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Tebipenem pivoxil as an alternative to ceftriaxone for clinically non-responding children with shigellosis: a randomised non-inferiority trial protocol

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ABSTRACT

Introduction Shigellosis is the second leading cause of diarrhoeal deaths among children worldwide. Oral azithromycin and intravenous ceftriaxone are the recommended first-line and second-line therapies for shigellosis in Bangladesh, respectively, but growing antibiotic resistance will require new antibiotic options. Tebipenem pivoxil, an orally administered carbapenem antibiotic with activity against many strains of antibiotic-resistant bacteria, may be a viable option.

Methods A phase IIb randomised controlled trial was planned to determine the efficacy and safety of oral tebipenem pivoxil, compared with intravenous ceftriaxone, for children with *Shigella* diarrhoea unresponsive to the first-line antibiotic therapy. We will enrol 132 children in the trial (66 in each arm). Children from Bangladesh aged 24–59 months suspected of having *Shigella* diarrhoea, with no clinical improvement within 48 hours of starting first-line therapy, will be randomised to a 3-day course of intravenous ceftriaxone (50 mg/kg, once a day) or a 3-day course of oral tebipenem pivoxil (4 mg/kg, three times a day). The children will be evaluated for key clinical, microbiological and safety outcomes during the subsequent 30-day period. Clinically, failure at day 3 will be defined as the presence of fever (axillary temperature ≥38°C), diarrhoea (three or more abnormally loose or watery stools in the last 24 hours), blood in stool, or abdominal pain/tenderness at day 3 of follow-up or death or hospitalisation prior to day 3. It is hypothesised that children treated with tebipenem pivoxil will have no worse clinical and microbiological failure rates compared with ceftriaxone.

Ethics and dissemination This study protocol was approved by the institutional review board of the International Centre for Diarrhoeal Disease Research, Bangladesh, which comprises a research review committee and an ethics review committee. In addition, the use of tebipenem pivoxil in shigellosis was approved by the Directorate General of Drug Administration of Bangladesh.

Trial registration number NCT05121974.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be a pioneer study comparing the clinical and microbiological efficacy of tebipenem with ceftriaxone in Bangladesh for the treatment of shigellosis.
⇒ This study will use microbiological and molecular techniques to ensure a valid comparison between the two arms.
⇒ The non-blinded design of the trial may lead to observer bias and biased estimates of the treatment effect.
⇒ The long-term effects of tebipenem on children will not be assessed in this trial due to its short duration, including follow-ups (30 days in total).

INTRODUCTION

Shigellosis stands as the second highest contributor to deaths caused by diarrhoeal diseases worldwide, resulting in over 200 000 fatalities each year.[1] In 2016, *Shigella* accounted for 60 000 deaths and 74 000 000 cases of diarrhoea among children under 5 years of age, with approximately 20% of these cases occurring in South Asia.[2] The global burden of shigellosis is mainly attributable to *Shigella flexneri* and *Shigella sonnei*. *Shigella dysenteriae* type 1, although rare in occurrence, has caused multiple epidemics.[3 4] While the mortality rate attributed to shigellosis has decreased over the past decade, the development of resistance to multiple antibiotics by the bacteria raises significant concerns.[4]

In its severe manifestation, *Shigella* invades the intestinal tissue, leading to clinical symptoms such as dysentery characterised by bloody or mucoid stool.[5] The WHO advises antibiotic therapy to children with *Shigella* dysentery. This recommendation is supported by evidence from randomised trials, highlighting the significant clinical

and microbiological benefits of antibiotic therapy in managing dysentery, where *Shigella* infections constitute the majority, accounting for over 60% of cases.[6] As per WHO guidelines, oral ciprofloxacin is the preferred first-line treatment, while intravenous or intramuscular ceftriaxone is recommended as the second-line option.[7] In Bangladesh, due to the high prevalence of *Shigella* isolates resistant to ciprofloxacin (approximately 70%), azithromycin, a macrolide antibiotic, is prioritised as the first-line therapy and ceftriaxone is reserved as the second-line treatment for the most severe cases.[8–10] Around 20% of *Shigella* isolates demonstrate resistance to azithromycin, indicating that a significant portion of affected children may need second-line treatment (unpublished data from a Dhaka hospital), while the study from the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) indicates low resistance to ceftriaxone in shigellosis cases in Bangladesh, ranging from 2% to 5%.[11] However, the potential for rapid emergence of resistance to this third-generation cephalosporin, coupled with its resource-intensive delivery, underscores the urgent need for evidence-based alternative antibiotic regimens for multidrug-resistant *Shigella* infections.[12–15]

