ISRCTN14829414 https://doi.org/10.1186/ISRCTN14829414

Typhoid vaccine follow-up study – Nepal

Submission date
11/05/2023

Recruitment status
No longer recruiting

Registration date
20/09/2023

Overall study status
Completed

Last Edited
10/10/2023

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
A certain type of bacteria causes typhoid fever. You can catch typhoid fever when you drink water or eat food that has these bacteria in it. The bacteria can get from the gut into the blood and can cause high fever, diarrhoea, upset stomach and headache. The infection can become serious and should be treated with antibiotics to kill the bacteria. In this study we want to improve our understanding of typhoid fever and how to prevent it. One of the ways that we can protect against typhoid is through vaccines. The site for this study is in a specific area in Kathmandu, Nepal called Lalitpur. We previously studied a typhoid conjugate vaccine in Lalitpur and found that over a 2-year study period the vaccine prevented around 80% of typhoid cases. We now want to know how this vaccine prevents typhoid in the children after the first 2 years and what impact it has on the rates of the whole population getting typhoid.

Who can participate?
All children who previously participated in the typhoid conjugate vaccine trial will be invited to take part in this study. In addition, anyone who lives in the defined study area in Lalitpur will be invited to attend study clinics if they have a fever meeting certain criteria and will also be included in a census and a qualitative sub-study.

What does the study involve?
For all consenting residents in the study area:
1. Census
2. Community surveillance of fevers and typhoid cases
3. Qualitative sub-study to understand participants' perception of participation in the typhoid vaccine study
In addition, for all children who were previously enrolled in the vaccine trial and whose parents have given consent to be a part of this ongoing study:
1. Follow-up phone calls every 3 months
For an additional sub-group of children who were previously enrolled in the vaccine trial and whose parents give consent:
1. Blood sample collection at one or two timepoints to understand the response their bodies make to the vaccine and how this changes over time

What are the possible benefits and risks of participating?
If participants develop typhoid fever, the costs of their treatment will be covered by the study. If

participants have a blood sample taken, there may be a small bruise afterwards, which should fade in a few days. There are no other risks in participating in the study.

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

When is the study starting and how long is it expected to run for?
January 2021 to December 2023

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

Who is the main contact?
Sarah Kelly, sarah.kelly@paediatrics.ox.ac.uk

Contact information

Type(s)
Scientific

Contact name
Ms Sarah Kelly

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
OxTREC Ref: 11-21, NHRC Ref: 240/2021

Study information

Scientific Title

Assessing the medium-term impact of a Vi-Polysaccharide Conjugate Vaccine in preventing typhoid infections among Nepali children

Acronym
TyVOID Nepal

Study objectives
This study aims to assess the change in medium-term efficacy of the new Typhoid Conjugate Vaccine (TCV) in children by comparing the relative risk of typhoid fever in a TCV cohort initially vaccinated in 2017/2018 with TCV cohorts vaccinated in 2020 and 2021. This study will address whether the new TCV will provide control of typhoid beyond the short-term efficacy demonstrated in healthy volunteers, or whether booster doses may be required. This study will also assess the decay in total and functional anti-typhoid antibodies in children 3 to 5 years after vaccination, and compare community-based typhoid clinical- and sero-incidence with these immune responses.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/07/2021, Oxford Tropical Research Ethics Committee (University of Oxford Research Services, University Offices, Wellington Square, Oxford OX1 2JD, UK; +44 (0) 1865 (2) 82106; oxtrec@admin.ox.ac.uk), ref: OxTREC Ref: 11-21

Study design
Prospective cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Community, Hospital

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
Typhoid fever

Interventions
This is a prospective cohort study, alongside the continuation of a community surveillance study, which will include conducting healthcare facility-based passive surveillance for typhoid fever in vaccinees and non-vaccinees, immunogenicity study of children to assess waning immunity to Vi-

TCV and WASH surveys along with a demographic census. Along with this a qualitative component, to assess the perception of the community regarding TCV vaccination, will be conducted in parallel. All the participants who were enrolled in the initial TyVAC study will be eligible for inclusion in this study. The entire population within the study catchment area will be included in the background typhoid surveillance and WASH assessment.

Prospective cohort study:
All the participants who were previously enrolled in the TyVAC study will be contacted via phone call and will be invited to be a part of the study. They will be provided with information about the study and if willing to take part, will be contacted every 3 months via phone call or home visit.

Community surveillance:
All patients attending fever clinics at wards or Patan Hospital with a history of fever ≥2 days with or without objective fever and residing in the catchment area will be identified. They will be provided with information about the study and if willing to take part consent for sample collection for blood culture will be sought.

