ISRCTN11643110 https://doi.org/10.1186/ISRCTN11643110

TyVAC Bangladesh: Typhoid Vaccine Trial

Submission date
05/02/2018

Recruitment status
No longer recruiting

Registration date
07/02/2018

Overall study status
Completed

Last Edited
04/03/2025

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Typhoid fever is a bacterial infection that can cause severe disease and even death. Typhoid is spread through contaminated food and water, due to poor hygiene and sanitation conditions. In Bangladesh, typhoid fever causes a lot of disease, mostly in children. Previous vaccines have not provided long-term protection for children. A new typhoid vaccine, Vi-TCV, has been developed and has been WHO pre-qualified and is licensed for use in India and Nepal. This vaccine is safe for children and may provide long-term protection. However, this vaccine is not yet available through the routine childhood immunisation programme. Before the government introduces the vaccine into the routine programme, more information is needed on the level of protection that the vaccine provides. The aim of this study is to find out whether the typhoid vaccine Vi-TCV reduces the incidence of typhoid fever in children.

Who can participate?
Children under the age of 16 years

What does the study involve?
As per local regulations, a pilot phase will be carried out initially, where 200 children between the ages of 9 months and <16 years will be vaccinated with either the typhoid vaccine or a vaccine that protects against Japanese encephalitis. At the same time, a census will be conducted, in order to identify who is currently living in the study catchment area. The study catchment area will then be divided up into 150 clusters or areas. These clusters of households will then be randomly allocated for participants living in them to either receive the typhoid vaccine (Vi-TCV) or a vaccine which protects against Japanese encephalitis. Participants will be followed up for up to 2 years following vaccination. When participants develop a fever during that time, they will be asked to come to the local hospital or the study clinics in the community. If they have a fever over 38 degrees C or if they have had a fever for 2 or more days they receive treatment and a blood test to check if they have typhoid fever. The cost of treatment for suspected or confirmed typhoid is covered by the study. All participants are also monitored for side effects associated with the vaccine. At the end of the study, all of the children who first received the Japanese encephalitis vaccine will be offered the typhoid vaccine too.

What are the possible benefits and risks of participating?
Participants benefit from the study by receiving the typhoid vaccine for free, which is not currently available through the routine immunisation system in Bangladesh. Participants also

have free treatment for any suspected or confirmed typhoid infections. The vaccine has been found to be safe in all previous studies, but since this is the largest study of this vaccine to date, there is a risk for participants that a rare side effect, not yet identified, may become apparent in this study.

Where is the study run from?
International Centre for Diarrhoeal Disease Research (Bangladesh)

When is the study starting and how long is it expected to run for?
February 2018 to February 2020

Who is funding the study?
Bill and Melinda Gates Foundation (USA), grant number: OPP1151153

Who is the main contact?
Prof. Andrew Pollard

Contact information

Type(s)
Scientific

Contact name
Prof Andrew Pollard

ORCID ID
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Contact details
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
OVG 2017/11

Study information

Scientific Title

Assessing the impact of a Vi-Polysaccharide Conjugate Vaccine in preventing typhoid infection among Bangladeshi children – a Phase IV trial

Study objectives
The typhoid vaccine, Vi-TCV, will reduce the incidence of laboratory confirmed typhoid fever in children receiving the vaccine, compared to those receiving a control vaccine.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. RRC, 19/12/2017
2. ERC, 22/01/2018
3. Oxford Tropical Research Ethics Council (OxTREC), 08/02/2018, ref: 5 -18

Study design
Parallel cluster-randomized controlled trial with 2-year follow-up to assess the change in medium-term vaccine protection

Primary study design
Interventional

Secondary study design
Cluster randomised trial

Study setting(s)
Community

Study type(s)
Prevention

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

Health condition(s) or problem(s) studied
Blood culture confirmed typhoid fever

Interventions
Current intervention as of 09/03/2021:
Intervention: Vi Typhoid conjugate vaccine (Vi-TCV), trade name: TyBar
Control: Japanese Encephalitis vaccine: trade name: SA14-14-2, Japanese Encephalitis Vaccine, Live

A baseline census innumerates all households within the geographically defined catchment area.

A pilot phase, prior to the main study, individually randomises 200 children, in an area separate from the main trial site, in an age-stratified manner to receive either Vi-TCV or the JE vaccine. Safety data is presented to the local DSMB (LDSMB), IRB and to the Directorate General of Drug Administration (DGDA), the National Regulatory Authority of Bangladesh prior to initiating the main cluster randomised trial.

For the pilot phase, two sequential groups of children are studied: children aged 3-15 years (n=100) followed by children aged 9 months to <3 years (n=100), with movement to the next phase contingent only on safety at 1 week post dosing. After approval by the LDSMB, IRB and the DGDA in Bangladesh, the main Vi-TCV study is initiated.

The main trial is participant- and observer-blinded, cluster-randomised study of the typhoid conjugate vaccine (Vi-TCV), brand name: Tybar-TCV, in Bangladeshi children. The population within a selected geographical catchment area of Mirpur, Dhaka, are offered entry into the study. The aim is to enrol 43,350 eligible, consenting children/guardians within the target age range (9 months to <16 years) residing in the target area at baseline. 150 Residential clusters of ca. 1250 people each are randomised in a 1:1 ratio to receive Vi-TCV or the control vaccine (SA 14-14-2).

Surveillance for enteric fever are undertaken in health care facilities in Mirpur for all residents of the participating clusters for 4 months preceding baseline and continuing for approximately 2 years after vaccination, until the end of the study. In this surveillance, all consenting residents from the participating clusters who present with a subjective history of ≥2 days fever and a temperature of ≥38°C have a blood culture taken, and receive appropriate clinical management. Those with positive blood cultures are visited at home to confirm their identity given at the treatment center, to collect information about their illness, and to review the treatment given, and adjust as necessary, based on laboratory testing.

At 6-month intervals during the 2 years after baseline, census updates of the population are done in all clusters, and children fulfilling the eligibility criteria for participation who have not received the study vaccines allocated to the cluster will be offered the vaccine, whilst retaining blinding.

Every 6 months, vaccinated participants will have a follow-up contact to collect data on fevers, episodes of clinically diagnosed and culture confirmed typhoid, school/work absenteeism and other significant illness till unblinding of the study population.

At ~3 years after the initial vaccination campaign (due to the interruption of COVID-19 pandemic), all participants will be unblinded. At this point, pilot study participants and both control and intervention groups of the main trial will be informed of their vaccination status and have their vaccines documented on the patient record. All participants in the control group will then be offered vaccination with the Vi-TCV vaccine. The study follow-up period has now been extended. A further 2 years of surveillance for enteric fever will be conducted, with additional censuses over the extended study period. Methods of surveillance, consent forms, questionnaire and data capturing will be the same as before.

Duration of participation is 5 years from enrolment (shorter than 5 years for subjects enrolled and vaccinated during the post-baseline, 6-monthly census updates).

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Previous intervention:
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For the pilot phase, two sequential groups of children are studied: children 3-15 years of age (n=100) followed by children 9 months to <3 years of age (n=100), with movement to the next phase contingent only on safety at one week post dosing. After approval by the LDSMB, IRB and the DGDA in Bangladesh, the main Vi-TCV study is initiated.

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Surveillance for enteric fever are undertaken in health care facilities in Mirpur for all residents of the participating clusters for four months preceding baseline and continuing for approximately 2 years after vaccination, until the end of the study. In this surveillance, all consenting residents from the participating clusters who present with a subjective history of ≥2 days fever and a temperature of ≥38°C have a blood culture taken, and receive appropriate clinical management. Those with positive blood cultures are visited at home to confirm their identity given at the treatment center, to collect information about their illness, and to review the treatment given, and adjust as necessary, based on laboratory testing.

At six month intervals during the two years after baseline, census updates of the population are done in all clusters, and children fulfilling the eligibility criteria for participation who have not received the study vaccines allocated to the cluster will be offered the vaccine, whilst retaining blinding.

Intervention Type
Biological/Vaccine

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Vi-TCV

Primary outcome measure
The efficacy and rate reduction of the Vi-TCV in preventing blood culture-confirmed symptomatic infection caused by S. typhi, measured through the incidence of blood culture confirmed typhoid fever in vaccinees in intervention clusters compared to control clusters.

Secondary outcome measures
Current secondary outcome measures as of 09/03/2021:
1. Vi-TCV vaccine safety, measured as the proportion of participants developing local and solicited adverse events within the first 7 days post-vaccination, and serious adverse events

within 6 months of vaccination, as determined through sub-sample at 7 days, and self-reporting at follow-up contact
2. The efficacy and rate reduction of the Vi-TCV in preventing blood culture-confirmed symptomatic infection caused by S. typhi among all residents in the clusters allocated to Vi-TCV (overall vaccine protection), measured through the incidence of blood culture confirmed typhoid fever in all residents of the intervention clusters compared to control clusters
3. Rates of participants with a history of ≥2 days of persistent fever, and a temperature of >38°C upon presentation, together with abdominal discomfort, at all study surveillance sites in vaccinees in intervention clusters compared to control clusters
4.Rates of residents with a history of ≥2 days of persistent fever, and a temperature of >38°C upon presentation, together with abdominal discomfort, at all study surveillance sites among all residents of the Vi-TCV clusters compared to the control vaccine clusters
5. Rates of patients with clinical diagnoses of typhoid fever at a study surveillance site in vaccinees in intervention clusters compared to control clusters
6. Rates of patients with clinical diagnoses of typhoid fever at a study surveillance site among all residents of the Vi-TCV clusters compared to the control vaccine clusters
7. Paratyphoid infection rates in each vaccination arm as measured by incidence of blood culture confirmed paratyphoid fever in vaccinees in intervention clusters compared to control clusters
8. Incidence of blood culture confirmed typhoid fever in vaccinees in previously Vi-TCV vaccinated clusters (original Vi-TCV clusters) compared with recently Vi-TCV vaccinated clusters (original control clusters) at 2 years post-vaccination and 2 years after unblinding
9. Persistence of antibodies induced by Vi-TCV in stratified age groups assessed by assay of anti-Vi IgG in blood samples collected at baseline, 28 day, 12 months, 18 months, 24 months post baseline vaccination, and 12 months and 24 months post unblinding visit in a subset of participants receiving Vi-TCV and control vaccine
10. Sero-incidence of typhoid fever, and therefore the sero-efficacy of Vi-TCV, assessed using assay of antibodies against the typhoid toxin (CdtB) in blood samples collected at baseline, 28 day, 12 months, 18 months, 24 months post baseline vaccination, and 12 months and 24 months post unblinding visit in a subset of participants receiving Vi-TCV and control vaccine

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Previous secondary outcome measures:
1. Vi-TCV vaccine safety, measured as the proportion of participants developing local and solicited adverse events within the first 7 days post-vaccination, and serious adverse events within 6 months of vaccination, as determined through sub-sample at 7 days, and self-reporting at follow-up contact
2. The efficacy and rate reduction of the Vi-TCV in preventing blood culture-confirmed symptomatic infection caused by S. typhi among all residents in the clusters allocated to Vi-TCV (overall vaccine protection), measued through the incidence of blood culture confirmed typhoid fever in all residents of the intervention clusters compared to control clusters
3. The impact of vaccination with Vi-TCV on rates of participants with a history of ≥2 days of persistent fever, and a temperature of >38°C upon presentation, together with abdominal discomfort, at all study surveillance sites in vaccinees in intervention clusters compared to control clusters.
4. The impact of vaccination with Vi-TCV on all residents of the clusters, as measured by rates of participants with a history of ≥2 days of persistent fever, and a temperature of >38°C upon presentation, together with abdominal discomfort, at all study surveillance sites among all residents of the Vi-TCV clusters compared to the control vaccine clusters
5. The impact of vaccination with Vi-TCV as measured by rates of patients with clinical diagnoses of typhoid fever at a study surveillance site in vaccinees in intervention clusters compared to control clusters
6. The impact of vaccination with Vi-TCV as measured by rates of patients with clinical diagnoses

of typhoid fever at a study surveillance site among all residents of the Vi-TCV clusters compared to the control vaccine clusters
7. Paratyphoid infection rates in each vaccination arm as measured by incidence of blood culture confirmed paratyphoid fever in vaccinees in intervention clusters compared to control clusters

Overall study start date
01/10/2016

Completion date
30/09/2023

Eligibility

Key inclusion criteria
1. Parent/guardian is willing and competent to provide informed consent. If the participant is 11 to <16 years of age, informed assent will also be sought
2. Aged between 9 months (or eligible for measles vaccination according to local protocol) and <16 years (i.e. up to 15 years 364 days) at time of vaccination
3. Apparently healthy (no complaints of febrile illness) on the day of vaccination
4. Parent/guardian confirms that their child will be willing and be able to comply with study requirements including follow-up contact, according the schedule (Appendix B)
5. Living within the study catchment area at the time of vaccination

Participant type(s)
Healthy volunteer

Age group
Child

Lower age limit
9 Months

Upper age limit
16 Years

Sex
Both

Target number of participants
At least 32500 eligible participants

Key exclusion criteria
Current participant exclusion criteria as of 13/08/2018:
1. Has knowingly received a typhoid or Japanese encephalitis vaccine in the last three years
2. Known allergy to any of the vaccine components
3. Medical or social reasons that will prevent the participant from conforming to the study requirements as judged by a medical professional
4. Planning to move away from the catchment area within the next month
5. Pregnant at the time of vaccination, as confirmed by a urine test (urine pregnancy test will be done in girls who are married)

Temporary exclusion criteria:
1. Receipt of any other vaccines in the last 30 days
2. Current temperature of at least 38°C or reported fever within 24 hours prior to vaccination
3. Use of antipyretics within 4 hours prior to vaccination
4. Unmarried girls between the ages of ≥12 and <16 years old whose first day of their last menstrual period (LMP) is more than 28 days ago or who do not know the date they last menstruated upon presentation

Previous participant exclusion criteria:
1. Has knowingly received a typhoid or Japanese encephalitis vaccine in the last three years
2. Known allergy to any of the vaccine components
3. Medical or social reasons that will prevent the participant from conforming to the study requirements as judged by a medical professional
4. Planning to move away from the catchment area within the next month
5. Pregnant at the time of vaccination, as confirmed by a urine test (urine pregnancy test will be done in girls who are married)

Date of first enrolment
12/02/2018

Date of final enrolment
02/08/2019

Locations

Countries of recruitment
Bangladesh

Study participating centre
International Centre for Diarrhoeal Disease Research, Bangladesh
68, Shaheed Tajuddin Ahmed Sharani
Mohakhali
Dhaka
Bangladesh
1212

Sponsor information

Organisation
University of Oxford

Sponsor details
University Offices
Wellington Square
Oxford

England
United Kingdom
OX1 2JD

Sponsor type
University/education

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

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
It is planned that the results of this trial will be published in high-impact peer reviewed journals within one year of the conclusion of the trial, around February 2021.

Intention to publish date
01/02/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Andrew Pollard.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		07/03/2019	29/05/2020	Yes	No
Other publications	"Fried egg" analysis	04/04/2023	24/04/2023	Yes	No
Other publications		15/11/2022	04/03/2025	Yes	No
Other publications	5-year follow-up	12/10/2024	04/03/2025	Yes	No
Other publications	Prospective cohort study	20/11/2023	04/03/2025	Yes	No
Results article		21/08/2021	04/03/2025	Yes	No