BiVISTA
Bivalent Vaccination against *Salmonella* Typhi and Paratyphi A

PARTICIPANT INFORMATION SHEET

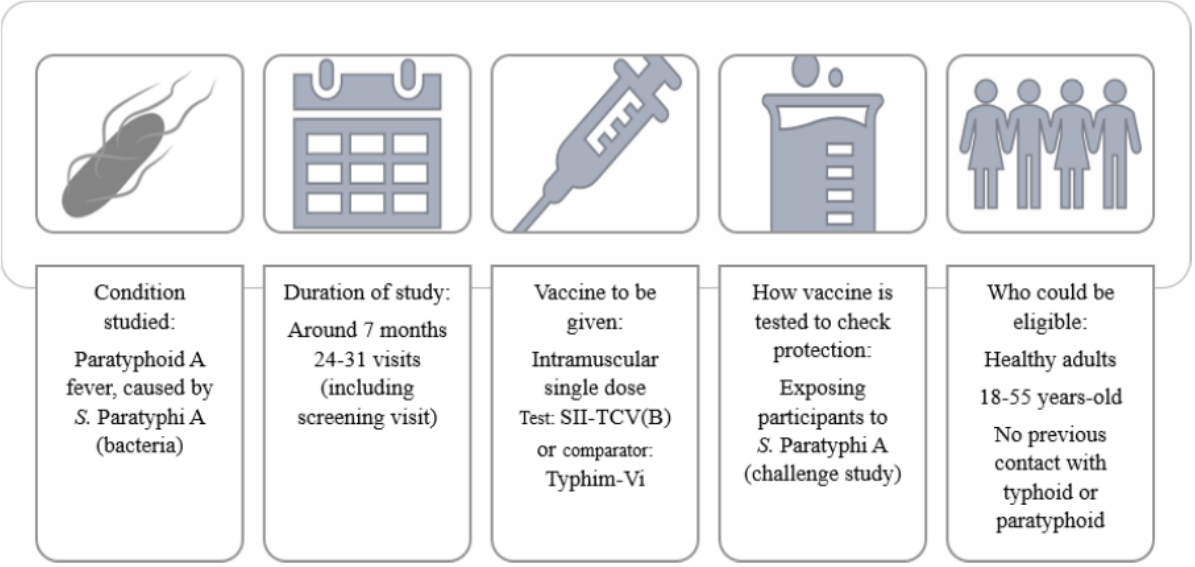
You are invited to take part in a study to investigate whether a new vaccine against typhoid and paratyphoid fever (Bivalent Typhoid Conjugate Vaccine, SII-TCV(B)), protects against infection with *Salmonella* Paratyphi A in a controlled human infection model.

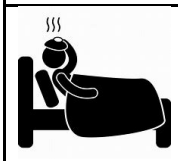
The Oxford Vaccine Group, which is part of the University of Oxford, is running the study across several sites in the UK with funding from the Serum Institute of India.

Before you decide whether to take part, it is important for you to understand what the study is about and what participation would involve. Please take time to read the information carefully and discuss with others if you wish. If anything is unclear or you would like further information, please contact the study team (details below). Participation in this study is entirely voluntary.

Thank you for taking the time to consider taking part in the study.

Contact details can be found at the end of this booklet



	**Study site**	The University Hospital of Wales, Cardiff and Vale University Health Board
	**Location for challenge site**	The Oxford Vaccine Group
	**Principal Investigator**	Dr Matthijs Backx
	**Chief Investigator**	Professor Andrew Pollard Professor Andrew Pollard is chair of the UK Department of Health and Social care's Joint Committee on Vaccination and Immunisation and a member of WHO Technical Advisory Group on Salmonella Vaccines
	**Study Sponsor**	University of Oxford. The sponsor takes on legal responsibility for the management of the research, ensuring the study is conducted in accordance with the protocol and good clinical practices.
	**Study Funder**	Serum Institute of India Pvt. Ltd., Pune, India
	**Who can take part in this study?**	We are looking to recruit healthy volunteers who are willing to be available for all necessary visits and are healthy, aged 18 to 55 and have not been exposed to *Salmonella* Typhi or Paratyphi A before.
	**What happens in this study?**	In this study we will be assessing if a new vaccine, SII TCV(B), can protect against *Salmonella* Paratyphi A infection by intentionally exposing participants to *Salmonella* Paratyphi A (*controlled human infection* or *challenge* model).
	**Reimbursement**	Participants will receive up to £4410 if they remain in the study for the entire period (includes payment for screening) and attend all the scheduled visits required for them. Payments will be made via bank transfer. Participants will be required to provide banking details including account name, sort code and account number.
	**Risks of participation**	Short-lived post vaccine symptoms such as mild discomfort of the arm and fever and muscle aches may occur. Following challenge, it is possible that participants may develop paratyphoid infection; this will be carefully managed, and treatment is available. A full discussion of the risks can be found on page 19.
	**Benefits of participation**	By taking part in this study, you will help research into the development of a new vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A. You will not directly receive any other personal health benefit from the study or its procedures.

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What is the purpose of this study?

In this study we will be assessing if a new vaccine, SII TCV(B), can protect against *Salmonella* Paratyphi A infection. We will also be evaluating whether this vaccine produces adequate immune responses against *Salmonella* Typhi, compared to an existing licensed typhoid vaccine. Results from this study may be used for licensing of the SII TCV(B) vaccine.

We will also collect data looking at:

- How safe and well tolerated the SII TCV(B) vaccine is.
- How the immune system responds to vaccination and challenge in those participants who have received SII TCV(B) vaccination compared to a control vaccine

We are looking to recruit 192 healthy volunteers aged 18-55.

What are *Salmonella* Typhi and Paratyphi A?

Typhoid and paratyphoid fever are both forms of an illness called Enteric fever. Their names come from the bacteria that cause them: *Salmonella* Typhi and *Salmonella* Paratyphi – specifically, *Salmonella* Paratyphi A is thought to be responsible for almost all cases of paratyphoid fever. Although they are from the same family as the *Salmonella* bacteria that causes gastroenteritis (for example food poisoning) in the UK, they are quite different.

Enteric fever causes individuals to feel generally unwell, sometimes with high fevers, headache, muscle and joint aches, abdominal pain and constipation. If severe or left untreated, it can result in complications, long-term carriage of the bacteria or death.

There are approximately 13 million cases of Enteric fever every year. Over two thirds are due to typhoid, for which there are vaccines available. Just under a third of cases (approximately 3.8 million per year) are due to paratyphoid, for which there is no vaccine. Both typhoid and paratyphoid are spread by the faeces of an infected person, typically via contaminated water or food. They are found in parts of the world where people don't have access to clean water and sanitation.

Where is this study taking place?

The study is taking place in multiple sites across the UK. Study visits will take place at the University Hospital of Wales. The challenge appointment will take place at the Oxford Vaccine Group. Travel from the University Hospital of Wales to the challenge site for the challenge visit will be arranged by the study teams and time expenses will be reimbursed.

Are there vaccines against *Salmonella* Paratyphi A?

There are currently no licensed vaccines against *Salmonella* Paratyphi A. However, there are effective vaccines to protect against *Salmonella* Typhi which are licenced and widely used.

What is the vaccine being tested in this study?

The Serum Institute of India (SII) have developed a Bivalent Conjugate Vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A. Bivalent means that the vaccine targets two organisms. In this case, the vaccine contains tiny amounts of the sugars from the surface of both *Salmonella* Typhi and *Salmonella* Paratyphi A that have been conjugated (attached) to other proteins (carriers), to induce a stronger immune response: in this vaccine, the carriers are tetanus and diphtheria toxoids, present in other widely used vaccines.

