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Development of a vaccine against Salmonella Paratyphi A

Submission date	Recruitment status	[X] Prospectively registered
14/02/2022	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
14/02/2022	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
20/12/2024	Infections and Infestations	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Typhoid and Paratyphoid fever are both forms of an illness called enteric fever. Their names come from the bacteria that cause them: Salmonella Typhi (typhoid) and Salmonella Paratyphi A (paratyphoid). They both cause high fevers, headache, muscle and joint aches, abdominal pain, constipation and feeling generally unwell. If severe or left untreated, it can result in complications, long-term carriage of the bacteria or death.

There are approximately 14.3 million cases of enteric fever every year, with 3.3 million of these due to paratyphoid. It is spread by the faeces of an infected person, typically via contaminated water or food. It is found in parts of the world where people have inadequate access to clean water and sanitation.

Effective vaccines against typhoid fever already exist but there are no licensed vaccines against paratyphoid fever yet. The University of Maryland have developed an oral paratyphoid vaccine. It has already been given to humans and was shown to be safe. It now needs testing to see if it might prevent disease.

The Oxford Vaccine Group has developed a method of testing enteric fever vaccines called controlled infection or “challenge” studies whereby participants are given the vaccine and later a dose of the bacteria which can cause disease. Participants are then monitored closely to see if they become unwell and then treated with effective antibiotics. This model of studying vaccines has been undertaken by participants in previous Oxford Vaccine Group studies since 2011.

This study aims to assess the efficacy of a new oral paratyphoid vaccine using a human challenge study. It will also extend our knowledge on the immune response to paratyphoid infection and oral vaccination against paratyphoid.

Who can participate?

Healthy adult volunteers aged 18 - 55 years

What does the study involve?

In this study we will give participants either two doses of the oral paratyphoid vaccine that is

being tested (CVD 1902) or a placebo, 14 days apart. Twenty-eight days after the second vaccine or placebo dose all participants will then be given the “challenge”(a dose of Salmonella Paratyphi A). We will be looking to see if the vaccine prevents disease.

Following challenge, all participants are monitored closely and are treated with antibiotics if they become unwell, or 14 days after drinking the bacteria, whichever is sooner.

The planned study visits will take place over a period of 14 months and during this period participants will be seen multiple times, including daily for 2 weeks during the period of challenge. Participants will also be asked to keep an online diary of their symptoms during both the vaccination and challenge period.

What are the possible benefits and risks of participating?
The risks to participants in this study are low but are associated with the potential side effects of the vaccine, symptomatic infection following challenge and the risk of subsequent complications, for example chronic carriage of S. Paratyphi A. These risks are all minimised by strict inclusion and exclusion criteria to the trial, recording of symptoms by participants in a daily e-diary, presence of an on-call 24-hour team, regular in-person reviews by the study team including daily during challenge and prompt treatment of all cases of infection. In addition, there is a very small risk of onward transmission of paratyphoid to close contacts of participants. Again, this is minimised by strict inclusion and exclusion criteria and by emphasising the importance of good hand hygiene to the participants throughout the trial.
There is no direct benefit to participants taking part in this study. Participants may benefit from being informed about their general health status, for example from study tests such as blood tests.

Where is the study run from?
Oxford Vaccine Group at the Centre for Clinical Vaccinology and Tropical Medicine (CCTVM) at the Churchill Hospital in Oxford (UK)

When is the study starting and how long is it expected to run for?
June 2021 to February 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
1. Miss Sophie Vernon, sophie.vernon@paediatrics.ox.ac.uk
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3. Dr Naina McCann, naina.mccann@paediatrics.ox.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2021-003259-41

IRAS number
249094

ClinicalTrials.gov number

Nil known

Secondary identifying numbers
CPMS 50702, MR/R025347/1, IRAS 249094

Study information

Scientific Title
Development of a live attenuated vaccine against Salmonella Paratyphi A

Acronym
VASP

Study objectives
The purpose of this study is to assess the efficacy of the orally-administered live-attenuated vaccine CVD 1902 and extend our knowledge of the immune response both to S. Paratyphi A infection and vaccination.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/11/2021, South Central - Berkshire Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 207 104 8121; berkshire.rec@hra.nhs.uk), ref: 21/SC/0330

Study design
Interventional randomized controlled trial (multi-centre)

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Development of a live attenuated vaccine against Salmonella Paratyphi A

Interventions

Vaccination days and post vaccination visits
Vaccine randomisation will be completed on the 1st vaccination day. We will also complete an interim medical assessment; check vital signs, urine test for participants of childbearing potential, and collect blood, saliva and stool samples. We will take blood and stool samples on all visits whilst saliva samples will only be taken on selected visits.
We ask that all participants drink a solution of sodium bicarbonate to neutralise their stomach acid. Then, one minute later the CVD 1902 vaccine (or placebo) will be given to participants to drink.
We would also give participants access to a web-based electronic diary (e-diary), and a thermometer to take daily temperatures. We ask participants to record their temperature twice daily and any symptoms every day for one week after each vaccination.

