART at baseline (1). ℨMissing values: Season of sampling (1), Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (9), BMI-for-age z-score (5), Height-for-age z-score (5). ϴMissing values: Viral load suppression at enrolment (1), Duration of ART at baseline (2). ΨMissing values: Season of sampling (2), Weight-for-age-z-score (1), Viral load suppression at enrolment (5), Duration of ART at baseline (6),

BMI-for-age z-score (1), Height-for-age z-score (1). $\mathcal{M}$Missing values: Weight-for-age-z-score (1), Viral load suppression at enrolment (1), Duration of ART at baseline (4), BMI-for-age z-score (1), Height-for-age z-score (1). BMI-for-age z-score and Height-for-age z-score were not included in the multivariate analysis because of colinearity. Adherence to study drug and Trial arm were colinear with Adherence and Trial arm hence excluded from multivariate analysis. Statistical model applied is generalised logistic regression.

Table S7: Factors associated with carriage of *Staphylococcus aureus* isolates at 48 weeks and 72 weeks in trial participants

	NASOPHARYNGEAL SWABS											
	48 weeks						72 weeks					
			Univariate analysis		Multivariate analysis				Univariate analysis		Multivariate analysis	
Variable	No. observations (n=312)#	No. isolates (n=65)*	Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value	No. observations (n=223)§	No. isolates (n=49)ω	Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value
Site												
Malawi	31% (96)	45% (29)	Reference		Reference		20% (44)	20% (10)	Reference		Reference	
Zimbabwe	69% (216)	55% (36)	0.46 [0.26–0.81]	0.007	0.65 [0.24–1.7]	0.38	80% (179)	80% (39)	0.95 [0.44–2.17]	0.893	0.81 [0.19–3.28]	0.77
Sex												
Female	48% (151)	52% (34)	Reference		Reference		45% (100)	45% (22)	Reference		Reference	
Male	52% (161)	48% (31)	0.82 [0.47–1.42]	0.479	0.79 [0.41–1.53]	0.484	55% (123)	55% (27)	1 [0.53–1.9]	0.993	0.97 [0.46–2.06]	0.931
Season of sampling												
May-Oct-Dry	58% (180)	43% (28)	Reference		Reference		37% (82)	31% (15)	Reference		Reference	
Nov-Apr-Rainy	42% (132)	57% (37)	2.11 [1.22–3.7]	0.008	1.71 [0.91–3.21]	0.095	63% (141)	69% (34)	1.42 [0.73–2.87]	0.313	1.16 [0.55–2.51]	0.71
Weight-for-age-z-score												
Not underweight	51% (158)	52% (32)	Reference		Reference		47% (104)	51% (25)	Reference		Reference	
underweight	49% (149)	48% (30)	0.99 [0.57–1.74]	0.979	0.89 [0.46–1.73]	0.735	53% (117)	49% (24)	0.82 [0.43–1.54]	0.529	0.69 [0.32–1.49]	0.347
Age at enrolment												
6-9y	9% (28)	8% (5)	Reference		Reference		11% (24)	8% (4)	Reference		Reference	
10-12y	20% (61)	22% (14)	1.37 [0.46–4.66]	0.29	1.18 [0.34–4.44]	0.48	18% (41)	18% (9)	1.41 [0.4–5.75]	0.22	1.52 [0.39–6.72]	0.17
13-16y	43% (133)	51% (33)	1.52 [0.57–4.8]		1.32 [0.45–4.49]		43% (96)	55% (27)	1.96 [0.67–7.19]		1.79 [0.56–7.01]	

17-19y	29% (90)	20% (13)	0.78 [0.26–2.63]		0.7 [0.21–2.56]		28% (62)	18% (9)	0.85 [0.25–3.41]		0.66 [0.17–2.93]	
Viral load suppression at enrolment												
Suppressed (<1000 copies/ml)	58% (177)	47% (30)	Reference		Reference		60% (130)	53% (26)	Reference		Reference	
Unsuppressed (>1000 copies/ml)	42% (130)	53% (34)	1.74 [1–3.03]	0.051	1.52 [0.79–2.94]	0.213	40% (88)	47% (23)	1.42 [0.74–2.69]	0.288	2.06 [0.98–4.42]	0.059
Adherence and Trial arm												
Adherence AZM	39% (122)	31% (20)	Reference		Reference		42% (94)	39% (19)	Reference		Reference	
Adherence Placebo	37% (114)	34% (22)	1.22 [0.62–2.39]	0.05	1.13 [0.55–2.35]	0.53	38% (94)	47% (23)	1.49 [0.74–3.01]	0.44	1.61 [0.76–3.48]	0.45
Not Adherent AZM	12% (37)	22% (14)	3.1 [1.36–7.06]		2 [0.74–5.25]		11% (24)	8% (4)	0.79 [0.21–2.39]		0.79 [0.18–2.92]	
Not Adherent Placebo	13% (39)	14% (9)	1.53 [0.61–3.64]		0.96 [0.3–2.78]		9% (21)	6% (3)	0.66 [0.14–2.21]		0.66 [0.13–2.48]	
MRC dyspnoea score												
< 2	65% (204)	55% (36)	Reference		Reference		71% (159)	71% (35)	Reference		Reference	
2 and above	35% (108)	45% (29)	1.71 [0.98–2.99]	0.058	0.99 [0.38–2.48]	0.989	29% (64)	29% (14)	0.99 [0.48–1.97]	0.982	0.8 [0.24–2.47]	0.71
ART regimen												
ATV/LPV/PI	26% (81)	23% (15)	Reference		Reference		31% (70)	33% (16)	Reference		Reference	
EFV/NVP	74% (230)	77% (50)	1.22 [0.66–2.39]	0.54	1.16 [0.55–2.57]	0.702	69% (153)	67% (33)	0.93 [0.48–1.86]	0.829	0.85 [0.4–1.82]	0.667
Duration of ART at baseline												
6m-<2y	10% (31)	5% (3)	Reference		Reference		8% (18)	6% (3)	Reference		Reference	
2y-<4y	18% (53)	21% (13)	3.03 [0.88–14.12]	0.38	4.96 [1.16–34.68]	0.25	16% (35)	15% (7)	1.25 [0.3–6.45]	0.93	1.59 [0.33–9.21]	0.93
4y-<6y	21% (64)	25% (15)	2.86 [0.85–13.1]		4.37 [1.07–29.89]		21% (46)	23% (11)	1.57 [0.42–7.68]		1.67 [0.39–8.88]	
6y+	51% (154)	49% (30)	2.26 [0.74–9.88]		3.5 [0.9–23.23]		55% (119)	55% (26)	1.4 [0.42–6.36]		1.56 [0.4–7.87]	
Adherence to study drug												
Adherence	76% (236)	65% (42)	Reference				80% (178)	86% (42)	Reference			

