Antibiotics for Children with Severe Diarrhea (the ABCD trial)

Statistical Analysis Plan

Version 1.0.12.05.2020

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1 Version history

Version number	Version date	Prepared by	Description of the completed editions
00.1	03.09.2017	Per Ashorn	First draft
00.2	24.09.2017	Per Ashorn, Chris Sudfeld Patty Pavlinac Naor Bar-Zeev	Additional detail on primary objective 1 and on secondary objectives
00.3	08.11.2017	Chris Sudfeld	Updated mortality and growth analyses based on Geneva investigator and TAG meeting
00.4	02.12.2017	Patty Pavlinac	Updated AMR analyses
00.5	04.10.2018	Per Ashorn	Review of SAP in light of observed low mortality event rate: Mortality outcome changed from 90-day to 180-day mortality to increase event rate. Secondary outcomes clarified: • Hospitalization to be more specifically defined as "at least one hospitalization:" • Include composite outcome of "hospitalization or death" events to day 90. • Include wasting (ΔWLZ and ΔMUAC) outcomes Registration of above changes on clinicaltrials.gov Other analytical addition: • Consider including time to event analysis for death outcomes
00.6	09.09.2019	Ayesha De Costa	Update after SAP drafting group written comments (23-2nd Sept 2019) and subsequent meeting for discussion on 6th Sept 2019. Meeting chaired by Naor Bar-Zeev
00.7	17.09.2019	Ayesha De Costa	Updated with PI input at the annual meeting of 17-19 Sept 2019
00.8	08.05.2020	Naor Bar-Zeev	Regression model formulae explicated more fully Rules for dealing with missingness and outliers defined. Hypothesis testing method outlined for non-inferiority outcome Text edited for readability and consistency
1.0	12.05.2020	Ayesha De Costa	Alignment of SAP with trial protocol. Edits in response to COVID-19 impact on AMR testing capacity.

2 Introduction

Mortality among young children with acute watery diarrhea who additionally have dehydration or malnutrition is high in low-income countries. Linear growth faltering is another important consequence of diarrhea, with potentially long-term effects on school performance, cognitive development and earning potential. Multi-country evidence shows that bacterial pathogens contribute substantially to mortality and linear growth faltering and with the widespread introduction of rotavirus vaccine, these bacteria will likely make a proportionally greater contribution to childhood diarrhea.

The ABCD Trial (AntiBiotic treatment of moderate to severe Childhood Diarrhea to reduce diarrhea-related mortality and stunting in children: multi-country randomized double-blinded placebo-controlled trial) is a WHO-sponsored 7-country double-blind randomized placebo-controlled 2-arm trial of a directly observed 3-day course of azithromycin vs placebo, powered for detection of 35% relative reduction in mortality and a 0.04 increase in length for age Z-score among children with medically-attended moderate to severe gastroenteritis. The trial will recruit in total 11,500 children (5,750 per treatment arm), in Bangladesh, Pakistan, India, Malawi, Tanzania, Kenya and Mali. Randomization was conducted using permuted blocks stratified by country.

This document outlines the plans for the statistical analysis of the primary and secondary objectives of the trial.

DSMB meeting and update of the SAP: This document was updated in Aug 2019 after the DSMB took a decision in their June 2019 meeting to halt recruitments into the ABCD trial because of (a) very small numbers of deaths (the primary outcome) and the strong likelihood of futility (b) a statistically significant but clinically less relevant difference in LAZ scores between the groups.

While the DSMB received information on allocations, the study teams, WHO coordinators and data management group (RTI) remained blind to the allocation until receipt of the DSMB report of 27th June 2019 which recommended that further recruitment be stopped. Sites were notified by Trial Sponsor on July 1, and all sites ceased recruiting in subsequent days, with last participants recruited on July 10.

3 Study objectives

3.1 Primary Objectives:

1. To compare rates of all-cause mortality in the 180 days following enrolment for an episode of high risk diarrhea without dysentery among children 2 to 23 months of age living in low resource settings who are randomized to receive a 3-day course of azithromycin or placebo.

2. To compare the change in linear growth (ΔLAZ) in the 90 days following an episode of high risk diarrhea without dysentery among children 2 to 23 months of age living in low resource settings who are randomized to receive a 3-day course of azithromycin or placebo.

3.2 Secondary Objectives:

Following an episode of high risk diarrhea without dysentery among children 2 to 23 months of age living in low resource settings who are randomized to receive a 3-day course of azithromycin or placebo, comparison by trial allocation arm of:

1. proportion of children with at least one hospitalization in the 90 days following enrolment
2. proportion of children with at least one hospitalization or who died in the 90 days following enrolment.
3. proportion of children with at least one hospitalization or who died in the initial 10 days following enrolment.
4. change in weight-for-length Z-score (ΔWLZ) in the 90 days following enrolment.
5. change in weight-for-length Z-score (ΔWAZ) in the 90 days following enrolment.
6. change in mid-upper arm circumference (ΔMUAC) in the 90 days following enrolment.
7. Prevalence of azithromycin resistant *E.coli* at baseline among a random subsample of enrolled participants.
8. Prevalence of azithromycin resistant *E.coli* and azithromycin resistant *S. pneumoniae* at D90 and D180 among a random subsample of enrolled participants and their household contacts.
9. Describe cause-specific mortality rates (as determined by verbal autopsy) in the 90 days following enrolment.

3.3 Trial implementation process outcomes:

By trial allocation arm:

1. Describe baseline characteristics
2. Describe dose compliance

3. Proportion of children with a documented serious adverse event in the initial 10 days following enrolment
4. Describe protocol deviations

By country of enrolment:

5. Describe baseline characteristics by country of enrolment
6. Describe dose compliance by country of enrolment

4 General approach to data analysis

4.1 Intention to treat (ITT) analysis:

Primary analysis will be by intended random treatment allocation. All randomized participants will be included in this analysis. Those with a missing mortality outcome will be assigned 'alive'. LAZ outcome will only be analyzed for those children with an outcome. (See Sections 8.1 and 8.2)

4.2 Per protocol (PP) analysis and definition of protocol deviation

The following participants will be excluded from the per protocol analysis:

(i) participants with a primary outcome missing for each respective outcome

(ii) Participants who have been non-adherent to treatment. Adherent participants are defined as those receiving all 3 doses of the study regimen in the first three days of trial participation. The exception to this is if a participant died during this 3-day period. Such participants will be included in the PP analysis.

