OXFORD VACCINE GROUP

Investigating Enteric Fever

Study Information Booklet – Part A

You are invited to take part in a study to investigate how people respond to enteric fever. The study is being run by the Oxford Vaccine Group which is part of the University of Oxford.

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 the 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).

Thank you for considering taking part in this study.

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Who are the Oxford Vaccine Group?

The Oxford Vaccine Group, which is part of the **University of Oxford**, is an independent research team of doctors, nurses and play assistants. We carry out research studies of new and improved vaccines for babies, young children, teenagers and adults and teach doctors and nurses about immunisations. In the past 5 years alone, over 7000 participants in the Thames Valley area have taken part in our research studies.

Why have I been invited to take part?

We are inviting healthy adults aged 18 to 60 years old to take part in this study. We use various ways to contact potential volunteers, including the Electoral Roll or the National Health Applications and Infrastructure Services (NHAIS) who hold the central NHS patient database (Open Exeter). This database identifies all persons within the local area who are in the appropriate age range. Please note that we do not have your contact details unless you have provided us with these.

What is enteric fever and what is the study about?

Salmonella Typhi (typhoid) and *Salmonella* Paratyphi (paratyphoid) cause an infection called enteric fever, responsible for over 30 million infections worldwide each year and approximately 200,000 deaths, mostly affecting children. Enteric fever is a particular problem in developing countries due to inadequate sanitation and water supplies. Disease is spread when bacteria from an infected individuals' faeces contaminates food and water supplies. Although rare in the UK, it can be picked up by travellers to developing countries. Symptoms include fever, headache and generally feeling unwell; however, if not treated properly with antibiotics, enteric fever can lead to severe complications and even death.

In this study, we are aiming to understand more about enteric fever and how it affects the immune system. This knowledge will help us better understand enteric fever, develop new diagnostic tests, and help develop a vaccine against the disease.

Are there vaccines against enteric fever?

Partly. A vaccine for *Salmonella* Typhi does exist but only prevents 30-60% of infections. Whilst these two bacteria sound similar and cause similar symptoms, no vaccine is currently available to protect against *Salmonella* Paratyphi infection and there is no combined vaccine.

What is the purpose of this study?

In this study, we are investigating how the immune system responds when a person is given either *Salmonella* Typhi or *Salmonella* Paratyphi. To do this we will be deliberately infecting participants by asking them to swallow a solution containing one of these bacteria, then treating them as soon as they show any symptoms of infection. This process is known as a 'challenge' and has been undertaken by 173 participants in previous Oxford Vaccine Group studies since 2009.

We have two main groups in this study. The first group of volunteers are 'naïve' to enteric fever, meaning they have never had enteric fever or received *Salmonella* Typhi or *Salmonella* Paratyphi as a part of a research study (this applies to you). The second group of volunteers have had *Salmonella* Typhi or *Salmonella* Paratyphi as part of the previous challenge studies performed by the Oxford Vaccine Group. We will then study these participants to see how their gut and immune systems respond to their first or second exposure to these bacteria. This will give us valuable information on how to prevent and diagnose infections in the future.

Another small number of individuals would be recruited to act as 'controls'. This means they would have the same procedures as outlined in this booklet but would not receive the bacteria.

Who can take part in the study?

We are looking for people who are healthy, aged 18 to 60 years of age and have not been exposed to *Salmonella* Typhi or Paratyphi before. If you had any significant medical conditions, a history of alcohol or drug abuse, or are pregnant, planning on becoming pregnant, or breastfeeding, you would not be able to participate. If you live or work with vulnerable people (e.g. people with poor immune systems and young children), or work in a profession which handles food, then you may not be able to take part in the 'challenge' but could act as a 'control' participant.

You would need to be available for an intensive period of 4 weeks where you would

attend daily visits with study doctors and nurses for 2 weeks, take a 2 week course of antibiotics, and remain in contact with the study team.

In addition, you would also need to be available for two endoscopies (a procedure where a camera looks down into the stomach and first part of the small intestine; this would be a half-day procedure). The first would be 6 weeks before the 'challenge' day and the second approximately a month afterwards.

Visits occur either at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) at the Churchill Hospital site or at the Endoscopy Unit, John Radcliffe Hospital.

We would prefer people not to be planning an extended trip in the first month following challenge. Follow-up visits would then be at 1, 3, 6 and 12 months after the 'challenge' day. If you are in the control group, follow-up finishes after 3 months.

You would also need to be contactable by mobile telephone and have access to the internet at home. If you have or had a significant psychiatric illness or a drug or alcohol problem you could not participate in the study.

How many other participants are there in the study?

We are aiming to enrol up to 60 participants to receive the challenge bacteria in this 'naïve' group, and up to 10 'control' participants in the study. A further possible up to 100 participants who have participated in previous typhoid or paratyphoid challenge studies will be recruited as a part of a separate group.

