ISRCTN65855590 https://doi.org/10.1186/ISRCTN65855590

# Bivalent vaccination against Salmonella Typhi and Paratyphi A

**Submission date**
11/10/2024

**Recruitment status**
No longer recruiting

**Registration date**
09/12/2024

**Overall study status**
Ongoing

**Last Edited**
16/09/2025

**Condition category**
Infections and Infestations

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

## Plain English summary of protocol

Background and study aims
Typhoid and Paratyphoid fever are forms of an illness called enteric fever. Their names come from the bacteria that cause them: Salmonella Typhi (typhoid) and Salmonella Paratyphi (paratyphoid, mostly caused by S. Paratyphi A). Enteric fever can cause high temperatures, headache, muscle and joint aches, abdominal pain, constipation and feeling generally unwell. If severe or left untreated, it can result in complications, including long-term carriage of the bacteria or even death. There are approximately 13 million cases of enteric fever every year, with 3.8 million of these due to paratyphoid infection. It spreads by the faeces of an infected person, typically through contaminated water or food. It is prevalent in regions of the world where people have inadequate access to clean water and sanitation. Effective vaccines against S. Typhi already exist, but there are no licensed vaccines against S. Paratyphi A. The Serum Institute of India (SII) has developed a vaccine targeting both Salmonella Typhi and Salmonella Paratyphi A, called SII TCV(B). SII-TCV(B) is given as an injection in the upper arm muscle. The vaccine has already been tested in humans, which showed the vaccine is safe and well-tolerated, and able to induce an immune response against Salmonella Typhi and Salmonella Paratyphi A. This study will test if this vaccine can prevent paratyphoid A infection, using a controlled human infection model (CHIM). It will also look at whether the vaccine induces a similar immune response against typhoid fever as a comparator vaccine (a licensed vaccine against S. Typhi). This study will be used to better understand how protection against paratyphoid A is developed.

Who can participate?
Healthy volunteers aged between 18 and 55 years, inclusive, at time of vaccination

What does the study involve?
In this CHIM, participants are given a single dose of either the SII TCV(B) vaccine (test vaccine) or Typhim Vi vaccine (comparator vaccine against S. Typhi) in the upper arm muscle, and later they are given a dose of S. Paratyphi A bacteria to drink, which can cause disease. They are closely monitored and treated with antibiotics 14 days after drinking the bacteria, or sooner, if they develop paratyphoid infection. This model of studying vaccines has been safely undertaken by around 500 participants in previous Oxford Vaccine Group studies, and this type of study was recommended by the World Health Organisation (WHO) to study how well new paratyphoid A vaccine candidates work to prevent paratyphoid infection.

What are the possible benefits and risks of participating?
By taking part in this study, participants will help with research into the development of a new vaccine against Salmonella Typhi and Salmonella Paratyphi A.

There are risks associated with taking part in this study. Post-vaccination, there may be short-lived symptoms such as mild discomfort of the arm, and fever and muscle aches may occur; there is also a small risk of allergic reaction. Following the challenge, participants may develop a paratyphoid infection, which may involve symptoms like fever, headache, nausea/vomiting, and muscle or joint aches. Paratyphoid A infection will be carefully managed, and treatment is available and provided for all participants, even if not becoming unwell. Severe problems are rare, as the infection is treated early on in the course of the illness.

Where is the study run from?
University of Oxford, Oxford Vaccine Group, UK

When is the study starting and how long is it expected to run for?
October 2024 to September 2027

Who is funding the study?
The Serum Institute of India, India

Who is the main contact?
Professor Sir Andrew J Pollard, info@ovg.ox.ac.uk

# Contact information

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Principal investigator

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# Additional identifiers

**Clinical Trials Information System (CTIS)**
Nil known

**Integrated Research Application System (IRAS)**
1007772

**ClinicalTrials.gov (NCT)**
Nil known

**Protocol serial number**
OVG2023/09, CPMS 65587

# Study information

**Scientific Title**
A phase II, multicentre, double-blind, randomised, controlled study of a bivalent conjugate vaccine against Salmonella enterica serovar Typhi and Paratyphi A to evaluate the efficacy, immunogenicity and safety using a human challenge model of Paratyphoid A infection

## Acronym
BiVISTA

## Study objectives
The Serum Institute of India has developed a new vaccine against the bacteria that cause typhoid and paratyphoid A fever (enteric fever). This study aims to evaluate if this vaccine can protect against paratyphoid A by exposing participants to the bacteria that cause paratyphoid A fever.

The study will also compare blood samples of the group who received this new vaccine with a group who received another vaccine against typhoid fever, to check if they can stimulate a similar immune response against typhoid fever.