Not Adherent	24% (76)	35% (23)	2 [1.1–3.61]	0.021		20% (45)	14% (7)	0.6 [0.23–1.36]	0.248
Trial arm									
Azithromycin	51% (159)	52% (34)	Reference			53% (118)	47% (23)	Reference	
Placebo	49% (153)	48% (31)	0.93 [0.54–1.61]	0.807		47% (105)	53% (26)	1.36 [0.72–2.58]	0.344
BMI-for-age z-score									
Wasted	20% (62)	21% (13)	Reference			24% (54)	27% (13)	Reference	
Normal	80% (245)	79% (49)	0.94 [0.48–1.93]	0.865		76% (167)	73% (36)	0.87 [0.43–1.84]	0.699
Height-for-age z-score									
Not stunted	46% (140)	48% (30)	Reference			43% (94)	45% (22)	Reference	
Stunted	54% (167)	52% (32)	0.87 [0.5–1.52]	0.622		57% (127)	55% (27)	0.88 [0.47–1.69]	0.704

#Missing values: Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (10), BMI-for-age z-score (5), Height-for-age z-score (5). *Missing values: Weight-for-age-z-score (3), Viral load suppression at enrolment (1), Duration of ART at baseline (4), BMI-for-age z-score (3), Height-for-age z-score (3). §Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (5), Duration of ART at baseline (5), BMI-for-age z-score (2), Height-for-age z-score (2). ωMissing values: Duration of ART at baseline (2). ℑMissing values: Season of sampling (1), Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (9), BMI-for-age z-score (5), Height-for-age z-score (5). ϑMissing values: Weight-for-age-z-score (1), Viral load suppression at enrolment (1), Duration of ART at baseline (2), BMI-for-age z-score (1), Height-for-age z-score (1). ΨMissing values: Season of sampling (2), Weight-for-age-z-score (1), Viral load suppression at enrolment (5), Duration of ART at baseline (6), BMI-for-age z-score (1), Height-for-age z-score (1). ℳMissing values: Season of sampling (1), Viral load suppression at enrolment (2), Duration of ART at baseline (2). BMI-for-age z-score and Height-for-age z-score were not included in the multivariate analysis because of colinearity. Adherence to study drug and Trial arm were colinear with Adherence and Trial arm hence excluded from multivariate analysis. Statistical model applied is generalised logistic regression.

Table S7: Factors associated with carriage of *Staphylococcus aureus* isolates at 48 weeks and 72 weeks in trial participants cont'd

	SPUTUM											
			48 weeks						72 weeks			
Variable	No. observations (n=290)ℑ	No. isolates (n=83)ϑ	Univariate analysis		Multivariate analysis		No. observations (n=224)Ψ	No. isolates (n=77)ℳ	Univariate analysis		Multivariate analysis	
			Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value			Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value
Site												
Malawi	29% (83)	32% (27)	Reference		Reference		25% (56)	25% (19)	Reference		Reference	
Zimbabwe	71% (207)	67% (56)	0.77 [0.44–1.35]	0.352	1.24 [0.49–3.15]	0.652	75% (168)	75% (58)	1.03 [0.55–1.97]	0.935	0.66 [0.21–2]	0.467
Sex												
Female	49% (142)	46% (38)	Reference		Reference		46% (104)	42% (32)	Reference		Reference	
Male	51% (148)	54% (45)	1.2 [0.72–2]	0.493	1.18 [0.64–2.18]	0.593	54% (120)	58% (45)	1.35 [0.78–2.37]	0.291	1.3 [0.68–2.5]	0.424
Season of sampling												
May-Oct-Dry	58% (167)	64% (53)	Reference		Reference		37% (82)	36% (27)	Reference		Reference	
Nov-Apr-Rainy	42% (122)	36% (30)	0.69 [0.41–1.17]	0.172	0.59 [0.32–1.06]	0.083	63% (140)	64% (49)	1.11 [0.63–1.98]	0.729	1.1 [0.58–2.11]	0.777
Weight-for-age-z-score												
Not underweight	53% (150)	50% (41)	Reference		Reference		50% (111)	48% (37)	Reference		Reference	
underweight	47% (135)	50% (41)	1.16 [0.69–1.94]	0.572	0.92 [0.5–1.68]	0.784	50% (112)	52% (40)	1.11 [0.64–1.93]	0.709	0.81 [0.41–1.59]	0.545
Age at enrolment												
6-9y	9% (27)	11% (9)	Reference		Reference		10% (23)	5% (4)	Reference		Reference	

