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Understanding the burden of enteric fever in Africa and Asia: a study of transmission and antibiotic resistance to improve diagnostics and inform vaccine strategies

Submission date
10/10/2016

Recruitment status
No longer recruiting

Registration date
20/10/2016

Overall study status
Completed

Last Edited
04/02/2022

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Enteric fever is a generalised illness which can cause a variety of symptoms including fever, tiredness, headache, stomach pain, diarrhoea and constipation due to infection with certain types of bacteria (for example, Salmonella). These bacteria are passed between humans and infection occurs after ingesting them in contaminated food or water. In certain parts of the world where enteric fever is common, there are many other illnesses that can cause similar symptoms. Finding out to what degree enteric fever affects a population is important, as this information is needed to determine how and when to use prevention methods, including vaccines. For enteric fever, this is made more complicated as many people don't come to hospital when they are sick or only have a mild illness. Some people can also carry the bacteria for a long period of time without becoming sick at all. Identifying these individuals is likely to be important for reducing the amount of enteric fever in these areas. The overall aim of this study is to collect together information needed to determine how a vaccine may help in controlling enteric fever.

Who can participate?
Participants who live in specific study areas with known high levels of enteric fever cases, irrespective of age or sex.

What does the study involve?
This study involves running a number of population surveys and surveillance studies, collecting, for example, general information on households (age and gender of people in households and also relationships), information on the usage of healthcare facilities (such as water sanitation and hygiene services), information on cases of enteric fever reported by healthcare centres and immunity testing for antigens that cause enteric fever.

What are the possible benefits and risks of participating?
There are no immediate benefits to taking part in the study, although it is believed that these

studies will help researchers to understand how to prevent the disease and therefore reduce the number of cases that occur. There are no risks to taking part.

Where is the study run from?
The study is run from Oxford University in the United Kingdom. Recruitment to the study and the census areas of interest are located in Malawi in Africa and Nepal and Bangladesh in South Asia.

When is the study starting and how long is it expected to run for?
June 2015 to December 2020

Who is funding the study?
1. Wellcome Trust
2. Bill and Melinda Gates Foundation

Who is the main contact?
1. Prof. Andrew J Pollard (scientific)
2. Miss Sarah Kelly (public)

Contact information

Type(s)
Scientific

Contact name
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Type(s)
Public

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Miss Sarah Kelly

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
OVG 2015/04

Study information

Scientific Title
Prospective, epidemiological, clinical and laboratory programme to plan and evaluate strategies to control enteric fever in different settings in Africa and Asia

Acronym
STRATAA: STRAtegic Typhoid alliance across Africa and Asia

Study objectives
The overall aim of this research is to provide the science to underpin the implementation of new vaccines for the control of invasive Salmonella diseases in different epidemiological settings in Africa and Asia by:
1. Providing missing data on disease burden, antibiotic resistance and transmission needed to support and implement conjugate vaccines for enteric fever and NTS, using epidemiological data collection and application of knowledge from typhoid and paratyphoid human challenge models
2. Establishing the host-factors that determine susceptibility to enteric fever and NTS, to inform vaccine implementation strategies
3. Providing a comprehensive approach to diagnostics to allow a more accurate assessment of disease burden, vaccine impact and to inform epidemiological models
4. Investigating the mechanisms of natural and vaccine-induced protection in human challenge models (UK), test in human-to-mouse studies, and validate in field settings (Nepal, Bangladesh and Malawi) and to develop correlates of protection to drive vaccine implementation
5. Model disease dynamics and the balance between direct and indirect vaccine impact in different settings using the biological and epidemiological data emerging from the programme
6. Strengthen research capacity in enteric fever endemic regions of the world and provide the data for vaccine implementation advocacy

The study will employ field sites with different patterns of disease, co-morbidities, force of infection, transmission and carriage and integrate expertise from different scientific disciplines to provide the essential data required to achieve a measurable impact on disease through introduction of conjugate typhoid vaccines.

Ethics approval required
Old ethics approval format

Ethics approval(s)

1. Oxford, United Kingdom: Tropical Research Ethics Committee, 13/10/2015, ref: 39-15
2. Dhaka, Bangladesh: icddr,b Research Review Committee, 23/02/2016, ref: PR-15119
3. Blantyre, Malawi: National Health Sciences Research Committee, 19/05/2016, ref: 15/5/1599
4. Patan, Nepal: Nepal Health Research Council, 20/01/2016, ref: 306/2015

Study design
Prospective epidemiological clinical and laboratory programme

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Community

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Enteric fever

Interventions
1. A population census of ~100,000 individuals to establish baseline demographic data on a per household basis; to be updated at regular intervals with migration, births and deaths during the study period. Approximately 20,000 households at each site will be visited by study staff and consent sought from the head of the household or key informant. With their assistance a brief questionnaire will be completed by researchers to provide data such as age, sex and relationship structure of those resident within the household.

2. Water sanitation and hygiene (WASH) and healthcare utilisation (HUS) surveys in households included in the census. Study staff will gather information from the consenting head/key informant of >700 randomly selected households from within the site census area. This will include data describing the actual and hypothetical usage of healthcare facilities for febrile illness episodes.

3. Passive surveillance performed at serving healthcare centres for cases of febrile illness and identification of culture-positive enteric fever illness. All individuals presenting at local health care facilities serving the census populations with a history of fever >72 hours will be eligible. Census identifier and screening information, including area of residence and clinical symptoms will be recorded following consent. Blood, stool, and other clinical samples will be collected for confirmation of diagnosis and development of diagnostic and serosurveillance tools. Patients with blood culture confirmed invasive Salmonella disease (S. Typhi, S. Paratyphi A or Non-Typhoidal Salmonellae) whose household is included in the census will be considered as index cases for further investigation (see 5, below). Research teams will collect further clinical

information from index cases at day 8 and, with addition of further samples, at months 1, 6 and in some cases 12 months at the relevant health care facility.

4. Population serosurveillance study including ~10,000 individuals at each census site selected by age-stratification, to look for subclinical and/or background immunising exposure to typhoidal Salmonella antigens in addition to identifying recent exposure and chronic carriers. Members of the research teams will collect blood samples from consenting participants. Serological assays for (immunoglobulin G) antibody to typhoid Virulence factor (Vi) will be performed on all samples; if raised this antibody can be used as an indicator of chronic typhoid carriage. Those with 'high' titres will have further blood and stool samples collected 6 and 12 months after the initial visit.

5. Household contact tracing of individuals presenting in the passive surveillance study (index cases) and identified as being chronic carriers in the serosurveillance study. Researchers will visit ≥73 households of cases identified by passive surveillance to enrol members as household contacts. Following consent procedures, blood and stool samples will be collected at the first visit and 1 month later. If a participant is found to have elevated anti-Vi IgG antibody levels, two further stool samples (collected at least 48 hours apart) will be collected at a six 6 month visit and the participant will be treated according to local and national guidelines. Further stool samples will be collected at 12 months to ensure treatment has been successful. Household contacts of suspected chronic carriers, identified during the serosurvey, will be approached by researchers (in an opportunistic sampling strategy) at the six-month follow-up visit to the household. Blood and stool samples will be collected with individual consent. No attempts will be made to carry out repeat visits to contact members of the household not present at the initial visit.

Intervention Type
Other

Primary outcome measure
The burden of enteric fever (typhoid and paratyphoid) in Africa and Asia, within the census populations, over a 2-year observation period, as determined by:
1. The number of new cases confirmed by blood culture
2. The rate of carriage per 1000 head of population
3. The infection rate amongst household contacts of confirmed cases

Secondary outcome measures
Antibody detection rates per 1000 head of population during the 2-year observation period to determine:
1. Rate of chronic carriage
2. Incidence of non-clinical typhoid
3. Rates of infection arising from close contact with confirmed enteric fever and chronic carriers

Overall study start date
22/06/2015

Completion date
31/12/2020

Eligibility

Key inclusion criteria

Census study, WASH and HUS survey:
Census participants will be the population (n ≥100,000, all ages) residing in a demarcated geographic area that is a known catchment population for each of the 3 typhoid surveillance sites. Participants will be recruited and consented as households.
1. Head of household / key informant is willing and competent to give informed consent for participation of the household in the study
2. Head of household / key informant is Male or Female, aged 18 years or above
3. Household is within the census area

Passive surveillance:
This component will include all patients presenting at any of the clinical surveillance sites in each country with a history of subjective fever >72 hours with or without objective fever on presentation.
1. Individual willing and competent to give informed consent if ≥18 years or the parent/legal guardian if participant <18 years;
2. Able to comply with study requirements
3. In addition those considered index cases (for the household contact component) must be resident in a household enrolled in the census survey

Household contacts (index cases):
From each site at least 73 households with index cases identified by the hospital surveillance component will be visited and all individual members of the household enrolled for the household contact study.
(Resident in same household as index case (identified from passive surveillance study) in whom enteric fever has been confirmed by a positive blood culture for S. Typhi or S. Paratyphi;
1. Individual willing and competent to give informed consent if ≥18 years or the parent/legal guardian if participant <18 years
2. Able to comply with study requirements

Serosurveillance:
Individual, age stratified participants (0-4 years, 5-9 years, 10-14 years >14 years) will be randomly selected from the census population.
1. Individual willing and competent to give informed consent if ≥18 years or the parent/legal guardian if participant <18 years
2. Male or female
3. Able to comply with study requirements
4. Resident in census area

Household contacts (of suspected chronic carriers identified in serosurvey):
Individuals resident in 50 households of suspected chronic carriers will be approached to request blood and stool samples in order to assess risk of infection in this group.
1. Resident in the same household as suspected chronic carrier identified in the serosurvey;
2. Individual willing and competent to give informed consent if ≥18 years or the parent/legal guardian if participant <18 years;
3. Able to comply with study requirements.

Participant type(s)

All

Age group

All

Sex
Both

Target number of participants
Census: 100,000 at 3 sites. Other surveys (passive surveillance, WASH, HUS, serosurvey and contact tracing) performed within this.

Total final enrolment
423618

Key exclusion criteria
Census study, WASH and HUS survey:
1. Head of household/key informant not willing for household to participate
2. Unable to identify Head of household/key informant

Passive surveillance:
1. Previous enrolment into this component (e.g. from previous attendance at healthcare facility with persistent fever)
2. Other underlying disease which can be rapidly diagnosed such as Malaria in children (Blantyre)

Household contacts (index cases):
1. Not a resident of household of index case at time of his/her primary illness
2. Fever at presentation in index case confirmed not due to S. Typhi or Paratyphi fever
3. Deemed clinically unsuitable by the survey team (e.g. terminally ill)

Serosurveillance:
1. Not resident in the census area
2. Deemed clinically unsuitable by the survey team (e.g. terminally ill)

Household contacts (of suspected chronic carriers identified in serosurvey):
1. Not a resident of household of suspected chronic carrier at time of the visit
2. Deemed clinically unsuitable by the survey team (e.g. terminally ill)

Date of first enrolment
29/05/2016

Date of final enrolment
31/01/2019

Locations

Countries of recruitment
Bangladesh

Malawi

Nepal

Study participating centre
International Centre for Diarrhoea Research, Bangladesh
68, ShaheedTajuddin Ahmed Sarani
Mohakhali
Dhaka
Bangladesh
1212

Study participating centre
Malawi-Liverpool-Wellcome Trust
Queen Elizabeth Central Hospital
College of Medicine
P.O. Box 30096
Chichiri
Blantyre
Malawi
3

Study participating centre
Oxford University Clinical Research Unit - Nepal
Patan Academy of Health Sciences
Lagankhel
Lalitpur
Nepal
26500

Sponsor information

Organisation
University of Oxford

Sponsor details
Clinical Trials and Research Governance
Joint Research Office, Block 60, Churchill Hospital
Oxford
England
United Kingdom
OX3 7LJ

Sponsor type
University/education

Website

https://www.admin.ox.ac.uk/researchsupport/ctrg/

ROR
https://ror.org/052gg0110

Organisation
International Centre for Diarhoea and Diarrhoeal Research, Bangladesh

Sponsor details
68, ShaheedTajuddin Ahmed Sarani
Mohakhali
Dhaka
Bangladesh
1212

Sponsor type
Research organisation

Website
http://www.icddrb.org

Organisation
Unviersity of Liverpool

Sponsor details
Research Support Office
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3 Brownlow street
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England
United Kingdom
L69 3GL

Sponsor type
University/education

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Publication and dissemination plan
Publication date for the main paper is aiming for September 2020, with numerous publications planned after this once all the trial data is analysed.

Intention to publish date
01/09/2020

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	02/07/2017		Yes	No
Results article		01/12/2021	03/02/2022	Yes	No