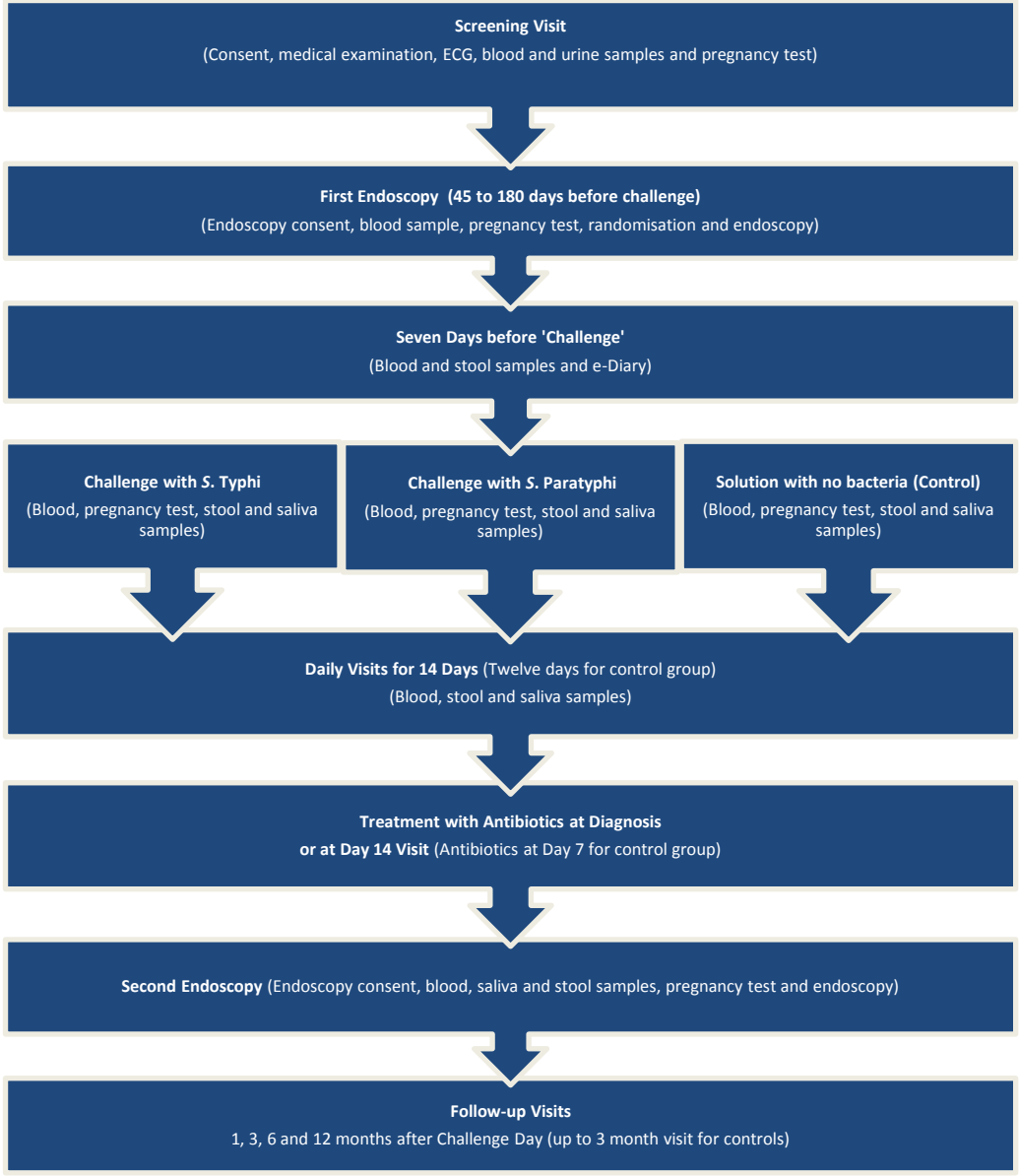
What happens in this study?

An outline of the study visits can be found in the chart below. If you expressed an interest in taking part, a member of the Oxford Vaccine Group would contact you by telephone to discuss the study. If you are still interested after this then we would organise for you to come to the CCVTM for a screening visit. If you met the study recruitment criteria, you would have:

- An endoscopy
- Approximately 6 weeks later would drink a solution containing the Salmonella Typhi or Paratyphi bacteria (or neither, for controls)

- Daily visits for 2 weeks following challenge, treatment with antibiotics and a second endoscopy
- The option of additional tests such as the wireless capsule endoscopy or enteric string test

These all are explained below in more detail.