10-12y	19% (56)	16% (13)	0.6 [0.22–1.7]	0.68	0.62 [0.2–1.96]	0.73	20% (44)	21% (16)	2.71 [0.84–10.61]	0.38	2.6 [0.72–11.18]	0.56
13-16y	43% (125)	42% (35)	0.78 [0.33–1.96]		0.8 [0.3–2.22]		44% (98)	45% (35)	2.64 [0.91–9.65]		2.19 [0.69–8.58]	
17-19y	28% (82)	31% (26)	0.93 [0.37–2.42]		1.02 [0.37–2.94]		26% (59)	29% (22)	2.82 [0.92–10.7]		2.37 [0.69–9.74]	
Viral load suppression at enrolment												
Suppressed (<1000 copies/ml)	57% (162)	45% (37)	Reference		Reference		58% (127)	57% (43)	Reference		Reference	
Unsuppressed (>1000 copies/ml)	43% (123)	55% (45)	1.95 [1.16–3.29]	0.012	1.94 [1.07–3.57]	0.031	42% (92)	43% (32)	1.04 [0.59–1.83]	0.887	1.2 [0.62–2.3]	0.59
Adherence and Trial arm												
Adherence AZM	39% (114)	35% (29)	Reference		Reference		42% (93)	42% (32)	Reference		Reference	
Adherence Placebo	36% (105)	29% (24)	0.87 [0.46–1.61]	0.018	0.86 [0.44–1.68]	0.02	38% (84)	34% (26)	0.85 [0.45–1.6]	0.52	0.75 [0.38–1.49]	0.33
Not Adherent AZM	11% (34)	20% (17)	2.93 [1.33–6.53]		3.49 [1.37–9.15]		11% (24)	10% (8)	0.95 [0.35–2.42]		0.94 [0.3–2.77]	
Not Adherent Placebo	13% (37)	16% (13)	1.59 [0.7–3.49]		2 [0.77–5.16]		10% (23)	14% (11)	1.75 [0.69–4.43]		2.1 [0.73–6.17]	
MRC dyspnoea score												
< 2	66% (192)	60% (50)	Reference		Reference		68% (153)	74% (57)	Reference		Reference	
2 and above	34% (98)	40% (33)	1.44 [0.85–2.44]	0.175	1.7 [0.74–3.93]	0.208	32% (71)	26% (20)	0.66 [0.35–1.21]	0.184	0.41 [0.14–1.14]	0.099
ART regimen												
ATV/LPV/PI	25% (73)	24% (20)	Reference		Reference		30% (68)	27% (21)	Reference		Reference	
EFV/NVP	75% (216)	76% (63)	1.09 [0.61–2.01]	0.773	0.95 [0.48–1.91]	0.887	70% (156)	73% (56)	1.25 [0.69–2.34]	0.468	1.31 [0.66–2.65]	0.45
Duration of ART at baseline												
6m-<2y	9% (27)	6% (5)	Reference		Reference		9% (19)	7% (5)	Reference		Reference	
2y-<4y	17% (49)	22% (18)	2.55 [0.87–8.67]	0.4	3.28 [1–12.35]	0.17	16% (34)	21% (16)	2.49 [0.76–9.13]	0.21	2.19 [0.59–9.04]	0.44
4y-<6y	22% (61)	22% (18)	1.84 [0.64–6.17]		2.15 [0.66–8.07]		23% (50)	17% (13)	0.98 [0.31–3.52]		0.98 [0.28–3.78]	

6y+	51% (144)	49% (40)	1.69 [0.64–5.32]		1.6 [0.53–5.64]	53% (115)	55% (41)	1.55 [0.55–5.08]		1.42 [0.44–5.12]
Adherence to study drug										
Adherence	76% (219)	64% (53)	Reference			79% (177)	75% (58)	Reference		
Not Adherent	24% (71)	36% (30)	2.29 [1.3–4.03]	0.004		21% (47)	25% (19)	1.39 [0.71–2.69]	0.327	
Trial arm										
Azithromycin	51% (148)	55% (46)	Reference			52% (117)	52% (40)	Reference		
Placebo	49% (142)	45% (37)	0.78 [0.47–1.3]	0.344		48% (107)	48% (37)	1.02 [0.58–1.77]	0.951	
BMI-for-age z-score										
Wasted	20% (56)	23% (19)	Reference			22% (48)	18% (14)	Reference		
Normal	80% (229)	77% (63)	0.74 [0.4–1.4]	0.343		78% (175)	82% (63)	1.37 [0.69–2.81]	0.379	
Height-for-age z-score										
Not stunted	44% (125)	51% (42)	Reference			42% (94)	45% (35)	Reference		
Stunted	56% (160)	49% (40)	0.66 [0.39–1.1]	0.113		58% (129)	55% (42)	0.81 [0.47–1.42]	0.469	

#Missing values: Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (10), BMI-for-age z-score (5), Height-for-age z-score (5). *Missing values: Weight-for-age-z-score (3), Viral load suppression at enrolment (1), Duration of ART at baseline (4), BMI-for-age z-score (3), Height-for-age z-score (3). §Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (5), Duration of ART at baseline (5), BMI-for-age z-score (2), Height-for-age z-score (2). ωMissing values: Duration of ART at baseline (2). ℑMissing values: Season of sampling (1), Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (9), BMI-for-age z-score (5), Height-for-age z-score (5). ϴMissing values: Weight-for-age-z-score (1), Viral load suppression at enrolment (1), Duration of ART at baseline (2), BMI-for-age z-score (1), Height-for-age z-score (1). ΨMissing values: Season of sampling (2), Weight-for-age-z-score (1), Viral load suppression at enrolment (5), Duration of ART at baseline (6), BMI-for-age z-score (1), Height-for-age z-score (1). 𝓜Missing values: Season of sampling (1), Viral load suppression at enrolment (2), Duration of ART at baseline (2). BMI-for-age z-score and Height-for-age z-score were not included in the multivariate analysis because of colinearity. Adherence to study drug and Trial arm were colinear with Adherence and Trial arm hence excluded from multivariate analysis. Statistical model applied is generalised logistic regression.

Table S8: Factors associated with carriage of azithromycin resistant *Streptococcus pneumoniae* isolates at 48 weeks and 72 weeks in trial participants