The safety and tolerability of the vaccine will be evaluated in participants receiving the new vaccine, compared with an existing licensed typhoid vaccine. We will investigate what kind of response the body produces and how this will lead to protection against disease.

## Ethics approval required
Ethics approval required

## Ethics approval(s)
approved 28/11/2024, South Central - Berkshire Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8178; berkshire.rec@hra.nhs.uk), ref: 24/SC/0309

## Study design
Phase II multicentre double-blind parallel-group randomized controlled study

## Primary study design
Interventional

## Study type(s)
Safety, Efficacy

## Health condition(s) or problem(s) studied
A study in healthy volunteers testing a new vaccine against Typhoid and Paratyphoid A infection.

## Interventions
The study will recruit 192 participants, randomised 1:1 to receive a single intramuscular dose of 0.5mL of either:
• The test vaccine (SII TCV(B)) - a bivalent conjugate vaccine against Salmonella Typhi and Paratyphi A developed and manufactured by the Serum Institute of India or;
• The comparator vaccine (Typhim Vi) - a licensed vaccine against Salmonella Typhi manufactured by Sanofi Pasteur.
28 days after vaccination, participants will be challenged with Salmonella Paratyphi A, manufactured by GenIbet BioPharmaceuticals.

Vaccination and post-vaccination visits
Vaccine randomisation will be completed at the vaccination visit (D-28) using a web-based randomisation system. Participants will also complete an interim medical assessment, check vital signs, complete a urine pregnancy test for participants of childbearing potential, and provide blood and stool samples. Saliva samples will be collected from a subset of participants.

Participants will then be vaccinated with either the test vaccine (SII TCV (B)) or comparator (Typhim Vi) according to the randomisation. The research team will give participants access to a web-based electronic diary (e-diary), and a thermometer to take daily temperatures. Participants are asked to record their temperatures twice daily and answer if they had pre-specified solicited symptoms, use of medication and any additional fevers for 7 days after vaccination. They will also have access to input additional symptoms into the diary for 28 days after receiving the vaccine. After receiving the vaccine, participants will be seen after one week (D-21) and two weeks (D-14) for post-vaccination visits during which additional blood samples will be collected from all participants, and stool and saliva samples collected in a subset of participants. Around 28 days after vaccination, participants will be seen in the clinic (post-vaccine immunology visit) for a blood test - this visit may be combined with the pre-challenge visit (D-2) if the visit windows allow.

Challenge visits
A pre-challenge visit will be completed up to 48 hours before the challenge visit. Blood and stool samples will be collected for all participants, and saliva samples taken for some participants. On challenge day (D0), a urine pregnancy test will be performed for participants of childbearing potential. An electronic diary will be set up for the challenge period. Participants will be asked to fast for 90 minutes before and after the challenge administration. They will be given a solution of sodium bicarbonate to drink (to neutralise stomach acid), followed by a drink containing Salmonella Paratyphi A bacteria.

Participants will be seen for daily follow-up visits where e-diary entries will be reviewed, observations taken, and blood and stool samples collected. The two outcomes for this period are as follows:
1. Some participants will not develop infection. They will be seen daily for 14 days. On day 14 post-challenge, they will be given a treatment course of antibiotics. Participants of childbearing potential will have a urine pregnancy test prior to starting antibiotics. They will then be telephoned on day 21 after the challenge to check their progress and reviewed in person on day 28 post-challenge.
2. For the remaining participants, they will be seen daily until the point at which they receive a diagnosis of paratyphoid A infection, according to pre-specified criteria:
o A positive blood culture for S. Paratyphi A from 72 hours post-challenge, or
o A positive blood culture for S. Paratyphi A within 72 hours post-challenge, with one or more signs/symptoms of paratyphoid A infection (such as recorded oral temperature ≥38.0oC), or
o Persistent positive blood cultures (two or more blood cultures taken at least 4 hours apart) for S. Paratyphi A within 72 hours post-challenge, or
o Oral temperature ≥38.0oC persisting for 12 hours or longer, not necessarily continuously
At this point, these participants will be asked to come back for a diagnosis visit, where blood and stool samples will be taken. They will start on a course of antibiotics at this point. Participants of childbearing potential will have a urine pregnancy test before they start antibiotics. For safety reasons, participants are seen at approximately 12, 24, 48, 72 and 96 hours after diagnosis. If no other visit is scheduled for day 14 post-challenge, they will also be seen on this day. They will then be telephoned on day 21 after the challenge to check on progress and reviewed in person on day 28 post-challenge.

Long-term follow-up visits
All participants will have follow-up visits on day 90 and day 180 after the challenge, where blood and stool samples will be collected, and saliva samples collected in a subset of participants.

