**Tebipenem-pivoxil as an alternative to ceftriaxone for clinically non-responding children with shigellosis: A randomized non-inferiority trial**

**The Tebi Trial**



**A collaboration between the:**
**International Center for Diarrheal Disease Research (icddr,b) &**
**University of Washington (UW) & and Supported by GSK**

**Statistical Analysis Plan**
**Version 2.0**

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## SECTION 1. ADMINISTRATIVE INFORMATION

**Title:** Tebipenem-pivoxil as an alternative to ceftriaxone for clinically non-responding children with shigellosis: a randomized non-inferiority trial

**ClinicalTrials.gov Registration: NCT05121974**

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**SAP Version:** 2.0 (03Aug2025)

**Protocol Version:4**

**SAP Revision History:**

| SAP version (date) | Justification for Revision | Timing of SAP in relation to interim analysis |
|---|---|---|
| 2.0 03 Aug 2025 | Non-inferiority hypothesis was based on a clinical benefit vs. the clinical failure definition therefore we needed to change difference in proportions in null and alternative hypotheses to a positive instead of negative value and to articulate the upper rather than lower bound of 95% confidence interval, accordingly. | After interim analysis before final analysis |
| | | |
| | | |

**Roles and Responsibilities in SAP and Signatures**

| Name | Trial Role | SAP Role |
|---|---|---|
| Sharika Nuzhat | Principal Investigator | Chief Investigator |
| Mohammod Jobayer Chisti | Co-Investigator | Co-Chief Investigator |
| | | |
| Patricia Pavlinac | Co-investigator | Draft |
| Amy Newlands | Statistical support | Reviewer |

## SECTION 2. INTRODUCTION

### Background and Rationale

Shigellosis is the second leading cause of death due to diarrheal diseases worldwide (>200,000 deaths/year). Though the mortality rate associated with Shigellosis has decreased, the fact that the bacteria have acquired resistance to multiple antibiotics, is a cause for major concern. Oral azithromycin and intravenous ceftriaxone are the recommend first and second line therapies, respectively, in Bangladesh. Approximately 20% of *Shigella* isolates are resistant to azithromycin suggesting that a substantial number of children will require second-line therapy. While resistance to ceftriaxone in shigellosis is low in Bangladesh at 5%, the potential for rapid emergence of antibiotic resistance to this third-generation cephalosporin and ceftriaxone's resource-intensive delivery method, underscore the need for evidence-based alternative antibiotic regimens for multidrug resistant *Shigella* infections.

Rigorous pre-clinical studies have established tebipenem-pivoxil as efficacious against *Shigella* infection[1,2]. Tebipenem (brand name: Orapenem) is a broad-spectrum orally administered antibiotic, from the carbapenem subgroup of β-lactam antibiotics[3,4]. It was developed as a replacement drug to combat bacteria that had acquired antibiotic resistance to commonly used antibiotics[4]. Tebipenem-pivoxil is a prodrug that is metabolized to tebipenem, its therapeutically active form. The safety of tebipenem-pivoxil was evaluated in approximately 1,100 subjects supporting the application for approval in Japan[5-7]. In this safety data set, there are 741 adult subjects across 17 trials and 440 paediatric subjects across six trials[8,9]. These 23 trials in total included one double-blind, comparator-controlled trial in children, five open-label trials in children, five trials enrolling adult patients (including two open-label cUTI trials), and 12 Phase 1 clinical pharmacology trials.

Assessing the need for new therapeutic regimes to counter the growing threat of development of antimicrobial resistance and development of multi-drug resistant strains, we propose a phase IIb randomized controlled trial (RCT) to determine the efficacy and safety of oral tebipenem-pivoxil, compared to IV ceftriaxone, for children with *Shigella* infections unresponsive to first-line antibiotic therapy.

**Primary Aim**

1. To determine whether tebipenem-pivoxil is clinically non-inferior to the currently WHO-recommended second line *Shigella* therapy (ceftriaxone) 3 days after treatment initiation.

   *Hypothesis: Children randomized to tebipenem-pivoxil experience no more clinical failures than children treated with ceftriaxone 3 days after treatment initiation.*

**Secondary Aim:**

1. To determine whether tebipenem-pivoxil is clinically non-inferior to the currently WHO-recommended second line *Shigella* therapy (ceftriaxone) 7 and 30 days after treatment initiation.