	NASOPHARYNGEAL SWABS										
	48 weeks						72 weeks				
			Univariate analysis		Multivariate analysis				Univariate analysis		Multivariate analysis	
Variable	No. observations (n=312)#	No. resistant isolates (n=26)*	Adjusted Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value	No. observations (n=223)§	No. resistant isolates (n=15)ω	Adjusted Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value
Site												
Malawi	31% (96)	54% (14)	Reference		Reference		20% (44)	40% (6)	Reference		Reference	
Zimbabwe	69% (216)	46% (12)	0.49 [0.19–1.23]	0.128	0.12 [0.01–1.44]	0.115	80% (179)	60% (9)	0.38 [0.11–1.33]	0.121	0.06 [0–1.26]	0.091
Sex												
Female	48% (151)	73% (19)	Reference		Reference		45% (100)	53% (8)	Reference		Reference	
Male	52% (161)	27% (7)	0.37 [0.13–0.96]	0.048	0.19 [0.02–1.06]	0.073	55% (123)	47% (7)	0.91 [0.28–2.84]	0.863	1.46 [0.29–8.13]	0.646
Season of sampling												
May-Oct-Dry	58% (180)	54% (14)	Reference		Reference		37% (82)	33% (5)	Reference		Reference	
Nov-Apr-Rainy	42% (132)	46% (12)	1.16 [0.46–2.9]	0.745	1.48 [0.27–8.98]	0.656	63% (141)	67% (10)	1.19 [0.37–4.23]	0.776	0.47 [0.06–3.14]	0.446
Weight-for-age-z-score												
Not underweight	51% (158)	36% (9)	Reference		Reference		47% (104)	47% (7)	Reference		Reference	
underweight	49% (149)	64% (16)	2.07 [0.81–5.55]	0.133	2.43 [0.37–19.71]	0.371	53% (117)	53% (8)	1.1 [0.35–3.53]	0.863	0.78 [0.11–5.31]	0.795

Age at enrolment												
6-9y	9% (28)	0% (0)	Reference		Reference		11% (24)	13% (2)	Reference		Reference	
10-12y	20% (61)	27% (7)	22908745.07 [0–3.67998020768624E+85]	NA	68564812.43 [0–NA]	0.69	18% (41)	27% (4)	3 [0.47–25.62]	0.29	7.41 [0.49–192.04]	0.23
13-16y	43% (133)	62% (16)	24311321.3 [0–NA]		48087742.57 [0–NA]		43% (96)	53% (8)	2.09 [0.44–15.3]		6.74 [0.64–124.62]	
17-19y	29% (90)	12% (3)	7977152.3 [0–1.28143335973616E+85]		14669776.62 [0–NA]		28% (62)	7% (1)	0.38 [0.02–4.36]		0.6 [0.01–17.84]	
Viral load suppression at enrolment												
Suppressed (<1000 copies/ml)	58% (177)	50% (12)	Reference		Reference		60% (130)	60% (9)	Reference		Reference	
Unsuppressed (>1000 copies/ml)	42% (130)	50% (12)	1.2 [0.47–3.08]	0.702	0.82 [0.16–4.14]	0.807	40% (88)	40% (6)	0.85 [0.25–2.65]	0.777	1.22 [0.18–8.73]	0.838
Adherence and Trial arm												
Adherence AZM	39% (122)	54% (14)	Reference		Reference		42% (94)	47% (7)	Reference		Reference	
Adherence Placebo	37% (114)	23% (6)	0.09 [0.02–0.28]	0.0002	0.07 [0.01–0.41]	0.01	38% (94)	40% (6)	0.86 [0.24–2.97]	0.89	2.24 [0.34–18.33]	0.18
Not Adherent AZM	12% (37)	15% (4)	0.76 [0.13–4.69]		0.02 [0–0.55]		11% (24)	7% (1)	0.55 [0.03–4.03]		0.8 [0.02–17.56]	
Not Adherent Placebo	13% (39)	8% (2)	0.07 [0.01–0.33]		0.01 [0–0.09]		9% (21)	6% (1)	0.47 [0.02–3.35]		0.03 [0–0.71]	
MRC dyspnoea score												
< 2	65% (204)	50% (13)	Reference		Reference		71% (159)	47% (7)	Reference		Reference	

2 and above	35% (108)	50% (13)	1.44 [0.58–3.63]	0.429	0.9 [0.08–9.67]	0.932	29% (64)	53% (8)	2.41 [0.76–7.83]	0.135	2.51 [0.12–56.6]	0.536
ART regimen												
ATV/LPV/PI	26% (81)	31% (8)	Reference		Reference		31% (70)	53% (8)	Reference		Reference	
EFV/NVP	74% (230)	69% (18)	0.86 [0.32–2.41]	0.769	1.49 [0.21–11.92]	0.692	69% (153)	47% (7)	0.27 [0.08–0.88]	0.03	0.05 [0.01–0.34]	0.005
Duration of ART at baseline												
6m-<2y	10% (31)	13% (3)	Reference		Reference		8% (18)	20% (3)	Reference		Reference	
2y-<4y	18% (53)	33% (8)	2.67 [0.58–15.02]	0.36	4.4 [0.28–88.31]	0.74	16% (35)	20% (3)	0.78 [0.11–5.38]	0.8	3.75 [0.22–96.05]	0.4
4y-<6y	21% (64)	21% (5)	1.28 [0.25–7.48]		1.5 [0.11–20.26]		21% (46)	20% (3)	0.58 [0.09–3.92]		1.05 [0.05–23.23]	
6y+	51% (154)	33% (8)	0.92 [0.22–4.81]		1.94 [0.15–28.02]		55% (119)	40% (6)	0.47 [0.1–2.62]		0.35 [0.02–5.3]	
Cotrimoxazole prophylaxis												
No	10% (31)	8% (2)	Reference		Reference		12% (27)	13% (2)	Reference		Reference	
Yes	90% (279)	92% (24)	1.2 [0.26–8.58]	0.83	0.34 [0.03–4.62]	0.382	88% (196)	87% (13)	0.47 [0.08–3.67]	0.415	0.28 [0.01–6.09]	0.39
Adherence to study drug												
Adherence	76% (236)	77% (20)	Reference				80% (178)	87% (13)	Reference			
Not Adherent	24% (76)	23% (6)	0.74 [0.24–2.06]	0.58			20% (45)	13% (2)	0.54 [0.08–2.32]	0.459		
Trial arm												
Azithromycin	51% (159)	69% (18)	Reference				53% (118)	53% (8)	Reference			

Placebo	49% (153)	31% (8)	0.09 [0.03–0.25]	<0.0001		47% (105)	47% (7)	0.85 [0.26–2.65]	0.773
BMI-for-age z-score									
Wasted	20% (62)	16% (4)	Reference			24% (54)	7% (1)	Reference	
Normal	80% (245)	84% (21)	1.07 [0.32–4.19]	0.916		76% (167)	93% (14)	5.21 [0.93–98.19]	0.125
Height-for-age z-score									
Not stunted	46% (140)	56% (14)				43% (94)	47% (7)		
Stunted	54% (167)	44% (11)				57% (127)	53% (8)		