Tebipenem pivoxil, marketed under the brand name Orapenem, belongs to the carbapenem subgroup of β-lactam antibiotics and is administered orally as a broad-spectrum antibiotic.[16 17] Rigorous preclinical studies have established that tebipenem pivoxil can be an effective agent against *Shigella* infection.[18 19] The safety profile of tebipenem pivoxil was assessed in around 1100 individuals, of whom 440 were children, providing evidence for its approval for application in Japan.[20–22] Throughout these studies, tebipenem pivoxil demonstrated a favourable safety profile and was well tolerated, exhibiting adverse event (AE) characteristics similar to widely used oral β-lactam antibiotics and intravenously administered carbapenems. In addition, no reports of the inducement of seizures due to the administration of tebipenem pivoxil in clinical trials have been reported.[17]

Considering the escalating challenge posed by the rapid emergence of antimicrobial resistance and the rise of multidrug-resistant strains in Gram-negative bacteria, we propose a phase IIb randomised controlled trial (RCT) to evaluate the safety and efficacy of oral tebipenem pivoxil in comparison to intravenous ceftriaxone for treating children with *Shigella* infections unresponsive to first-line antibiotic treatment. Bangladeshi children aged 24–59 months, suspected of *Shigella* infections, with no clinical improvement after 48 hours of first-line therapy, will be randomly assigned to receive either a 3-day course of oral tebipenem pivoxil (4 mg/kg, three times a day) or 3 days of intravenous ceftriaxone (50 mg/kg, once a day). Throughout the subsequent 30 days, we will extensively assess the children for essential clinical, microbiological and safety parameters. Furthermore, we will vigilantly monitor the development of antibiotic resistance, specifically focusing on extended-spectrum β-lactamase (ESBL)-producing and carbapenemase-producing *Escherichia coli*, which are common Gram-negative bacteria in the gut flora, to evaluate both the clinical implications and potential public health risks associated with the administration of carbapenem antibiotics in this context.

AIMS AND OBJECTIVES

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 randomised to tebipenem pivoxil experience no more clinical failures than children treated with ceftriaxone, 3 days after treatment initiation.

Secondary aims

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

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

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

3. Describe the number of AEs among children with shigellosis treated with oral tebipenem pivoxil or intravenous ceftriaxone.
4. Compare the prevalence of ceftriaxone and tebipenem pivoxil resistance, as well as ESBL-producing and carbapenemase-producing *E. coli*, in children treated with tebipenem pivoxil or ceftriaxone 7 days and 30 days after initiation of second-line therapy.

Hypothesis: Children randomised to tebipenem pivoxil experience a higher prevalence of carbapenem resistance than children randomised to ceftriaxone 7 days *after randomisation; however, this difference goes away by day 30. Children randomised to ceftriaxone experience a higher prevalence of resistance to β-lactams other than carbapenems than children randomised to tebipenem pivoxil* 7 days *after randomisation; however, this difference goes away by day 30.*

METHODS AND ANALYSIS

Description of the study

This is a phase IIb non-inferiority RCT employing a factorial group design with an allocation ratio of 1:1. The study aims to determine the efficacy and safety of oral tebipenem pivoxil compared with intravenous ceftriaxone for treating 132 children, aged 24–59 months with Shigella infections that do not respond to first-line antibiotic therapy.