   *Hypothesis: Children randomized to tebipenem-pivoxil experience no more clinical failures than children treated with ceftriaxone 7 and 30 days after treatment initiation.*

2. To determine whether tebipenem-pivoxil is microbiologically non-inferior to the currently WHO-recommended second line *Shigella* therapy (ceftriaxone) 7 and 30 days after treatment initiation.

   ***Hypothesis****: Children randomized to tebipenem-pivoxil experience no more microbiologic failures than children treated with ceftriaxone, both 7 and 30 days after treatment initiation.*

3. Describe the number of adverse events, between children with shigellosis treated with oral tebipenem-pivoxil or IV ceftriaxone.

4. Compare the prevalence of ceftriaxone and carbapenam resistance, as well as ESBL-and carbapenemase-producing *Escherichia coli*, in children treated with tebipenem-pivoxil or ceftriaxone 7 and 30-days after initiation of second-line therapy.

   ***Hypothesis****: Children randomized to tebipenem-pivoxil will have higher proportion of carbapenem resistant E.coli isolates than children randomized to ceftriaxone 7-days after randomization, however this difference will go away by day 30. Children randomized to ceftriaxone will have a higher proportion of ceftriaxone resistant E.coli isolates, 7-days after randomization, however this difference will also go away by day 30.*

## SECTION 3. STUDY METHODS

### Trial Design

This will be a single-blind, randomized trial to determine the non-inferiority of tebipenem-pivoxil, an oral antibiotic, to the current WHO recommended second line antibiotic, ceftriaxone in reducing clinical and microbiologic failure. Bangladeshi children aged 24 to 59 months with suspected *Shigella* infections and no clinical improvement within 48 hours of first-line therapy will be randomized to a 3-day course of oral tebipenem-pivoxil (4 mg/kg 3x daily) or 3-days of IV ceftriaxone (50 mg/kg 1x daily). The children will be evaluated for key clinical, microbiologic, and safety outcomes during the subsequent 30-day period.

### Randomization

Block randomization (1:1) in random sized blocks of will be used to assign treatment groups at study enrollment by an independent statistician. Treatment allocation (once assigned) will be known to the managing clinician and the participant due to the differing drug delivery mechanisms of the two antibiotics (oral vs. injectable). However, the team conducting the statistical analyses will be blinded to treatment allocation (allocation will appear A and B).

### Sample Size

To the best of our knowledge, no randomized clinical trials have compared treatment options for clinically non-responding children with shigellosis or children with drug resistant (or presumed drug-resistant) *Shigella*. Therefore, the sample size estimation was derived from the most recent of the three trials of IV/IM ceftriaxone for shigellosis[10-12] which compared a 3-day course of oral ciprofloxacin to IM ceftriaxone in Israeli children with invasive diarrhea (73 of whom had Shigella) and found 97% microbiologic success and 100% clinical success on day 5 [12]. We therefore assumed a clinical and microbiologic success rate of 97%. We chose an absolute 10% non-inferiority margin as the maximum risk difference in clinical success between tebipenem-pivoxil or ceftriaxone that would be clinically acceptable, by consultation with infectious disease and paediatric clinical specialists at the icddr,b.

Assuming an equal cure rate of 97% for both arms, an absolute 10% non-inferiority margin and a 2.5% one-sided alpha level, the study would require 46 confirmed *Shigella* patients per treatment arm to have 80% power. To achieve 92 children with *Shigella*-confirmed infection we will need to recruit 124 children in the RCT (approximately 75% of whom will have Shigella infection confirmed by PCR). We anticipate a low (5%) dropout rate because of the short follow-up time period for the primary outcome and the close monitoring of these children, requiring we enroll 132 children in the trial (66 in each arm).

### Framework

Aim 1 and 2 will be tested for non-inferiority and aim 4 as a superiority hypothesis test. Aim 3 will be presented descriptively.