#Missing values: Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (10), Cotrimoxazole prophylaxis (2), BMI-for-age z-score (5), Height-for-age z-score (5). *Missing values: Weight-for-age-z-score (1), Viral load suppression at enrolment (2), Duration of ART at baseline (2), BMI-for-age z-score (1), Height-for-age z-score (1). §Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (5), Duration of ART at baseline (5), BMI-for-age z-score (2), Height-for-age z-score (2). ωMissing values: None missing. ℑMissing values: Season of sampling (1), Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (9), Cotrimoxazole prophylaxis (2), BMI-for-age z-score (5), Height-for-age z-score (5). ϴMissing values: Duration of ART at baseline (1), Cotrimoxazole prophylaxis (1). ΨMissing values: Season of sampling (2), Weight-for-age-z-score (1), Viral load suppression at enrolment (5), Duration of ART at baseline (6), Cotrimoxazole prophylaxis (1), BMI-for-age z-score (1), Height-for-age z-score (1). ℳMissing values: None missing. BMI-for-age z-score and Height-for-age z-score were not included in the multivariate analysis because of colinearity. Adherence to study drug and Trial arm were colinear with Adherence and Trial arm hence excluded from multivariate analysis. *The number of observations was too few for model convergence for AZM-resistant SP at both 48 and 72 weeks. Statistical model applied is generalised logistic regression.

Table S8: Factors associated with carriage of azithromycin resistant *Streptococcus pneumoniae* isolates at 48 weeks and 72 weeks in trial participants cont'd

Variable	*SPUTUM							
	48 weeks				72 weeks			
	No. observations (n=290)ℑ	No. resistant isolates (n=7)θ	Univariate analysis		No. observations (n=224)Ψ	No. resistant isolates (n=5)ℳ	Univariate analysis	
			Adjusted Odds ratio, 95% CI	*p* value			Adjusted Odds ratio, 95% CI	*p* value
Site								
Malawi	29% (83)	86% (6)	Reference		25% (56)	60% (3)	Reference	
Zimbabwe	71% (207)	14% (1)	0.06 [0–0.41]	0.014	75% (168)	40% (2)	0.24 [0.03–1.66]	0.15
Sex								
Female	49% (142)	71% (5)	Reference		46% (104)	80% (4)	Reference	
Male	51% (148)	29% (2)	0.31 [0.04–1.64]	0.194	54% (120)	20% (1)	0.2 [0.01–1.47]	0.16
Season of sampling								
May-Oct-Dry	58% (167)	86% (6)	Reference		37% (82)	60% (3)	Reference	
Nov-Apr-Rainy	42% (122)	14% (1)	0.19 [0.01–1.27]	0.143	63% (140)	40% (2)	0.43 [0.05–2.84]	0.379
Weight-for-age-z-score								
Not underweight	53% (150)	71% (5)	Reference		50% (111)	20% (1)	Reference	
underweight	47% (135)	29% (2)	0.38 [0.05–1.99]	0.28	50% (112)	80% (4)	3.27 [0.44–67.09]	0.308
Age at enrolment								
6-9y	9% (27)	0% (0)	Reference		10% (23)	0% (0)	Reference	

10-12y	19% (56)	43% (3)	69389275.89 [0–NA]	NA	20% (44)	20% (1)	28912198.6 [0–NA]	NA
13-16y	43% (125)	29% (2)	11564879.31 [0–NA]		44% (98)	40% (2)	11014170.9 [0–NA]	
17-19y	28% (82)	29% (2)	21027053.3 [0–NA]		26% (59)	40% (2)	21027053.53 [0–NA]	
Viral load suppression at enrolment								
Suppressed (<1000 copies/ml)	57% (162)	43% (3)	Reference		58% (127)	60% (3)	Reference	
Unsuppressed (>1000 copies/ml)	43% (123)	57% (4)	1.33 [0.26–7.5]	0.728	42% (92)	40% (2)	0.6 [0.07–4.02]	0.601
Adherence and Trial arm								
Adherence AZM	39% (114)	57% (4)	Reference		42% (93)	40% (2)	Reference	
Adherence Placebo	36% (105)	29% (2)	0.16 [0.02–0.97]	0.29	38% (84)	40% (2)	0.74 [0.08–6.76]	0.94
Not Adherent AZM	11% (34)	14% (1)	0.67 [0.03–7.45]		11% (24)	0% (0)	0 [NA–5.4279267380445E+145]	
Not Adherent Placebo	13% (37)	0% (0)	0 [NA–1.0410563068989E+126]		10% (23)	20% (1)	1.75 [0.07–23.69]	
MRC dyspnoea score								
< 2	66% (192)	29% (2)	Reference		68% (153)	60% (3)	Reference	
2 and above	34% (98)	71% (5)	4.33 [0.82–32.96]	0.102	32% (71)	40% (2)	1.44 [0.17–9.71]	0.71
ART regimen								
ATV/LPV/PI	25% (73)	0% (0)	Reference		30% (68)	60% (3)	Reference	
EFV/NVP	75% (216)	100% (7)	75881451.83 [0–NA]	0.995	70% (156)	40% (2)	0.24 [0.03–1.66]	0.15
Duration of ART at baseline								