Study site

The study will take place in the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). The hospital partly caters to the needs of Dhaka city having a population of more than 13 million. This hospital stands as the largest facility globally specialising in diarrhoeal disease treatment. Located in the capital city of Bangladesh, Dhaka, it predominantly serves patients hailing from impoverished socioeconomic backgrounds residing in both urban and peri-urban areas of the city. The hospital features separate wards, including a specialised nutrition rehabilitation unit, comprehensive laboratory facilities capable of conducting various clinical tests, and an intensive care unit equipped with both invasive and non-invasive ventilatory support, as well as other critical care resources for managing seriously ill patients. With a distinguished history, the hospital has conducted numerous clinical trials and studies, some of which are internationally renowned for their significant contributions to enhancing the health and nutrition of infants and young children.[23]

Study participants

Children aged 24–59 months with suspected *Shigella* infection (clinical features of mucus and/or blood in stools and/or fever or tenesmus, and RBC and leucocytes >10 per high power field) will be identified as potential participants[24] in the study, and those interested in participating will provide informed consent. We will exclude participants on the basis of the following criteria:

- The child received study antibiotics (azithromycin, ceftriaxone and/or tebipenem) for the illness directly before coming to the hospital (as confirmed by the bottle or prescription).
- Severe acute malnutrition (SAM), defined as weight-for-height z-score less than −3 or mid-upper arm circumference less than 115 mm, and/or other signs of infections requiring antibiotics.
- Patients with additional infectious foci who may not respond adequately to orally administered medication.
- Patients with underlying diseases that are progressive, complicated or severe, which are believed to significantly impact the onset of the infection, its clinical progression, and the effectiveness and safety evaluation of the study drug.
- Patients presenting with convulsive disorders, such as epilepsy, as an underlying condition.
- Patients diagnosed with a lipid metabolism disorder or congenital carnitine deficiency.
- Patients exhibiting clinically diagnosed severe hepatic or renal dysfunction.
- Patients with a known allergic history to β-lactam antibiotics, including carbapenems, penicillin and cephems.
- Patients who have been treated with alternative antibiotics for their illness and have shown signs of improvement.
- Patients considered unsuitable for inclusion in this study by the attending physician.
- Clinically improved after first-line therapy.
- Patients unable to provide a stool sample at enrolment.

After written informed consent is received, children will be screened, monitored and enrolled (on meeting all the inclusion criteria) in the study during their stay in icddr,b Dhaka hospital despite not yet being randomised (day −2) (figure 1). Children will immediately be given first-line antibiotic therapy in addition to the local standard of care (oral rehydration solution or intravenous rehydration depending on the patient's condition; necessary medication if the patient has symptoms of fever; zinc supplementation) for suspected shigellosis (azithromycin 10 mg/kg once per day for 5 days). At or within 48 hours of treatment initiation, the study physician will examine the child and determine whether or not the child has clinically failed first-line therapy (at least one or more event/s of the following: clinical deterioration within early 24 hours, presence of fever, blood in stool, ≥3 loose/watery stools 48 hours after initiation of therapy). We will determine clinical deterioration based on clinical history, including the development of any morbid conditions such as sepsis, severe sepsis, septic shock, pneumonia, convulsion, SAM, etc. If a patient develops any clinical deterioration, they will not be enrolled in the study. Fever is a common presentation of shigellosis with mucoid and bloody stools. Patients often present to the hospital with a history of fever as their first symptom of shigellosis. We will observe the patient for 24 hours after the completion of 2 doses of azithromycin, and if the fever is still persistent, we will consider the patient to have clinically failed. Also, we will monitor the patient for 24 hours after the completion of two doses of azithromycin, and if there is still blood in the stool, or if the patient passes three or more loose/watery stools within 24 hours we will deem the patient as clinically failed to the first-line treatment of azithromycin.

Children who have clinically failed at 48 hours[7] will be randomised (day 0) to one of the two treatment arms: oral tebipenem pivoxil (4 mg/kg, three times a day × 3 days) or intravenous ceftriaxone (50 mg/kg, once per day × 3 days). The dosing rationale for tebipenem pivoxil was based on the established safety and efficacy of tebipenem pivoxil for treatment of upper respiratory tract infections in children at a total daily dose of 12 mg/kg. In addition, the dosing selection was further supported by simulations incorporating a previously published paediatric population pharmacokinetic model for tebipenem pivoxil and tebipenem minimum inhibitory concentration (MIC) values for *Shigella* clinical isolates.[25 26] The dose selection for the trial will be further reviewed and validated through a small pilot study where pharmacokinetics of tebipenem in this population will be investigated. Therapies will be delivered by study staff. When a child is stable, he/she will be discharged from the hospital according to the hospital's policy and guidelines. Their discharge will not be influenced by their participation in the study. Children will be followed up for 30 days with scheduled visits