After receiving the first vaccine (day -42), we will see participants after a week (day-35). A second vaccination will be given 14 days after the first vaccine (day -28). Participants will then have a further follow up visits prior to challenge (Day -21). During these post-vaccination visits we would review the e-diary for symptoms, ask if any medications have been taken, and obtain further blood and stool samples to make sure the bacteria has been cleared. At some visits saliva samples will also be taken (both vaccination days, day 0 (challenge), day 1 and day 2, at day 28, day 90, day 180, day 365).

Challenge day (day 0) Start of the intense monitoring period
Participants are asked to provide stool samples and blood is collected from all participants. Participants of childbearing potential will have a urinary pregnancy test performed. We would perform a mood assessment and set up the electronic diary for the challenge period. Participants will be asked to fast for 90 minutes before the visit. They will be given a solution of sodium bicarbonate (to neutralise stomach acid) followed by a drink containing Salmonella Paratyphi A bacteria.
At follow up visits e-diary entries will be reviewed, observations will be taken plus blood and stool samples.

Participants will be seen daily until one of two outcomes:
1. We anticipate some participants will not develop infection (anticipated one third in the placebo arm). 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 before they start antibiotics. They will then be telephoned on day 21 after challenge to check on their progress and reviewed in person at day 28 post challenge.
2. For the remaining participants (anticipated two thirds in the placebo arm) they will be seen daily, until 14 days post challenge until the point at which they receive a diagnosis of paratyphoid infection (either from the result of a blood test result or reaching the diagnostic criteria by symptoms). At this point they will be asked to come back for a diagnostic visit where blood and stool samples will be taken. They will be started on a course of antibiotics at this visit. 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 their diagnostic visit. If no other visit is scheduled for day 14 post challenge date they will also be seen (this would only occur in those diagnosed before day 10). They will then be telephoned on day 21 after challenge to check on their progress and reviewed in person at day 28 post challenge.
For safety reason pregnancy tests will be performed on participants of childbearing potential before both vaccinations, prior to challenge, prior to starting antibiotics ie at day 14 if not diagnosed, or at the diagnostic visit if participants are diagnosed.

Long term follow up
All participants will have follow up visits at day 90, day 180, day 365 where blood, saliva and stool samples will be taken.
Mood assessment will be performed at baseline (-42), at challenge visit (day 0), at day 7 post challenge and at day 14 post challenge or at paratyphoid diagnosis.
Vital signs, physical examination, blood and urine sampling, ECG, and mood assessment can be performed at any stage in the study if felt to be clinically indicated.
From these procedures we will collect data including:
- proportion of participants diagnosed with infection following challenge in the vaccine and placebo groups
- safety and tolerability of the CVD 1902
- the immune response to the vaccine alone and following challenge which may correlate with protection from disease.

1. Vaccine: CVD 1902
CVD 1902 is a live attenuated strain of Salmonella Paratyphi A, an unlicensed, experimental oral vaccine for Salmonella Paratyphi A infection developed by the Center for Vaccine Development at the University of Maryland in Baltimore. A dose contains not less than 2 x 10^10 CFU and vaccine recipients in this trial will receive 2 doses delivered in 30 mL carrier sodium bicarbonate solution, 14 days apart.

2. Placebo:
The vaccine placebo is 30 mL 1.3% w/v sodium bicarbonate solution made up using BP sodium bicarbonate powder with sterile water.

3. Pre-treatment: Sodium bicarbonate solution for both vaccine and placebo arms.
Both groups will receive 120 mL of sodium bicarbonate solution prior to vaccine or placebo. Sodium bicarbonate solution will be reconstituted from pharmaceutical grade sodium bicarbonate powder and sterile water at a concentration of 1.3% w/v. Sodium bicarbonate powder and sterile water for the pre-treatment bicarbonate solution prior to vaccine and challenge administration will be stored in a secure drug cupboard within a temperature-controlled room.