### Interim Statistical Analysis and Stopping Guidance

One interim analyses of the primary outcome (clinical failure) will occur when one-half (n=66) of the children have been enrolled in the trial which will mean approximately 50 children with laboratory confirmed *Shigella* are in the trial. Safety stopping criteria are based on the assessment of clinical failure rates for Tebipenim and Ceftriaxone where the DSMB may recommend to stop the study early if there is a statistically significantly greater clinical failure rate in Tebipenim versus Ceftriaxone at the 1-sided 0.03% level of significance. The DSMC will consider the totality of evidence from the interim analysis and descriptive data to make a determination about continuing the study

At the interim, the following rule will be assessed:
Prob (Risk Difference > 0) >=99.7%, (where the Risk Difference is defined as number of day 3 clinical failures on Tebipenim/number of children taking tebipenem – number of day 3 clinical failures on Ceftriaxone/number of children taking Ceftriaxone). If the proability is >50% but < 99.7%, the DSMC can also have the option to recommend pausing recruitment based on their assessment of the safety data as a whole.

The DSMC will be provided with the risk differences in each treatment group, the difference in proportions, the 99.7% confidence interval and the probability the risk difference is greater than 0. A Risk Difference > 0 indicates Tebipenim has a higher rate of clinical failures than Ceftriaoxone.The DSMC will make a judgment based on this information along with the totality of the safety information about continuing the study.The DSMC is empowered to continue or stop the trial based on the stopping rules and totality of safety evidence.

If the DSMC decides to continue the trial after the interim analysis, a 1-sided alpha of 0.025 will be used as the statistical significance boundary at the final analysis for the primary hypothesis tests as no alpha spending for the outcome of non-inferiority is being spent at the interim.

**Timing of Final Analysis**
The first main report/ publication of the trial will be prepared for the primary aim when every enrolled child has completed their 30-day follow-up visit or is deemed lost to follow-up and all primary endpoint data has been cleaned (anticipated publication in June 2025).

**Timing of Final Outcome Assessment**
Regularly scheduled visits include those at Enrollment and days 3, 7, and 30 days post-randomization. All visits will occur in the clinic. Participants who miss a day 3 or day 7 visit will be contacted daily for 3 days and participants missing a day 30 visit, will be contacted daily for 7 days to attempt the visit. If a visit occurs after the visit window, relevant data will be ascertained when possible, but will not be included in primary analyses. The start date/time for each participant is the date/time of randomization.

## SECTION 4. STATISTICAL PRINCIPLES

### Confidence Intervals and P-values

Level of Statistical Significance
All hypotheses will utilize a 2-sided test with 95% confidence interval (alpha of 0.05).

Type I Errors
We will not adjust the alpha for multiple testing. Instead we will clearly state primary and secondary analyses and interpret secondary analyses as hypothesis-generating rather than confirmatory.

Confidence Intervals to be Reported
All analyses will utilize two-sided 95% confidence intervals. When assessing non-inferiority, the upper bound of the 95% confidence interval will be compared to the non-inferiority margin.

### Adherence and Protocol Deviations

Definition of adherence intervention and assessment including extent of exposure

The study medications will be administered in the hospital by study staff therefore adherence will be recorded in daily record forms completed by study staff. Complete adherence will be defined as completion of 3 days worth of the study medications. Partial adherence as at least 1 day of completion of the study medication (all doses in a given day).

Description of how adherence to the intervention will be presented

Adherence data will be reported by randomization arm (complete adherence and partial adherence). In an analysis secondary to the intention to treat analysis, we will exclude children who did not have complete adherence.

Definition of protocol deviations for the trial

The following are pre-defined major protocol deviations with a direct bearing on the primary outcome:

- Change in treatment from the originally assigned randomization arm. Per clinical protocols, this will necessarily occur when a child has clinically failed on Day 3-if they were randomized to the tebipenem arm they will be given ceftriaxone and if randomized to ceftriaxone, the dose will extend to 5 days.
- Errors in applying inclusion/exclusion criteria that are discovered after randomization

*The following are pre-defined minor protocol deviations*:

- Missed sample collection (stool/rectal swab, blood spot) due to participant refusal or other barrier to sample collection (such as visit occurring over phone).
- Missed anthropometry assessment due to follow-up visit occurring over the phone

Description of which protocol deviations will be summarized

Protocol deviations will be classified as major and minor prior to unblinding of randomization allocation. After unblinding, verification of treatment arm assignment will take place and any violations also reported. The number (and percentage) of participants with major and minor protocol deviations will be summarized by study arm in relevant analyses with details of the deviation provided. The patients that are randomized will be used as the denominator to calculate percentages. No statistical tests will be performed.