Screening Visit
(Consent, medical examination, ECG, blood and urine samples and pregnancy test)
First Endoscopy (45 to 180 days before challenge)
(Endoscopy consent, blood sample, pregnancy test, randomisation and endoscopy)
Seven Days before 'Challenge'
(Blood and stool samples and e-Diary)
Challenge with S. Typhi
(Blood, pregnancy test, stool and saliva samples)
Challenge with S. Paratyphi
(Blood, pregnancy test, stool and saliva samples)
Solution with no bacteria (Control)
(Blood, pregnancy test, stool and saliva samples)
Daily Visits for 14 Days (Twelve days for control group)
(Blood, stool and saliva samples)
Treatment with Antibiotics at Diagnosis
or at Day 14 Visit (Antibiotics at Day 7 for control group)
Second Endoscopy (Endoscopy consent, blood, saliva and stool samples, pregnancy test and endoscopy)
Follow-up Visits
1, 3, 6 and 12 months after Challenge Day (up to 3 month visit for controls)

Screening Visit

The **purpose of the screening visit is to assess whether you are able to participate in the study** without taking any extra risk to your health.

At the screening visit we would sit with you and go through the study in detail. This visit would provide an opportunity for you to ask any further questions you might have about the study and what's involved. You would be allowed as much time as you feel necessary before making any decision on whether to take part.

If you are keen to proceed, we would ask you to sign an **informed consent form** and complete a short consent quiz to assess your understanding of what the study involves. Only once this is signed would we then start any study procedures.

We would ask you questions about your health, undertake a physical examination including an ECG ('heart tracing') and take a urine and a blood sample to ensure you are healthy. Blood will be screened for HIV and Hepatitis B and C, coeliac disease as well as for a type of antibody that some people lack without knowing (called IgA deficiency). All participants are asked to complete a questionnaire to assess anxiety and depression. In addition, you would be asked to attend a separate appointment for an abdominal ultrasound to check for gallstones, which can cause you to carry *Salmonella* Typhi or Paratyphi in your gallbladder. We would also contact your GP to confirm your eligibility. For all females, we would perform a pregnancy test.

We would also seek your consent to register you on the 'The Over-volunteering Prevention System' (**TOPS**) national database. This is designed to prevent the potential for harm by volunteering in too many clinical trials involving investigational medicinal products and blood donations. This would be done using your National Insurance number (or passport number if you do not have a National Insurance number). We would also require your National Insurance number for your reimbursement processing.

Once the study team have confirmed your suitability for the study, we would inform you and arrange a date for your endoscopy and then further visits.

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 make a decision there and then.

Endoscopy

An important aspect of this study is to look at how the gut (gastrointestinal system) defends the body against infection. The gut has a large part to play in the immune defence against microbes (or 'bugs') that enter the body from the mouth. To study how the gut defends the body against infection, we will be asking participants to have two endoscopies where we will be collecting tissue samples (called biopsies) from the gut lining. As the gut lining does not have sensation, taking biopsies is painless. From these samples we aim to answer questions on how the bacteria cause illness and why some people are protected and others become unwell.

The two endoscopies are performed by the Gastroenterology team at the Endoscopy Unit, John Radcliffe Hospital. If you are taking part in this study you will receive a separate information booklet about the procedure and would need to sign a specific consent form if you are happy to proceed. To prepare, you would be asked to fast for 6 hours. For comfort, an anaesthetic spray would be used to numb the throat and a sedative would be offered. A flexible endoscope with a camera on the end goes in the mouth, through to the stomach and to the first part of the small intestine. Intestinal fluid and tissue samples from the lining of the small intestine will be taken. The endoscopy and biopsy takes approximately 20-25 minutes in total. You would be observed for up to 2 hours after the procedure to ensure any anaesthetic or sedation has worn off and ensure you are able to eat and drink as normal (allow a maximum of four hours for this visit) .

If you receive sedation you will not be permitted to drive home or use public transport. You must arrange for a family member or friend to collect you. The study team will need to be given their phone number so that we can contact them when you are ready.

What are the risks of endoscopy?

An endoscopy is a simple and safe examination for most people. Serious problems are rare. The risks can be associated with the procedure itself or with the sedation.

The main risks are:

- A tear (perforation) in the lining of the stomach or oesophagus. This happens to approximately 1 in 10,000 people and is most commonly

associated with biopsy of an underlying cancer or other abnormality which usually, but not always, has caused symptoms before endoscopy. Perforation can be treated with rest, antibiotics and fluids or may require surgery to repair the hole.

- Bleeding may occur at the site of biopsy and nearly always stops on its own. Very rarely this could result in an admission to hospital.
- Problems with breathing, heart rate and blood pressure – such problems are normally very short lived and unlikely in healthy volunteers. We will monitor you carefully so that if any problems do occur they can be treated quickly.
- Mechanical damage caused by the endoscope to teeth – this is very rare.