(iii) Participants whose follow-up visit for anthropometry was outside the window allowed by protocol will be excluded from per protocol analysis of Primary Outcome 2 (change in length-for-age z-score) and Secondary Outcome 1 (acute wasting), but will be included in Primary Outcome 1 (mortality).

(iv) Participants who were ineligible or should not have otherwise been enrolled into the study

4.3 Accounting for stratified randomization by study site

The trial utilizes a stratified randomization scheme by country. As a result, all primary and secondary analyses will account for the randomization schema and adjust for country of enrolment by including unconditional fixed effects for country of enrolment in all analyses.

4.4 Sensitivity analyses examining potential baseline imbalances

We will report baseline characteristics of participants by trial allocation arm (Table 1), we will exam imbalance by trial arm, accepting that these arose by random chance, and will not conduct hypothesis tests for difference by allocation arm. However we will include any apparent imbalances in sensitivity analyses for all primary and secondary outcomes. In sensitivity analyses, we will include as model covariates characteristics which on univariable analysis are associated with the outcome of interest with a p-value <0.10. If the point-estimates for the unadjusted and adjusted analyses of the primary outcomes differ by more than 10%, the adjusted analysis will be presented as primary.

4.5 Effect modification of treatment effects

We will examine whether treatment effects on the outcomes (primary and secondary) differ by *a priori* determined effect modifiers. We will examine modification of treatment effects by trial site by including effect modifying covariates in the regression models.

Effect modifiers of interest include:

1. The participant's age (examined as a continuous variable, but reported as <6 months of age, 6-11 months, 12 months or older)
2. The participant's sex
3. Reason for enrolment: dehydration, moderate wasting or severe stunting considered as non-mutually exclusive categories
4. Participant's wealth quintile with respect to country-specific national wealth distribution (see derivation in Section 7.7)

4.6 Adjusting for baseline measure in change from baseline outcomes

Primary Objective 2 is change from baseline in length-for-age Z-score. Change from baseline outcomes will be adjusted for the baseline value in order to avoid the phenomenon of regression to the mean. In an analysis of covariance (ANCOVA) framework, this can be achieved by including baseline metric in the model. Identically, the same adjustment is achieved by including participant level covariates as random effects in a mixed effects model. This accounts for the clustering of length-for-age and weight-for-length across the two timepoints (enrolment and day 90) within each enrolled participant.

5 Hypotheses to be tested

Primary Objective 1 – 180 day mortality:

Null hypothesis: Among children 2-23 months of age with moderate to severe diarrhea, 180 day mortality is independent of treatment allocation to placebo or to a 3-day course of oral azithromycin.

Alternative hypothesis: Among children 2-23 months of age with moderate to severe diarrhea, 180 day mortality is not independent of exposure i.e. those allocated to receive a 3-day course of oral azithromycin compared to those allocated to receive oral placebo..

Primary Objective 2 – Change in Length-for-age z-score:

Null hypothesis: Among children 2-23 months of age with moderate to severe diarrhea, the mean change from baseline in length-for-age z-score (ΔLAZ) over the 90 day follow-up period is independent of treatment allocation to placebo or to a 3-day course of oral azithromycin.

Alternative hypothesis: Among children 2-23 months of age with moderate to severe diarrhea, the mean change from baseline in ΔLAZ over the 90 day follow-up period is not independent of exposure i.e. among those treated with a 3-day course of oral azithromycin than those treated with a placebo preparation.

Secondary objective 1 – Hospitalization by day 90

Null hypothesis: Among children 2 to 23 months of age with moderate to severe diarrhea, the proportion of children hospitalized by day 90 after enrolment, is independent of treatment allocation to placebo or to a 3-day course of oral azithromycin.

Alternative hypothesis: Among children 2 to 23 months of age with moderate to severe diarrhea, the proportion of children hospitalized by day 90 after enrolment, is not equal in the placebo arm and the arm receiving 3-day course of oral azithromycin.

Secondary objective 2 – Hospitalization or death by day 90

Null hypothesis: Among children 2 to 23 months of age with moderate to severe diarrhea, the proportion of children hospitalized or dying by D90 after enrolment, is independent of treatment allocation to placebo or to a 3-day course of oral azithromycin.

Alternative hypothesis: Among children 2 to 23 months of age with moderate to severe diarrhea, the proportion of children hospitalized or dying by D90 after enrolment, is not equal in the placebo arm and the arm receiving 3-day course of oral azithromycin.

Secondary objective 3 – Hospitalization or death by day 10

Null hypothesis: Among children 2 to 23 months of age with moderate to severe diarrhea, the proportion of children hospitalized or dying by day 10 after enrolment, is independent of treatment allocation to placebo or to a 3-day course of oral azithromycin.

Alternative hypothesis: Among children 2 to 23 months of age with moderate to severe diarrhea, the proportion of children hospitalized or dying by day 10 after enrolment, is not equal in the placebo arm and the arm receiving 3-day course of oral azithromycin.

Secondary Objective 4, 5 & 6 - Acute wasting:

Null hypothesis: Among children 2-23 months of age with moderate to severe diarrhea, the mean change from baseline in weight-for-length z-score (ΔWLZ), weight-for-age z-score (ΔWAZ) and mid-upper arm circumference (ΔMUAC) over the 90 day follow-up period is independent of treatment allocation to placebo or to a 3-day course of oral azithromycin.

Alternative hypothesis: Among children 2-23 months of age with moderate to severe diarrhea, the mean change from baseline in weight-for-length z-score (ΔWLZ), weight-for-age z-score (ΔWAZ) and mid-upper arm circumference (ΔMUAC) over the 90 day follow-up period is not independent of treatment allocation to placebo or to a 3-day course of oral azithromycin.

Secondary objective 7: descriptive report of prevalence of azithromycin resistant E.coli from stools provided at baseline by a sub sample of children enrolled into the trial.

Secondary Objective 8- Antibiotic resistance:

Null hypothesis: Among the subset of children 2-23 months of age with moderate to severe diarrhea selected to be in the AMR sub-study, the prevalence of resistance to azithromycin in *E. coli* and *S. pneumoniae* is greater than or equal to 10% points higher in the group randomized to a 3-day course of oral azithromycin than those randomized to placebo.

Alternative hypothesis: Among the subset of children 2-23 months of age with moderate to severe diarrhea selected to be in the AMR sub-study, the prevalence of resistance to azithromycin in *E. coli* and *S. pneumoniae* in the group randomized to a 3-day course of oral azithromycin is less than 10% points higher than in the group randomized to placebo.