**Analysis Populations**

Analysis of primary and secondary outcomes will be by intention-to-treat (ITT), modified intention-to-treat (mITT), and per protocol. The Primary analyses will be intention-to-treat (ITT). The ITT population will include all randomized children according to the treatment they were randomized to receive, irrespective of *Shigella* confirmatory results. In the mITT population, children who do not have *Shigella* confirmed by culture or PCR (Ct<30) at the time of randomization will be excluded, as will any who were deemed ineligible, post-randomization. Per protocol analyses will exclude children who did not receive full treatment course, missed the relevant visit,day 7 for day 7 outcomes and day 30 for day 30 outcomes), and those who withdrew consent. Children who withdrew consent or missed the relevant follow-up visit will be retained in ITT and mITT analyses to preserve randomization, but will be assigned the outcome of interest (clinical or microbiologic failure). Also in secondary analyses, we will compare treatment effects between groups defined by self-reported adherence to the intervention as well as in groups based on treatment received (rather than treatment randomized to).

## SECTION 5. TRIAL POPULATIONS

**Screening Data**

The total number screened will be reported along with summary of reasons for exclusion into the trial.

**Eligibility**

Children aged 24-59 months with suspected *Shigella* infection (clinical features of fever, mucus and/or blood in stools, tenesmus, and RBC and leucocytes >10 per hpf) will be identified as potential participants[13] in the study and informed consent will be administered for those interested in participating. Table 4 describes the inclusion/exclusion criteria.

| **Table 4.** Description of study population and criteria for the inclusion and exclusion of study participants. | |
|---|---|
| Study Population: | Children aged 24-59 months with suspected *Shigella* infection (clinical features of fever, mucus and/or blood in stools, tenesmus, and RBC and leucocytes >10 per hpf) who have clinically failed at 48-hours since 1st line therapy initiation (azithromycin 10 mg/kg). |
| Inclusion Criteria: | Children aged 24-59 months with suspected *Shigella* infection (clinical features of fever, mucus and/or blood in stools, tenesmus, and RBC and leucocytes >10 per hpf) will be identified as potential participants[13] in the study and informed consent will be administered for those interested in participating. |
| Exclusion Criteria | • Child received study antibiotics (azithromycin, ceftriaxone, and/or tebipenem) for the illness prior to presentation (as confirmed by bottle or prescription)<br>• Severe acute malnutrition (SAM), defined as weight-for-height z-score less than -3 or mid upper arm circumference less than 115mm, and/or other signs of infections requiring antibiotics<br>• Patients with other infectious foci who are potentially unresponsive to treatment with orally administered medication<br>• Patients in whom the efficacy and safety of the study drug is difficult to determine because of a progressive, complicated, or severe underlying disease believed to critically influence the onset of the infection, its clinical course, and therapeutic efficacy<br>• Patients with convulsive disorders, such as epilepsy, as an underlying disease<br>• Patients with a known lipid metabolism disorder or congenital carnitine deficiency<br>• Patients with severe hepatic or renal dysfunction<br>• Patients with a history of allergy to β-lactam antibiotics (e.g., carbapenems, penicillin, and cephems)<br>• Patients who have received other antibiotics for the illness and exhibited improvements<br>• Patients deemed inappropriate for this study by the attending physician<br>• Clinically improved after first-line therapy<br>• Unable to provide a stool sample at enrolment |

**Recruitment**

Children will be recruited from inpatient departments where they will be admitted for suspected *Shigella*. To ensure potentially eligible children are identified by study staff, staff will identify potential participants at the point of presentation to care with suspected Shigella infection (clinical features of fever, mucus and/or blood in stools, tenesmus/straining and RBC and leucocytes >10 per hpf in stool). Children will be screened and the caregivers of potentially eligible children will undergo informed consent. Children will be managed according to standard of care (which includes first line antibiotic therapy [azithromycin]) after consent is received and observed for 48 hours. Children who clinically failed after 48 hours since initial management will be randomized into the trial.