Pre-challenge visit (7 days before challenge)

You would be given a date, time and place to come to at the Oxford Vaccine Group at the Churchill Hospital. We would start by checking that you are happy to remain in the study and ask if anything had changed medically since we last saw you.

We collect blood and stool samples from you and get you set up with an electronic diary card (e-Diary) that you fill in for 28 days, recording your temperature and any symptoms you may have. The control group are also asked to fill in this diary as other illnesses or the antibiotic treatment we give you can cause symptoms.

We will also ask you to record information about your diet for seven days before challenge. We are interested in studying how the bacteria in your gut affects challenge with the Typhoid/Paratyphoid bacteria and vice-versa. Collecting information about your diet will help us to determine if differences in diet can also have an impact on your response to challenge.

We then arrange the date and time for your challenge visit one week later.

Challenge visit (Day 0)

The challenge visit occurs between 45 and 180 days after the first endoscopy to allow your intestine to fully recover from the procedure. The challenge day involves having two appointments at the Churchill Hospital, Oxford. You would be asked to come to the clinic first thing in the morning with a fresh stool sample. You would have blood, saliva and urine tests taken and women would have a further urine pregnancy test performed. You would be asked to fast for 90 minutes before the visit.

Prior to the challenge visit, the study team will randomly allocate you to receive either *Salmonella* Typhi or Paratyphi. This means a computer programme will randomly assign participants on a 1:1 ratio to receive either bacteria, similarly to tossing a coin. The study team would not be able to influence which challenge bacteria you are to receive. You would not find out what challenge bacteria you received until after you completed treatment with antibiotics.

We would give you a drink to counteract the acid in your stomach (as stomach acid can kill *Salmonella* Typhi and Paratyphi) followed by a drink containing either *Salmonella* Typhi or Paratyphi bacteria. You would then be asked to fast for a further 90 minutes. The control group would receive the drink to counteract stomach acid but would not receive a drink containing either bacteria. We make sure that your e-Diary is working and provide you with a thermometer before you leave.

We then see you 12 hours after the challenge to collect a blood sample. It is really important that you do not take paracetamol, ibuprofen or any other medication that may lower your temperature, unless instructed to by a study doctor, as this will interfere with the diagnosis of enteric fever.

Do I need to prepare in any way for the challenge?

You should not take any medication other than hormonal contraceptive ('the pill') leading up to the challenge unless discussed with a study doctor. In certain circumstances it would be acceptable to continue to take long term medications – one of the study doctors will discuss this with you during screening. Your health and well-being is much more important than the conduct of this study and if at any time you required any medication then you should take it and inform the study team before you started on any treatment. For example, antibiotics could affect the *Salmonella* bacteria and the day you were challenged might have to be rescheduled. If during the study any other treatment becomes 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 ask you to keep a record of all the medications (including vaccines) that you take during the study.

What are the risks of undergoing challenge?

The risks of taking part in this study are very low provided that you follow all study procedures and attend visits as outlined in this booklet. If left untreated, enteric fever could result in serious illness or even death. However, nearly 2,000 people

have been challenged with typhoid bacteria during studies conducted in the United States in the 1960's and at the Oxford Vaccine Group since 2009 and all have made a complete recovery.

Based on previous studies, we expect between half and two thirds of the group who have not been previously exposed to *Salmonella* Typhi or Paratyphi to develop enteric fever. Even if diagnosed with enteric fever, some individuals will remain well and experience minimal symptoms.

Risks of enteric fever

Common symptoms of enteric fever include:

- Fever and chills
- headache;
- muscle or joint aches,
- abdominal pain (tummy upset), nausea and/or loss of appetite.
- tiredness and/or feeling generally unwell

If enteric fever is left untreated, possible complications include bleeding from the gut, a hole developing in the gut, becoming a carrier of typhoid or paratyphoid, altered consciousness, coma or death. Severe complications are unlikely as we treat participants very early on in the course of illness (within 12 hours of onset of fever or if a participant has the bacteria in their blood). 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.

You would be required to provide the study team a 24 hour contact of someone who lives near you, who would know where you were for the duration of the study and who are willing to have the study team contact them. You would give the study information to this contact and ask them to sign a letter with their name and contact details. If you failed to attend a visit and we were unable to contact you, your 24 hour contact would be called. If your whereabouts were still unknown, study staff would make every effort to ascertain your whereabouts, e.g. attending your home. If study staff still could not locate you, study staff would inform the police to ensure your safety.

Risk of Carriage

Some people who contract enteric fever can go on to carry the bacteria and excrete the bacteria in their stools. When this happens, it is almost always in people with gallstones. For this reason we do an ultrasound scan of your gallbladder prior to challenge. If you did have gallstones you would be unable to take part. In the very unlikely event that you did become a carrier you would be referred to an infectious diseases doctor for further antibiotic treatment. Those in the control group will not require a gallbladder ultrasound as they will not be challenged with the bacteria.