The same hypothesis are also applicable to contacts

6 Data management and analysis processes, and procedures on breaking the intervention code

6.1. The data set on the WHO server called the 'WHO dataset' will be the final data set from which all ABCD analyses will be done, consistent with analyses for a multicentric trial.

6.2. The WHO coordination team will coordinate the analyses. The intellectual input for the analyses will be provided by all site PIs within the statistical analysis plan – dummy tables drawn up (which will be populated by a study statistician) and initial models specified. The WHO will ensure there is a statistically competent data analyst to support the analyses. A preliminary cleaning of the data required to confirm the main analyses (death and linear growth outcomes) will be done by the analyst. At this point, all investigators will remain blinded to the intervention each participant has been receiving.

6.3. The analyst makes a preliminary dataset that contains clean data required for the confirmatory main analyses (as in V9 of the protocol and table 2 and row 1 of table 3). The dataset and summary statistics for each variable, including missingness tables, are distributed to the principal investigators on the trial. Once these individuals agree that the data are sufficiently comprehensive and clean, the study statistician will run an analysis by blinded trial allocation arm.

6.4. The analyst will complete and present the preliminary analyses for the two created groups. Based on these analyses, the study statistician + investigators will make suggestions for the amendment of the Statistical Analysis Plan (SAP) (e.g. on the treatment of missing values). The plan is to break the code after the AMR analysis is completed. However, this may change if the AMR analysis is delayed beyond March 2020.

6.5. Before the intervention code is fully broken, mistakes found in the data can be corrected in the database, as long as there is an audit trail that indicates the date of correction, the old and new value, justification for the correction and the identity of the person authorizing the change (this is not necessary for the correction of entry errors). Any changes in the dataset will be incorporated into the WHO dataset after the discussion with the site and approval of the site PI and the WHO coordinator. After the code is broken, the data on main outcomes will be "frozen" and data can no longer be corrected in the database. Instead, all corrections (also entry errors) will be reviewed and need to be approved by the responsible investigator and WHO coordinator and documented.

6.6. A data analysis workshop is planned tentatively in March 2020, but was canceled as a result of the COVID pandemic. Instead this will done online in May-June. The idea is that the initial analysis as specified in the SAP has been completed and shared with all sites. Therefore, this workshop will facilitate further exploration of questions that arise

from the initial analyses, modification of models etc. and development of the manuscript. Ideally, the plan is to finalize the main trial paper and AMR analyses (resistance to azithromycin) at the same time, if this is possible.

6.7. Country level analyses: To ensure integrity of multiple reports/ publications from the ABCD trial, the same WHO dataset should be used for all analyses. No enrolments may be added to or deleted from this dataset. For country level analyses, where additional variables may be available, these should be appended onto the WHO dataset for the specific site and then analyzed.

7 Definition of the outcomes

7.1 180 day mortality (and 10 day and 90 day mortality outcomes)

Definition of 180 day Mortality: Death due to any cause occurring ≤180 days post-randomization. The day of enrolment in the trial is termed "Study Day 1" therefore 180 days post enrollment is Study Day 181. All deaths or censoring events occurring from enrolment and up to and including Study Day 181 will be included in the primary analysis of the mortality outcome. Deaths and censoring events occurring on or after Study Day 182 (181 days since enrolment) will not be included in the analysis. Other mortality outcomes such as death by day 10 (part of Secondary Outcome 4) and day 90 (part of Secondary Objective 6) will also be defined on basis that say of enrolment is termed "Study Day 1", making these outcomes on Study Day 11 and 91 respectively.

Date of death:

The date of death may be extracted *in ordered preference* from:

1. Death certificate
2. Hospital or clinic record
3. Caregiver other official written record
4. Caregiver recall

Note that forms do not currently record source of death date. Local SOP's should outline the above ordered preference.

Date of death currently appears on three forms ("Form 08-Vital Status"; "Form 11-SAE"; and on the verbal autopsy form). In cases of conflict among forms, the date appearing on Form 08-Vital Status should be prioritized over other forms.

7.2 Length-for-age Z-score (LAZ):

Length for age will be determined from age, sex, and length information at the date of enrolment (day 1) and date of D 90visit (day 91 up to day 101) of participant age, using the macro developed by the WHO using the WHO 2006 multi-centre growth standard. The LAZ values will be rounded to two decimal points.

7.3. Weight-for-age Z-score (WAZ):

Weight for age will be determined from age, sex, and weight information at the date of enrolment (day 1) and date of final visit (day 91 up to day 101) of participant age, using the macro developed by the WHO using the WHO 2006 multi-centre growth standard. The WAZ values will be rounded to two decimal points.

7.3 Weight-for-length Z-score (WLZ):

Weight for length will be determined from age, sex, length and weight information at the date of enrolment (day 1) and date of final visit (day 91 up to day 101) of participant age, using the macro developed by the WHO using the WHO 2006 multi-centre growth standard. The WLZ values will be rounded to two decimal points.

7.4 Hospitalization:

First episode of overnight stay in a health facility per child occurring within 10 days from enrolment by trial records

First episode hospitalizations per child occurring within 90 days from enrolment by trial records or parent or caregiver report of overnight stay in a health facility

7.5 Azithromycin resistance

Clinical Minimum inhibitory concentrations (MIC) cut-offs corresponding to non-susceptibility from the 2020 Clinical and Laboratory Standards Institute (CLSI) will be used for defining azithromycin resistance. MICs exceeding the established cut-points corresponding to resistance and intermediate will be considered as “resistant” to maximize likelihood of detected potential signals of declining susceptibility.

7.6 Serious adverse event

At least one episode within 10 days from enrolment of any event defined as a serious adverse event in Standard Operating Procedure 10, of 14 February 2019. Other serious events (anaphylactic reaction, convulsions, severe colitis, other) will be described by trial arm.

7.7 Wealth quintiles

Socioeconomic questions were collected through a household survey questionnaire. Data from this trial will be compared to each ABCD country's most recent Demographic & Health Survey (DHS) coding for the corresponding wealth/asset variable in the corresponding country. By appending ABCD data and DHS household dataset for each country, DHS wealth index guidelines will be used to perform Principal Component Analysis (PCA) to compute a wealth index score for each observation in the DHS and ABCD datasets all together for a particular country and then take quintiles of that score to assign each participant household a quintile. Since the DHS are nationally representative, the wealth quintile for each ABCD participant is normed to each participant's country standards. Further exploratory analysis by rural vs urban site may also be undertaken.