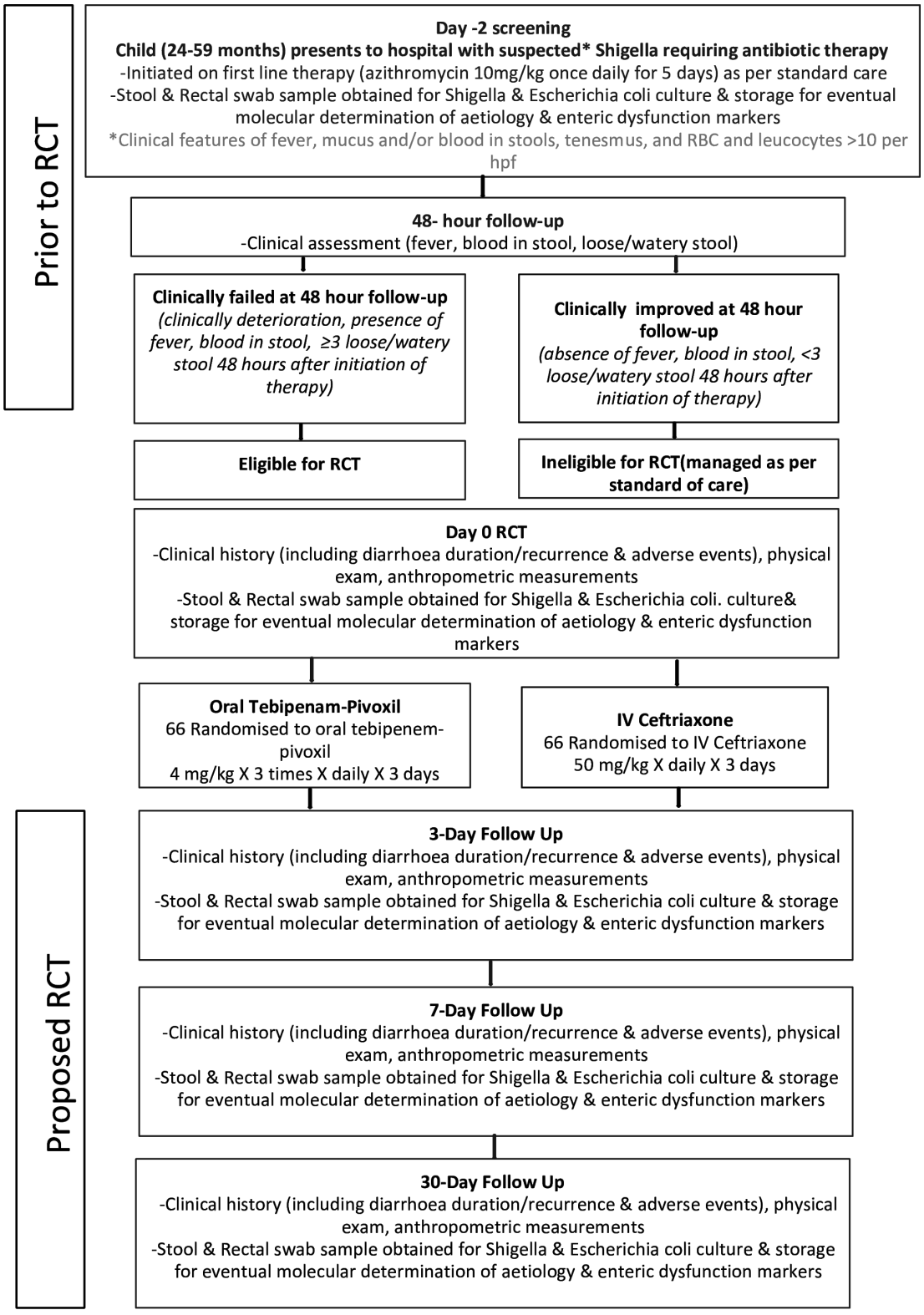

Figure 1 Trial design. IV, intravenous; RCT, randomised controlled trial.

at 3 days, 7 days and 30 days after randomisation. During these visits, as well as at the day 0 visit, a physical examination will be performed by the study physician, anthropometric measurements will be taken and caregivers will be interviewed about the clinical history of the child in addition to collecting sociodemographic information.