Participants who reside in the catchment area who experience a fever lasting for ≥2 days and/or a fever of ≥38ºC, as subjectively reported by a parent/guardian in case of children or the patient ≥18 years of age, will be asked to present to Patan Hospital or established ward clinics. Regular community engagement activities will take place throughout the study period in order to remind and encourage participants to attend the clinics.

Immunogenicity:
In the TyVAC trial, blood samples were collected from 1500 participants who were enrolled in the study and separately randomized. Blood samples will be collected from these participants at 42 months to 60 months after the original TyVAC vaccination campaign. Samples will be collected for serological assay from additional 500 participants vaccinated in the early cohort in the original TCV arm and 250 participants collected from the cohorts vaccinated in 2020 and 2021 with TCV who previously received the MenA vaccine. The participants who had not withdrawn from the immunogenicity component of the TyVAC trial will be approached by a research member first via phone call or home visit. They will then be invited for a blood draw at the ward clinics or at Patan Hospital. Informed consent will be sought, after which the participants will be enrolled in this component of the study. If there is a substantial loss to follow-up of participants who were previously enrolled in the immunogenicity sub-study, new participants will be enrolled to meet the target.

Immunogencity – Vi-TCV & Vi-CRM197:
TyVAC participants who have received both Vi-TCV and Vi-CRM197 or have only received Vi-CRM197 will be approached by a research member first via phone call. They will then be invited for a blood draw at a ward clinic or at Patan Hospital. Informed consent will be sought, after which the participants will be enrolled in this component of the study.

Census:
Field workers will approach the head or identified key informant of each household within the defined catchment area Lalitpur, Kathmandu with information about the studies. Details regarding demographic characteristics, sanitation features (WASH) and socioeconomic status will be taken from the head of household or key informant. Data will be collected by trained study personnel at each individual’s household.

Qualitative Component:
Participant recruitment will be different depending on the objective of each qualitative sub-component.
1. For focus group discussions (FGDs) with parents/guardians of vaccinated children or participants ≥18 years, 4 – 8 parents/guardians or vaccinated participants from each study ward will be contacted by phone and will be invited to participate. The parents/guardians or vaccinated participants will be first approached for FGDs and if there are insufficient numbers for FGDs, they will be approached for IDIs.
2. In-depth interviews (IDI) or key informant interviews (KII) with the community leaders will be conducted to explore their perceptions regarding the typhoid vaccine study and research in general.
3. After their periodic home visit, THPs will be contacted in person and will be invited to participate in the FGD.
4. For IDI, all the children and adults ≥18 years who are asked for blood draw while they visit the passive surveillance clinic at Patan Hospital will be contacted in person and invited to participate.
5. The research medical officers and research nurses, who are involved in consent taking process and blood draw will be invited to participate in the IDIs.

Intervention Type
Biological/Vaccine

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Typhoid Conjugate Vaccine (TCV)

Primary outcome measure
The incidence rate of culture-positive typhoid fever in the late-vaccinated cohorts and the early-vaccinated cohort, measured using the number of blood culture confirmed cases during the 2 years of follow-up

Secondary outcome measures
1. Immunity to Vi-TCV measured using anti-Vi IgG and anti-Vi IgA antibody levels in blood samples collected during 2 years of follow up
2. Immunogenicity of Vi-TCV followed by Vi-CRM197 vs Vi-CRM197 alone, measured using anti-Vi IgG and anti-Vi IgA antibody levels in blood samples collected from participants who have received both Vi-TCV and Vi-CRM197 with participants who have received Vi-CRM197 alone at one timepoint
3. Immunogenicity of Vi-CRM197 compared to Vi-TCV, measured using anti-Vi IgG and anti-Vi IgA levels in participants who have received one dose of Vi-CRM197 and participants who have received Vi-CRM197 following Vi-TCV with participants previously enrolled in immunogenicity and have received one dose of Vi-TCV at one timepoint
4. Incidence rate of culture-confirmed typhoid fever from passive surveillance in all residents, measured using the number of blood culture confirmed cases during the 2 years of follow-up
5. Sero-incidence of typhoid infection and sero-efficacy of Vi-TCV, measured using typhoid toxin (CdtB) antibody levels in blood samples collected during 2 years of follow up