To ensure clearance after challenge, you must provide three stool samples after the completion of antibiotics. The first sample is taken 1 week after you have completed antibiotics and the next two samples are collected at least 48 hours apart.

Participants in the control group would not be at risk of getting enteric fever or passing it to their contacts.

What happens at the follow-up visits?

Follow up visits would be at the CCVTM or in a dedicated area on the adjacent John Warin Ward (infectious diseases ward). It is essential that you are available in Oxford until you have completed antibiotic treatment. We would ask each participant to attend every visit, complete the e-Diary, and to keep in contact with the study team who are there for your safety.

After drinking the typhi or paratyphi bacteria, you may develop symptoms of enteric fever or remain well. Some people are diagnosed with enteric fever without having any symptoms. For two weeks after challenge we would like to see you every day in the morning for 30 to 45 minutes and would also contact you in the evening by text message or telephone call. We would ask you to bring a fresh stool sample to each visit.

At each visit we would review your symptoms and e-Diary, measure your temperature, pulse and blood pressure and take blood stool and saliva samples. These samples would be examined for typhi or paratyphi bacteria and used to study your body's immune response to infection. Blood tests will also be taken for genetic testing to see whether a particular genetic makeup can protect against enteric fever. For this reason it is necessary for us to record your ethnicity as this influences how we interpret your genetic tests.

What happens if I get enteric fever?

The main symptom of enteric fever is a temperature. Some people will also feel very tired, have a headache, have muscle or joint aches, go off their food, have stomach pain, and/or feel sick. If you developed a temperature you would need to let one of the study team know immediately. If you have a fever for 12 hours or if we found bacteria in your blood then you would be diagnosed with enteric fever. You would then be treated with a course of antibiotics to clear the infection. Women would have a pregnancy test before being started on antibiotics.

Once you had started the course of antibiotics, paracetamol could be taken to lower your temperature and will be provided. If you do develop enteric fever, you could feel unwell for a couple of days.

If we have concerns about your symptoms or your well-being, we can admit you to a hospital ward, but it is unlikely that this would be necessary.

We are very interested in what happens in the first couple of days after diagnosis of enteric fever so we would like to see you when you are first diagnosed and then 12, 24, 48, 72 and 96 hours later.

What happens if I do not get enteric fever?

If you had not been diagnosed with enteric fever after 14 days we would give you antibiotics. This would ensure elimination of any *Salmonella* Typhi or Paratyphi bacteria from your body.

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

We would use an antibiotic called ciprofloxacin which comes as a tablet taken twice a day for 14 days. This is recognised as being amongst the best treatments for enteric fever and is widely used for treatment of many different types of bacterial infections.

The vast majority of people do not have any side effects from ciprofloxacin. Ciprofloxacin can occasionally cause diarrhoea, stomach upset and stomach pains. Very rarely can it cause rash, mood disturbance, heart rhythm abnormalities, liver

and kidney problems, headache, problems with the blood and sleepiness. If after starting ciprofloxacin it was found that you were unable to continue taking it, there are several other effective antibiotics we can use.

Non-specific side effects of antibiotics can sometimes occur. These might include nausea, vomiting, diarrhoea, headache or thrush. In order to monitor your response to antibiotics and any potential side effects, we would ask you to continue completing an online diary after starting treatment. If you were to develop any symptoms after starting antibiotics, we would ask you to contact one of the on-call doctors who would be able to advise you on the most appropriate course of action, which might include switching you to an alternative antibiotic.

Female participants using oral hormonal contraceptives should use additional barrier contraception (such as condoms) whilst taking the antibiotics, in case absorption through the gut lining has been affected by the bacteria. 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.

Will I need to take any other medicines?

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

What blood, urine, saliva and stool tests will I have?

We would take blood and urine samples as part of the screening visit, to help us assess your general health. Blood, stool and saliva samples would also be taken on the majority of your study visits, in order for us to monitor your immune response and for safety reasons. Some of the samples are for research tests, and we would not be able to provide these results, but we would give you the results of your other tests, if you would like them. We would only send the results to your GP if you consented for us to do so and would not report them to anyone without your permission.

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 infection

or not. No more than 1263ml of blood will be taken over 15 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 1410ml per year, and men 1880ml per year.

Will there be any additional procedures?

A small group of participants may also be asked to participate in optional additional tests such as a video capsule endoscopy (swallowing a camera the size of a vitamin pill which takes images of the stomach and small intestine) or a 'string test' (swallowing a capsule attached to a long string, then later withdrawing the string and collecting liquid from the small intestine). These tests are optional and would not affect your participation in the enteric fever study. If you are interested in these procedures, we can provide you with more information.

What would happen to any samples I give?