During their inpatient stay, children will be continuously monitored for potential AEs by the physician. Children randomised to tebipenem pivoxil who do not respond to treatment after 72 hours will be declared as clinical failure, evidenced by the presence of fever (axillary temperature ≥38°C) or diarrhoea (three or more abnormally loose or

watery stools in the last 24 hours), or blood in stool, or abdominal pain/tenderness (defined by localisation of pain by a child in response to query of parent/caregiver or during an examination/palpation if there is any facial expression while compressing any part of the abdomen) after 72 hours of second-line drug treatment. We will monitor the patient for 8–12 hours after completion of the last dose of second-line treatment (ceftriaxone or tebipenem). For those whose symptoms worsen, they will be switched to intravenous ceftriaxone for an additional 3 days (6 days of total therapy). Symptoms worsening will be assessed by clinical history (frequency of diarrhoea/recurrence and AE), physical exam and anthropometric measures. Similarly, children randomised to the ceftriaxone treatment arm who do not respond to treatment after 72 hours or are evidenced by any symptoms of clinical failure will receive a further two doses of ceftriaxone for an additional 2 days as a rescue therapy (5 days of total therapy). If the child fails to respond after a total of 5 days of ceftriaxone therapy, the investigators will decide the next step of management based on clinical decision.

The study medicine will be administered in the hospital by the study staff, therefore adherence will be recorded in daily forms completed by study staff. Throughout the intervention, the patient will stay and be monitored in the hospital. Complete adherence will be defined as completion of 3 days' worth of study medications.

Allocation concealment and randomisation

Block randomisation (1:1) is used to assign treatment groups at study enrolment by an independent statistician. Envelopes are concealed by the independent statistician, and the study physician will open the envelope containing the treatment allocation on participant enrolment. To be robust, the envelopes are truly opaque, sequentially numbered and opened in the correct order. Treatment allocation will be known to the managing clinician and the participants due to the differing drug delivery mechanisms of two antibiotics (oral vs injectable). Data managers and analysts will be unblinded also as they will recognise which arm the child is in from the dose frequency; tebipenem three times/day, ceftriaxone once/day. The statistician from our collaborator's side will perform a blinded analysis of the data set where we will remove the variables that might let him recognise which arm the patient was in.

Data collection management and storage

All children with shigellosis, within the defined age group, eligible for enrolment will be screened and examined by study physicians. Data collection tools included case record forms, daily clinical records forms, medicine administration forms, laboratory reports and so on. The case record form (online supplemental file 3) will be used to collect relevant sociodemographic characteristics, WASH practice and clinical information including duration, nature and medication for current illness. Clinical examination measurements will be performed and recorded by the study physician. Daily follow-ups will be systematically carried out and documented to effectively track the progression of the disease. All data regarding study participants will also be recorded in password-protected computer files. During screening, participants will be provided with a unique study ID, and all reports, study data and administrative forms will be identified by the study ID. The privacy, anonymity and confidentiality of data/information identifying the participant will be strictly maintained. All medical information, description of treatment and results of the laboratory tests performed are confidential, under lock and key, and none other than research staff will have access to this information. The participant's name and identity will not be disclosed while analysing or publishing the results of this study.

Children are followed up on day 3, day 7 and day 30 after randomisation. Clinical examination during the follow-up visit will be performed and recorded by the physician. Follow-up visit data also includes the onset of new illness, its duration, history of hospitalisation and history of antibiotics for illness. As the patients will be treated as inpatients and will be provided the standard care for their ailment, full participant retention is expected. No outcome data will be collected from participants who discontinue or deviate from the intervention.