4. S. Paratyphi A challenge strain.
A parent seed lot, S888P5SP01, was established in March 2010 after serial colony selections on Luria Broth PTK agar plates and stored in the Novartis Vaccines and Diagnostics bacterial seed bank (Siena, Italy). This lot was used to establish the GMP Master Cell Bank, SA-13-002. Under GMP conditions in GenIbet BioPharmaceuticals, Portugal, 3 dose levels of the challenge agent were produced in chemically-defined media, using sucrose as the carbon source, to prepare a bulk bacterial suspension (Active Substance, 00513). Prepared vials containing the challenge agent were stored at -80°C ± 5°C and transferred to the Oxford Vaccine Group Laboratory in 2013.

5.. Antibiotics.
Antibiotics are used to treat diagnosed Salmonella Paratyphi A infection or at day 14 post challenge for those who have not been diagnosed.

6. Other medications
These will be used, if required, to treat symptoms that may occur during symptomatic Salmonella Paratyphi A infection (for example, paracetamol, etc).

Updated 12/09/2023: Female participants changed to participants of childbearing potential.

Intervention Type
Biological/Vaccine

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
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Primary outcome measure
Development of clinical or microbiologically proven paratyphoid infection following oral challenge with 1-5x10^3 S. Paratyphi A (strain NVGH308) delivered in a sodium bicarbonate solution at 14 days after the administration of the challenge agent:
Paratyphoid fever is diagnosed if ANY of the following apply:
1. A positive blood culture for S. Paratyphi A from 72 h post-challenge
2. A positive blood culture for S. Paratyphi A within 72 h post-challenge, with one or more signs /symptoms of paratyphoid infection (such as recorded temperature ≥38.0°C)
3. Persistent positive blood cultures (two or more blood cultures taken at least 4 h apart) for S. Paratyphi A within 72 h post-challenge.
4. Oral temperature ≥38.0°C persisting for 12 h

Secondary outcome measures
Current secondary outcome measures as of 12/02/2024:

1. Clinical course of paratyphoid infection after challenge between placebo and CVD 1902 groups, in particular:
1.1. time to onset of symptoms
1.2. duration of illness
1.3. symptom severity
1.4. time to onset of bacteraemia
1.5. time to onset of stool shedding
1.6. inflammatory response
Evaluated using clinical reporting, physical examination findings, microbiological assays to detect S. Paratyphi A in blood and stool, and laboratory assays to monitor inflammatory responses.
2. Innate, humoral, cell-mediated and mucosal responses to vaccination at baseline (Day -42) and post-vaccination time points (D-35, D-28, D-21 and D0) measured using immunological laboratory assays. These may include:
2.1. S. Paratyphi A antigen specific antibodies and serum bactericidal antibody titres
2.2. Cell-mediated responses (including antigen specific cell frequencies, description of lymphocyte populations, B and T cell repertoire)
2.3. Cytokine and acute phase reactant profile and kinetics
3. Immunological laboratory assays to assess innate, humoral, cell-mediated and mucosal responses to challenge will be taken at various time points following challenge. Baseline samples will be taken on D0 and post-challenge samples will be taken on D1, D2, D4, D7, D14, D28, D90, D180 and D365. Post-diagnosis samples will be taken on day of paratyphoid diagnosis, 12-24 hours following diagnosis and 96 hours following diagnosis. A variety of sample types will

be taken, these may include:
3.1. Cell-mediated responses (including antigen specific cell frequencies, description of lymphocyte populations, B and T cell repertoire)
3.2. Cytokine and acute phase reactant profile and kinetics
3.3. S. Paratyphi A antigen-specific IgA, IgM and IgG antibodies
4. Clinical observation and participant recording of symptoms, both solicited and unsolicited plus safety laboratory data. This will be evaluated using vaccination e-diaries completed by the participant daily for 7 days following each vaccine and then with any additional symptoms. Laboratory data will be taken at post-vaccination visits (D-35, D-28, D-21, D0).
5.Immunological response data post-vaccination (including S. Paratyphi A specific antibody titres, cell-mediated responses) will be combined with vaccine efficacy data following S. Paratyphi A challenge to investigate if particular immunological markers could be used to predict protection from paratyphoid infection.