Per CONSORT guidelines, we will report the number of individuals who:

1. Underwent screening
2. Met inclusion criteria
3. Did not meet inclusion criteria (and reasons)
4. Enrolled in the study and were randomized (ITT)
5. Were included in the mITT
6. Were included in the per-protocol population

**Withdrawal/Follow-Up**

Level of withdrawal (from intervention and/or from follow-up)
Withdrawal of consent will be tabulated using the following categories: withdrawal from follow-up but allow prior collected data/ samples to be used; withdrawal from follow-up and disallow already collected data/samples to be utilized; withdrawal from study intervention but continue with follow-up/data collection; withdrawal from study intervention and discontinue with follow-up/data collection.

*Timing of withdrawal/lost to follow-up data*
Tabulation of withdrawals will include withdrawals by each follow-up timepoint (3, 7, and 30 days)

Reasons and details of how withdrawal/lost to follow-up data will be presented. The numbers and reasons (if available) of losses to follow-up and withdrawals will be summarized by treatment arm.

## SECTION 6. ANALYSIS

**Outcome Definitions**

Primary Study End-Point:

1. **Clinical Failure at Day 3** will be defined as presence of fever (axillary temperature ≥38°C), diarrhoea (3 or more abnormally loose or watery stools in the last 24 hours), blood in stool, or abdominal pain/tenderness (defined by localization of pain by a child in response to query of parent/caregiver or an examination during palpation there is any facial expression during compression of any part of abdmen) at Day 3 of follow-up or a death or hospitalization prior to Day 3.

Secondary Study End-Point:

1. **Clinical Failure at Day 7 and Day 30** will be defined as presence of fever (axillary temperature ≥38°C), diarrhoea (3 or more abnormally loose or watery stools in the last 24 hours), blood in stool, or abdominal pain/tenderness (defined by localization of pain by a child in response to query of parent/caregiver or an examination during palpation there is any facial expression during compression of any part of abdmen) at Day 7 or 30, respectively of follow-up or a death or hospitalization prior to Day 30. If a child changed treatment at day 3 due to clinical failure, then the day 3 outcome (failure) value will be carried forward to the Day 7 and Day 30 timepoint in primary analyses. If a failure occurred by Day 7, the failure will be carried forward to Day 30.
2. **Microbiological Failure** will be defined as the presence of *Shigella* DNA at Ct values of 30 or less enrolment OR *Shigella* isolated by microbiologic culture, at the follow-up visit. Microbiologic failure will be assessed at Day 7 and Day 30. If a child changed treatment at day 3 due to clinical failure, then the day 3 microbiological outcome will be carried forward to the Day 7 and Day 30 timepoints. If a failure occurred by Day 7, the failure will be carried forward to Day 30.
3. **Adverse Events.** Adverse events will be ascertained by caregiver report or identified by the study clinicians during clinical exams in hospital, at scheduled follow-up visits or during unscheduled visits. Severity (grades 1–5) will be defined according to 2014 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events by the clinical team.

4. **Carbapenem-resistant and cephalosporin resistant *Shigella* and *Enterobacteriaceae coli* isolates.** Carbapenem resistance will be defined as resistance to any of the following: meropenem (MIC ≥4), imipenem (MIC ≥4) or ertapenem (MIC ≥2) under CLSI guidelines. Cephalsporin resistance will be determined defined as ceftriaxone MIC ≥4.
5. **ESBL-producing *Shigella* and *Enterobacteriaceae coli* isolates** will be defined according to the BioMerieux software version 9.0 manufacturer instructions

Exploratory Study End-Points

6. **Change in length-for-age z-score** (LAZ) and will be defined as the difference in LAZ between enrolment and follow-up time points.
7. **Change in mid-upper arm circumference** (MUAC) will be defined as the difference in LAZ and MUAC between enrolment and follow-up time points.