Microbiological testing

Children will provide stool samples on day −2 before commencing first-line therapy. Among those randomised, samples will also be collected prior to the first dose of second-line therapy on day 0, and subsequently on days 3, 7 and 30 during follow-up. Stool samples will be divided into three, with one part allocated for microbiological culture and the remaining two parts stored at −80°C. Additionally, for the initial sample on day −2, an extra portion will be used for microscopy and faecal leucocyte assessment. Although the majority of *E. coli* are innocuous, diarrhoeagenic *E. coli* can cause significant diarrhoea. The ESBL-producing *E. coli* are a major multidrug-resistant bacterium.[27] Including *E. coli* in the investigations will allow us to look at antibiotic resistance in similar gut bacteria, bacteria that may share antibiotic-resistant conferring mobile plasmids with *Shigella*, and this strategy has been used in two recent trials of azithromycin.[28 29] Microbiological culture, including the isolation of *Shigella* and *E. coli* along with antibiotic susceptibility testing (AST), will be carried out on fresh stool samples on day −2, day 0, day 3, day 7 and day 30. Additionally, quantitative PCR to identify the ipaH gene,[30 31] indicative of *Shigella* DNA presence, will be performed on frozen stool samples collected on day −2, day 0, day 3, day 7 and day 30 in a single batch at the end of the study. AST will be performed (*in real time or on stored isolates*) using the automatic Vitek 2 system (tables 1 and 2 list antibiotics tested). Resistance thresholds for MICs will adhere to the Clinical and Laboratory Standards Institute (CLSI) 2021 standards. Consequently, ceftriaxone resistance will be classified as MIC≥4 in accordance with CLSI guidelines.

Table 1 List of antibiotics for which susceptibility against *Shigella* will be tested

Ampicillin	Ertapenem	Tigecycline
Amoxicillin/clavulanic acid	Imipenem	Nitrofurantoin
Piperacillin/tazobactam	Meropenem	Colistin
Cefuroxime	Amikacin	Trimethoprim/sulfamethoxazole
Ceftriaxone	Gentamicin	Ciprofloxacin
Cefoperazone/sulbactam	Nalidixic acid	Cefepime

Carbapenemase resistance will be characterised by resistance to any of the following: meropenem (MIC≥4), imipenem (MIC≥4) or ertapenem (MIC≥2).

Data safety and monitoring

Prior to the study's initiation, a data safety and monitoring board (DSMB) will be convened to oversee severe AEs (SAEs) and decide on the study's continuation following interim analysis. The DSMB, to be established by the ethics review committee (ERC) of icddr,b will preferably include at least five members with expertise in *Shigella*, clinical trials, statistics, paediatrics, ethics and antibiotic resistance. The DSMB will meet virtually/in person at least every 6 months or as desired by the ERC. The members of the DSMB will be independent; none of them will be affiliated to the sponsor or the study team.

SAEs related to study participation will be monitored in real time by the study team and will be reported to the relevant institutional review boards (IRBs) and the DSMB within 48 hours of occurrence. Furthermore, SAE reports (cumulative) will be transferred monthly to the DSMB. The severity of AEs, graded from 1 to 5, will be determined by the clinical team using the 2014 Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events. This grading table offers descriptions for each AE severity level as follows: grade 1 signifies a mild event, grade 2 denotes a moderate event, grade 3 indicates a severe event, grade 4 represents a potentially life-threatening event and grade 5 stands for death.

Data analysis plan

The detailed statistical analysis plan can be found on clinicaltrials.gov: NCT05121974.

Outcome definitions

We will use the following primary and secondary study endpoints:

Primary study endpoint

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

Secondary study endpoint

1. **Clinical failure at day 7 and day 30** will be defined as the presence of fever (axillary temperature ≥38°C), diarrhoea (three or more abnormally loose or watery stools in the last 24 hours), blood in stool, or abdominal pain/tenderness (defined by localisation of pain by a child in response to query of parent/caregiver or on examination during palpation if there is any facial expression during compression of any part of the abdomen) at day 7 or day 30, respectively, of follow-up or death or hospitalisation 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 timepoints in primary analyses.
2. **Microbiological failure** will be defined as the presence of *Shigella* DNA at Ct values of 30 or less or less than the enrolment Ct value or *Shigella* isolated by microbiological culture at the follow-up visit. Microbiological 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.