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Previous secondary outcome measures:

1. Clinical course of paratyphoid infection after challenge between placebo and CVD 1902 groups, in particular:
1.1. time to onset of symptoms
1.2. duration of illness
1.3. symptom severity
1.4. time to onset of bacteraemia
1.5. time to onset of stool shedding
1.6. inflammatory response
Evaluated using clinical reporting, physical examination findings, microbiological assays to detect S. Paratyphi A in blood and stool, and laboratory assays to monitor inflammatory responses.
2. Innate, humoral, cell-mediated and mucosal responses to vaccination at baseline (Day -42) and post-vaccination time points (D-35, D-28, D-21 and D0) measured using immunological laboratory assays. These may include:
2.1. S. Paratyphi A antigen specific antibodies and serum bactericidal antibody titres
2.2. Cell-mediated responses (including antigen specific cell frequencies, description of lymphocyte populations, B and T cell repertoire)
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3. Immunological laboratory assays to assess innate, humoral, cell-mediated and mucosal responses to challenge will be taken at various time points following challenge. Baseline samples will be taken on D0 and post-challenge samples will be taken on D1, D2, D4, D7, D14, D28, D90, D180 and D365. Post-diagnosis samples will be taken on day of paratyphoid diagnosis, 12-24 hours following diagnosis and 96 hours following diagnosis. A variety of sample types will be taken, these may include:
3.1. Cell-mediated responses (including antigen specific cell frequencies, description of lymphocyte populations, B and T cell repertoire)
3.2. Cytokine and acute phase reactant profile and kinetics
3.3. S. Paratyphi A antigen-specific IgA, IgM and IgG antibodies
4. Clinical observation and participant recording of symptoms, both solicited and unsolicited plus safety laboratory data and microbiological data from blood and stool cultures following vaccination. This will be evaluated using vaccination e-diaries completed by the participant daily for 7 days following each vaccine and then with any additional symptoms. Laboratory and microbiological data will be taken at post-vaccination visits (D-35, D-28, D-21, D0).
5.Immunological response data post-vaccination (including S. Paratyphi A specific antibody

titres, cell-mediated responses) will be combined with vaccine efficacy data following S. Paratyphi A challenge to investigate if particular immunological markers could be used to predict protection from paratyphoid infection.

Overall study start date
01/06/2021

Completion date
28/02/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 23/03/2023:

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 judgment of the study team
4. Willing to be available for all required appointments and if applicable to travel to vaccination and challenge site
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 his or her GP or equivalent NHS databases 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 and participant identifiable data as required for study purposes
8. Agree to allow his or her GP (and/or Consultant if appropriate), to be notified of participation in the study
9. Agree to allow Public Health England to be informed of their participation in the study
10. Agree to give his or her close household contacts written information informing them of the participant's 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 4 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 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. Participants must have received at least one dose of a SARS-CoV-2 vaccine that has been approved for use by the MHRA (or other national regulatory authority) >4 weeks prior to enrollment
17. Agree to not receive other vaccinations (eg Covid-19 vaccines) during the 7 days before and after study vaccination and during the 21 days post-challenge

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Previous inclusion criteria as of 14/04/2022:

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 judgment of the study team
4. Willing to be available in Oxford 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 his or her 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 as required for study purposes
8. Agree to allow his or her GP (and/or Consultant if appropriate), to be notified of participation in the study
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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. Participants must have received at least one dose of a SARS-CoV-2 vaccine that has been approved for use by the MHRA (or other national regulatory authority) >4 weeks prior to enrollment
17. Agree to not receive other vaccinations (eg Covid-19 vaccines) during the 7 days before and after study vaccination and during the 21 days post-challenge

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Previous inclusion criteria:

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 judgment of the study team.
4. Live or reside within the Thames Valley Area.
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 his or her 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 as required for study purposes.
8. Agree to allow his or her GP (and/or Consultant if appropriate), to be notified of participation in the study.
9. Agree to allow Public Health England to be informed of their participation in the study.

10. Agree to give his or her close household contacts written information informing them of 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 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. Participants must have received at least one dose of a SARS-CoV-2 vaccine that has been approved for use by the MHRA (or other national regulatory authority) > four weeks prior to enrollment.
17. Agree to not receive other vaccinations (eg Covid-19 vaccines) during the 7 days before and after study vaccination and during the 21 days post-challenge.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Both

Target number of participants
UK Sample Size: Up to 76 participants

Total final enrolment
72

Key exclusion criteria
Updated 12/09/2023: Female participants changed to participants of childbearing potential.