6m-<2y	9% (27)	33% (2)	Reference		9% (19)	20% (1)	Reference	
2y-<4y	17% (49)	17% (1)	0.67 [0.03–8.68]	0.7	16% (34)	0% (0)	0 [NA–4.5372465105451E+196]	1
4y-<6y	22% (61)	33% (2)	0.89 [0.09–8.88]		23% (50)	0% (0)	0 [NA–3.913788066561E+282]	
6y+	51% (144)	17% (1)	0.24 [0.01–2.81]		53% (115)	80% (4)	1.33 [0.15–29.4]	
Cotrimoxazole prophylaxis								
No	10% (30)	0% (0)	Reference		11% (25)	20% (1)	Reference	
Yes	90% (258)	100% (6)	6899158.76 [0–NA]	0.994	89% (198)	80% (4)	0.32 [0.03–7.21]	0.364
Adherence to study drug								
Adherence	76% (219)	86% (6)	Reference		79% (177)	80% (4)	Reference	
Not Adherent	24% (71)	14% (1)	0.69 [0.03–4.88]	0.745	21% (47)	20% (1)	1.03 [0.05–8.26]	0.979
Trial arm								
Azithromycin	51% (148)	71% (5)	Reference		52% (117)	40% (2)	Reference	
Placebo	49% (142)	29% (2)	0.15 [0.02–0.79]	0.034	48% (107)	60% (3)	1.17 [0.18–9.64]	0.868
BMI-for-age z-score								
Wasted	20% (56)	29% (2)	Reference		22% (48)	0% (0)	Reference	
Normal	80% (229)	71% (5)	0.7 [0.13–5.48]	0.701	78% (175)	100% (5)	18653031.07 [0–NA]	0.994
Height-for-age z-score								
Not stunted	44% (125)	29% (2)			42% (94)	100% (5)		
Stunted	56% (160)	71% (5)			58% (129)	0% (0)		

#Missing values: Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (10), Cotrimoxazole prophylaxis (2), BMI-for-age z-score (5), Height-for-age z-score (5). *Missing values: Weight-for-age-z-score (1), Viral load suppression at enrolment (2), Duration of ART at baseline (2), BMI-for-age z-score (1), Height-for-age z-score (1). §Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (5), Duration of ART at baseline (5), BMI-for-age z-score (2), Height-for-age z-score (2). ωMissing values: None missing. ℑMissing values: Season of sampling (1), Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (9), Cotrimoxazole prophylaxis (2), BMI-for-age z-score (5), Height-for-age z-score (5). ϴMissing values: Duration of ART at baseline (1), Cotrimoxazole prophylaxis (1). ΨMissing values: Season of sampling (2), Weight-for-age-z-score (1), Viral load suppression at enrolment (5), Duration of ART at baseline (6), Cotrimoxazole prophylaxis (1), BMI-for-age z-score (1), Height-for-age z-score (1). ℳMissing values: None missing. BMI-for-age z-score and Height-for-age z-score were not included in the multivariate analysis because of colinearity. Adherence to study drug and Trial arm were colinear with Adherence and Trial arm hence excluded from multivariate analysis. *The number of observations was too few for model convergence for AZM-resistant SP at both 48 and 72 weeks. Statistical model applied is generalised logistic regression.

Table S9: Factors associated with carriage of azithromycin resistant Staphylococcus aureus isolates at 48 weeks and 72 weeks in trial participants

*NASOPHARYNGEAL SWABS								
Variable	48 weeks				72 weeks			
	No. observations (n=312)#	No. resistant isolates (n=32)*	Univariate analysis		No. observations (n=223)§	No. resistant isolates (n=9)ω	Univariate analysis	
			Adjusted Odds ratio, 95% CI	*p* value			Adjusted Odds ratio, 95% CI	*p* value
Site								
Malawi	31% (96)	66% (21)	Reference		20% (44)	44% (4)	Reference	
Zimbabwe	69% (216)	34% (11)	0.17 [0.05–0.48]	0.001	80% (179)	56% (5)	0.2 [0.04–1.01]	0.048
Sex								
Female	48% (151)	53% (17)	Reference		45% (100)	56% (5)	Reference	
Male	52% (161)	47% (15)	0.94 [0.35–2.49]	0.897	55% (123)	44% (4)	0.68 [0.15–2.97]	0.606
Season of sampling								
May-Oct-Dry	58% (180)	44% (14)	Reference		37% (82)	33% (3)	Reference	
Nov-Apr-Rainy	42% (132)	56% (18)	0.95 [0.35–2.54]	0.914	63% (141)	67% (6)	0.85 [0.19–4.57]	0.833
Weight-for-age-z-score								
Not underweight	51% (158)	41% (13)	Reference		47% (104)	67% (6)	Reference	
underweight	49% (149)	59% (19)	2.52 [0.92–7.22]	0.076	53% (117)	33% (3)	0.53 [0.1–2.32]	0.413
Age at enrolment								
6-9y	9% (28)	9% (3)	Reference		11% (24)	11% (1)	Reference	
10-12y	20% (61)	28% (9)	1.2 [0.13–9.91]	0.37	18% (41)	11% (1)	0.43 [0.01–13.33]	0.93
13-16y	43% (133)	50% (16)	0.63 [0.08–4.26]		43% (96)	56% (5)	0.71 [0.07–16.13]	
17-19y	29% (90)	13% (4)	0.3 [0.03–2.46]		28% (62)	22% (2)	1 [0.06–26.86]	
Viral load suppression at enrolment								

Suppressed (<1000 copies/ml)	58% (177)	58% (18)	Reference		60% (130)	56% (5)	Reference	
Unsuppressed (>1000 copies/ml)	42% (130)	42% (13)	0.41 [0.15–1.11]	0.085	40% (88)	44% (4)	0.94 [0.2–4.11]	0.935
Adherence and Trial arm								
Adherence AZM	39% (122)	56% (18)	Reference		42% (94)	78% (7)	Reference	
Adherence Placebo	37% (114)	0% (0)	0 [0–1.26969432296415E+39]	0.005	38% (94)	0% (0)	0 [NA–1.716182395961E+138]	0.89
Not Adherent AZM	12% (37)	41% (13)	1.44 [0.13–33.05]		11% (24)	22% (2)	2.86 [0.23–68.91]	
Not Adherent Placebo	13% (39)	3% (1)	0.01 [0–0.12]		9% (21)	0% (0)	0 [NA–Inf]	
MRC dyspnoea score								
< 2	65% (204)	44% (14)	Reference		71% (159)	56% (5)	Reference	
2 and above	35% (108)	56% (18)	2.57 [0.95–7.21]	0.066	29% (64)	44% (4)	2.16 [0.46–9.87]	0.315
ART regimen								
ATV/LPV/PI	26% (81)	16% (5)	Reference		31% (70)	11% (1)	Reference	
EFV/NVP	74% (230)	84% (27)	2.35 [0.72–8.47]	0.166	69% (153)	89% (8)	4.87 [0.77–95.34]	0.155
Duration of ART at baseline								
6m-<2y	10% (31)	7% (2)	Reference		8% (18)	11% (1)	Reference	
2y-<4y	18% (53)	33% (10)	1.67 [0.06–24.88]	0.13	16% (35)	22% (2)	0.8 [0.04–23.23]	0.76
4y-<6y	21% (64)	23% (7)	0.44 [0.02–5.56]		21% (46)	11% (1)	0.22 [0.01–7.24]	
6y+	51% (154)	37% (11)	0.29 [0.01–3.36]		55% (119)	56% (5)	0.53 [0.04–12.67]	
Cotrimoxazole prophylaxis								
No	10% (31)	6% (2)	Reference		12% (27)	11% (1)	Reference	
Yes	90% (279)	94% (29)	1.45 [0.22–11.62]	0.695	88% (196)	89% (8)	0.97 [0.12–20.34]	0.979
Adherence to study drug								
Adherence	76% (236)	56% (18)	Reference		80% (178)	78% (7)	Reference	

