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Assessing optimal timing for childhood vaccines in Nepal

Submission date 07/12/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 07/01/2021	**Overall study status** Completed	
Last Edited 28/06/2024	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims
Vaccines help protect our bodies against diseases. When a child comes into contact with a disease against which they have been vaccinated, their body will be able to recognise and fight the disease. Without vaccines, children are at increased risk of catching many serious diseases. The World Health Organization (WHO) recommends that all children receive a number of different vaccines at specific ages. One of the vaccines recommended protects against 5 diseases called diphtheria, tetanus, whooping cough, hepatitis B and Haemophilus influenzae type b (Hib) infection, which can cause pneumonia and meningitis. This vaccine is sometimes called a DTP-containing vaccine. Many countries around the world gives this vaccine at different time points and it is not known which schedule is best.

Who can participate?
Children aged 42 - 50 days

What does the study involve?
Participants will be randomly allocated to receive one of five different immunisation schedules containing the vaccine containing DTP. The timing of doses and whether a child receives two or three doses (both have been shown to be effective) will vary between trial arms. Children will then have blood tests taken to see whether they have antibodies for DTP before their booster doses.

What are the possible benefits and risks of participating?
The benefit include the opportunity to receive vaccines for Typhoid and Varicella which are not currently included as part of the Expanded Programme on Immunisation. The risks are those associated with phlebotomy (blood-drawing), and include pain and discomfort.

Where is the study run from?
The trial is run at two sites in Kathmandu, Patan Hospital and Tribhuvan University Teaching Hospital (Nepal).

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

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

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
OxTREC 12-20

Study information

Scientific Title
Optimising diptheria, tetanus toxoids and pertussis (DTP)-containing vaccine infant immunisation schedules in Nepal

Acronym
OptImms-Nepal

Study objectives
The aim of this project is to identify an optimal immunisation schedule for infants by comparing the immunogenicity of 5 different immunisation schedules including the current WHO recommended “accelerated” schedule, investigating the effect of number, spacing and timing of doses of routine infant vaccines in the different schedules. Each schedule has been selected based on positive immunogenicity data from previous research. We will use the WHO recommended EPI schedule as the reference schedule.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 20/09/2020, Nepal Health Research Council ethics committee (Ethical Review M&E Section, Ramshah Path, Kathmandu, Nepal; +977-1-4254220; approval@nhrc.gov.np), ref: 95 /2020 P
2. Approved 28/02/2020, Patan Institutional Review Committee (Patan Academy of Health Sciences IRC, Patan Academy of Health Sciences, Lagankhel, Lalitpur, Nepal; +977-1-5545112; irc-pahs@pahs.edu.np), ref: none provided
3. Approved 17/12/2020, OxTREC (Research Services, University Of Oxford, University Offices, Oxford, OX1 2JD, UK; +44 (0)1865 282585; oxtrec@admin.ox.ac.uk), ref: 12-20

Study design
Multi-site randomized 5-arm non-inferiority clinical trial

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Optimising diphtheria, tetanus toxoids and pertussis (DTP) immunity through infant immunisation schedules in Nepal

Interventions
Participants will be recruited across 2 sites; at Patan Hospital and the Tribhuvan University Teaching Hospital (TUTH), both in Kathmandu. Recruitment and randomisation will take place at the time of attendance for the child's 6-week immunisations. Participants will be enrolled at immunisation clinics linked to both health facilities. The study will be open-label for participants and clinical trial staff but blinded for laboratory staff. The study will assess the immunogenicity of the current DTP-Hib-HBV-containing vaccine administered in 5 different immunisation schedules

Following informed parent/legal guardian consent, enrolled infants will be randomly allocated to one of 5 main vaccination groups, and one of four booster dose schedule.
The first two schedules (Groups 1 and 2) are two 'Early Pertussis' schedules and correspond to the WHO standard, and a modified, EPI schedules (two rather than 3 early doses).
Group 3 will be vaccinated according to the OptImms-proposed schedule (which is also the E-CDC recommended schedule).
Groups 4 and 5 correspond to the programs currently in use in the UK and Americas.

Blood tests will be performed at standard time points considered necessary for evaluation of vaccine responses.

The primary outcome Pertussis IgG immune response will be measured at the pre-booster dose time point, i.e. at 9 or 12 months of age. Children will receive varicella and typhoid vaccination as a benefit of participation in the study.