The blood, saliva, stool, gut secretions and tissue samples collected during this study would be analysed in laboratories of the Oxford University Hospital and University of Oxford research laboratories. We would also send data and samples to other researchers working with us on this project, including researchers outside the European Union. The data and samples would be anonymised.

What else do I need to know?

If you chose to take part in this study, we will be asking for your separate permission to store samples obtained, including DNA, in a collection of samples called a BioBank. Details of this will be provided in a separate booklet provided to you after you are enrolled into this study. You are free to say no to this and continue to take part in the enteric fever study if you wish.

If you went ahead and took part in the study, you may be eligible for 'rechallenge' in the second group of the study. If you are happy, we would contact you again a year after your first challenge to see if you are interested in taking part in this group.

Would any genetic tests be done?

Some blood would be used to look at the pattern of genes being actively used by your body during *Salmonella* Typhi or Paratyphi 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 the responses to enteric fever.

What if any of my test results were abnormal?

We would notify your GP that you were taking part in this study. If abnormal results or undiagnosed conditions are found in the course of the study these would be discussed with you and, if you agreed, your GP would be informed of these results. For example, a new diagnosis of high blood pressure might be made. Any newly diagnosed conditions would be looked after by your GP within the NHS.

Can I give enteric fever to anyone else?

Enteric fever is transmitted to other people principally through poor hygiene practices such as not thoroughly washing hands after using the toilet and before preparing food. Most transmitted cases are within the household or other close contacts but this is extremely unlikely if good hygiene practices are followed. We would give you detailed advice on how to make sure you don't give enteric fever to other people and also provide you with liquid soap and disposable towels to help. It is very unlikely that anyone could contract this 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* Typhi or Paratyphi. This would occur after you had started antibiotics but we would provide you with information to give to your close contacts to explain the risks before this.

There is no risk of transmission if you are in the control group.

Pregnancy

Enteric fever and certain antibiotics can potentially be dangerous during pregnancy both to the mother and to the foetus. Women would therefore be asked to use an effective method of contraception until the tests show that the *Salmonella* Typhi or Paratyphi bacteria have been cleared. A pregnancy test would be carried out at the screening visit, again before the challenge process and before starting antibiotics.

The next three points apply to those to be challenged with Salmonella Typhi *or Salmonella* Paratyphi *and not the control group.*

Contact with young children and people with problems with their immune system

You should not have close contact with young children (those in pre-school or nursery or those aged less than two years old) or with anyone who has a problem with their immune system until we were absolutely sure that you did not have the *Salmonella* Typhi or Paratyphi bacteria in your body (at least two months after challenge). This is because young children and the immunocompromised catch illnesses more easily and can become more unwell.

Food handlers

Salmonella Typhi and Paratyphi can be spread in food handled by people who are infected with these bacteria. If your work involves handing or preparing unwrapped food that is not subject to further heating then you would not be able to participate in this study.

Clinical and social care occupations (including healthcare students)

If you work in these areas you would have to agree to stay away from your work or studies for the entire challenge period. We would need to inform your employer (or occupational health department) of your participation in the study. If you have direct contact with people or patients who are susceptible to infection (including those under two years of age) or in whom enteric fever would have particularly serious consequences then you would not be allowed to return to work until cleared of infection. This involves obtaining three consecutive negative stool samples, 48 hours apart, commencing one week after completion of antibiotics.

Reimbursement

All participants will be reimbursed for their time, travel and the inconvenience based on the following figures:

- Travel expenses: £15 per visit
- Inconvenience of blood tests: £10 per blood donation
- Time required for visit: £20 per visit
- Time off work reimbursement: £150 per day if applicable
- Endoscopy reimbursement: £100 each
- Enteric string test (optional): £45 each
- Wireless video capsule endoscopy (optional): £45 each

Participants will receive between £3,340 and £3,655 if they remain in the study for the entire period.

Control participants will receive £1345 if they remain in the study for the entire period.

Payments are made directly by bank transfer. For this reason we would require participants to provide their bank details at screening. Bank details would be kept confidential.

Participant payments will be requested at the following visits: screening, Day 14, second endoscopy, Day 90, Day 180, and Day 365.

If you chose to leave the study early or were withdrawn from the study you would be reimbursed according to the length of your participation based on these figures.

Medical photography and film

If you were to have any clearly visible signs of enteric fever we may ask your permission to take a photograph/film. Medical photography/film can be useful in clinical discussions, scientific publications and educational events. We would need your consent to take any photograph/film and if you chose to withhold this, it would not affect your participation in the study in any way. If you did give consent, you would still be able to decide exactly what the images could be used for. We will keep your identity confidential and the storage and access to any images would be tightly controlled to maintain your privacy. In exceptional cases, we may request to take an identifiable image, such as the face. In this case we would request your explicit consent.