This vaccine will be administered as an injection in the muscle of the upper arm. In this study we will be testing the vaccine to see if it can prevent paratyphoid A infection, and to see if it produces an adequate immune response against typhoid infection.

This vaccine has already been tested in humans. In a Phase I trial, the vaccine induced an immune response against both components. The study showed that the vaccine was safe and well-tolerated. There were no serious adverse events related to the vaccine. In this study, participants will be randomised to receive either the study vaccine (SII TCV(B)) or a control vaccine, Typhim Vi, which is approved for use around the world including in the UK to protect against typhoid fever.

What is a human infection ('challenge') study?

Human infection or challenge studies involve deliberately exposing participants to an infectious agent (such as a bacterium). We will be asking participants to drink a solution that contains bacteria. 'Challenge' using bacteria that cause enteric fever (*Salmonella* Typhi and *Salmonella* Paratyphi A) has been performed safely at the Oxford Vaccine Group since 2011. Around 500 participants have been involved in these studies.

Human challenge is done in a very controlled way using a specific dose. Participants are then closely monitored for signs of infection. **All** participants are treated with antibiotics at the end of the observation period, regardless of whether they develop signs of infection, to make sure that the challenge bacteria are eradicated. This type of study is very powerful as it can be used to look at diseases that are hard to study when they occur naturally.

For this challenge study, the Oxford Vaccine Group will use *Salmonella* Paratyphi A. We know that by giving a specific dose of *Salmonella* Paratyphi A, approximately 58% of people exposed to the bacteria will develop paratyphoid infection. By using this very controlled setting to expose people to *Salmonella* Paratyphi A, we can test vaccines to determine how well they protect against infection.

Why have I been invited?

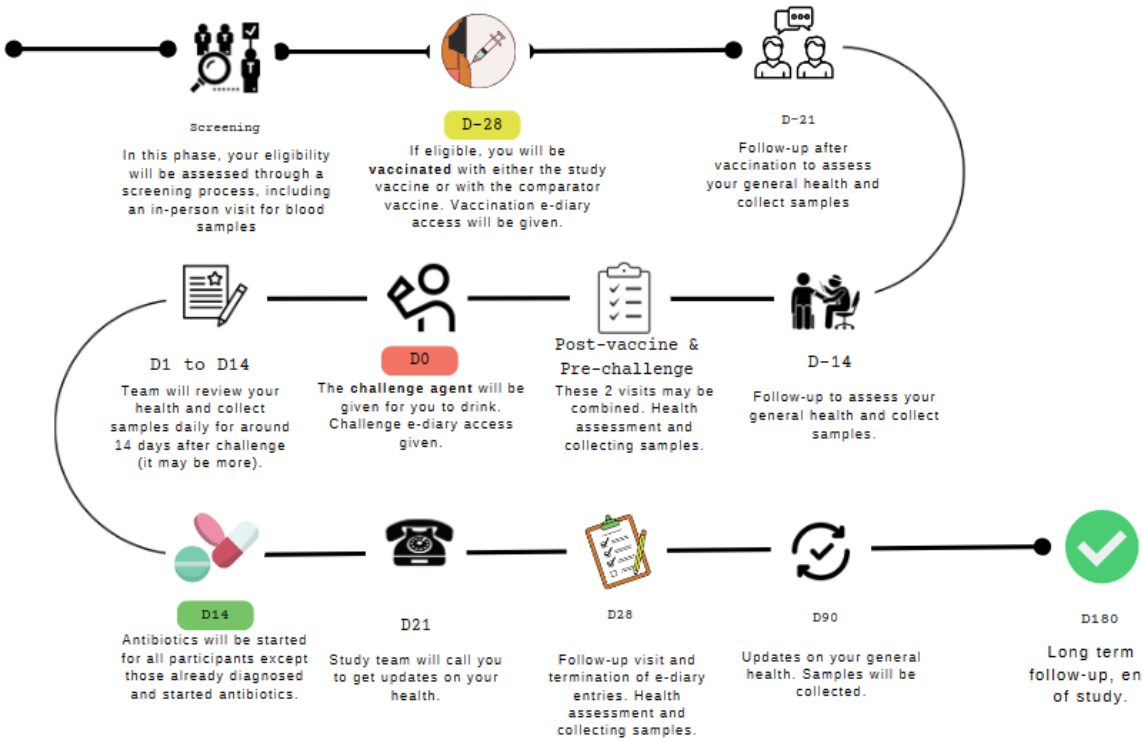
We are looking to recruit healthy volunteers who are aged between 18 and 55 years. We use various ways to contact anyone who may be interested in this study, including via the Electoral Roll, by requesting a data extract from NHS patient databases, or using a relevant mailing list(s) or registry(s) that individuals may have independently signed up to.

In the case of NHS databases, we will only request identification of persons based on postcode and appropriate age range. This information is shared with CFH Docmail or an equivalent company (who have been assessed under the NHS Data Security and Protection Toolkit) solely for the purpose of arranging for the invitations to be sent.

Please note that we **do not** have your contact details, unless you have been contacted using the open version of the electoral register or you have previously provided us with this information.

What does this study involve?

The following diagram gives a simplified outline of the key study visits and what will be done during each visit.



Please note that you must be willing to travel to the Oxford Vaccine Group for the challenge visit, which may take an entire day with travel times. Transport to the challenge site will be provided. Following challenge, you would need to attend the University Hospital of Wales for **daily visits for approximately 2 weeks**. During the challenge period you will **not** need to self-isolate, but you will be asked to **follow strict hygiene measures**.

Everyone will need to complete a course of antibiotics for 14 days. You would also need to remain in contact with the study team during this period (contactable by mobile telephone and have access to the internet). We will also ask you to provide us the details of a person who lives close to you and would be willing to know where you were during the vaccine and the challenge phase, in case we have any concerns and cannot contact you.
Follow up visits would then be at 1, 3, and 6 months after 'challenge' day. The total study duration would be approximately 7 months. You must agree to comply with the requirements of the study.

Do I have to take part?

No. **Taking part is entirely voluntary**. We are looking for volunteers. Should you volunteer and later change your mind (for whatever reason) it is your right to do so and you would not need to provide an explanation to the study team or anyone else, but because of the nature of this study you may need follow up and treatment even if you chose to withdraw, depending on the stage of the study you were at when you chose to withdraw.

Whatever you choose it is important that you are happy with your decision, and it is not the role of the study team to decide for you. We would help present the details of the study and answer all your questions so you could make an informed decision.

If you decide not to participate in the study or discontinue the study participation, this will not affect your standard medical care.

Who can take part in the study?

We are looking to recruit volunteers who are healthy and aged 18 to 55. Volunteers will also need to be willing to be available for all necessary visits, and live/stay within approximately a 60-minute commute to your local study site during the challenge period.

Certain things may mean you are **not able to take part** in the study, which will be explained in the section below.

Why might I be excluded from taking part?

Pregnancy

Paratyphoid infection can potentially be dangerous during pregnancy both to the mother and to the unborn child. Participants that can get pregnant will therefore be asked to use an effective method of contraception. There is no data on the use of this vaccine in pregnancy or whilst breast feeding. It is therefore a requirement of participation that volunteers who could become pregnant must use contraception. Exceptions to this are below:

- Absence of female reproductive system;
- Post-menopausal;
- Surgical sterilisation.