Vaccinations will occur over a 15-month time period, with a 24-month follow-up period for all study arms.
Randomisation will occur electronically via a plugin on RedCAP.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
DTwP-HBV-Hib vaccine (Serum Institute of India), Oral Polio Vaccine – Bi-valent, Injectable Polio Vaccine, Pneumococcal conjugate vaccine (Synflorix), Measles Rubella vaccine, Typhoid

conjugate vaccine (Typbar-TCV®, Bharat-Biotech.), Japanese encephalitis vaccine (JE), Varicella vaccine - TBC, Rotavirus vaccine (Rotarix)

Primary outcome(s)

Pertussis IgG immune response measured in Multiplexed Immune Assay (MIA)-5 plex at the pre-booster dose time point, i.e. at age 9 or 12 months

Key secondary outcome(s))

Current secondary outcome measures as of 28/06/2024:

1. Pertussis IgG immune response measured in an MIA 4-plex at the post-prime dose time point, (i.e. at age 10, 12, 14 or 16 weeks), 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months.
2. Diphtheria IgG immune response measured on an MIA 5-plex using in-house reference sera calibrated against the WHO standard, at age 14 or 16 weeks, 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months. The MIA 5-plex uses in-house reference sera as standard, which are calibrated against the WHO standard (van Gageldonk et al., 2008; van Gageldonk et al., 2011)
3. Tetanus IgG immune response measured on an MIA 5-plex using in-house reference sera calibrated against the WHO standard, at age 14 or 16 weeks, 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months
4. Hep B virus S antigen, mIU/ml measured using an assay currently under development at the Dutch Institute of Public Health, at age 14 or 16 weeks, 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months
5. PRP (Hib) IgG immune response measured using a multiplexed immune assay, at age 14 or 16 weeks, 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months.
6. Serotype specific anti-pneumococcal IgG measured in an MIA x-plex in 1a, 2, 3 and 4 blood samples in all arms and booster groups. IVIG that has been calibrated against the 89-S serum is used as reference serum (Elberse et al., 2010).
7. Polio type I-III IgG immune response measured using a 3-plex inhibition assay, at the pre-booster timepoint (i.e. at age 9 or 12 months) and at age 24 months (Schepp et al., 2017)
8. Typhoid vi-IgG will be measured using an assay currently under development at the Dutch Institute of Public Health, in blood 2 in Arm 5 at 28 weeks, in blood 3 & 4 in booster groups 2, 3, and 4 (12 and 24 months).
9. Serum volumes permitting JE response will be measured using plaque reduction neutralization titre (PRNT) assays, by ELISA and/or indirect fluorescent antibody test (IFA) at age 13 and 24 months.

Exploratory outcome measures:
10. Measles IgG antibody concentrations are measured in an MIA 4-plex at all time points up to the first measles and rubella vaccine dose, if possible given blood sample volumes
11. For measles only, serum volumes permitting, serum will also be analysed using plaque reduction neutralization titre (PRNT) assay at the same timepoints
12. Rubella IgG response measured in an MIA 4-plex at all time points up to the first measles and rubella vaccine dose, if possible given blood sample volume
As standard, the international rubella standard (RUBI-1-94) is used, which has been calibrated

against the international reference serum for measles (Smits et al.,2012)
Measle and rubella titres will only be measured prior to administration of the first MR vaccine

13. Rotavirus IgG will be measured using MIA 4-plex in all blood samples of all arms and booster groups.
14. SARS-COV2 IgG and RAV IgG will be measured using MIA 4-plex in all blood samples of all arms and booster groups.

Safety outcome measures:
15. Descriptive summary of self-reported local and systemic vaccine reactions occurring within 7 days post-vaccination collected verbally at each point of contact, using Brighton Collaboration case definitions.