Current exclusion criteria as of 23/03/2023:

1. History of significant organ/system disease that could interfere with trial conduct or completion. Including, for example, but not restricted to:
1.1. Cardiovascular disease including a diagnosis of hypertension
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 previous cholecystectomy
1.7. Gastro-intestinal disease including requirement for antacids, H2-receptor antagonists, proton pump inhibitors or laxatives
1.8. Neurological disease
1.9. Metabolic disease
1.10. Autoimmune disease
1.11. Psychiatric illness requiring hospitalisation
1.12. Known or suspected drug misuse
1.13. Known or suspected alcohol misuse (alcohol misuse defined as an intake exceeding 42 units per week)
1.14. Infectious disease
2. Have any known or suspected impairment of immune function, alteration of immune function, or prior immune exposure that may alter immune function to typhoid resulting from, for example:
2.1. Congenital or acquired immunodeficiency, including IgA deficiency
2.2. Human Immunodeficiency Virus infection or symptoms/signs suggestive of an HIV-associated condition
2.3. Receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 12 months or long-term systemic corticosteroid therapy.
2.4. Receipt of immunoglobulin or any blood product transfusion within 3 months of study start
2.5. History of cancer (except squamous cell or basal cell carcinoma of the skin and cervical carcinoma in situ)
3. HLA-B27 positive
4. 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
5. Weight less than 50kg
6. Presence of implants or prosthesis
7. Anyone taking long-term medication (e.g. analgesia, anti-inflammatories or antibiotics) that may affect symptom reporting or interpretation of the study results
8. Contraindication to fluoroquinolones, macrolide antibiotics, co-trimoxazole or ceftriaxone
9. Family history of aneurysmal disease
10. Participants of childbearing potential 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 at least one week after completion of antibiotic treatment
11. Full-time, part-time or voluntary occupations involving:
11.1. Clinical or social work with direct contact with young children (defined as those attending pre-school groups or nursery or aged under 2 years), or
11.2. Clinical or social work with direct contact with highly susceptible patients or persons in whom typhoid infection would have particularly serious consequences
11.3. Commercial food handling (involving preparing or serving unwrapped foods not subjected to further heating)
11.4. (unless willing to avoid work from vaccination until demonstrated not to be infected with S. Paratyphi A after challenge by clearance samples in accordance with guidance from Public Health England and willing to allow study staff to inform their employer)
12. Close household contact with:
12.1. Young children (defined as those attending pre-school groups, nursery or those aged less than 2 years)
12.2. Individuals who are immunocompromised (including pregnancy)
13. Scheduled elective surgery or other procedures requiring general anaesthesia during the study period

14. Participants who have participated in another research study involving an investigational product that might affect risk of paratyphoid infection or compromise the integrity of the study within the 30 days prior to enrolment (e.g. significant volumes of blood already taken in previous study)
15. Detection of any abnormal results from screening investigations (at the clinical discretion of the study team)
16. Inability to comply with any of the study requirements (at the discretion of the study staff and the participant's General Practitioner)
17. Any other social, psychological or health issues which, in the opinion of the study staff, may
17.1. put the participant or their contacts at risk because of participation in the study,
17.2. adversely affect the interpretation of the primary endpoint data,
17.3. Impair the participant's ability to participate in the study
18. Have any history of allergy to vaccine components
19. Having been resident in an enteric fever endemic country for 6 months or more
20. Have previously been diagnosed with laboratory-confirmed typhoid or paratyphoid infection or been given a diagnosis compatible with enteric fever
21. Have participated in previous typhoid or paratyphoid challenge studies (with ingestion of challenge agent)
22. Have received any oral typhoid vaccination (eg Ty21a or M01ZH09) at any time
23. Have a prolonged corrected QT interval (> 450 milliseconds) on ECG screening
24. Significant blood donation or planned blood donation within 3 months of enrollment

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Previous exclusion criteria:

1. History of significant organ/system disease that could interfere with trial conduct or completion. Including, for example, but not restricted to:
1.1. Cardiovascular disease including a diagnosis of hypertension
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 previous cholecystectomy
1.7. Gastro-intestinal disease including requirement for antacids, H2-receptor antagonists, proton pump inhibitors or laxatives
1.8. Neurological disease
1.9. Metabolic disease
1.10. Autoimmune disease
1.11. Psychiatric illness requiring hospitalisation
1.12. Known or suspected drug misuse
1.13. Known or suspected alcohol misuse (alcohol misuse defined as an intake exceeding 42 units per week)
1.14. Infectious disease
2. Have any known or suspected impairment of immune function, alteration of immune function, or prior immune exposure that may alter immune function to typhoid resulting from, for example:
2.1. Congenital or acquired immunodeficiency, including IgA deficiency
2.2. Human Immunodeficiency Virus infection or symptoms/signs suggestive of an HIV-associated condition
2.3. Receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation

therapy within the preceding 12 months or long-term systemic corticosteroid therapy.
2.4. Receipt of immunoglobulin or any blood product transfusion within 3 months of study start
2.5. History of cancer (except squamous cell or basal cell carcinoma of the skin and cervical carcinoma in situ)
3. HLA-B27 positive
4. 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
5. Weight less than 50kg
6. Presence of implants or prosthesis
7. Anyone taking long-term medication (e.g. analgesia, anti-inflammatories or antibiotics) that may affect symptom reporting or interpretation of the study results
8. Contraindication to fluoroquinolones, macrolide antibiotics, co-trimoxazole or ceftriaxone
9. Family history of aneurysmal disease
10. Female 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
11. Full-time, part-time or voluntary occupations involving:
11.1. Clinical or social work with direct contact with young children (defined as those attending pre-school groups or nursery or aged under 2 years), or
11.2. Clinical or social work with direct contact with highly susceptible patients or persons in whom typhoid infection would have particularly serious consequences
11.3. Commercial food handling (involving preparing or serving unwrapped foods not subjected to further heating)
11.4. (unless willing to avoid work from vaccination until demonstrated not to be infected with S. Paratyphi A after challenge by clearance samples in accordance with guidance from Public Health England and willing to allow study staff to inform their employer)
12. Close household contact with:
12.1. Young children (defined as those attending pre-school groups, nursery or those aged less than 2 years)
12.2. Individuals who are immunocompromised (including pregnancy)
13. Scheduled elective surgery or other procedures requiring general anaesthesia during the study period
14. Participants who have participated in another research study involving an investigational product that might affect risk of paratyphoid infection or compromise the integrity of the study within the 30 days prior to enrolment (e.g. significant volumes of blood already taken in previous study)
15. Detection of any abnormal results from screening investigations (at the clinical discretion of the study team)
16. Inability to comply with any of the study requirements (at the discretion of the study staff and the participant's General Practitioner)
17. Any other social, psychological or health issues which, in the opinion of the study staff, may
17.1. put the participant or their contacts at risk because of participation in the study,
17.2. adversely affect the interpretation of the primary endpoint data,
17.3. Impair the participant's ability to participate in the study
18. Have any history of allergy to vaccine components
19. Having been resident in an enteric fever endemic country for 6 months or more
20. Have previously been diagnosed with laboratory-confirmed typhoid or paratyphoid infection or been given a diagnosis compatible with enteric fever
21. Have participated in previous typhoid or paratyphoid challenge studies (with ingestion of challenge agent)
22. Have received any oral typhoid vaccination (eg Ty21a or M01ZH09) at any time
23. Have a prolonged corrected QT interval (> 450 milliseconds) on ECG screening

24. Significant blood donation or planned blood donation within 3 months of enrollment

Date of first enrolment
25/02/2022

Date of final enrolment
20/11/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
Headington
Oxford
United Kingdom
OX3 7LE

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
University Hospitals Bristol and Weston NHS Foundation Trust
Trust Headquarters

Marlborough Street
Bristol
United Kingdom
BS1 3NU

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Study participating centre
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
United Kingdom
L3 5QA

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
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United Kingdom
B15 2GW

Sponsor information

Organisation
University of Oxford

Sponsor details
Research Governance, Ethics and Assurance (RGEA)
Joint Research Office
1st floor, Boundary Brook House
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United Kingdom
OX3 7GB
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RGEA.Sponsor@admin.ox.ac.uk

Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/03/2025

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.1	30/11/2021	14/02/2022	No	No
Protocol file	version 3.1	11/04/2022	14/04/2022	No	No
Protocol file	version 3.0	07/03/2022	14/04/2022	No	No
Protocol article		24/05/2023	25/05/2023	Yes	No
Protocol file	version 4.0	04/11/2022	12/06/2023	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 4.1	03/07/2023	12/09/2023	No	No
Protocol file	version 5.0	12/10/2023	12/02/2024	No	No
Protocol file	version 5.1	23/02/2024	07/03/2024	No	No
Protocol file	version 5.2	26/04/2024	20/05/2024	No	No