Acceptable contraception methods include:

- Oral, injected or implanted hormonal contraceptives that prevent ovulation;
- Intrauterine device (IUD);
- Intrauterine system (IUS);
- Sole sexual partner is a vasectomised male;
- Barrier methods of contraception;
- Complete abstinence from sex with a male partner for the whole duration of the study.

There is no evidence that the vaccine can be shed into semen.

Contact with young children and other vulnerable people (including household contact)

You would be advised not to have close contact with young children (those in pre-school care/nursery or under 2 years of age) or with anyone who may be especially vulnerable to infection until we have confirmed that you have cleared the *Salmonella* Paratyphi A from your stool after challenge.

Clinical and social care occupations (including healthcare students)

If you work in these areas, you will have to agree to stay away from your work or studies for the entire challenge period (or to be redeployed to alternative work which does not involve direct contact with individuals). We would need to inform your employer (or occupational health department) of your participation in the study.

Food handlers

Salmonella Paratyphi A can be transmitted in food handled by people who are infected with it. If your work or voluntary activities involves handling or preparing unwrapped food that is not subject to further heating, then you would not be able to participate in this study unless you were willing and able to confirm that you are not working in this role from challenge until we have confirmed that you have cleared the *Salmonella* Paratyphi A from your stool after challenge. If you are responsible for taking care of meals in your household, you would need to arrange for someone else to do this during the challenge phase, until clearance.

Those who may have been exposed to *Salmonella* Typhi or *Salmonella* Paratyphi previously

This includes anyone who has previously lived in an area of the world where the bacteria are common. It also includes anyone who has received a vaccine against *Salmonella* Typhi (there are no existing vaccines against *Salmonella* Paratyphi A) or taken part in one of our previous enteric challenge studies. This is because we will be testing how a person's immune system responds to the new SII TCV(B) vaccine. To do this, we need people who have not already developed antibodies to the bacteria.

Other causes for exclusion

- History of any significant medical condition, such as diabetes (amongst others);
- Any known or suspect immune system impairment or function abnormality such as HIV infection, auto-immune conditions (like Graves or coeliac) or history of cancer (bar some types of skin cancer);
- Gallbladder problems, like stones or polyps or surgical removal of gallbladder in the past;
- Presence of implants or prosthetic material, like screws/pins/plates;
- Moderate or severe depression or anxiety or other uncontrolled mental health conditions;
- Weight less than 50 kg;
- If you are taking certain medications on a regular basis, that could affect the study outcome;
- Contraindication to any of the antibiotics used in the study (ciprofloxacin, azithromycin, co-trimoxazole or ceftriaxone);
- History of allergic reactions to vaccines;
- Family history of aneurysm;
- Scheduled elective surgery or other procedures requiring general anaesthesia during the

study period;

- Abnormal results from screening investigations (please see the section "Face-to-face screening visit" which details which tests are done at screening).

There are also some situations in which we may need to delay the start of the study for you.

If you are unsure about any of the conditions listed, a member of the study team can help you.

We would also like to know if you are expecting to receive any vaccines during the study period as this may affect whether you are able to participate in the study.

What will happen to me if I decide to take part?

If you choose to take part, you would be screened for the applicable eligibility study criteria. If found eligible, you would be involved in the study for approximately 7 months in total. The different stages of the study will now be considered in detail.

Study Procedures

Online pre-screening questionnaire and medical records consent

If you decide that you would like to take part in this study, then you may be asked to complete a short set of online questions that cover some of the key criteria for participation in the study. If the study is right for you at this point, we will contact you to provide further instructions on the next steps. In addition, we will ask you to provide consent for the study team to access your medical records via the electronic patient records or through your GP. This consent is only to allow access to your medical records, and not the consent for enrolment into the study. If you choose to participate in the study, you will need to sign a separate consent.

If, based on these online questions, you are not eligible to participate in the study, you will be informed.

Face to Face Screening Visit (Up to 2 hours)

The purpose of screening is to assess whether you can participate in the study. This visit will occur at your local study site.

At the screening visit, we will outline the nature of the clinical study in person, and this will explain what to expect by taking part, the risks involved and what side-effects you might expect to experience. This visit would provide an opportunity for you to ask any further questions you might have to a member of the study team about what is involved. You would be allowed as much time as you needed before making any decision on whether or not to take part.

If you wished to proceed, we would ask you to complete a **short quiz** to ensure you had understood the study and sign an **informed consent form**. Only after the informed consent form is signed, can we proceed with any study procedures.

We would ask you questions about your health, or review any information given by phone, undertake a physical examination including **an ECG** ('heart tracing') and take **urine and blood samples**. We would

also arrange an ultrasound scan of your gallbladder to check for any abnormalities (e.g., the presence of any gallstones would mean you were unable to take part). This is a non-invasive and painless procedure.

Blood would be screened for general health (to check your blood count, kidney, and liver function), HIV, hepatitis B and C and coeliac disease as well as for a congenital immune deficiency that some people have without knowing (called IgA deficiency). Your blood would also be tested for the presence of the **HLA-B27** gene, which can be associated with some autoimmune conditions. All participants are also asked to complete a mood assessment to screen for **anxiety and depression**. Urine will be tested for the presence of blood, protein, and glucose. For all participants of childbearing potential, we would also perform a **pregnancy test** on your urine sample.

Following the screening tests, if an abnormal result was found on one of the tests, we would discuss this with you. **We may provide you with the information and ask you to attend your GP**. **Alternatively, with your permission, we would share this information with your GP** or other relevant healthcare provider.

During your screening, you would be asked to provide your National Insurance number (or passport number if you are not a UK national). This would be entered onto a national database which helps prevent volunteers from taking part in too many clinical trials. **The Over-volunteering Prevention System (TOPS)** ensures the safety of all our participants in this study; therefore, if you are unwilling to have your information submitted on TOPS, you would not be able to take part in our study. If you withdraw from the study before you receive a vaccine, the database will show that you never received a dose. For more information on this, you can access:https://www.hra.nhs.uk/about-us/committees-and-services/the-over-volunteering-prevention-system/

If the study team found any reason why you could not take part in the study this would be discussed with you.

Once the study team have confirmed your suitability for the study, we would inform you and arrange a date for your vaccination visit. If more than 120 days have elapsed from your screening visit to vaccination, we would repeat your face-to-face screening visit including some of the procedures.