**Analysis Methods**

Statistical Analysis of Primary Aim

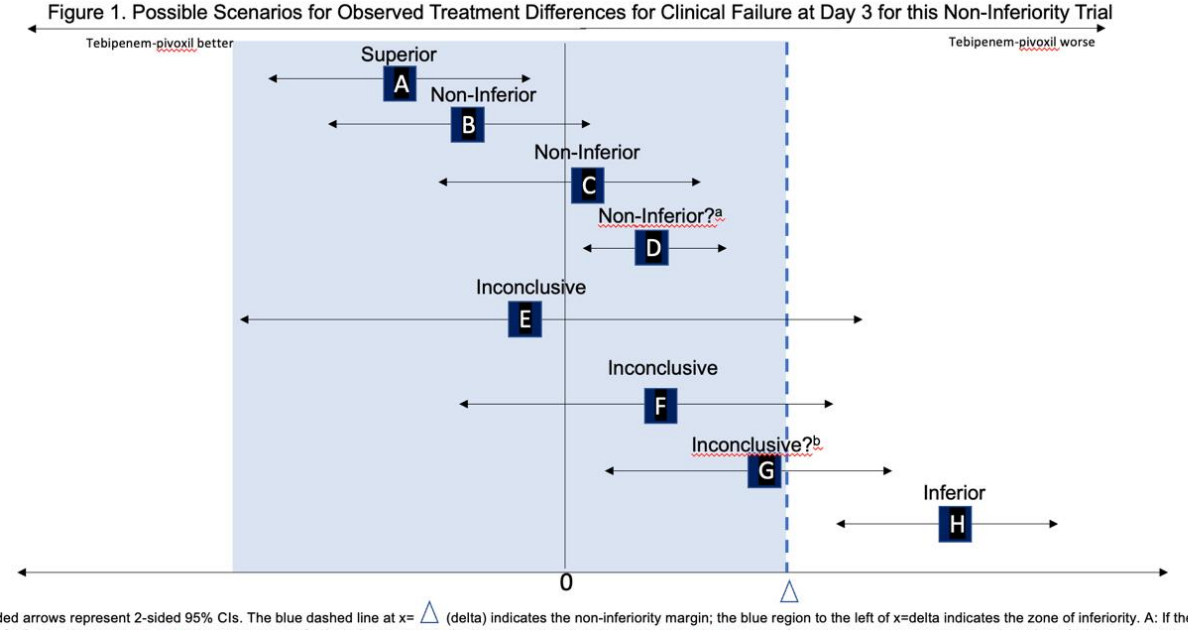
***Aim 1.*** *To determine whether tebipenem-pivoxil is clinically non-inferior to the currently WHO-recommended second line Shigella therapy (ceftriaxone) 3 days after treatment initiation.*

*Statistical Analysis:* We will calculate the proportion with clinical failure at day 3 between randomization arms, with the absolute risk differences determined using ceftriaxone as the reference. The proportion of clinical failures will be compared using Fisher's exact tests for descriptive purposes. A Miettinen and Nurminen two sided 95% confidence interval for the risk difference will be calculated assuming a binomial distribution. The hypotheses of the study for the non-inferiority of tebipnemen vs. ceftriaxone are as follows:

$$H0: \mu1 - \mu2 \geq \Delta$$
$$H1: \mu1 - \mu2 < \Delta$$

Where $\mu1$ and $\mu2$ are the proportion of clinical failure at day 3 in tebipenem and ceftriaxone arms, respectively and $\Delta$ is value determined as the confidence interval bound. The value of $\Delta$ has been set as 10%. Therefore if the upper bound of the confidence interval (2.5% one-sided significance level) of the statistical testing should fall below 10% then tebipenem will be deemed to be statistically non-inferior to ceftriaxone. Figure 1 outlines possible scenarios for observed treatment differences for clinical failure at day 3 for this non-inferiority trial.

Figure 1. Possible Scenarios for Observed Treatment Differences for Clinical Failure at Day 3 for this Non-Inferiority Trial




The double-sided arrows represent 2-sided 95% CIs. The blue dashed line at x= △ (delta) indicates the non-inferiority margin; the blue region to the left of x=delta indicates the zone of inferiority. A: If the CI lies wholly to the left of zero, Tebipenem-pivoxil is superior. B and C: If the CI lies to the left of delta and includes 0, Tebipenem-pivoxil is non-inferior but not shown to be superior. D: If the CI lies wholly to the left of delta and wholly to the right of 0, Tebipenem-pivoxil is non-inferior but also inferior since a null treatment difference is excluded. This is rare because it requires a very large sample size, or can result from a non-inferiority margin that is very wide and so will be unlikely for this study. E and F: If the CI includes delta and 0, the difference is nonsignificant but the result regarding noninferiority is inconclusive. G: If the CI includes delta and is wholly to the right of 0, the difference is statistically significant, but the result is inconclusive regarding possible inferiority of magnitude delta or worse. H: If the CI is wholly above delta, Tebipenem-pivoxil is inferior.

a This CI indicates non-inferiority as it does not include delta, but Tebipenem-pivoxil is significantly worse than Ceftriaxone. This result is unlikely as requires very large sample sizes
b This CI is inconclusive in that it is still plausible that the true treatment difference is less than delta, but Tebipenem-pivoxil is significantly worse than Ceftriaxone.