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Previous secondary outcome measures:

1. Pertussis IgG immune response measured in an MIA 4-plex at the post-prime dose time point, (i.e. at age 10, 12, 14 or 16 weeks), 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months.
2. Diphtheria IgG immune response measured on an MIA 5-plex using in-house reference sera calibrated against the WHO standard, at age 14 or 16 weeks, 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months. The MIA 5-plex uses in-house reference sera as standard, which are calibrated against the WHO standard (van Gageldonk et al., 2008; van Gageldonk et al., 2011)
3. Tetanus IgG immune response measured on an MIA 5-plex using in-house reference sera calibrated against the WHO standard, at age 14 or 16 weeks, 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months
4. Hep B virus S antigen, mIU/ml measured using an assay currently under development at the Dutch Institute of Public Health, at age 14 or 16 weeks, 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months
5. PRP (Hib) IgG immune response measured using a multiplexed immune assay, at age 14 or 16 weeks, 1-month post-primary series (i.e. age 18, 20, or 28 weeks), pre-booster timepoint (i.e. at age 9 or 12 months), post-booster timepoint (i.e. at age 10 or 13 months) and at age 24 months.
6. Serotype specific anti-pneumococcal IgG measured in an MIA x-plex, at the pre-booster timepoint (i.e. at age 9 months), post-booster timepoint (i.e. at age 10 months) and at age 24 months. IVIG that has been calibrated against the 89-S serum is used as reference serum (Elberse et al., 2010)
7. Polio type I-III IgG immune response measured using a 3-plex inhibition assay, at the pre-booster timepoint (i.e. at age 9 or 12 months) and at age 24 months (Schepp et al., 2017)
8. Typhoid vi-IgG will be measured using an assay currently under development at the Dutch Institute of Public Health, at age 13 and 24 months
9. Serum volumes permitting JE response will be measured using plaque reduction neutralization titre (PRNT) assays, by ELISA and/or indirect fluorescent antibody test (IFA) at age 13 and 24 months.

Exploratory outcome measures:
10. Measles IgG antibody concentrations are measured in an MIA 4-plex at all time points up to

the first measles and rubella vaccine dose, if possible given blood sample volumes
11. For measles only, serum volumes permitting, serum will also be analysed using plaque reduction neutralization titre (PRNT) assay at the same timepoints
12. Rubella IgG response measured in an MIA 4-plex at all time points up to the first measles and rubella vaccine dose, if possible given blood sample volume
As standard, the international rubella standard (RUBI-1-94) is used, which has been calibrated against the international reference serum for measles (Smits et al.,2012)
Measle and rubella titres will only be measured prior to administration of the first MR vaccine

Safety outcome measures:
13. Descriptive summary of self-reported local and systemic vaccine reactions occurring within 7 days post-vaccination collected verbally at each point of contact, using Brighton Collaboration case definitions.

Completion date
31/07/2025

Eligibility

Key inclusion criteria
1. Age of 42 - 50 days old at time of first visit
2. Generally healthy as determined by a medical history and examination
3. Resident in the Kathmandu Valley, Nepal study area and planning to remain in the study area for the 2 years of the study

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Child

Lower age limit
42 days

Upper age limit
50 days

Sex
All

Total final enrolment
956

Key exclusion criteria
1. Born at less than 36 weeks gestation
2. Birth weight <2.5 kg, or a current weight of <3 kg at 6 weeks of age, as determined by a medical professional

3. Prior receipt of any vaccination except Polio, Hepatitis B, or BCG
4. Planned administration of vaccines other than the study vaccines (with the exception of vaccines against rotavirus, hepatitis A & B, inactivated influenza and varicella, which can be administered 14 days before or after study vaccines; polio and measles/rubella vaccines as part of national campaigns; and BCG vaccines which will be administered when indicated by national programme)
5. Parents who plan to move out of the geographical study area
6. Concurrently participating in another clinical study, which includes blood draws or IMPs, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device)
7. Any major congenital defects, serious chronic illness, significant disease, disorder, family history or diagnosis of immunosuppressive condition, or medical treatments which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study
8. Use of any investigational or non-registered product (drug or vaccine) within 30 days preceding the vaccination, or planned use during the study period; Known allergy to any vaccine components

Date of first enrolment
05/12/2021

Date of final enrolment
27/02/2023

Locations

Countries of recruitment
Nepal

Study participating centre
Patan Academy of Health Sciences, Patan Hospital
Satdobato Road
Kathmandu
Nepal
44700

Study participating centre
Institute of Medicine
Tribhuvan University Teaching Hospital
Dept of Child Health
Maharajgunj Road
Kathmandu
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44600

Sponsor information

Organisation
University of Oxford

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, Gates Learning Foundation, William H. 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

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to their size, but analyses will be published with summary data.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		21/07/2023	24/07/2023	Yes	No
Participant information sheet	version 2.0	17/11/2020	11/02/2022	No	Yes