Other study procedures:
Other medications will also be used, if required, to treat symptoms that may occur during

symptomatic Salmonella Paratyphi A infection (for example paracetamol).
Mood assessment will be performed at screening, prior to vaccination, prior to challenge and before starting antibiotics.

### Intervention Type
Biological/Vaccine

### Phase
Phase II

### Drug/device/biological/vaccine name(s)
SII-Typhoid Conjugate Vaccine (Bivalent) (SII-TCV(B)), Vi capsular polysaccharide vaccine (Typhim Vi)

### Primary outcome(s)
1. The proportion of participants developing S. Paratyphi A infection within 14 days following the challenge (in case any of the pre-specified criteria as mentioned under the Intervention section (Challenge Visits) are satisfied)
2. The Geometric Mean Concentration of S. Typhi Vi antigen-specific IgG measured by ELISA at day 28 following vaccination

### Key secondary outcome(s))
1. Occurrence of local solicited events in the 7 days following vaccination, systemic solicited events in the 7 days following vaccination, unsolicited events in the 28 days following vaccination and serious adverse events following vaccination throughout study participation. These will be measured using data recorded in the vaccination e-diary by participants and AEs and SAEs will be recorded and reviewed at all visits.
2. Quantification of S. Paratyphi A antigen-specific antibodies measured using in-house ELISA and /or Luminex-based quantification at 28 days following vaccination, including anti-LPS IgG, IgA and IgM and SBA titres
3. Quantification of S. Typhi antigen-specific antibodies measured using ELISA at 28 days following vaccination, for anti-Vi IgG and IgA

### Completion date
30/09/2027

## Eligibility

### Key inclusion criteria
Participants must satisfy all of the following criteria to be considered eligible for the study:
1. Willing and able to give informed consent for participation in the study
2. Aged between 18 and 55 years, inclusive, at time of vaccination
3. In good health as determined by medical history, physical examination and clinical judgement of the study team
4. Willing to be available at designated site for all required appointments
5. Agree (in the study team’s opinion) to comply with all study requirements, including capacity to adhere to good personal hygiene and infection control precautions
6. Agree to allow study staff to contact their GP to access the participant’s vaccination records, medical history and have their opinion solicited as to the participant’s appropriateness for inclusion
7. Agree to allow study staff to access NHS health records (medical and vaccination history) as

required for study purposes
8. Agree to allow their GP (and/or Consultant if appropriate), to be notified of participation in the study
9. Agree to allow national public health agency to be informed of their participation in the study
10. Agree to give their close household contacts written information about the participants' involvement in the study and offering them voluntary screening for S. Paratyphi A carriage
11. Agree to have 24-hour contact with study staff during the four weeks post challenge and are able to ensure that they are contactable by mobile phone for the duration of the vaccination and challenge period until antibiotic completion
12. Have internet access to allow completion of the e-diary and real-time safety monitoring
13. Agree to avoid antipyretic/anti-inflammatory treatment from challenge until advised by a study doctor or until 14 days after the challenge
14. Agree to refrain from donating blood for the duration of the study
15. Agree to provide their National Insurance/Passport number for the purposes of TOPS registration and for payment of reimbursement expenses
16. Agree to not receive any inactivated vaccine within 7 days before and after vaccination and 7 before and 21 days after challenge
17. Agree to not receive any live vaccine or vaccine containing DT or TT within 28 days before vaccination to 28 days after challenge
18. For participants of childbearing potential: willing to ensure that they or their partner use effective contraception 30 days prior to vaccination and continue to do so until clearance is confirmed

### Participant type(s)
Healthy volunteer

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
18 years

### Upper age limit
55 years

### Sex
All

### Key exclusion criteria
The participant will not be eligible if any of the following apply:
1. History of significant organ/system disease that could interfere with study conduct or completion, in the opinion of the study team. Including, for example, but not restricted to:
1.1. Cardiovascular disease
1.2. Respiratory disease
1.3. Haematological disease
1.4. Endocrine disorders
1.5. Renal or bladder disease, including history of renal calculi
1.6. Biliary tract disease, including biliary colic, asymptomatic gallstones or polyps or previous