Not Adherent	24% (76)	44% (14)	2.07 [0.74–6.01]	0.168	20% (45)	22% (2)	2.36 [0.29–14.86]	0.372
Trial arm								
Azithromycin	51% (159)	97% (31)	Reference		53% (118)	100% (9)	Reference	
Placebo	49% (153)	3% (1)	0 [0–0.02]	<0.0001	47% (105)	0% (0)	0 [NA–1.4000330786506E+115]	0.995
BMI-for-age z-score								
Wasted	20% (62)	22% (7)	Reference		24% (54)	22% (2)	Reference	
Normal	80% (245)	78% (25)	0.89 [0.25–3.07]	0.856	76% (167)	78% (7)	1.3 [0.26–9.69]	0.769
Height-for-age z-score								
Not stunted	46% (140)	59% (19)			43% (94)	44% (4)		
Stunted	54% (167)	41% (13)			57% (127)	56% (5)		

#Missing values: Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (10), Cotrimoxazole prophylaxis (2), BMI-for-age z-score (5), Height-for-age z-score (5). *Missing values: Viral load suppression at enrolment (1), Duration of ART at baseline (2), Cotrimoxazole prophylaxis (1). §Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (5), Duration of ART at baseline (5), BMI-for-age z-score (2), Height-for-age z-score (2). ωMissing values: None missing. ℑMissing values: Season of sampling (1), Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (9), Cotrimoxazole prophylaxis (2), BMI-for-age z-score (5), Height-for-age z-score (5). ϴMissing values: Duration of ART at baseline (1). ΨMissing values: Season of sampling (2), Weight-for-age-z-score (1), Viral load suppression at enrolment (5), Duration of ART at baseline (6), Cotrimoxazole prophylaxis (1), BMI-for-age z-score (1), Height-for-age z-score (1). ℳMissing values: Viral load suppression at enrolment (1) . BMI-for-age z-score and Height-for-age z-score were not included in the multivariate analysis because of colinearity. Adherence to study drug and Trial arm were colinear with Adherence and Trial arm hence excluded from multivariate analysis. *The number of observations was too few for model convergence for AZM-resistant SP at both 48 and 72 weeks. Statistical model applied is generalised logistic regression.

Table S9: Factors associated with carriage of azithromycin resistant *Staphylococcus aureus* isolates at 48 weeks and 72 weeks in trial participants cont'd

	SPUTUM											
	48 weeks						72 weeks					
			Univariate analysis		Multivariate analysis				Univariate analysis		Multivariate analysis	
Variable	No. observations (n=290)ℑ	No. resistant isolates (n=33)ϑ	Adjusted Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value	No. observations (n=224)Ψ	No. resistant isolates (n=20)ℳ	Adjusted Odds ratio, 95% CI	*p* value	Adjusted Odds ratio, 95% CI	*p* value
Site												
Malawi	29% (83)	64% (21)	Reference		Reference		25% (56)	30% (6)	Reference		Reference	
Zimbabwe	71% (207)	36% (12)	0.06 [0.02–0.19]	<0.0001	0 [0–0.2]	0.042	75% (168)	70% (14)	0.69 [0.22–2.26]	0.522	0.42 [0.01–10.3]	0.599
Sex												
Female	49% (142)	45% (15)	Reference		Reference		46% (104)	50% (10)	Reference		Reference	
Male	51% (148)	56% (18)	0.98 [0.4–2.39]	0.96	0.53 [0.03–7]	0.627	54% (120)	50% (10)	0.63 [0.22–1.77]	0.375	3.34 [0.68–22.85]	0.169
Season of sampling												
May-Oct-Dry	58% (167)	64% (21)	Reference		Reference		37% (82)	45% (9)	Reference		Reference	
Nov-Apr-Rainy	42% (122)	36% (12)	1.08 [0.42–2.7]	0.877	0.03 [0–0.71]	0.065	63% (140)	55% (11)	0.56 [0.2–1.62]	0.282	1.25 [0.27–6.17]	0.773
Weight-for-age-z-score												
Not underweight	53% (150)	48% (16)	Reference		Reference		50% (111)	70% (14)	Reference		Reference	
underweight	47% (135)	52% (17)	1.06 [0.44–2.59]	0.893	0.12 [0–1.65]	0.135	50% (112)	30% (6)	0.29 [0.09–0.83]	0.026	0.11 [0.02–0.65]	0.02
Age at enrolment												