Table 2 List of antibiotics for which susceptibility against *E. coli* will be tested

Amikacin	Ciprofloxacin	Nalidixic acid
Amoxicillin/clavulanic acid	Colistin	Piperacillin+Tazobactam
Ampicillin	Cotrimoxazole	Tigecycline
Cefepime	Ertapenem	Meropenem
Cefoperazone/sulbactam	Gentamicin	Cefuroxime
Ceftriaxone	Imipenem	

3. **AEs** will be detected through caregiver reports or identified by study clinicians during clinical examinations, scheduled follow-up visits or unscheduled visits in the hospital. Severity levels (grades 1–5) will be determined by the clinical team using the 2014 Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events.
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. Cephalosporin resistance will be defined as ceftriaxone MIC≥4.
5. ***ESBL-producing Shigella and Enterobacteriaceae coli isolates*** will be defined according to the BioMerieux software V.9.0 manufacturer instructions.

Statistical analysis

We will calculate the proportion with clinical failure at day 3 between randomisation 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. A two-sided 95% CI for the risk difference will be calculated assuming a binomial distribution and the lower bound of the CI will be compared with the non-inferiority margin of −10%. We will follow the same analysis approach for testing for non-inferiority in secondary outcomes (clinical failure on day 7 and day 30 as well as microbiological failure on day 7 and day 30). If a child changed, or extended, treatment at day 3 due to clinical failure, then the day 3 value will be carried forward to day 7 and day 30 in primary analyses. We will compare the proportion of children in whom *E. coli* is isolated with carbapenem and cephalosporin resistance, as well as ESBL-producing and carbapenemase-producing *E. coli*, within each randomisation arm at day 7 and day 30 using GEE with a logit link (or Poisson link if it fails to converge).

Analysis of primary and secondary outcomes will be by intention-to-treat (ITT), modified intention-to-treat (mITT) and per protocol. The ITT population will include all randomised children according to the treatment they were randomised 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 randomisation will be excluded, as will any who were deemed ineligible, postrandomisation. Per protocol analyses will exclude children who did not receive the full treatment course, missed the relevant visit, day 7 for day 7 outcomes and day 30 for day 30 outcomes), and/or 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 randomisation but will be assigned the outcome of interest (clinical or microbiological 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 randomised to).

Interim statistical analysis and stopping guidance

A DSMB will be assembled prior to study initiation to monitor SAEs. One interim analysis 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. The study team will have access to the study data and will perform interim analysis. Safety stopping criteria are based on the assessment of day 3 clinical failure rates for tebipenem and ceftriaxone where the DSMB may recommend stopping the study early if there is a statistically significantly greater clinical failure rate in tebipenem versus ceftriaxone at the one-sided 0.03% level of significance. The result of the interim analysis will be shared with the DSMB. The DSMB will consider the totality of evidence from the interim analysis and descriptive data to make a determination about continuing the study.

Data will be analysed using STATA V.15.0 IC (College Station, Texas, USA). A detailed statistical analysis plan can be found at ClinicalTrials.gov Identifier: NCT05121974.

Sample size

As per our current understanding, there are no randomised clinical trials that have directly compared treatment regimens for children showing clinical non-response to shigellosis treatment or those with drug-resistant (or presumed drug-resistant) *Shigella*. Hence, the sample size calculation was based on the latest among three trials investigating intravenous/intramuscular ceftriaxone for shigellosis.[32–34] This particular trial compared a 3-day course of oral ciprofloxacin to intramuscular ceftriaxone in Israeli children with invasive diarrhoea (73 of whom had *Shigella*) and reported 97% microbiological success and 100% clinical success by day 5.[34] Thus, we assumed a clinical and microbiological success rate of 97%. A non-inferiority margin of 10% was selected as the maximum acceptable risk difference in clinical and microbiological failure between tebipenem pivoxil or ceftriaxone. With an equal assumed cure rate of 97% for both arms, a 10% non-inferiority margin, and a one-sided α level of 2.5%, the study would necessitate 46 confirmed Shigella patients per treatment arm to achieve 80% power. To reach a total of 92 children with confirmed Shigella infection, we will aim to recruit 124 children for the RCT. Approximately 75% of these participants are expected to have *Shigella* infection confirmed by PCR. We expect a minimal dropout rate of 5% due to the short follow-up duration for the primary outcome and the diligent monitoring of these children. Therefore, we plan to enrol 132 children in the trial, with 66 allocated to each arm.