8 Data missingness and outliers

8.1 Missingness

Every effort will be made to ensure as complete data recording as possible. Inbuilt database checks on missing fields are pre-programmed and regular quality assurance checks will be conducted at sites. Missingness prevalence and pattern will be reviewed by trial statisticians. In describing the trial cohorts, where missingness is >10% the missing will be reported as a separate category. Missingness of primary outcomes is addressed in Section 4.1. Participants with no recorded death events will be presumed alive for analysis of Primary Outcome 1. Participants with missing anthropometry or age data at day 1 or at day 90, for which change in length-for-age z-score is not possible, will be excluded from analysis for Primary Outcome 2 (change in length-for-age z-score) and Secondary Outcome 1 (acute wasting). Children who develop bi-pedal edema and cannot have a weight associated z-score will be included in Primary Outcome 1 but excluded from Secondary Outcome 1. Complete case analyses will be performed and missing anthropometry data will not be imputed. The investigators considered imputation methods to be unlikely to result in valid predictions of individual level anthropometric measures.

8.2 Outliers

The WHO Growth Standards 2006 (Page 14 in https://www.who.int/childgrowth/software/anthro_pc_manual_v322.pdf) consider the following metrics as biologically implausible and recommend excluding these from analysis of nutritional surveys:

WAZ <-6 or >5, or LAZ <-6 or >6, or WLZ <-5 or >5

Data points outside these bounds will be considered missing and excluded from analysis for Primary Objective 2 and Secondary Objective 1, both for the Per Protocol and the Intention to Treat cohorts. It should be noted that trial inclusion/exclusion criteria excluded from enrolment children with WLZ≤-3 at baseline.

Participants whose length on day 90 is less than their length on day 1 will have the respective z-scores calculated and will remain included in analysis for Primary outcome 2. This is because there is likely to be bidirectional bias in repeated measurements. Negative deviances in length are likely to occur only rarely, while similar sized positive deviance in length are difficult to distinguish from correctly recorded gains in length over time. Excluding the negative results only would bias the total cohort towards a larger difference from baseline. Keeping them in the cohort is the more conservative option.

9 Statistical analyses

9.1 Primary outcome 1 - 180 day Mortality

We will report the unadjusted risk ratio (RR) of all-cause death by trial allocation arm, which will be the number of deaths over number of persons in each trial allocation arm, and report either a χ^2 -test of [(death/placebo)/(death/azithromycin)] or a Z-test of the log[(death/placebo)/(death/azithromycin)].

We will examine the 180-day fatality by randomized treatment groups using log-binomial mixed effects models to calculate the risk ratio and 95% confidence bound. Models will include trial site indicators as fixed effects to account for the randomization schema. The primary analysis would only include site as this is the stratified randomization factor. Fatality effect estimates will be presented in Table 2.

Regression model for the outcome of mortality in the ABCD trial will be defined as the following log-binomial mixed effects model:

$$log\ Pr(Y_i = 1) = \beta_{0_c} + \beta_1 C_i + \beta_2 Z_i \times 1_{\{t>t_0\}} + \varepsilon_i$$

– Model 1

Where

$$Y_i = \begin{cases} 1 & died \\ 0 & alive\ at\ day\ 180 \end{cases}$$

And

$$\beta_{0_c} = \beta_0 + b_c$$

Under this definition we are accounting for clustering at clinic level The b term is a random effects for the c^{th} clinic, and take account of the variance due to clustering within clinic.

The term $\beta_1 C_i$ is the fixed effect of country, with C_i representing the country of enrolment for child *i.*

The term $\beta_2 Z_i$ is the fixed effect of azithromycin, with Z_i representing the treatment allocation for child *i* where

$$Z_i = \begin{cases} 1 & azithromycin \\ 0 & placebo \end{cases}$$

The term ε_{ij} is the variance component due to random error for child *i* at time *j*.

Now if $\mu_i = logPr(Y_i = 1)$ then Y is distributed as

$$Y_i \sim Binomial(\mu_i | b_c)$$

and Relative Risk of death by $Z_i = \exp(\beta_1)$

Extending Model 1 to admit child level covariates, we have:

$$log\ Pr(Y_i = 1) = \beta_{0_c} + \beta_1 C_i + \beta_2 Z_i \times 1_{\{t>t_0\}} + \beta_3 \boldsymbol{X}_{ij} + \varepsilon_{ij}$$

- Model 2

Where $\boldsymbol{X}_{ij}$ is the vector of effect-modifying covariates of child *i* at time *j*:

$$\boldsymbol{X}_{ij} = \begin{cases} age\ category\ (< 6m, 6-11m, \geq 12m) \\ + Sex \\ + Reason\ for\ enrolment \\ + Wealth\ quintile \end{cases}$$ (See Section 4.5)

Where randomization resulted in imbalanced covariates (p-value of t-test or χ^2 test of <0.2 on univariable analysis), sensitivity analysis will include in vector $\boldsymbol{X}_{ij}$ confounders that are imbalanced (e.g. but not limited to: sex, wasting, stunting, dehydration) where $\boldsymbol{X}_{ij}$ is a vector that includes imbalanced covariates of child *i* at time *j* (those shown are just exemplary):

$$\boldsymbol{X}_{ij} = \begin{cases} \ldots \\ + wasting \\ + dehydration \ldots \end{cases}$$

9.2 Primary outcome 2 - Change in Length-for-age z-score

The group means at baseline and endline and the mean ΔLFAZ will be presented by treatment group in Table 3. We will use generalized linear mixed models with ΔLAZ as the response variable and treatment group, fixed effects for study site and variable effects for child (which accounts for baseline LAZ) and clinic as the explanatory variables.

The primary analysis for this variable will only include the site since this is the stratified randomization..

Regression model for the outcome change from baseline in length for age Z-score (ΔLFAZ) in the ABCD trial is defined as the following linear mixed-effects model:

$$Y_{ij} = \beta_{0_{c_i}} + \beta_1 C_i + \beta_2 Z_i \times 1_{\{j=1\}} + \varepsilon_{ij} \quad \textbf{- Model 3}$$

Y_{ij} is ΔLFAZ in child *i* at time *j*, where

$$j = \begin{cases} 1 & day\ 90 \\ 0 & enrollment \end{cases}$$

$\beta_{0_{c_i}}$ is the random effect of child *i* at clinic *c*, where

$$\beta_{0_{c_i}} = \beta_0 + b_{c_i} + b_{0_i}$$

Under this definition we are accounting for clustering at clinic level and at child level. The *b* terms are random effects for the c^{th} clinic and the i^{th} child, and take account of the variance due to clustering within clinic or over time in a given child. The latter is effectively also an adjustment for baseline LFAZ and WFAZ for that child. Should these models not converge, we will allow clinic to remain the random effect, but adjust for baseline LFAZ as a fixed effect.