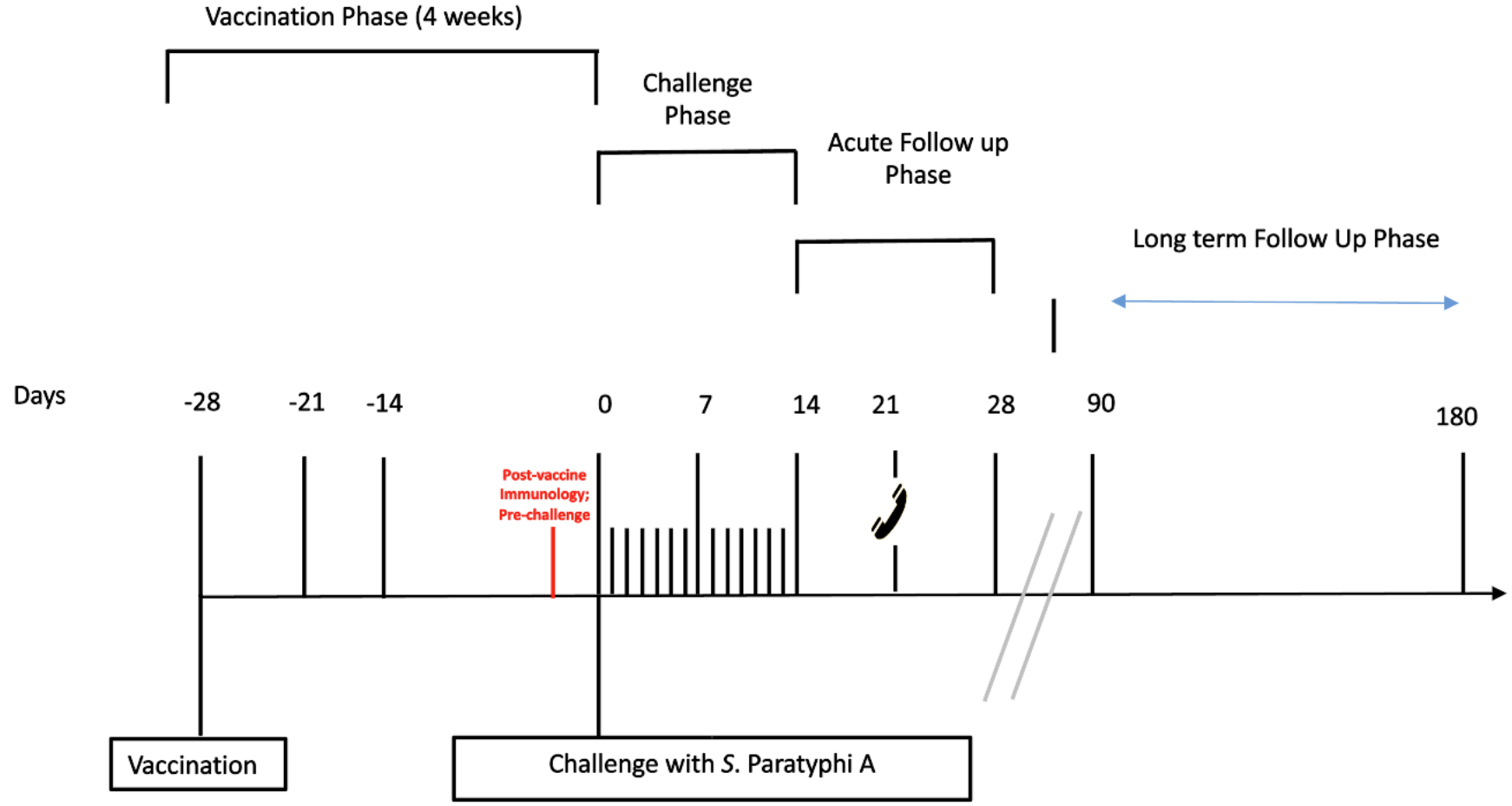
Your participation in this study is at the researchers' discretion.

Is coming to screening a commitment to taking part?

No. It is an opportunity to meet with the study staff and ask questions. You do not need to decide there and then.

Overview of the Study

This diagram shows an overview of the whole study. This information booklet will now go through each part of the study in detail.



Vaccination day visit (Up to 2 hours)

Your vaccination visit will take approximately 2 hours and will take place at your local study site. Before going ahead to receive vaccine, the study team will perform a safety review to ensure it is safe to proceed with vaccination. At this point, blood samples will be taken. In some participants, saliva and stool samples may also be taken. Participants with the potential to get pregnant will have a urinary pregnancy test.

At the point of vaccination, you will be either given the test or comparator vaccine, based on the pre-generated randomisation sequence. This is similar to flipping a coin. This is a double-blind study, which means neither you nor the study clinicians will know which vaccine you received until the end of the study. The vaccine will be administered in the deltoid muscle (upper arm) and then you will be observed for a minimum of 45 minutes by a member of the study team.

You will be set up with an electronic diary where we would ask you to record your temperature twice a day, in the morning and in the evening, and record any symptom you experience every day for 7 days following vaccination**.** The diary is a web-based electronic diary (e-diary), so you will be able to access it via a daily link which will be sent to your email. We ask that you let us know if you have a high temperature (greater than or equal to 38°C). You can take paracetamol and ibuprofen after vaccination if required**.** A clinical member of the study team will be checking your diary daily, so it is important that you fill it in regularly. For all e-diaries completed during the study, participants may be contacted by phone if the e-diaries are not completed or not working.

We will also give you a thermometer, a ruler, a paper back-up diary and an emergency contact card, with the 24hr contact details of the study team.

Post vaccination visits (Up to 30 minutes)

After receiving the vaccine, we would ask you to attend follow up visits one and two weeks after vaccination. These visits would take place at your local study site. During these post-vaccination visits, we would review your e-diary for symptoms, ask if you have taken any medications, and obtain further blood samples to assess your body's response to the vaccine. For some participants we may ask you to provide saliva and stool samples at these visits.

Post vaccine immunology (if required, 15 minutes)

You will only require this visit at a different date to the pre-challenge visit if it is decided to not proceed with challenge four weeks after vaccination, as planned. In that case, we would still like to take blood samples to check your immune response to the vaccine at this point. This visit would be a short visit to take blood samples, and the pre-challenge visit would then happen at a later stage, up to 2 days before challenge. In the visit schedule diagram, this visit (in red on the figure) is joined with the pre-challenge visit, as we expect both to occur on the same day. The post vaccine immunology and pre challenge visit procedures may both occur on the same day as the challenge day (D0), before the challenge administration.

Pre-challenge visit (Up to 30 minutes)

Before going ahead with challenge, you will have a pre-challenge visit with your local study site (this may occur up to 2 days before challenge). At this visit the study staff will perform some observations, ask some questions, take some blood samples and check that you are safe to proceed with challenge. A mood assessment will be carried out, and for participants that can get pregnant a urinary pregnancy test will be done.

This will happen around four weeks after vaccination. In the 'Overview of the Study' diagram, this visit is in red, as this may be done at the same time as the post-vaccine immunology visit. It is also possible that this visit may happen on the same day as the challenge day (Day 0), before the challenge administration.

Challenge day (Day 0) - Start of the intense monitoring period

The challenge visit would take place at The Oxford Vaccine Group under controlled conditions. Transport would be arranged for you to the challenge centre.

On the day of challenge, you would be asked to fast (i.e., not eat or drink anything) for 90 minutes before the appointment time.

We would first give you a drink to counteract the acid in your stomach (as stomach acid can kill *Salmonella* Paratyphi A) followed by the drink containing *Salmonella* Paratyphi A bacteria. You would then be asked to fast for a further 90 minutes. Once the 90 minutes are complete, lunch would be provided for participants. Participants should remain at the challenge site until 2 hours post challenge. This is because any vomit within this time would contain paratyphoid and would require careful cleaning. If vomiting did occur, you would need to be treated with antibiotics and kept in the study only for safety reasons (withdrawn from protocol-specified procedures).

We would set up a new challenge e-diary with you and check that you can use your e-diary and your thermometer. We would ask you to record your temperature in the e-diary twice a day, plus record any additional fevers you may have, and your symptoms once a day for the following 21 days. You will also be asked to record every antibiotic dose in this e-diary once you start antibiotics. We would also provide you with a paper backup challenge diary, to be used to record your symptoms, if you were unable to access the internet to complete the e-diary.

For the 14 days following challenge (or until you are diagnosed) it is very important that you do not take paracetamol, ibuprofen or any other medication that may lower your temperature unless instructed to do so by the study team, as this will interfere with the diagnosis of paratyphoid A infection. Your study doctor can give you options of medications to reduce pain, you just have to contact the study team for this.

We would also ask you to follow strict hygiene measures until we confirm clearance, which would usually happen around 6 weeks after challenge, but may be longer. Clearance is confirmed after 3 stool samples collected at least one week after completing antibiotics are tested negative for *S.* Paratyphi A.