DISCUSSION

Antibiotic resistance is growing in *Shigella*, despite *Shigella* being the second leading cause of diarrhoea and diarrhoea deaths among children worldwide. This non-inferiority clinical trial of tebipenem pivoxil as an alternative to ceftriaxone could expand treatment options for children with antibiotic-resistant *Shigella* infections. The prevalence of irrational antibiotic use is notably high in low-income and middle-income countries, including Bangladesh.[35] WHO endorses ciprofloxacin, azithromycin and ceftriaxone for the treatment of shigellosis, where the first two are recommended as first-line treatments[36] and the last one, ceftriaxone, is recommended as a second-line treatment option.[37 38] The susceptibility pattern of *Shigella* isolates to recommended antibiotics showed resistance at alarming rates and the percentage should not to be overlooked.[11 36 39] Establishing effective and obtainable antibiotics for treating shigellosis is now an enormous challenge. Data from this important trial will not only answer the important clinical question of whether tebipenem pivoxil can be used, but will also provide important microbiological data, including antibiotic resistance information, that will inform our understanding of the impact of antibiotic treatment for *Shigella* on longer-term antibiotic resistance patterns.

This study can lead to larger phase III studies that can address a new way of fighting against the development of bacterial resistance to the existing or commonly prescribed antibiotics. The results are expected to encourage further clinical studies to find alternatives to some other commonly prescribed antibiotics against enteric infectious micro-organisms. Additional uses of tebipenem could be further explored through the design of appropriately powered studies in other diseases.

ETHICS AND DISSEMINATION

Ethical approvals

This study protocol was approved by the IRB of icddr,b that comprises the research review committee and the ERC of icddr,b (protocol no: PR 21005; V.5.00; 15 October 2023). In addition, the use of tebipenem pivoxil in shigellosis was approved by the Directorate General of Drug Administration of Bangladesh. The study protocol adheres to the recommendations for interventional trials (SPIRIT) guidelines for reporting.

Consent

After confirming eligibility, the primary caregiver of participants provides written informed consent and will be monitored for 48 hours before randomisation. At or within 48 hours of treatment initiation, if the child is considered to have clinical failure with first-line therapy, the caregiver will provide another written informed consent form. Caregivers will sign the written informed consent form and the study physician will explain the purpose of the study, as well as all the study procedures, and possible risks and benefits. Documented witnessed verbal consent and fingerprints will be obtained for illiterate caregivers. Caregivers will also be informed that they can choose to participate in the trial or they can withdraw their participation at any time after enrolment in the study. One copy of the signed consent document will be given to the caregiver of each participant, and another copy will be kept for the study documentation.

Dissemination plan

We will be planning to disseminate the result of the trial findings to international and national scientific members and policymakers of the Bangladesh Government after the completion of the trial through national and international seminars and conferences. On completing data collection and analysis, the study results will be submitted for publication in an appropriate peer-reviewed journal.

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Contributors SN, MRI, SD, SJB, PBP, SLA, RG, TA, FQ, AN, JA, EFA, FK, DA and MJC conceived and designed the study. SN, MRI, SJB, PBP and SLA wrote the manuscript. SD, AN, RG, JA, EFA, FK, DA, MJC, FQ and TA critically reviewed and edited the manuscript. All the author(s) read and approved the final version of the manuscript for submission. The first author, SN is the guarantor.

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Competing interests AN, RG, EFA, and JA are employees of the GSK group of companies. AN and RG also own shares in the GSK group of companies. AN, RG, EFA, and JA declare no other financial and non-financial relationships and activities. The other authors declare that they have no competing interests.

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