The term $\beta_1 C_i$ is the fixed effect of country, with C_i representing the country of enrolment for child *i.*

The term $\beta_2 Z_i$ is the fixed effect of azithromycin, with Z_i representing the treatment allocation for child *i* where

$$Z_i = \begin{cases} 1 & azithromycin \\ 0 & placebo \end{cases}$$

The term ε_{ij} is the variance component due to random error for child *i* at time *j*.

Participants whose Day 90 visit occurred outside the protocol defined window will be included in the Intention to Treat Analysis. Sensitivity analysis will take account of the time varying nature of this visit by fitting a model that allows the effect of azithromycin to vary as a function of time is:

$$Y_{ij} = \beta_{0_{c_i}} + \beta_1 C_i + \beta_2 Z_i \times 1_{\{t>t_0\}} + \beta_3 Z_i t_{ij} \times 1_{\{t>t_0\}} + \varepsilon_{ij}$$

- Model 4

Model 4 allows for a proportional effect of fixed magnitude (parameter β_2) *and* for a time-varying effect (parameter β_3).

Under Model 2 the term $\beta_{0_{c_i}}$ is the random effect of child *i* at clinic *c*, as it was above, but where

$$\beta_{0_{c_i}} = \beta_0 + b_{c_i} + b_{0_i} + b_{1_i} t_{ij}$$

As before, should these models fail to converge, we will allow clinic to remain the random effect, but adjust for baseline LFAZ as a fixed effect.

Extending Model 4 to admit child level covariates, we have:

$$Y_{ij} = \beta_{0_{c_i}} + \beta_1 C_i + \beta_2 Z_i \times 1_{\{t>t_0\}} + \beta_3 Z_i t_{ij} \times 1_{\{t>t_0\}} + \beta_4 \boldsymbol{X}_{ij} + \varepsilon_{ij}$$

- Model 5

Where $\boldsymbol{X}_{ij}$ is the vector of effect-modifying covariates of child *i* at time *j*:

$$\boldsymbol{X}_{ij} = \begin{cases} age\ category\ (< 6m, 6-11m, \geq 12m) \\ + Sex \\ + Wealth\ quintile \end{cases}$$

Where randomization resulted in imbalanced covariates, sensitivity analysis will include in vector $\boldsymbol{X}_{ij}$ confounders that are imbalanced (e.g. but not limited to: sex, wasting, stunting, dehydration) as previously described.

9.3 Analysis of secondary objectives 1, 2 and 3 - Hospitalization

Following an episode of high risk diarrhea without dysentery among children 2 to 23 months of age living in low resource settings who are randomized to receive a 3-day course of azithromycin or placebo, comparison by trial allocation arm of:

1. proportion of children hospitalized or died in the initial 10 days following enrolment.
2. proportion of children hospitalized in the 90 days following enrolment.
3. proportion of children hospitalized or died in the 90 days following enrolment.

Primary event considered will be the first episode of hospitalization per child. Hospitalization rates will be reported by country to understand heterogeneity across sites. Risk ratio will be estimated from a model including trial allocation and country of enrollment. Adjusted analysis will include effect modifying covariates, and sensitivity analysis will include unbalanced potential confounders by trial arm.

Hospitalization data are available as binary outcomes only, and date of hospitalization is missing for all events after 10 days of follow-up. Time to event analysis is not possible for the hospitalization outcome.

Since likelihood of hospitalization may cluster by clinic, the following log-binomial mixed effects model is proposed:

$$log\ Pr(Y_i = 1) = \beta_{0_c} + \beta_1 C_i + \beta_2 Z_i \times 1_{\{t>t_0\}} + \varepsilon_i \qquad \textbf{– Model 6}$$

Where

$$Y_i = \begin{cases} 1 & hospitalized\ at\ least\ once\ by\ day\ 180 \\ 0 & not\ hospitalized \end{cases}$$

Under this definition we are accounting for clustering at clinic level The *b* term is a random effects for the c^{th} clinic, and take account of the variance due to clustering within clinic.

The term $\beta_1 C_i$ is the fixed effect of country, with C_i representing the country of enrolment for child *i.*

The term $\beta_2 Z_i$ is the fixed effect of azithromycin, with Z_i representing the treatment allocation for child *i* where

$$Z_i = \begin{cases} 1 & azithromycin \\ 0 & placebo \end{cases}$$

The term ε_{ij} is the variance component due to random error for child *i* at time *j*.

Adjusted analysis will include individual level effect modifiers, thus:

$$log\ Pr(Y_i = 1) = \beta_{0_c} + \beta_1 C_i + \beta_2 Z_i \times 1_{\{t>t_0\}} + \beta_{3_X} \boldsymbol{X}_{ij} + \varepsilon_i \qquad \textbf{– Model 7}$$

Where $\boldsymbol{X}_{ij}$ is the vector of effect-modifying covariates of child *i* at time *j*:

$$\boldsymbol{X}_{ij} = \begin{cases} age\ category\ (< 6m, 6-11m, \geq 12m) \\ + Sex \\ + Wealth\ quintile \end{cases}$$

Where randomization resulted in imbalanced covariates, sensitivity analysis will include in vector $\boldsymbol{X}_{ij}$ confounders that are imbalanced (e.g. but not limited to: sex, wasting, stunting, dehydration) as previously described.

9.4 Analysis of secondary endpoint 4, 5 & 6

Secondary endpoint 4 & 5: To compare ΔWLZ and ΔMUAC in the 90 days following an episode of high risk diarrhea without dysentery among children 2 to 23 months of age living in low resource settings who are randomized to receive a 3-day course of azithromycin or placebo.

9.4.1 Outcome Definitions

1. ΔWLZ = WLZ at endline visit *minus* WLZ at randomization visit
2. ΔWAZ = WAZ at endline visit *minus* WLZ at randomization visit
3. ΔMUAC = MUAC at endline day visit *minus* MUAC at randomization visit

In sensitivity analysis the endline visit date will be restricted to those who had the visit from study day 91 to 100.

The group means for WLZ, WAZ and MUAC at baseline, endline and mean change will be presented by group as indicated in Table 3. We will use generalized linear mixed models with ΔWLZ, ΔWAZ or ΔMUAC as response variables and treatment group and fixed effects for study country and random effects for clinic and child as the explanatory variables. A sensitivity analyses including potential effect modifiers and unbalanced confounders will be done. Modeling will be analogous to Models 3-5 listed in Section 9.2, but where Y_{ij} is ΔWLZ, ΔWAZ or ΔMUAC respectively, in child *i* at time *j*.

