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The azithromycin and cefixime treatment of typhoid in South Asia trial

Submission date
02/07/2023

Recruitment status
No longer recruiting

Registration date
06/07/2023

Overall study status
Completed

Last Edited
14/08/2025

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Typhoid and paratyphoid (enteric) fever affects more than 11 million children and adults globally each year including 7 million in South Asia. Up to 1% of patients who get typhoid may die of the disease and, in those that survive, a prolonged period of ill health and catastrophic financial cost to the family may follow. In the last 20 years, treatment of typhoid fever with a 7-day course of a single oral antimicrobial, such as ciprofloxacin, cefixime or azithromycin, given in an out-patient setting has led to a patient recovery in 4 to 6 days without the need for expensive hospitalization. Increasing antimicrobial resistance in Asia and sub-Saharan Africa threatens the effectiveness of these treatments and increases the risk of prolonged illness and severe disease. The recent emergence of a particularly resistant typhoid strain in Pakistan, and its subsequent international spread, adds urgency to this problem and Salmonella is now listed as a high (Priority 2) pathogen by the World Health Organisation.

Who can participate?
Patients aged 2 years or over (and weighing at least 10 kg) to 65 years with suspected uncomplicated typhoid fever

What does the study involve?
Treatment with combinations of antimicrobials may be more effective for treating typhoid fever and mitigating the problems of resistance. This suggestion is based on expert opinion but is not backed up by good-quality evidence. The ACT-South Asia study aims to compare a combination of azithromycin and cefixime with azithromycin alone in the outpatient treatment of clinically suspected and confirmed uncomplicated typhoid fever. The total recruitment will be more than 1500 (around 2150) patients with target of 400 blood culture positive cases across sites in Nepal, Bangladesh and Pakistan. A placebo (sugar pill) will be used instead of cefixime in the single-drug arm so that neither the patient nor the study team knows which patient is receiving which treatment. Investigators will assess whether treatment outcomes are better with the combination after one week of treatment and at one- and three-month follow-ups. Both antimicrobials are widely used and have excellent safety profiles. If the combination treatment is better than the single antibiotic treatment, this will be an important result for patients across South Asia and other typhoid-endemic areas. This study will additionally investigate the financial implications for families and the health system.

What are the possible benefits and risks of participating?
All participants will receive azithromycin which is a standard treatment choice for this disease in South Asia. Half of the patients will, in addition, receive cefixime, which is also a recommended treatment for typhoid in South Asia. For the duration of the study, all participants will have access to free and accurate health assessments and diagnostics at dedicated clinics in the hospitals at each of the study sites. Participants will also have access to medical staff for general health issues for the duration of the study.

Azithromycin and cefixime are widely used antimicrobials with a favorable safety profile. Both antimicrobials have been used in previous clinical trials of typhoid fever with minimal and mild adverse effects only. Safety monitoring will be conducted as a secondary outcome of this study.

Where is the study run from?
Oxford University Clinical Research Unit (Nepal)

When is the study starting and how long is it expected to run for?
November 2019 to December 2025

Who is funding the study?
UK Research and Innovation (UKRI) Joint Global Health Trials Scheme

Who is the main contact?
Buddha Basnyat, buddhabasnyat@gmail.com

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04349826

Protocol serial number

MR/TOO5033/1

Study information

Scientific Title
Azithromycin and cefixime combination versus azithromycin alone for the out-patient treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia; a randomized controlled trial (ACT-South Asia Trial)

Acronym
ACT-South Asia trial

Study objectives
1. Primary Hypothesis: The combination of azithromycin and cefixime is superior (i.e. it leads to fewer treatment failures) to azithromycin alone for the treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia

2. Secondary Hypothesis:
The combination of azithromycin and cefixime, when compared to azithromycin alone, for the treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia will significantly reduce the fever clearance time, the time to treatment failure, the duration of symptoms, and the occurrence and duration of faecal carriage of S. Typhi and S. Paratyphi. The combination will be more cost-effective than azithromycin alone and will not lead to more adverse events.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. Approved 16/07/2020, Oxford Tropical Research Ethics Committee (OxTREC) (Wellington Square, Oxford , OX1 2JD, United Kingdom; +44 (0) 1865 282106; oxtrec@admin.ox.ac.uk), ref: 28-20

2. Approved 02/03/2021, Nepal Health Research Council (NHRC) (Ramshah path, PO Box:7626,, Kathmandu, 44600, Nepal; +977 1 4254220; nhrc@nhrc.gov.np), ref: 781/2020 P

Primary study design
Interventional

Study design
Randomized participant-and observer-blind multi-centre phase IV study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
The out-patient treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia

Interventions

Potential participants attending the study site clinics with fever or a history of fever will be identified and approached for possible inclusion in this study. Trial staff will screen potential participants in a fever clinic for eligibility for the study. Those meeting the criteria for the history of illness will be asked for verbal consent to have blood samples taken to complete the eligibility assessment. Participants will be considered eligible for enrolment in the trial if they fulfil all the inclusion criteria and none of the exclusion criteria. Participants will be randomly allocated to one of two treatment arms resulting in a 1:1 final disposition. Before treatment allocation, the patient's eligibility and informed signed consent will be confirmed and entered into the database. A computer-generated randomization list will use block randomization with stratification by site and age (children (< 16 years) and adults (≥16 years). The recruitment in most sites will take place during working hours as these are uncomplicated typhoid patients.

Patients with suspected uncomplicated typhoid fever will be randomized to one of the two interventions:
Arm A: Azithromycin 20mg/kg/day oral dose once daily (maximum 1gm/day) and Cefixime 20mg to 30mg/kg/day oral dose in two divided doses (maximum 400mg bd) for 7 days
Arm B: Azithromycin 20mg/kg/day oral dose once daily (maximum 1gm/day) for 7 days and Cefixime-matched placebo for 7 days. Both antimicrobials are widely used and have excellent safety profiles. If the combination treatment is better than the single antibiotic treatment, this will be an important result for patients across South Asia and other typhoid-endemic areas. This study will additionally investigate the financial implications for families and the health system.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Azithromycin, cefixime

Primary outcome(s)
A composite outcome of treatment failure by the 28th day after the initiation of treatment will be defined by either of the following events:
1. Clinical failure: Persistence of fever on day 7 (168 h) post-treatment initiation or the need for rescue treatment as judged by the Trial Clinician or the development of any complication (e.g., clinically significant bleeding, fall in the Glasgow Coma Scale score, perforation of the gastrointestinal tract) or Syndromic enteric fever relapse within 28 days of initiation of treatment
2. Microbiological failure: A positive blood culture for S. Typhi or S. Paratyphi on day 7 of treatment regardless of the presence of fever (microbiological failure) or blood culture-confirmed typhoid fever relapse within 28 days of initiation of treatment

Key secondary outcome(s)
1.The FCT will be the time from the first dose of a study drug until a temperature of<37.5°C (axillary); <38.0°C (oral) has
been achieved for at least 48 h;
2.The time to treatment failure will be the time from the first dose of a study drug until an event occurs defined as a
Treatment failure
3.The time to treatment failure will be the time from the day of the first symptom until an event

occurs defined as a
Treatment failure
4.Adverse events will be graded(grade3/4 adverse events, serious adverse events, adverse events of any grade leading to modification of study drug dose or interruption/early discontinuation); 5.Postive culture of faeces sample for
S.Typhi or S.Paratyphi
6. The incremental cost-effectiveness ratio (ICER) will comprise of the total costs per case, real outpatient and in-patient costs, total direct and indirect costs for the family and healthcare system and health outcomes converted to Disability Adjusted Life Years (DALYs). The cost per DALY averted will be compared against multipliers of the GDP/capita, in each of the four countries to establish the cost- Effectiveness of the combination regimen.