*Adapted from JAMA, December 26, 2012 Vol 308 No.24*

Statistical Analysis of Secondary Aims

***Secondary Aim 1****. To determine whether tebipenem-pivoxil is clinically non-inferior to the currently WHO-recommended second line Shigella therapy (ceftriaxone) 7 and 30 days after treatment initiation.*

*Statistical Analysis:* We will calculate the proportion with clinical failure at day 7 and day 30 between randomization arms, with the absolute risk differences determined using ceftriaxone as the reference. The proportion of clinical failures will be compared using Fisher's exact tests for descriptive purposes.

A Miettinen and Nurminen two sided 95% confidence interval for the risk difference will be calculated assuming a binomial distribution. The hypotheses of the study for the non-inferiority of tebipnemen vs. ceftriaxone are as follows:

$$H0: \mu1 - \mu2 \geq \Delta$$
$$H1: \mu1 - \mu2 < \Delta$$

Where μ1 and μ2 are the proportion of clinical failure at day 7 or 30 (considered separately) in tebipenem and ceftriaxone arms, respectively and Δ is value determined as the confidence interval bound. The value of Δ has been set as 10%. Therefore if the upper bound of the confidence interval (2.5% one-sided significance level) of the statistical testing should fall below 10% then tebipenem will be deemed to be statistically non-inferior to ceftriaxone.

If a child changed, or extended, treatment at day 3 due to clinical failure, then the day 3 value will be carried forward to the Day 7 and Day 30 in primary analyses.

***Aim 2*** *To determine whether tebipenem-pivoxil is microbiologically non-inferior to the currently WHO-recommended second line Shigella therapy (ceftriaxone) 7 and 30 days after treatment initiation.*

*Statistical Analysis:* Analyses outlined in Primary Aim 1 and Secondary Aim 2 above will be used with the endpoint of microbiologic failure instead of clinical failure. Secondary analyses will use a less stringent cut-off of Shigella DNA (Ct <35) or detection by culture to consider *Shigella* presence.

***Aim*** *3. Describe the number of adverse events, between children with shigellosis treated with oral tebipenem-pivoxil or IV ceftriaxone.*

*Statistical Analysis*: No hypothesis tests will be performed but instead the graded events will be summarized by randomization arm.

***Aim 4.*** *Compare the prevalence of ceftriaxone and carbapenem resistance, as well as ESBL-and carbapenemase-producing Escherichia coli, in children treated with tebipenem-pivoxil or ceftriaxone 7- and 30-days after initiation of second-line therapy*

*Statistical Analysis*: We will compare the proportion of children in whom *E.coli* is isolated with carbapenem and cephalosporin resistance, as well as *as well as ESBL-and carbapenemase-producing Escherichia coli*, within each randomization arms at day 7 and day 30 using GEE with a logit link (or Poisson if failes to converge) link and two-way chi-squared tests. We will construct models utilizing an auto-regressive correlation structure and an exchangeable correlation structure, maintaining an exchangeable correlation structure if the estimates and standard errors are similar between the two options. Each type of resistance will be modelled separately. A paired test (e.g., McNemar's) test will be used to also determine whether the antibiotic resistance wanes over time within each of the intervention arms. Also, we will compare resistance proportions among children (as opposed to among isolates) where absence of *E.coli* is considered susceptible (to maintain randomization). We will additionally report the proportion of resistance in *Shigella* but because we expect near-perfect microbiologic efficacy, we anticipate very few *Shigella* isolates and therefore will only describe those findings.

**Statistical Software**
All analyses will be conducted using STATA or R and the software used reported in all analysis write-ups.

**References**
References to be Provided for Non-standard Statistical Methods
All methods being proposed are standard.

Data Management Plan
Procedures relating to data entry, management, QA/AC are outline in the Data Management Trial Standard Operating Procedure.

Trial Master File and Statistical Master File
The Statistical Master File is maintained by the Study PI.

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