What happens at the follow up visits?

Follow up visits during the challenge period will take place daily at your local study site for around 14 days following challenge for most volunteers, and up to 19 days for a few participants – please see section on "What happens if I get paratyphoid A infection?". At these visits, we would review the symptoms recorded in your e-diary, measure your vital signs, and take a blood and stool sample. These samples would be examined for the paratyphoid bacteria and to study your body's immune response to paratyphoid A infection, and may be sent to another study site for testing.

You would be diagnosed with paratyphoid A infection for the purposes of this study if you have a persistent fever or if the bacteria were found in your daily blood samples.

It is essential that you are available to attend the study visits after challenge, potentially at short notice until you have completed antibiotic treatment. We would ask each participant to attend every visit, complete the e-diary, and keep in contact with the team, who are there for your safety. We would then see you for visits at 1, 3 and 6 months after challenge. Additionally, we may request you to come for an unscheduled visit if we have any concerns around safety.

You can contact us on the telephone at any time if you are concerned about any medical conditions.

What happens if I get paratyphoid A infection?

The main symptom of paratyphoid infection is fever (a high temperature). Some people will also feel generally unwell or very tired, have a headache, have muscle or joint aches, go off their food, have stomach pain, and/or feel sick, like they had a very bad flu. If you develop a high temperature (of 38°C or above) you need to let one of the study team know immediately. If your temperature remains high for 12 hours or if we found bacteria in your blood tests, then you would be diagnosed with paratyphoid infection. You will then be treated with a course of antibiotics to clear the paratyphoid infection.

Once you have started the course of antibiotics, paracetamol can be taken to lower your temperature, which we will provide. If you develop paratyphoid A infection, you could feel unwell for several days. The majority of participants who develop paratyphoid infection in this setting, have only limited or mild symptoms, we do not expect you to become severely unwell during this time. However, if this did occur then we would arrange for you to be admitted to a hospital ward until you had recovered.

For safety reasons, we would need to see you when you are first diagnosed and then at 12, 24, 48, 72, and 96 hours later. Attending both the 12-hour and 24-hour visit may not always be required (you will need to attend at least one) – this will be up to the clinical team. These visits are to ensure that you are responding well to the antibiotic treatment. As at other times in the study, additional visits may be required for your safety and the study team would talk to you about these. Blood and stool samples from these visits may be sent to another study site for testing, if required.

Please check the section on the risks of taking part for more information.

What happens if I do not get paratyphoid infection?

If you are not diagnosed as having paratyphoid infection, at day 14 after challenge we would still give you a course of antibiotics. This is to ensure *Salmonella* Paratyphi A bacteria are eliminated from your body.

What antibiotics will I be taking and what are the potential side effects?

We will use two antibiotics called ciprofloxacin and azithromycin. They come as tablets, ciprofloxacin is taken on the first 4 days and azithromycin is taken for the following 10 days. They are both recognised as being the best treatments for paratyphoid infection and are widely used for treatment of many different types of infections. In order to monitor your response to antibiotics and any potential side effects, we would ask you to continue completing the e-diary after starting treatment. If you were to develop any symptoms after starting antibiotics, we would ask you to contact us. We would be able to advise you on the most appropriate course of action, which might include switching you to an alternative antibiotic.

Most people do not have any side effects from these antibiotics. General side effects of antibiotics can sometimes occur. These might include upset stomach, nausea, vomiting, diarrhoea, headache or thrush. Occasionally, ciprofloxacin can cause a rash, dizziness or itching and changes in the liver or kidney blood tests. Very rarely, ciprofloxacin causes sensitivity to sunlight, seizures, problems with the blood cells (reduced white cells or platelets), ringing sound in the ears, joint or muscle pains, tendon inflammation or areas of numbness/pins and needles. It can also trigger or worsen depression, or make people feel confused, or experience hallucinations or other strange sensations. At the screening visit, the study team will provide you with the MHRA patient information leaflet on ciprofloxacin; please read this for more information on the severe side effects associated with this antibiotic. To reduce the potential side effects, you would take a shorter course of ciprofloxacin, followed by azithromycin. With azithromycin, people can occasionally have insomnia, dizziness, vertigo, muscle pain, problems with the blood cells (e.g., reduced white cells). Rare azithromycin effects may include allergic reactions, sensitivity to sunlight, liver problems or skin becoming yellow (cholestatic jaundice). We will discuss these with you at your screening visit and would ask you to monitor for any of these symptoms (in particular: tendon pain, numbness of hands/feet, worsening mood) and let us know immediately if you developed any of them. It is vital that you keep good communication with your study team regarding any potential side effects, because the sooner they are sorted, the less severe they are. If after starting ciprofloxacin or azithromycin it was found that you were unable to continue taking either, there are several other effective antibiotics we can use, including trimethoprim/sulfamethoxazole or amoxicillin. If you needed an alternative antibiotic, we would discuss any potential side effects with you.

Participants using oral hormonal contraceptives (‘the pill’) should use additional barrier contraception (such as condoms) during the challenge period until shown to have cleared the bacteria (approximately 3 months in total), in case absorption through the gut lining has been affected by the bacteria from the challenge or by the antibiotics use.

The amount of antibiotic that is absorbed can be affected by antacids and iron supplements. We would therefore ask you not to take these whilst you were taking the antibiotics.

It is possible that the vaccine, paratyphoid A exposure and the antibiotics used to treat the infection have a transient effect on your gut and the balance of bacteria that naturally live in your body. One aspect of this study will be to look at the effect of these on the bacteria in the stool.

Will I need to take any other medicines?

Some people may experience symptoms after being 'challenged' and, if required, the study doctor can prescribe medication to help with these (e.g., laxative for constipation). Any such medicine, including its benefits and side effects, will be discussed with you beforehand.

In certain circumstances it is acceptable to continue to take long term medications (e.g., the 'pill') – one of the study doctors would discuss this with you during screening. If during the study any other treatment became necessary, it would be important to inform us immediately so that we could ensure that the antibiotics and treatment you had been given were safe. We would ask you to inform us of all the medications (including vaccines) that you took during the study, which will include keeping a record of the medications you take for 28 days after vaccination and after challenge in the e-diary.

What samples will be collected?

We would take blood and urine samples as part of the screening visit, to help us assess your general health. Stool samples would be collected at the study visits after the challenge and until clearance, for safety reasons, and some participants may also be asked to provide stool and saliva samples at some other visits. Some of the samples are for research tests and we would not be able to provide these results, but we can give you the results of your other tests, if you would like them.

The total volume of blood taken will not be the same for everyone. This is because we intend to take different samples depending on whether people develop paratyphoid infection or not. A maximum of 900 mL of blood will be taken over the study period of 7 months. As a comparison, if you were to give blood to the National Transfusion Service a woman would be able to give a maximum of 1410 mL per year over three visits and men 1880 mL per year over four visits. For this reason, participants will be asked not to donate any blood while participating in the study.

What will happen to the samples I give?

The blood, saliva (if applicable) and stool samples collected during this study would be transported locally to Study Centres, NHS Trust laboratories or other UK private laboratories for analysis or to the University of Oxford research laboratories or to UKHSA (the UK Health Security Agency) for research analyses. Those analysed in local study site laboratories or NHS laboratories will either be discarded once analysed, or where bacteria have been grown, the bacteria may be transferred to University of Oxford research laboratories or Oxford NHS Trust Laboratories for storage and further analysis for this study. We would also send some samples to other researchers working with us on this research project, including researchers within and outside the UK. All of the samples would be assigned a study code which is used instead of your name or other identifiers when sent outside of your local research centre, appointed laboratories and the University of Oxford. However, your DNA is unique to you so

it can never be completely anonymous. Samples transported to the University of Oxford may be stored at secure storage locations outside of the University of Oxford for the duration of the study. The University of Oxford would still retain overall responsibility for sample storage and handling.