As part of the endoscopy, pictures of the gut lining may be taken and stored under your anonymised study code. These images are to show if a change has occurred to the gut lining after ingestion of *S*. Typhi or *S*. Paratyphi.

If you have agreed to have a wireless video capsule endoscopy, the recorder device will capture and store images of the small intestine. These images will be kept under your anonymised study code.

What would be expected of me during the study?

Applies to all:

- You must stay in close contact with the study team until you have completed antibiotics.
- You need to attend all study visits.
- You should record all symptoms you have, medications you have taken, and your temperature twice a day for 28 days in the e-Diary.
- You must not take paracetamol, ibuprofen or any other medication that may lower your temperature unless instructed to by a study doctor.
- You must take a full course of antibiotics when prescribed to you by a study doctor.

Applies to those given Salmonella Typhi or Paratyphi:

- 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 contact study information and ask them to return a signed reply slip with their details and a 24 hour phone number to the study team.
- You must provide all household and sexual contacts with study information given to you by the study team which will offer them screening for *Salmonella* Typhi or Paratyphi infection.
- Female participants should use an effective method of contraception until the *Salmonella* Typhi or Paratyphi bacteria are cleared from their system, including barrier contraception whilst taking antibiotics.
- You must provide three stool samples after the completion of antibiotics so we can ensure you are clear of *Salmonella* Typhi or Paratyphi bacteria. The first sample is taken 1 week after you have completed antibiotics and the next two samples are collected at least 48 hours apart.

Do I have to take part?

No. 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.

Whatever you choose it's important that you are happy with your decision and it is not the role of the study team to help decide for you. We would help present the

details of the study and answer all your questions so you could make an informed decision.

What happens if I don't want to carry on with the study?

If you change your mind about being involved with this study, you would be free to withdraw without giving a reason. We would use the samples and data we have collected from you in our analysis of the study up until the point you informed us that you wanted to withdraw. If you have had the drink of *Salmonella* bacteria then we would need to treat you with antibiotics and make sure you have provided us with three clearance stool samples because of the potentially serious consequences of untreated enteric fever. Your reimbursement would be paid as a proportion of the total reimbursement according to the length of your participation.

If you have concerns about specific procedures you will have an opportunity to discuss these with the study team. In exceptional circumstances, it may be possible to participate in the study without undertaking all procedures.

Is there someone I can contact during the study?

You would have access to a study doctor 24 hours a day until you had been successfully treated for *Salmonella* Typhi or Paratyphi infection. It would be very important that you stay in touch with the study team and let us know as soon as you get a temperature or if you were unwell.

What are the advantages of taking part in the study?

This study will not be of direct benefit to you, but the information we obtain may help our understanding of enteric fever and its effect on the human body. We hope this information will help prevent enteric fever in those who live in areas where it is common or travellers who go to these areas.

Would my taking part in this study 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. Your information would be stored on a secure server, and paper notes would be held by the Oxford Vaccine Group in a locked filing cabinet. Once the study has completed, all documents would be archived in a secure facility for 15 years. Storage of this data

will be reviewed every 5 years and files will be confidentially destroyed if storage is no longer required.

Your data is retained in case we need to contact you regarding any study related matters or if you wish to contact us regarding your participation in the study. We may also contact you to inform you of future related studies.

In order to ensure that the study is being conducted correctly, 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), who are an independent panel of experts responsible for study safety.
- The Clinical Trials and Research Governance Office (CTRG), University of Oxford, who are responsible for ensuring the appropriate conduct of the research on behalf of the research sponsor (the University of Oxford).
- Representatives of the Oxford University Hospitals NHS trust

By signing the consent form for this study, you would be giving permission for these groups to look at your study records; however they would not be able to remove any information that identified you from the premises of the Oxford Vaccine Group.

In order to enrol into this study, you would be required to sign a form, documenting that you consent for us to contact your GP. This is to inform him/her that you would be entering the study, and to ensure there are no medical reasons that would put you at risk whilst taking part in this study.

For those recruited to have *Salmonella* Typhi or Paratyphi 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* Typhi or Paratyphi. We would inform the local Public Health England Unit of the names, addresses and dates of birth of all participants that were challenged with *Salmonella* Typhi or Paratyphi and those that developed enteric fever and/or have *Salmonella* bacteria found in their stools. This is to ensure that there is independent oversight of the public health aspects of this study. No one else would be told that you are involved in the study. As outlined earlier, we would only notify your GP of the results from any medical tests we performed with your permission. With the exception of correspondence with your GP and with Public Health England,

any information about you that leaves the clinic would have your name and address removed so that you could not be recognised from it.

During your screening visit you would be asked to provide your National Insurance number (or passport number if you do not have a National Insurance number). This would be entered on to a national database which helps prevent volunteers from taking part in too many clinical trials. More information can be found at *www.tops.org.uk*. Your NI number (or passport number) would also be stored securely for the duration of the study to be used to process your reimbursement.