9.5 Analysis of Secondary Objective 8 – Antibiotic resistance in enrolled participants

To compare prevalence of azithromycin resistant *E.coli* and azithromycin resistant *S. pneumoniae* respectively in stool and nasopharyngeal swabs submitted for antimicrobial resistance testing at D90 and D180 among a random subsample of enrolled participants, by trial allocation arm.

9.5.1 Outcome Definitions

E. coli = The proportion of children participating in the antimicrobial resistance substudy whose stool was submitted for antimicrobial resistance testing, among whom azithromycin resistant *E. coli* was detected in the day 90 (main analysis) and day 180 stool specimens.

S. pneumoniae = The proportion of children participating in the antimicrobial resistance substudy whose stool was submitted for antimicrobial resistance testing among whom azithromycin resistant *S. pneumoniae* was detected at day 90 (main analysis) and day 180 nasopharyngeal swab specimen.

9.5.2 Analysis

Four non-superiority hypothesis tests (2 samples and 2 timepoints) will be conducted to test whether the difference in prevalence of resistance at day 90 and day 180 in children assigned

to the azithromycin (R_{AZM}) and placebo ($R_{placebo}$) group exceeds a margin of 10% (one sided test).

E. coli Day 90	*E. coli* Day 180	*S. pneumoniae* Day 90	*S. pneumoniae* Day 180
H_0: $R_{AZM} - R_{placebo} > 10\%$	**H_0:** $R_{AZM} - R_{placebo} > 10\%$	**H_0:** $R_{AZM} - R_{placebo} > 10\%$	**H_0:** $R_{AZM} - R_{placebo} > 10\%$
H_1: $R_{AZM} - R_{placebo} \leq 10\%$	**H_1:** $R_{AZM} - R_{placebo} \leq 10\%$	**H_1:** $R_{AZM} - R_{placebo} \leq 10\%$	**H_1:** $R_{AZM} - R_{placebo} \leq 10\%$

Justification for the NI margin of 10%: this margin has been chosen based on clinical acceptability among infectious disease experts. Also, consultation with investigators in other trials of azithromycin accept a 10% (absolute difference) NI margin as reasonable. The non-inferiority hypothesis will be tested using the continuity corrected χ^2 test as suggested by Dunnett and Gent, Biometrics 1977.

In primary analysis, the prevalence denominator will be all children enrolled in the AMR sub-study whose stool was submitted for antimicrobial sensitivity testing (irrespective of whether the bacteria was isolated). Those children who were enrolled in the AMR study, who provided a sample, but whose sample could not be subject to an antibiotic sensitivity test because of external circumstances (COVID-19 related lockdowns of the lab), will be excluded from the denominator. At sites, that have experienced a lockdown, random distribution of selection of specimens for testing will be difficult to confirm, though examination for systematic bias (eg by date range) will be undertaken. If bias is suggested in sites that have not completed testing, these sites will be excluded from hypothesis testing. But other remaining sites will be included in non-inferiority test as outlined above.

In secondary analysis, the prevalence denominator will be defined as those children in whom the respective bacteria was isolated and tested (i.e. azithromycin resistance in E. coli as a proportion of E. coli isolates, and likewise for *S. pneumoniae*). Sites that have not completed testing as outlined above, will be dealt with as outlined above.

9.5.3. Exploratory analyses

For both the primary and secondary analyses, estimates of AMR prevalence will be adjusted for site and other potentially confounding covariates (including those listed in Section 4.5, and data on recent antibiotic use).Resistance analyses will be reported separately for Asia and African sites.

Change in resistance over time within individual participating children will be estimated using mixed effects models or by including baseline MIC in the model. If MICs will be reported as ordered categories then ordinal mixed effects models will be used. If reported categorically as Resistant/Sensitive then binomial mixed effects models will be used.

We will also describe the resistance prevalence in *E.coli* at baseline for both trial arms.

If azithromycin resistance is detected among participants' samples tested, then a separate exploratory analysis on resistance to one or more β-lactam antibiotics will be done.

9.6 Analysis of Outcome 8- Antibiotic resistance in contacts

To compare prevalence of azithromycin resistant *E. coli* and azithromycin resistant *S. pneumoniae* respectively in stool and nasopharyngeal swabs submitted for antimicrobial resistance testing at Day90 and Day180 among the siblings or close household contacts (children under five years of age living in the same household under the care of the same primary caregiver) of a random sub-sample of enrolled participants, by trial allocation arm. It should be noted that recruitment of the contacts themselves was non-random, biases by site and other factors are likely. Adjustments may be made using a modeling framework, but any arising results should be interpreted with caution and full caveats and limitations will be disclosed with any reporting of results. Such model adjusted outcomes will be described as exploratory.

9.6.1 Outcome Definitions

E. coli = The proportion of child contacts participating in the antimicrobial resistance substudy whose stool was submitted for antimicrobial resistance testing among whom azithromycin resistant *E. coli* was detected in the day 90 (main analysis) and day 180 stool specimen.
S. pneumoniae = The proportion of child contacts participating in the antimicrobial resistance substudy whose stool was submitted for antimicrobial resistance testing among whom azithromycin resistant *S. pneumoniae* was detected at day 90 (main analysis) and day 180 nasopharyngeal swab specimen.

9.6.2 Analysis

Four non-inferiority hypothesis tests (2 samples and 2 timepoints) will be conducted to test whether the difference in prevalence of resistance in children assigned to the azithromycin and placebo group exceeds 10% (one sided test).

E.coli Day 90	*E.coli* Day 180	*S. pneumoniae* Day 90	*S. pneumoniae* Day 1
H_0: $R_{AZM} - R_{placebo} > 10\%$	**H_0:** $R_{AZM} - R_{placebo} > 10\%$	**H_0:** $R_{AZM} - R_{placebo} > 10\%$	**H_0:** $R_{AZM} - R_{placebo} >$
H_1: $R_{AZM} - R_{placebo} \leq 10\%$	**H_1:** $R_{AZM} - R_{placebo} \leq 10\%$	**H_1:** $R_{AZM} - R_{placebo} \leq 10\%$	**H_1:** $R_{AZM} - R_{placebo} \leq$

Although this analysis is predefined, we anticipate low power for this analysis. Justification for the NI margin of 10%: this margin has been chosen based on clinical acceptability among

infectious disease experts. Also, consultation with investigators in other trials of azithromycin accept a 10% (absolute difference) NI margin as reasonable. The non-inferiority hypothesis will be tested using the continuity corrected χ^2 test as suggested by Dunnett and Gent, Biometrics 1977. Since all participants will not provide a contact for sampling (stool or swab), an examination for systematic bias among the contacts who provided samples that were submitted for testing (eg by date range, site) will be undertaken. Any apparent bias will be described, and potentially adjusted for using a modeling framework.