Would any genetic tests be done?

Some blood would be used to look at the pattern of genes being actively used by your body in response to the vaccine and during *Salmonella* Paratyphi A infection. The response to infection and to vaccines is in part genetically controlled, so knowing the pattern of genes that are being used may help us to understand how individuals respond to vaccination and paratyphoid infection.

What else do I need to know?

If you chose to take part in this study, we will be asking for your permission to store your samples in a collection of samples called a 'Biobank'. Details about this will be discussed at your screening visit, and you are free to say no to the Biobank and continue to take part in this study if you wish.

Should you consent to this, you will NOT be asked to donate extra samples and you will NOT be asked to undergo any extra procedures. All samples will be stored in a de-identified way.

What if we find something unexpected?

If abnormal results or undiagnosed conditions are found during the course of the study these would be discussed with you and, if you agree, your GP would be informed of these results (we would not report them to anyone else without your permission). For example, a new diagnosis of high blood pressure might be made.

In the UK, healthcare professionals are legally obliged to report any new suspected cases of acute hepatitis B and hepatitis C to the public health agency. If you are found to have acute hepatitis B or C, we will be required to send a report to the public health agency, including your name and personal contact information. It's important to note that you cannot opt out of this. This many also involve a referral to your GP or specialist for further testing.

Any newly diagnosed conditions would be looked after by your GP.

What are the advantages of taking part in the study?

There is no direct benefit from taking part in the study. As part of the screening investigations, you will receive information about your general health, but this is not a health check. We hope that the knowledge gained from this study will contribute to the understanding of paratyphoid disease and vaccine development. You may receive an experimental vaccine that could prevent you becoming unwell with paratyphoid A and typhoid infections, either as part of the study or at some future date. We **cannot guarantee** however that you will be protected from these infections either during the study or in the future.

Are there any disadvantages or risks from taking part?

Risks of vaccination

Both vaccines may cause side effects. These might be systemic such as headache, muscle or joint aches, reduced appetite, fever, chills/ rigors and feeling generally unwell; or local reactions such as redness, itching, swelling and pain at the injection site. Less common side effects could include cough, a cold, or allergic reactions such as a rash. We will observe everyone in the study for any side effects, particularly in the first seven days after receiving a vaccine by asking you to complete an electronic diary. Side effects may be mild or severe. Most effects will stop shortly after receiving the vaccine. In the Phase 1 study of this vaccine conducted in healthy participants in India, it was given to 30 participants and found to be safe and well tolerated. However, it is important to notify the study team if you are at all worried about your symptoms.

You may take medicines after you've received a vaccination to help lessen side effects; for example, if you have a fever after vaccination, you could take paracetamol to help treat it. Any medication you have taken during the study should be recorded in your e-diary.

With any vaccination, there is a very small risk of an allergic reaction which might be a serious one like an anaphylaxis reaction. However, there will be trained staff and facilities available to manage the situation if that arises.

Risks of undergoing challenge

The risks of taking part in this study are very low, provided that you comply with study visits and maintain close contact with the study team as outlined in this booklet. If untreated, paratyphoid infection can result in serious illness or even death. However, around 500 people have been successfully challenged with *Salmonella* Typhi and Paratyphi A bacteria that cause enteric fever at the Oxford Vaccine Group since 2011 and all have made a complete recovery from infection.

Paratyphoid Infection

While some individuals in the study would remain well and experience no symptoms, we would expect most people to experience symptoms of paratyphoid infection. Whilst symptoms differ from person-to-person, common symptoms include:

- fever
- chills
- headache
- feeling tired and generally unwell
- muscle or joint aches
- abdominal discomfort
- nausea or vomiting
- loss of appetite

You may need to take time away from work/study if you develop symptoms of paratyphoid infection, and in case of severe symptoms, such as vomiting/inability to take the antibiotic tablets, we would arrange for you to be admitted to hospital.

Severe problems are unlikely, as we would treat participants very early on in the course of illness (shortly after developing persistent fever or if a participant has bacteria in their blood tests). Severe complications are rare and mainly occur when paratyphoid fever is not treated properly or in a timely manner. If paratyphoid fever is left untreated, possible complications include bleeding from the gut, a hole developing in the gut, becoming a carrier of paratyphoid, altered consciousness, coma, or death. It is for these reasons that it would be crucial that you take the full course of antibiotics, stay in contact with the study team and let a study doctor know as soon as you developed a temperature or felt unwell.

There is also a small risk of relapse, when the infection may happen again within 2-4 weeks, after completing treatment. In the unlikely event this were to happen, you would require a second course of antibiotics. For this reason, if you develop a fever even after completing treatment, it is important to communicate to the study doctor.

Excretion of bacteria in the stools

A small percentage (up to 10%) of people who contract paratyphoid infection can go on to carry the bacteria and excrete the bacteria in their stools for 3 months or even longer periods. These people are known as 'carriers' and we know that people with gallstones are especially vulnerable to becoming carriers. For this reason, we would do an ultrasound scan of your gallbladder at screening and if we found that you had evidence of gallstones, you would not be able to take part in the study.

We also collect 3 stool samples after you have completed your antibiotics to prove that the paratyphoid bacteria have been fully cleared from your body (called clearance samples). Rarely, stool cultures can remain positive even after you have completed a course of antibiotics. In the unlikely event that this were to occur, you would receive further antibiotics to significantly reduce the risk of you becoming a carrier. If you became a carrier, you would be referred to an Infectious Diseases specialist for further antibiotic treatment.

Antibiotics

A small number of people may have side effects to the antibiotics used to treat the paratyphoid infection. We will discuss these with you when you come to screening. There is further information in the section above called '**What antibiotics will I be taking and what are the potential side effects?'**

General risks

This study involves blood tests at all visits. Taking blood samples may sometimes result in bruising to the area and some people can feel faint. If you were feeling faint, our staff would ask you to stay at the clinic until you felt well again. It is also possible that due to the volume of blood taken in the study you may become anaemic; your blood tests are closely monitored for this.

Can I give paratyphoid infection to anyone else?

Paratyphoid infection is transmitted to other people through them coming into contact with the faeces of infected individuals. This would only occur following poor hygiene practices such as not thoroughly washing hands after using the toilet and before preparing food. Most cases occur within a household and other close contact situations (e.g., sexual contact) but transmission is extremely unlikely if good hygiene practices are followed. We will discuss this with you at screening.

We would give you detailed advice on how to make sure you do not give paratyphoid infection to other people and provide you with liquid soap and disposable towels for the challenge phase. It is very unlikely that anyone could contract paratyphoid infection from you if you maintain good hand washing and food preparation habits. However, to offer peace of mind to your close contacts we would offer them a screening test to check that they are not infected with *Salmonella* Paratyphi A. This would occur after you have started antibiotics, but we would provide you with information to give to your close contacts to explain the risks before this.

In summary:

This study involves:

- Being given a single dose of an intramuscular vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A or a comparator vaccine
- One month later, drinking a solution containing a strain of *Salmonella* Paratyphi A which causes paratyphoid fever.
    - The aim of the study is to see if the vaccine we are testing can induce your body to produce an immune response against the bacteria and see if it can protect volunteers from developing paratyphoid A infection when exposed to it.
- Attending a number of study visits (24-31 visits), including an intensive period of at least two weeks after challenge where you would need to be seen **every day.**
    - There is no need for isolation, but we would ask you to follow strict hygiene measures.
- Having blood, and sometimes saliva and stool samples taken at visits.