6. The comparison of WASH indicators between surveys done during the TyVAC and TyVOID study at the end of TyVAC and TyVOID
7. Incidence rates of blood culture-confirmed paratyphoid from passive surveillance in all residents, measured using the number of blood culture confirmed cases during the 2 years of follow-up
8. Number of clinical diagnoses of typhoid fever, as determined by trial staff in Patan Hospital outpatient clinics and trial clinic using local clinical definitions during the 2 years of follow-up
9. Rates of hospital or clinic presentation with culture-confirmed typhoid fever illness of any duration, measured by hospital presentation logs, hospital records, trial clinic records and self-reporting during three monthly follow-ups

Overall study start date
01/01/2021

Completion date
31/12/2023

Eligibility

Key inclusion criteria
Prospective cohort study:
1. Individuals who were enrolled in the TyVAC trial
2. Parent/legal guardian/participant 18 years and older give informed consent
3. Parent/legal guardian/participant 18 years and older confirms that their child/they will be willing and able to comply with study requirements

Community surveillance:
1. Individuals presenting to the healthcare facility with a history of ≥2 days of fever, and/or a recorded temperature ≥38.0ºC
2. Individual willing and competent to give informed consent if ≥18 years or the parent/legal guardian if participant <18 years. Assent will be sought from children 7 years of age or older
3. Able to comply with study requirements

Immunogenicity:
1. Children enrolled and randomized in the TyVAC trial who have received Vi-TCV either in early or late cohorts
2. Parent/legal guardian is willing and competent to provide informed consent. If the participant is 7 years of age or older, assent will also be sought. If the participant is 18 years or older, consent will be sought from them.
3. Parent/legal guardian confirms that their child will be willing and able to comply with study requirements

Immunogencity – Vi-TCV & Vi-CRM197:
1. Children enrolled and randomized in the TyVAC trial who have received both Vi-TCV and Vi-CRM197 OR who have received the Vi-CRM197 only
2. Parent/legal guardian is willing and competent to provide informed consent. If the participant is 7 years of age or older, assent will also be sought. If the participant is 18 years or older, consent will be sought from them
3. Parent/legal guardian confirms that their child will be willing and able to comply with study requirements

Census:
1. Head of household/key informant is willing and competent to give informed consent for the 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

Qualitative Component:
For FGDs or IDIs to explore the perception of the overall study:
1. Parents/guardians of the vaccinated children or participants of TyVAC Nepal who received vaccination and are ≥18 years old who consent to participate
2. Tole health promoters willing to participate
3. Key-informant interview/in-depth interview with the community leaders

In-depth interview/FGD regarding blood draw during passive surveillance visit:
1. Vaccinated children ≥18 years along with adults presenting with fever at the passive surveillance clinic at Patan Hospital who are asked for a blood draw and those who consent for IDI will be included
2. Parents/guardians of vaccinated children less than 18 years presenting with fever at the passive surveillance clinic at Patan Hospital and those who consent for IDI will be included
3. Parents/guardians of children or participants themselves (≥18 years old) who present with fever at passive surveillance clinics and are asked for a blood draw will be included in the FGD if they provide consent for FGD
4. Research medical officers and research nurses involved in the consent-taking and blood draw procedure will be approached to explore their perceptions regarding blood draw for research purposes
5. FGDs or IDIs to describe the facilitators and barriers regarding vaccination
6. Parents/guardians of children or participants ≥18 years old who received TCV during the second round (2020-2021) of vaccination and will consent to participate in an interview
7. Parents/guardians of children or participants ≥18 years old who denied vaccination during the second round (2020-2021) but came for unblinding and consent to participate in an interview

Participant type(s)
Healthy volunteer

Age group
Mixed

Sex
Both

Target number of participants
20,019

Key exclusion criteria
Prospective cohort study:
1. Consent withdrawn from the TyVAC trial
2. Did not give consent for contact for future studies in the TyVAC trial

Immunogenicity:
1. Consent withdrawn for immunogenicity in the TyVAC trial
2. Deemed clinically unsuitable by the survey team (e.g. terminally ill)

Immunogenicity – Vi-TCV & Vi-CRM197:
1. Consent withdrawn for immunogenicity in the TyVAC trial
2. Deemed clinically unsuitable by the survey team (e.g. terminally ill)

Census:
1. Unable to identify the head of household/key informant

Qualitative Component:
1. Relatives other than parents/guardians

Date of first enrolment
01/08/2021

Date of final enrolment
30/07/2023

Locations

Countries of recruitment
Nepal

Study participating centre
Oxford University Clinical Research Unit - Nepal
Patan Academy of Health Sciences
PO Box 26500
Kathmandu
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26500

Sponsor information

Organisation
University of Oxford

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Sponsor type
University/education

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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
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
30/10/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available on request from Sarah Kelly (sarah.kelly@paediatrics.ox.ac.uk).

IPD sharing plan summary
Available on request