In the primary analysis, the denominator of these prevalence estimates will be all child contacts enrolled in the AMR sub-study whose stool was submitted for antimicrobial sensitivity testing (irrespective of whether the bacteria was isolated). Treatment of sites affected by COVID-19 lockdowns will be as outlined in Section 9.5.2.

In secondary analysis, the prevalence denominator will be defined as those contacts in whom the respective bacteria was isolated and tested (i.e. azithromycin resistance in E. coli as a proportion of E. coli isolates, and likewise for *S. pneumoniae*). Sites that have not completed testing as outlined above, will be dealt with s outlined in Section 9.5.2.

9.6.4 Exploratory analyses

For both the primary and secondary analyses, estimates of AMR prevalence will be adjusted for site and other potentially confounding covariates (including those listed in Section 4.5, and data on recent antibiotic use).

Resistance analyses will be reported separately for Asia and African sites.

Change in resistance over time within individual participating children will be estimated using mixed effects models or by including baseline MIC in the model. If MICs will be reported as ordered categories then ordinal mixed effects models will be used. If reported categorically as Resistant/Sensitive then binomial mixed effects models will be used.

If azithromycin resistance is detected among participants' samples or isolates tested, then a separate exploratory analysis on resistance to one or more B-lactam antibiotics in contacts will be done.

9.7 Analysis of Secondary Outcome 9: Cause-specific mortality

Describe cause-specific mortality rates (as determined by verbal autopsy) in the 90 days following enrolment.

Definitions of cause of death will be determined by method used for collecting and analyzing verbal autopsy data. These results will be descriptive. We will not undertake hypothesis testing or examine difference in causes of death by treatment allocation.

10 Other exploratory analyses

10.1 Time-to-event analysis of mortality
Time-to-event sensitivity analyses will be conducted. We will construct stratified Kaplan-Meier curves to graphically present the timing of participant deaths by treatment group. The stratified log rank test will be used to assess statistical difference between treatment groups to account the stratified randomization. We will also use Cox proportional hazard models with fixed effects for trial site to produce hazard ratio estimates. Date of loss to follow-up will be date of last recorded contact, and will censor further analysis.

Mean anthropometry at enrolment and other baseline covariates will be described for the cohort of deceased children. Given small number of deaths, further analysis (e.g. of effect modification of child level covariates or of seasonality on death outcome) may not be appropriate.

10.2 Outcome by age: Models will be constructed for restricted age bands (<6 months, 6-11 months, 12 months and older). In such models age will not be incorporated into vector $\boldsymbol{X}_{ij}$.

10.3 Outcome by reason for enrolment: Models will be constructed separately for participants enrolled for severe stunting, for moderate wasting and for dehydration.

10.4 Seasonality by country may be explored by adding a spline term to the models outlined, allowing outcome to vary seasonally by country.

10.5 Heterogeneity across countries may be expected to occur in underlying population (e.g. proportion stunted at baseline) and also for some trial outcomes. Heterogeneity may be explored by presenting country specific model as a forest plot, and using meta-analytic techniques providing a pooled weighted estimate, and heterogeneity metrics such as the I^2 statistic. Metaregression could be used to explore magnitude of impact of heterogeneous covariates. Although heterogeity will be explored, stratum specific testing is not envisaged (apart from adjusted models already described) as there is unlikely to be adequate power to test within a stratum. We will present the results of our defined Primary Outcomes as planned, describing any apparent heterogeneity.