The approximate study duration is 7 months.

What is expected of me during the study?

- You need to attend all study visits (including daily visits for 14 days post challenge).
- If your local study site is not a ‘challenge site’, you will need to travel to a challenge site for one visit (The Challenge visit).
- You must remain in mobile telephone contact throughout the study.
- You must have access to the internet.
- You must stay in close contact with the study team throughout the study.
- You must stay/ live within approximately a 60-minute commute to your local study site during the challenge period.
- You must nominate someone who lives near to you and who would know where you were for

the duration of the study as an alternative contact for the study team. You would give this person the study information and ask them to return a signed reply slip with their details and a 24-hour phone number. If for any reason we could not get hold of you or your 24-hour contact during the study and were concerned about your welfare we may visit the place you are staying and/or call the Police.

- You must provide all household contacts with study information given to you by the study team which will offer them screening for *Salmonella* Paratyphi A infection.
- You should record in the study e-diary all your symptoms once a day and your temperature twice a day for the first 7 days after vaccination and the first 21 days after challenge.
- You should record in the challenge e-diary every dose of antibiotics you take
- After *Salmonella* Paratyphi A **challenge**, you must **not** take paracetamol, ibuprofen or any other medication that may lower your temperature unless instructed to do so by a study doctor.
- You must take a full course of antibiotics when given to you.
- Participants that can get pregnant should use an effective method of contraception from one month prior to vaccination until they are shown to be clear of *Salmonella* Paratyphi A bacteria.
- Participants using oral hormonal contraceptives (e.g., the "pill") should use additional barrier contraception (such as condoms) during the challenge period until shown to have cleared the bacteria (approximately 2-3 months in total).
- You must provide at least 3 stool samples after the completion of antibiotics so we can ensure you are clear of paratyphoid. These would be obtained 1 week after you completed antibiotics and would be collected at least 48 hours apart.
- You must follow strict hygiene measures from challenge day until clearance is confirmed.

Who will be informed of my participation?

Your General Practitioner: In order to take part in this study, you would be required to consent for us to contact your GP.

This is to ensure there are no medical reasons that would prevent you from taking part in this study. If you subsequently took part, we would let them know of your participation and demonstrated stool clearance.

As outlined earlier, we would only notify your GP of the results from any other medical tests we performed with your permission.

Public Health Wales: We would inform the local PH Wales team of the names, addresses and dates of birth of all participants that were challenged with *Salmonella* Paratyphi A. This is to ensure that there is independent oversight of the public health aspects of this study. We will also tell them when you have demonstrated stool clearance.

Your close contacts: We would provide you with information about the study to distribute to anyone who is identified as a close contact (for example, members of your household) to invite them to be screened for *Salmonella* Paratyphi A following challenge if they wish.

Your employer: In certain circumstances (see "Why might I be excluded from taking part?"), it may be necessary to tell your Employer about your participation in the study.

Will my taking part be kept confidential?

Yes. All information that is collected about you during the course of the research would be coded with a study number and kept strictly confidential. Any information about you that leaves the clinic would have your name and address removed so that you could not be recognised (with the exception of letters sent to PH Wales, your GP, and your employer (in certain circumstances only) – see above, and documents used to request investigations such as ultrasounds).

Since results from this study may be used for licensing of the SII TCV(B) vaccine, we may be required to share data collected during the study, including information from which you may be able to be identified, with the study funder (Serum Institute of India) and regulators. We would only share identifiable information with the Serum Institute of India to the extent required for potential future licensing of the vaccine.

Responsible members of the University of Oxford team, local study team, NHS or other appointed laboratories, local study site laboratories, authorised representatives appointed by the Sponsor, and regulatory authorities may be given access to data, to ensure your safety as well as for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. The following groups may inspect the study records without violating your confidentiality:

- Monitors who check that the study is being conducted to a high standard, including the Data and Safety Monitoring Committee (DSMC) - an independent panel of experts responsible for study safety.

Pseudo-anonymised data and samples would be sent to other researchers working with us on this research project, including researchers within and outside of the United Kingdom. The data and samples would be pseudo-anonymised, this means that information from which participants could be identified has been removed and stored separately from the dataset or samples which are shared with these researchers. Therefore, these researchers would not receive your personal data.

University of Oxford is the data controller and is responsible for looking after your information and using it properly.

How much will I get paid?

All participants will be reimbursed for their time, travel and for inconvenience.

Payments are made directly by bank transfer in instalments during the study. For this reason, we require participants to provide their bank details (including account name, sort code and account number) at screening. Consent will be obtained prior to requesting and storing personal bank account details.

All personal banking details will be stored confidentially and retained while the participant is actively involved in the study and participants' bank details will be stored to align with local site financial policy.

Personal information such as your name, bank details and national insurance number may be shared with the site finance team to process or verify your reimbursement payments. Financial auditors may also audit the records where this information is held. All confidential data will be stored according to the UK General Data Protection Regulation.

Reimbursement Information

Study visit number	Visit type	Amount	
Screening **(including ultrasound if this is conducted)[1]**	Screening assessment	£110	Payment Trigger 1 after screening complete
D-28	Vaccination	£110	
	Full completion of Diary	£30	
D-21, D-14, Post-vaccine immunology, pre-challenge visits (as required)[2]	Follow-up	£90/visit	Payment Trigger 2 after vaccine follow up visits
D0	Challenge visit[3]	£110	
	Days off work - 10 days[3]	£150/day	
D 1- D14	Follow-up visits[3]	£90/visit	
PD to D14PD, as required	Diagnosis visits[3]	£90/visit	
	Full completion of Challenge Diary	£30	Payment Trigger 3 at the end of diagnosis, or D14 post challenge visits
D28		£90/ visit	
Stool samples 1-3		£30/ sample	Payment Trigger 4 after the 3 clearance stool samples
D90, D180	Follow-up visits	£90/ visit	Payment Triggers 5 and 6 after D90 and D180 visits, respectively
Unscheduled visit(s)	If required, as per PI discretion only	£90/ visit	If unscheduled visits have occurred, they will be paid at the next payment trigger point.
Per participant total (not including unscheduled)		Up to £4410	

[1] *The ultrasound visit may occur on a separate day from the screening visit. The total payment for completing screening will be the same (£110) regardless of whether the visit occurred on the same day or a separate day.*

[2] *The post-vaccine immunology visit, the pre-challenge visit and the D0 visit may all happen separately or (most commonly) they may all be combined into one or two visits. In the event that all*

three visits are held on one day, the highest amount of £110 will be paid to the participant. If the three visits are spread across two days, participants will be paid for both days, as applicable.

[3]All participants who are challenged will be paid for the Challenge visit, receive the 10 days off work reimbursement, reimbursement for D1 to D14 and reimbursement for the PD visit only (not subsequent PD visits), regardless of whether they are diagnosed.

Travel for participants travelling from the parent site to the challenge site will be arranged for the participant and therefore does not require reimbursement.

Payments will be made in accordance with the table above. All payments will be made via bank transfer and can take 6-8 weeks to be processed and may take longer around bank holidays.

Participants will receive a maximum total of £4410 for the scheduled visits if they remain in the study for the entire period (includes payment for screening), depending on the visits that are required for them.