cholecystectomy
1.7. Gastrointestinal disease including chronic diarrhoea, inflammatory bowel disease, irritable bowel syndrome or diseases requiring the use of regular antacids, H2-receptor antagonists, proton pump inhibitors, laxatives or prokinetic agents
1.8. Neurological disease
1.9. Metabolic disease
1.10. Psychiatric illness requiring hospitalisation, or history of schizophrenia and manic depressive psychosis
1.11. Known or suspected drug use
1.12. Known or suspected alcohol misuse
1.13. Infectious disease
1.14. Coagulation disorders
2. Have any known or suspected impairment of immune function, alteration of immune function or prior immune exposure that may alter immune function resulting from, for example:
2.1. Congenital or acquired immunodeficiency, including IgA deficiency
2.2. History of auto-immune disease
2.3. Human Immunodeficiency Virus or symptoms/signs suggestive of an HIV-associated condition
2.4. Receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 12 months or long-term systemic corticosteroid therapy
3. Receipt of immunoglobulin or any blood product transfusion within 3 months of study vaccination
4. History of cancer (except squamous cell or basal cell carcinoma of the skin and cervical carcinoma in situ)
5. HLA-B27 positive
6. Moderate or severe depression or anxiety as classified by the Hospital Anxiety and Depression Score at screening or challenge that is deemed clinically significant by the study doctors
7. Weight less than 50 kg
8. Presence of implants or prosthetic material
9. Taking long-term medication (e.g. analgesia, anti-inflammatories or antibiotics) that may affect symptom reporting or interpretation of the study results or that may interact with antibiotics used for the treatment of paratyphoid A (in particular drugs that could prolong corrected QT interval).
10. Contraindication to fluoroquinolones, macrolide antibiotics, co-trimoxazole or ceftriaxone
11. Family history of aneurysmal disease
12. Participants who are pregnant, lactating or who are unwilling to ensure that they or their partner use effective contraception 30 days prior to vaccination and continue to do so until three negative stool samples have been obtained after completion of antibiotic treatment
13. Full-time, part-time or voluntary occupations involving the below (unless willing to avoid work from challenge day until demonstrated not to be infected with S. Paratyphi A by clearance samples in accordance with guidance from national public health agency and willing to allow study staff to inform their employer):
13.1. Direct contact with young children (defined as those attending preschool groups or nursery or aged under 2 years, or
13.2. Direct contact with highly susceptible patients or persons in whom paratyphoid A infection would have particularly serious consequences
13.3. Commercial food handling (involving preparing or serving unwrapped foods not subjected to further heating).
14. Close household contact with:
14.1. Young children (defined as those attending preschool groups, nursery or those aged less than 2 years)
14.2. Individuals who are immunocompromised (including pregnancy)

15. Scheduled elective surgery or other procedures requiring general anaesthesia during the study period.
16. Participation in another research study involving an investigational product that might affect the risk of paratyphoid A infection or compromise the integrity of the study within the 30 days prior to study vaccination (e.g., significant volumes of blood already taken in previous study), including an interval between trials of a minimum of 5 half-lives of the investigational product's last administration; or plan to enrol in another research study during the follow-up study period
17. Detection of any abnormal results from screening investigations (at the clinical discretion of the study team)
18. Having been resident in an enteric fever endemic country for 6 months or more
19. Previous diagnosis with laboratory-confirmed typhoid or paratyphoid infection or a diagnosis compatible with enteric fever
20. Participation in previous typhoid or paratyphoid challenge studies (with ingestion of challenge agent)
21. Receipt of any typhoid vaccination at any time
22. Prolonged corrected QT interval (>450 milliseconds) or significant clinical abnormality on ECG
23. Presence of gallbladder abnormalities such as stones/calculi or polyps, as seen on ultrasound.
24. Significant blood donation or planned blood donation prior to study vaccination
25. Known serious reactions, allergy, hypersensitivity or any life-threatening reaction to any of the vaccine components, including reactions to previous receipt of tetanus or diphtheria-containing vaccines.
26. Evidence of HIV, Hepatitis B or Hepatitis C infection
27. Inability to comply with any of the study requirements (at the discretion of the study staff and the participant's General Practitioner)
28. Any other social, psychological or health issues which, in the opinion of the study staff, may:
28.1. Put the participant or their contacts at risk because of participation in the study
28.2. Adversely affect the interpretation of the primary endpoint data
28.3. Impair the participant's ability to participate in the study

### Date of first enrolment
01/02/2025

### Date of final enrolment
30/11/2025

## Locations

### Countries of recruitment
United Kingdom

England

Wales

### Study participating centre
### Oxford Vaccine Group
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**Study participating centre**
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**Study participating centre**
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**Study participating centre**
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**Study participating centre**
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**Study participating centre**
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**Study participating centre**
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# Sponsor information

**Organisation**
University of Oxford

**ROR**
https://ror.org/052gg0110

# Funder(s)

**Funder type**
Industry

### Funder Name
Serum Institute of India

### Alternative Name(s)
Serum Institute of India Pvt. Ltd, SII

### Funding Body Type
Private sector organisation

### Funding Body Subtype
For-profit companies (industry)

### Location
India

## Results and Publications

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request directed to Professor Sir Andrew J Pollard (andrew.pollard@paediatrics.ox.ac.uk) or upon written approval of the Sponsor.

### IPD sharing plan summary
Available on request