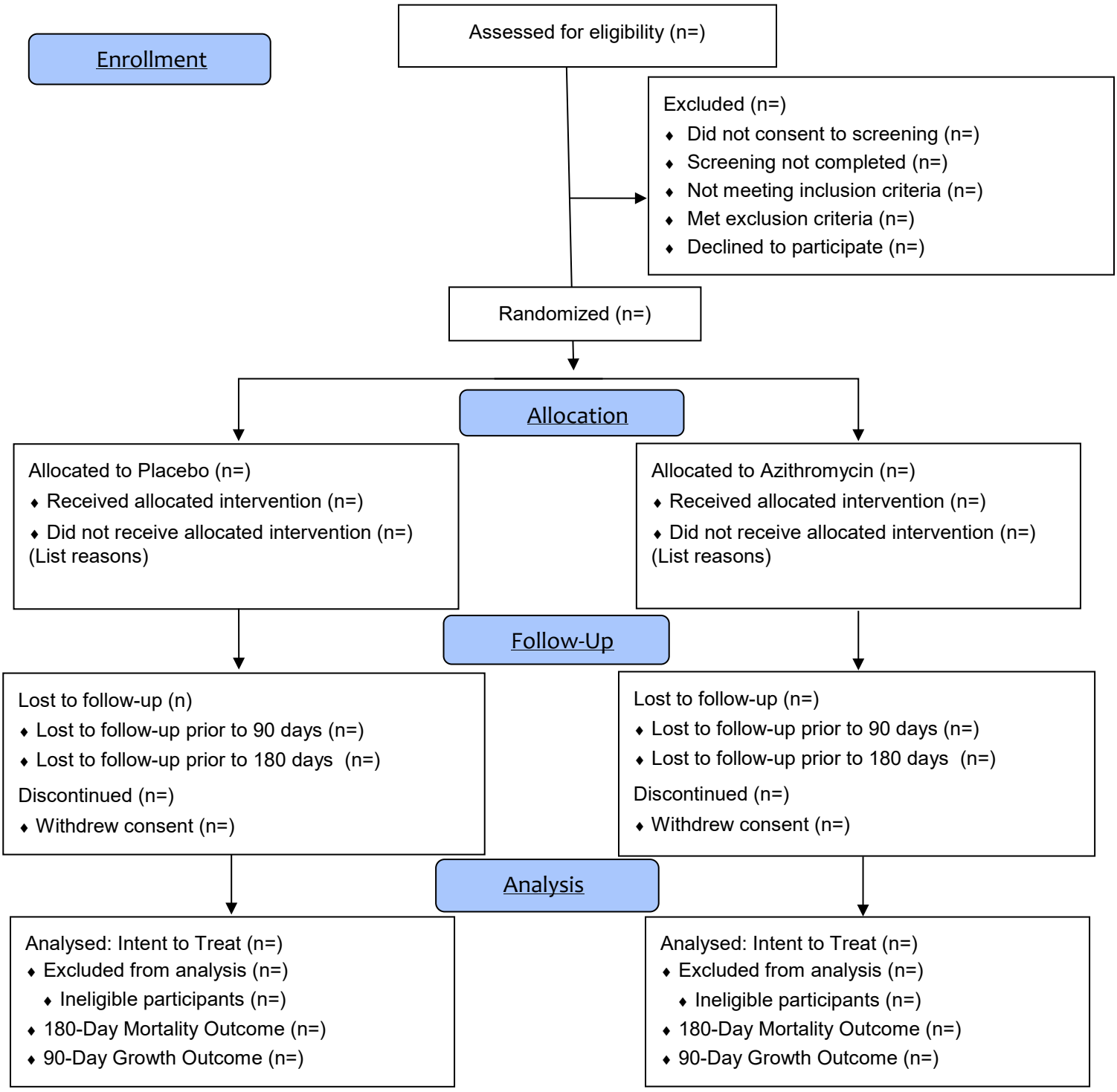
11 Software

Software: The study statistician will employ the software that s/he is experienced with using. The analyses provided by the statistician (on the direction of the site PIs) will be considered final. No parallel analyses of the same data/ question will be considered.

12. Figures and tables

Figure 1. Participant flow in CONSORT recommended format (Lancet 2001: 357: 1193)

ABCD Consort Flow Diagram



Tables

Table 1. Participant characteristics at enrolment by trial allocation arm

Variable	**Placebo**	**Azithromycin**
Number of participants	xxx	xxx
Mean (SD) age, months	xx.x (xx.x)	xx.x (xx.x)
Proportion male, %	xx.x%	xx.x%
Mean (SD) weight, kg	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) length, cm	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) MUAC, cm	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) LAZ, z-score units	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) WLZ, z-score units	xx.xx (xx.xx)	xx.xx (xx.xx)
Prevalence of moderate stunting (-3.0<LAZ≤-2.0), %	xx.xx (xx.xx)	xx.xx (xx.xx)
Prevalence of severe stunting (LAZ≤-3.0), %	xx.xx (xx.xx)	xx.xx (xx.xx)
Prevalence of moderate wasting (-3.0<WLZ≤-2.0), %	xx.xx (xx.xx)	xx.xx (xx.xx)
Prevalence of some or severe dehydration, %	xx.xx (xx.xx)	xx.xx (xx.xx)
Mean (SD) maternal age, years	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal height, cm	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal weight, kg	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal BMI, kg / m^2	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal MUAC, cm	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal education, years	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) number of children below 5 years of age in the household	xx.x (xx.x)	xx.x (xx.x)

SD = standard deviation; MUAC = mid-upper arm circumference; LAZ = length-for-age Z-score; WLZ = weight-for-length Z-score; BMI = body mass index

Table 2. Primary outcomes

Outcome	Placebo	Azithromycin	RR (95% CI)*	p-value
180 day mortality	n/N (%)	n/N (%)		
ΔLAZ mean (sd)			NA	

* from adjusted generalized linear mixed model
RR = Risk Ratio; CI = confidence interval; ΔLAZ = mean change in length-for-age Z-score

Table 3. Anthropometric parameters

Anthropometric parameter	Placebo	Azithromycin	Effect (95% CI)	P-value
Day 90 anthropometry performed, N (%)				
LAZ at day 90, Mean (sd)				
WAZ at day 90, Mean (sd)				
ΔWAZ (95%CI)				
WLZ at day 90, Mean (sd)				
ΔWLZ (95%CI)				
MUAC at day 90 (cm), Mean (sd)				
ΔMUAC (95%CI)				

Δ = mean change in anthropometric parameter between day 1 and day 90; LAZ = length-for-age Z-score; WAZ = weight-for-age Z-score; WLZ = weight-for-length Z-score; MUAC = mid-upper arm circumference

Table 4. Secondary outcomes

Outcome	Placebo	Azithromycin	RR (95% CI)*	Wald test p-value
Day 10 hospitalization or death	n/N (%)	n/N (%)		
Day 90 hospitalization or death	n/N (%)	n/N (%)		
Day 90 hospitalization	n/N (%)	n/N (%)		

* from adjusted generalized linear mixed model
RR = Risk Ratio; CI = confidence interval

Table 5

	Baseline	Placebo group			Treated group		
		D90	D180	Adjusted p value	D90	D180	Adjusted p value
E. Coli -AZM resistance (mean, 95% CI) in partcipants							
By stool sample							
By isolates tested							
S. Pneumoniae - AZM resistance (mean, 95% CI) in participants							
By stool sample							
By isolates tested							
E. Coli -AZM resistance (mean, 95% CI) in community contacts							
By stool sample	NA						
By isolates tested	NA						
S. Pneumoniae - AZM resistance (mean, 95% CI) in community contacts							
By stool sample	NA						
By isolates tested	NA						

Table 6. Other reportable outcomes by trial arm

Outcome	Placebo	Azithromycin
Dosing adherence	n/N (%)	n/N (%)
Protocol deviations	n/N (%)	n/N (%)

Table 6. Baseline characteristics and other reportable outcomes by country of enrolment

Variable	**Bangladesh**	**India**	**Pakistan**	**Mali**	**Tanzania**
Number of participants	xxx	xxx	xxx	xxx	xxx
Mean (SD) age, months	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Proportion male, %	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
Mean (SD) weight, kg	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) length, cm	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) MUAC, cm	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) LAZ, z-score units	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) WLZ, z-score units	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Prevalence of moderate stunting (-3.0<LAZ≤-2.0), %	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Prevalence of severe stunting (LAZ≤-3.0), %	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Prevalence of moderate wasting (-3.0<WLZ≤-2.0), %	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Prevalence of some or severe dehydration, %	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Mean (SD) maternal age, years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal height, cm	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal weight, kg	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal BMI, kg / m^2	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal MUAC, cm	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) maternal education, years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD) number of children below 5 years of age in the household	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Dosing adherence to protocol	n (%)	n (%)	n (%)	n (%)	n (%)
Protocol deviations	n (%)	n (%)	n (%)	n (%)	n (%)

SD = standard deviation; MUAC = mid-upper arm circumference; LAZ = length-for-age Z-score; WLZ = weight-for-length Z-score; BMI = body mass index