6-9y	9% (27)	15% (5)	Reference		Reference		10% (23)	5% (1)	Reference		Reference	
10-12y	19% (56)	24% (8)	1.6 [0.27–10.01]	0.071	0.18 [0–17.9]	0.41	20% (44)	30% (6)	1.8 [0.18–41.12]	0.42	0.03 [0–2.81]	0.3
13-16y	43% (125)	42% (14)	0.53 [0.11–2.35]		1.17 [0.03–63.22]		44% (98)	50% (10)	1.2 [0.13–25.87]		0.29 [0.01–16.6]	
17-19y	28% (82)	18% (6)	0.24 [0.04–1.17]		0.03 [0–3.91]		26% (59)	15% (3)	0.47 [0.04–11.3]		0.1 [0–7.65]	
Viral load suppression at enrolment												
Suppressed (<1000 copies/ml)	57% (162)	48% (16)	Reference		Reference		58% (127)	68% (13)	Reference		Reference	
Unsuppressed (>1000 copies/ml)	43% (123)	52% (17)	0.76 [0.31–1.85]	0.544	2.5 [0.16–66.17]	0.531	42% (92)	32% (6)	0.53 [0.17–1.55]	0.262	0.37 [0.05–2.09]	0.277
Adherence and Trial arm												
Adherence AZM	39% (114)	52% (17)	Reference		Reference		42% (93)	65% (13)	Reference		Reference	
Adherence Placebo	36% (105)	3% (1)	0.03 [0–0.18]	0.0001	0 [0–0.02]	0.085	38% (84)	10% (2)	0.12 [0.02–0.51]	0.056	0.08 [0–0.62]	0.24
Not Adherent AZM	11% (34)	39% (13)	3.06 [0.78–15.5]		0.14 [0–2.94]		11% (24)	15% (3)	0.88 [0.16–4.23]		0.59 [0.02–9.91]	
Not Adherent Placebo	13% (37)	6% (2)	0.13 [0.02–0.59]		0 [0–0.02]		10% (23)	10% (2)	0.32 [0.04–1.52]		1.14 [0.08–13.01]	
MRC dyspnoea score												
< 2	66% (192)	33% (11)	Reference		Reference		68% (153)	75% (15)	Reference		Reference	
2 and above	34% (98)	67% (22)	7.8 [2.95–22.23]	<0.0001	175.77 [1.27–202838.5]	0.082	32% (71)	25% (5)	0.93 [0.27–2.89]	0.908	0.38 [0.01–6.05]	0.524
ART regimen												
ATV/LPV/PI	25% (73)	12% (4)	Reference		Reference		30% (68)	25% (5)	Reference		Reference	

EFV/NVP	75% (216)	88% (29)	3.52 [1.14–13.35]	0.041	18.43 [1.15–705.81]	0.065	70% (156)	75% (15)	1.17 [0.38–4.07]	0.791	1.39 [0.27–8.06]	0.697
Duration of ART at baseline												
6m-<2y	9% (27)	13% (4)	Reference		Reference		9% (19)	20% (4)	Reference		Reference	
2y-<4y	17% (49)	22% (7)	0.18 [0.01–1.5]	0.3	0 [0–0.47]	0.36	16% (34)	20% (4)	0.08 [0–0.76]	0.12	0.01 [0–0.42]	0.1
4y-<6y	22% (61)	25% (8)	0.2 [0.01–1.69]		0.02 [0–1.76]		23% (50)	20% (4)	0.11 [0–1.05]		0.03 [0–0.6]	
6y+	51% (144)	41% (13)	0.12 [0.01–0.91]		0.02 [0–2.45]		53% (115)	40% (8)	0.06 [0–0.48]		0.01 [0–0.25]	
Cotrimoxazole prophylaxis												
No	10% (30)	9% (3)	Reference		Reference		11% (25)	5% (1)	Reference		Reference	
Yes	90% (258)	91% (30)	1.14 [0.26–5.87]	0.868	0.03 [0–6.24]	0.239	89% (198)	95% (19)	2.24 [0.35–43.68]	0.47	1.63 [0.1–50.05]	0.742
Adherence to study drug												
Adherence	76% (219)	55% (18)	Reference				79% (177)	75% (15)	Reference			
Not Adherent	24% (71)	45% (15)	2.08 [0.83–5.32]	0.119			21% (47)	25% (5)	1.02 [0.29–3.2]	0.969		
Trial arm												
Azithromycin	51% (148)	91% (30)	Reference				52% (117)	80% (16)	Reference			
Placebo	49% (142)	9% (3)	0.04 [0.01–0.15]	<0.0001			48% (107)	20% (4)	0.18 [0.05–0.57]	0.006		
BMI-for-age z-score												
Wasted	20% (56)	24% (8)	Reference				22% (48)	25% (5)	Reference			
Normal	80% (229)	76% (25)	0.93 [0.33–2.71]	0.89			78% (175)	75% (15)	0.56 [0.17–2.06]	0.362		
Height-for-age z-score												
Not stunted	44% (125)	58% (19)					42% (94)	45% (9)				

Stunted	56% (160)	42% (14)					58% (129)	55% (11)		

#Missing values: Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (10), Cotrimoxazole prophylaxis (2), BMI-for-age z-score (5), Height-for-age z-score (5). *Missing values: Viral load suppression at enrolment (1), Duration of ART at baseline (2), Cotrimoxazole prophylaxis (1). §Missing values: Weight-for-age-z-score (2), Viral load suppression at enrolment (5), Duration of ART at baseline (5), BMI-for-age z-score (2), Height-for-age z-score (2). ωMissing values: None missing. ℑMissing values: Season of sampling (1), Weight-for-age-z-score (5), Viral load suppression at enrolment (5), ART regimen (1), Duration of ART at baseline (9), Cotrimoxazole prophylaxis (2), BMI-for-age z-score (5), Height-for-age z-score (5). ϴMissing values: Duration of ART at baseline (1). ΨMissing values: Season of sampling (2), Weight-for-age-z-score (1), Viral load suppression at enrolment (5), Duration of ART at baseline (6), Cotrimoxazole prophylaxis (1), BMI-for-age z-score (1), Height-for-age z-score (1). ℳMissing values: Viral load suppression at enrolment (1) . BMI-for-age z-score and Height-for-age z-score were not included in the multivariate analysis because of colinearity. Adherence to study drug and Trial arm were colinear with Adherence and Trial arm hence excluded from multivariate analysis. *The number of observations was too few for model convergence for AZM-resistant SP at both 48 and 72 weeks. Statistical model applied is generalised logistic regression.