The reimbursement provided are considered to be reasonable amounts to cover the costs of participating in this research. There should not be any consequences for tax or benefit purposes.

Is there anything else I should know?

If you have private medical insurance, you are advised to contact your insurance company before participating in this study.

Where can I get advice on whether to take part?

We are happy to answer any questions you might have and contacting us does not commit you to taking part in the study. Please feel free to contact us by email: id.research.cav@wales.nhs.uk or by phone: 02921847059.

What will happen to my data?

An online screening questionnaire is used to determine your eligibility. For those participants who proceed to take part in the study, the data from the screening questionnaire will be kept with their study records. For those who do not proceed to participate in the study, all answers from the screening questionnaire will be kept until the end of the study recruitment period and then will be deleted. If you supplied your medical history or underwent screening but were not vaccinated in the study either because you were not eligible or decided not to take part, then any data collected will be kept until the end of the study.

Responsible members of the University of Oxford, regulatory authorities, study monitors and the relevant NHS Trust(s) may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. Since results from this study may be used for licensing of the SII TCV(B) vaccine, we may be required to share data, including information from which you may be able to be identified, with the study funder (Serum Institute of India) and regulators.

We would only share identifiable information with the Serum Institute of India to the extent required for potential future licensing of the vaccine.

You will be given a study number, which will be used on study paperwork and samples. We will be using information from your medical records in order to undertake this study and will use the minimum personally identifiable information possible. We may need to view your ID (driver's license, passport or national ID card) and will record either your national insurance or passport number for TOPs database registration and payment processing. This will be taken at the screening visit. We will securely retain this information until the end of the study. Your bank details will be stored in line with the Cardiff and Vale University Health Board's financial policy.

General Data Protection Regulation (GDPR) requires that we state the legal basis for processing information about you. Medical research is regarded as "a task in the public interest". The University of Oxford is the Sponsor and the 'data controller' and will use your personal information to contact you about the research study and make sure that relevant information about the study is recorded for your care in relation to your health during the study, and to oversee the quality of the study. Your personal information will be kept confidential and handled in accordance with data protection laws in the UK.

Study staff will ensure that participants' data is pseudo-anonymised other than for uses (e.g., notification to PH Wales requesting investigations such as ultrasounds and communication with the GP) about which the participants will be consented for. Participants will be identified by initials and a participant ID number on the study paperwork. Your email address is required for the electronic diaries, in order for them to function. Only designated site staff and the data managers(s) will have access to view your email address and you will need to consent to this.

We may disclose your personal data to our third-party service providers to carry out activities specifically for the purpose of this research study and as explained in this information sheet, for example text messaging service providers/companies to send study-related text messages to you. Any third-party service providers are required to take appropriate security measures to protect your personal data in line with University of Oxford policies. We do not allow our third-party service providers to use your personal data for their own purposes, but rather to only process your personal data for specified purposes and in accordance with our instructions.

Study data may be stored electronically on a secure server by the University IT team and paper notes will be kept in a secure location at each study site or as outlined in local SOP's. We will store the research data and any research documents that contain personal information, such as consent forms, securely for up to 25 years after the end of the study, or as per national regulatory requirements. Anonymised research data may be kept indefinitely. It will not be possible to identify you in any publication or report.

You can stop being part of this study at any time, without giving a reason, but we will keep information about you that we already have, including samples and symptom diary data. If you prefer, you can request that your samples are destroyed (if they have not already been analysed).

If you have agreed that samples can be retained for future research, then your personally identifiable information will be kept with restricted access solely for the purposes of sample management. Samples will be provided for future research only in a form that does not identify you.

At the completion of the study, unless you consent otherwise (e.g., if you request to be informed of other studies), your personal details will not be used to contact you other than exceptional circumstances concerning your safety. If you consent to take part in another study carried out by the Cardiff and Vale University Health Board, personal information and medical information including blood test results may be accessed to avoid unnecessary repetition.

If you agree to future contact (e.g. to be informed of other studies) we will continue to store your consent form within the study records and personal information (e.g. name, DOB, contact details) in a password protected database. This will be archived on a university server with restricted access and kept indefinitely, or until the study team feel that it would no longer be required, at which point it will be deleted. This will be held separately from the study data and you can request at any time to have your details removed. If you have not consented to be approached for future studies, your contact details and consent form will be destroyed after 25 years as per national regulatory requirements.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at: https://cavuhb.nhs.wales/use-of-site/privacy-policy/

You can find out more about how we use your information:

- At www.hra.nhs.uk/patientdataandresearch
- By asking one of the research team
- By sending us an email to id.research.cav@wales.nhs.uk
- By ringing us on 02921847059 (Research Team)

What will happen if I do not want to carry on with the study?

If at any time after agreeing to participate you change your mind about being involved in this study, you would be **free to withdraw at any time** without giving a reason.

If you wish to leave after drinking the challenge (*Salmonella* Paratyphi A) bacteria, then you would need to:

- Take a full course of antibiotics.
- Provide 3 stool samples one week after completing the antibiotics to demonstrate clearance.

The reason for this is to ensure you would be treated and free of the bacteria, as very serious consequences can occur in individuals with untreated paratyphoid infection. We would also need to refer you for follow up with your own GP. We would also inform PH Wales of when you demonstrate clearance.

If you withdraw from the study after we have collected samples from you, unless you state otherwise, any biological samples, which have been collected whilst you have been in the study, will be used for research as detailed in this participant information sheet.

What if there is a problem?

The investigators recognise the important contribution that volunteers make to medical research and will make every effort to ensure your safety and wellbeing. The University of Oxford, as the research sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your taking part in this study. If something does go wrong, you are harmed during the research, and this is due to someone's negligence, then you may have grounds for a legal action for compensation. While the Sponsor will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint. The study doctor can advise you of further clinical action and refer you to a doctor within the NHS for treatment, if necessary. NHS indemnity operates in respect of the clinical treatment provided.

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you can contact the PALS (Patient Advice and liaison Service), Patients Experience Directorate, Concerns Department Tel : 029 2074 4095, Email: concerns@wales.nhs.uk, Website: www.cardiffandvaleuhb.wales.nhs.uk/concerns-complaints or you may contact the University of Oxford Research Governance, Ethics and Assurance (RGEA) office (the Sponsor of the study) at rgea.complaints@admin.ox.ac.uk or on 01865 616480.

Who is organising the funding?

This study is funded by the Serum Institute of India.

Who has reviewed the study?

The study has been reviewed by the study sponsor (the University of Oxford). It has been approved by an independent research ethics committee (South Central – Berkshire Research Ethics Committee) and the Medicines & Healthcare products Regulations Agency (MHRA).

What will happen to the results of the study?

The results of the research will be published on the University of Oxford website, presented at conferences or published in a scientific medical journal(s), which can potentially take a few years. All publications will be available online and you may receive a letter containing these results. Your individual results would not be identifiable, nor would you be identified in any report or publication.

The results of the research and the data generated by the research will also potentially be used for future academic research

What do I do now?

Thank you for considering taking part in this study.

If you do not wish to participate in the study, you do not need to contact us. If we do not hear from you, we will assume that you do not want to take part in the study. However, you are welcome to contact us using the contact details below if you wish.

If you are interested in participating in the study, you do not need to make a final decision straight away. If you wish to discuss any element of the study further or clarify any doubts, please consider:

- Checking our website https://www.ovg.ox.ac.uk/studies/bivista/cardiff
- Contact us using the contact details below:

Email: id.research.cav@wales.nhs.uk

Phone: 02921847059

Yours sincerely,

Dr Matthijs Backx

Cardiff and Vale University Health Board