Who monitors the conduct of the study?

The study will be under continuous monitoring by the research team at the Oxford Vaccine Group. The Clinical Trials Research Governance (CTRG) on behalf of the Sponsor (The University of Oxford) and a Data and Safety Monitoring Committee (an independent panel of experts) will provide further oversight.

What will happen at the end of the research study?

The results of the research will be published in a scientific medical journal; this can potentially take a few years. All OVG publications will appear on the OVG website and you will 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 will also potentially be used for future academic research within the Oxford Vaccine Group.

Is there anything else I should know?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

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

Where can I take 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. For independent advice you can contact **INVOLVE** (www.invo.org.uk) which is a government funded national advisory group

supporting those considering involvement in NHS, public health and social care research. Please feel free to discuss this study before deciding whether or not to participate.

What if I wish to complain?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact info@ovg.ox.ac.uk or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email ctrg@admin.ox.ac.uk.

At any time during the study you would be entirely free to change your mind about taking part, and to withdraw from the study. This would not affect your subsequent medical care in any way.

Who is funding the study?

The study is funded by the Medical Research Council.

Who has reviewed and approved this study?

The study has been reviewed by the study sponsor (the University of Oxford). It has been approved by an independent research ethics committee (14/SC/1204) and has also been approved by the NHS (NHS R&D approval).

So, in summary, what would happen if I decide to take part in the study?

- We would ring you to arrange an appointment to discuss the study further and answer any questions you may have.
- You would then attend a screening visit at the CCVTM where you would have blood and urine tests (and a pregnancy test for women). An ultrasound scan of your abdomen would then be arranged (unless you are recruited to the control group). These are to assess your eligibility for the study.
- Following satisfactory screening results you would be booked for your first endoscopy which will take place at the Endoscopy Unit, John Radcliffe Hospital.
- 45 to 180 days later you would have a pre-challenge visit and then be randomised to either receive *Salmonella* Typhi or *Salmonella* Paratyphi on challenge day (randomisation not applicable to control group).

- You would be asked to fill in an electronic diary card twice a day for 28 days to record any symptoms you have and your temperature.
- You will then be challenged by drinking a solution that contains the bacteria. For those in the control group you will drink a sodium bicarbonate drink without any bacteria.
- You would attend clinic appointments at least once a day for 14 days during which time blood, saliva and stool samples would be collected.
- You would be treated with antibiotics if you were diagnosed with enteric fever or, if you did not become unwell/are in the control group, 14 days after challenge.
- After completing the antibiotics you would have a second endoscopy with the same procedures performed as the first endoscopy.
- We would continue to see you for the occasional clinic visit up to a year after the challenge visit (3 months for control group).

If you have been offered and agreed to have more information about additional tests as part of this study, that is, enteric string test and/or wireless video capsule endoscopy, further information is available in separate booklets.

What do I do now?

Thank you for considering taking part in this study. You do not need to make a final decision straight away. If you wish to discuss any element of the study further, then please contact us by either

- Telephone (**01865 611400**)
- Website (**www.ovg.ox.ac.uk/recruiting-studies**
- Email (**info@ovg.ox.ac.uk**)
- Reply slip (please find attached)

If you would prefer not to receive an invitation letter, please contact the Thames Valley and South Midlands – Primary Care team to join the opt out register by email: optout.tvsm@nihr.ac.uk or by phone on 07900 407260. Your full contact details would be required to ensure that you would be removed from future mailings. They will ensure research invitation letters are not sent by Open Exeter.

If you would like to change your mailing preferences on the electoral roll, you can contact the mailing preference service by: email mps@dma.org.uk or by phone 020 7291 3310.

Yours sincerely,

Prof. Andrew J Pollard
Professor of Paediatric Infection & Immunity
Clinical Tutor in Medicine
Honorary Consultant Paediatrician

Prof. Brian Angus
Clinical Tutor in Medicine
Honorary Consultant Physician

Malick Gibani
Lead Research Fellow

Lily Norman
Lead Research Nurse

Investigating Enteric Fever

Reply Slip

You can either e-mail us at: info@ovg.ox.ac.uk
OR
Visit our website: www.ovg.ox.ac.uk
OR
Telephone us on: 01865 611400
OR
Use the pre-paid envelope to return this reply slip

☐ **I would like to know more about the study.** Please contact me. I realise that this is not a commitment to taking part in the study.

Your details

Name	
Date of birth	
Your address	
Phone number (and best time to call Mon-Fri 9am-5pm)	
Email address	

OR

☐ **I do not wish to be included in this study**. We will assume that you do not want to take part in the study if we do not hear from you. However, you are still welcome to tick the 'No' box above and provide feedback if you wish.


oxford vaccine group