Completion date
30/12/2025

Eligibility

Key inclusion criteria
1. A history of fever at presentation for >48 hours and a documented fever(≥37.5oC (axillary))
2. Aged ≥2 years (and ≥10 kg) to 65 years old
3. No clear focus of infection on initial clinical evaluation
4. Malaria RDT negative; dengue NS1 RDT negative; scrub typhus RDT negative; CRP rapid test ≥10 mg/L. Able to take oral treatment (Exception case if any Of RDT is positive or CRP< 10, but blood/stool culture positive case).
5. Able to attend for follow-up and can be contacted by telephone
6. Written fully informed consent to participate in the study including assent for children in addition to parental/legal guardian consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
2 Years

Upper age limit
65 Years

Sex
All

Key exclusion criteria
1. History of fever for >14 days
2. Pregnant or positive pregnancy test or breast-feeding
3. Presence of clinical symptoms or signs indicating a focal infection such as pneumonia; urinary

infection, meningitis, eschar
4. Obtundation, haemodynamic shock, visible jaundice, gastrointestinal bleeding or any signs of severe disease that may require immediate hospitalization
5. Being treated for TB or HIV or severe acute malnutrition
6. Patients with cardiac disease
7. Patient requiring intravenous antibiotics for any reason
8. Previous history of hypersensitivity to any of the treatment options
9. Either of the trial drugs are contraindicated for any reason (e.g. drug interactions)
10. Has received azithromycin or cefixime in the last 5 days
11. Receiving another antimicrobial and responding clinically to the treatment as judged by the attending clinician.
12. Being on another drug (for example certain kinds of anti-depressants, or anticonvulsants) that may also cause prolonged QT interval
13. COVID-19 PCR/antigen positive

Date of first enrolment
09/05/2021

Date of final enrolment
30/09/2025

Locations

Countries of recruitment
Bangladesh

Nepal

Pakistan

Study participating centre
Patan Academy of Health and Sciences
Lagankhel
Kathmandu
Nepal
26500

Study participating centre
Civil Services Hospital
Banaeshwor
kathmandu
Nepal
44600

Study participating centre

Siddhi Memorial Hospital
Bhaktapur
Bhaktapur
Nepal
44600

Study participating centre
B.P.Koirala Institute of Health Science
Ghopa
Dharan
Nepal
44600

Study participating centre
Sukraraj Tropical and Infectious Disease Hospital
Teku
Kathmandu
Nepal
44600

Study participating centre
Kathmandu Model Hospital
Pradarshani Marg
Putalisadak
Kathmandu
Nepal
44600

Study participating centre
Aga Khan University
Stadium Road
Karachi
Pakistan
411102

Study participating centre
Aga Khan University Hospital for Women Garden
515 Gold street
Garden east Karachi

Karachi
Pakistan
411102

Study participating centre
Aga Khan University Karimabad
Karimabad block 3
Gulberg town
Karachi
Pakistan
411102

Study participating centre
National Institute Of Child Health
Rafique H.J.Shaheed Road
Karachi
Pakistan
75510

Study participating centre
International Center for Diarrheal Disease Research,Bangladesh
68 Shaheed Tajuddin Ahmed Sarani Mohakali
Dhaka
Bangladesh
16340

Study participating centre
Shaheed Suhrawardy Medical College
Sher-E-Bangla Nagar
Dhaka
Bangladesh
807

Study participating centre
Dhaka Shishu (Child) Hospital
Sher-E-Bangla Nagar
Dhaka
Bangladesh
807

Study participating centre
National Academy Of Medical Sciences, Bir Hospital
Mahabouddha
Kathmandu
Nepal
44600

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research council

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analyzed during the current study are/will be available on request from Dr Buddha Basnyat at ctu-nepal@oucru.org/buddhabasnyat@gmail.com

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		12/11/2021	03/07/2023	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes