ISRCTN43385161 https://doi.org/10.1186/ISRCTN43385161

TyVAC Nepal: typhoid vaccine study

Submission date
20/06/2017

Recruitment status
No longer recruiting

Registration date
26/09/2017

Overall study status
Completed

Last Edited
11/10/2023

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Current plain English summary as of 13/08/2018:
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 Nepal, 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 is licensed for use in 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 will introduce 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

What does the study involve?
Participants are randomly allocated to either receive the typhoid vaccine (Vi-TCV) or a vaccine which protects against meningitis. Participants are followed-up over a two-year period. When participants develop a fever during that time, they are 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 meningitis vaccine are 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 Nepal. 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?
Patan Hospital (Nepal)

When is the study starting and how long is it expected to run for?
November 2017 to August 2020

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

Who is the main contact?
Prof. Andrew Pollard

Previous plain English summary:
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 Nepal, 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 is licensed for use in 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 will introduce 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

What does the study involve?
Participants are randomly allocated to either receive the typhoid vaccine (Vi-TCV) or a vaccine which protects against meningitis. Participants are followed-up over a two-year period. When participants develop a fever during that time, they are 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 meningitis vaccine are 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 Nepal. 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?
Patan Hospital (Nepal)

When is the study starting and how long is it expected to run for?
November 2017 to August 2020

Who is funding the study?
Bill and Melinda Gates Foundation (USA)

Who is the main contact?
Prof. Andrew Pollard

Contact information

Type(s)
Scientific

Contact name
Prof Andrew Pollard

ORCID ID
http://orcid.org/0000-0001-7361-719X

Contact details
Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)
Churchill Hospital Old Road
Oxford
United Kingdom
OX3 7LE

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
OVG2017/05

Study information

Scientific Title
Assessing the impact of a Vi-Polysaccharide Conjugate Vaccine in preventing typhoid infection among Nepalese children – a Phase III 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. Nepal Health Research Council (NHRC), 16/08/2017, reference number: 386, registration number: 170/2017
2. Oxford Tropical Research Ethics Council (OxTREC), 10/08/2017, ref: 15-17

Study design
Participant- and observer-blind randomised-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled 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 interventions as of 13/08/2018:
Participants will be randomised (block randomisation) 1:1 to receive a single dose of either Vi-TCV or MenA vaccine:
Intervention: Vi Typhoid conjugate vaccine (Vi-TCV), trade name: TyBar
Control: Meningococcal group A vaccine (MenA), trade name: MenAfriVac
Neither the participants or the researchers will know which vaccine any child has received until the end of trial. At the end of the trial, once it is unblinded, and everyone knows which vaccine they received, all of the children who first received the control vaccine will be offered the typhoid vaccine too, and all children who received the intervention vaccine will also be offered the control meningococcal group A vaccine.

Participants will be followed-up over a two year period. When participants develop a fever during that time, they will be asked to come to the local hospital or the trial 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 will get treatment and a blood test to check if they have typhoid fever. The cost of treatment for suspected or confirmed typhoid will be covered by the trial. All participants will also be monitored for safety outcomes associated with the vaccine.

Previous interventions:
Participants will be randomised (block randomisation) 1:1 to receive a single dose of either Vi-TCV or MenA vaccine:
Intervention: Vi Typhoid conjugate vaccine (Vi-TCV), trade name: TyBar
Control: Meningococcal group A vaccine (MenA), trade name: MenAfriVac

Neither the participants or the researchers will know which vaccine any child has received until the end of trial. At the end of the trial, once it is unblinded, and everyone knows which vaccine they received, all of the children who first received the control vaccine will be offered the typhoid vaccine too.

Participants will be followed-up over a two year period. When participants develop a fever during that time, they will be asked to come to the local hospital or the trial 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 will get treatment and a blood test to check if they have typhoid fever. The cost of treatment for suspected or confirmed typhoid will be covered by the trial. All participants will also be monitored for safety outcomes associated with the vaccine.

Intervention Type
Biological/Vaccine

Phase
Phase III

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

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 participants presenting to hospital or clinic for the duration of the trial, in each vaccination arm

Secondary outcome measures
1. Vi-TCV vaccine safety, measured as the proportion of participants developing all adverse events within the first 7 days post-vaccination, and serious adverse events within 6 months of vaccination, as determined through self-reporting at three-monthly follow-up contact
2. The impact of vaccination with Vi-TCV on the incidence of inpatient/outpatient admission rates for fever, measured by the rates of participants with at least ≥2 days of subjective persistent fever, or a temperature of at least 38 degrees C, at presentation at Patan Hospital or trial clinics in each vaccination arm, stratified by duration and severity of fever
3. The difference in rates of hospital and clinic presentation for febrile illness in each vaccination arm, measured as the rates of hospital or clinic presentation with febrile illness of any duration in each vaccination arm, measured by hospital presentation logs, hospital records, trial clinic records and self-reporting during three monthly follow-up
4. Days spent in hospital from febrile illness, measured as the length of stay in hospital, collected from Patan hospital patient records, and parent/self-reported, in each vaccination arm
5. Incidence of clinically-suspected enteric fever, measured as the number of clinical diagnoses of typhoid fever, as determined by trial staff in Patan hospital outpatient clinics and trial clinic, in each vaccination arm throughout the two year follow-up period
6. Paratyphoid infection rates in each vaccination arm, measured as the rates of blood culture confirmed Paratyphoid cases in participants presenting to hospital or clinic for the duration of the trial, in each vaccination arm

Added 20/06/2019:
7. 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 participants presenting to hospital or clinic with at least 3 days of fever, for the duration of the trial in each vaccination arm

Overall study start date
01/11/2017

Completion date
01/08/2020

Eligibility

Key inclusion criteria
1. Parent/legal guardian is willing and competent to provide informed consent. If the participant is 12 years of age or older, 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. In good health on the day of vaccination
4. Parent/legal guardian confirms that their child will be wiling and be able to comply with study requirements including follow-up contact, according the trial schedule
5. Live 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
20,000

Total final enrolment
20019

Key exclusion criteria
The participant will not be enrolled if any of the following criteria apply:
1. They have knowingly received a typhoid vaccine in the last three years
2. They have a known allergy to any of the vaccine components
3. Any medical or social reasons that will prevent the participant from conforming to the study requirements as judged by a medical professional
4. They are planning to move away from the catchment area within the next 6 months

Participants will be temporarily excluded from being vaccinated if, at point of vaccination, any of the following apply:
1. Reported fever within 24 hours prior to vaccination
2. Use of anti-pyretics within 4 hours prior to vaccination
If these apply, the participant will be temporarily excluded for vaccination until 48 hours has passed. A re-assessment will be conducted to ensure these temporary exclusion criteria no longer exist

Date of first enrolment
01/11/2017

Date of final enrolment
09/04/2018

Locations

Countries of recruitment
Nepal

Study participating centre
Patan Hospital
Kathmandu
Nepal
-

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 August 2021.

Added 20/06/2019:
An interim analysis will be conducted after 45 cases have been identified and one year of follow-up has been reached. The results of the interim analysis will be published in a high impact journal.

Intention to publish date
01/08/2021

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	protocol	07/03/2019	08/03/2019	Yes	No
Results article	results	05/12/2019	06/12/2019	Yes	No

Results article		09/11/2021	26/10/2021	Yes	No
Results article	Under-detection of blood culture-positive enteric fever cases: The impact of missing data and methods for adjusting incidence estimates	16/01/2020	11/10/2023	Yes	No